The Visual Inspection Regulatory and Compendial Environment: Current Issues and Opportunities

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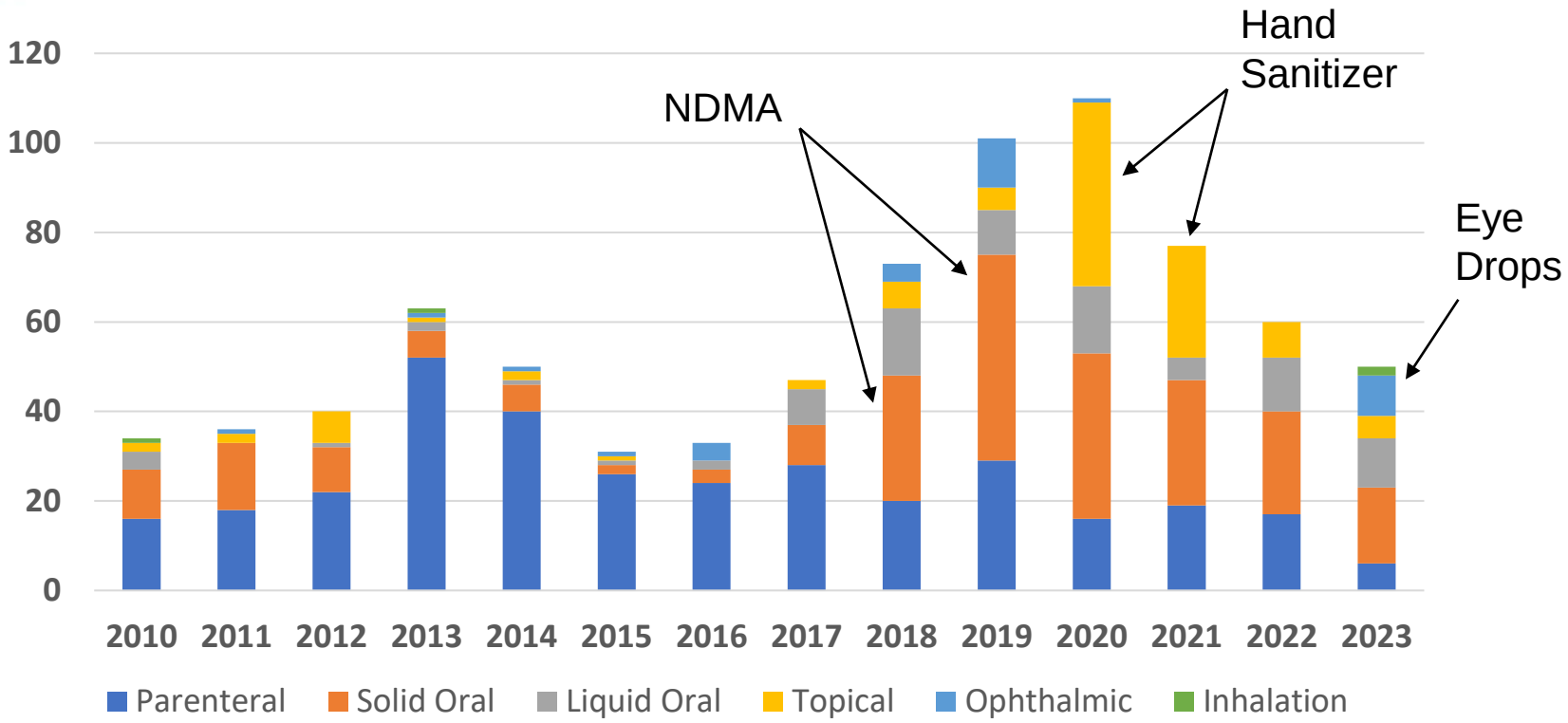
Agenda

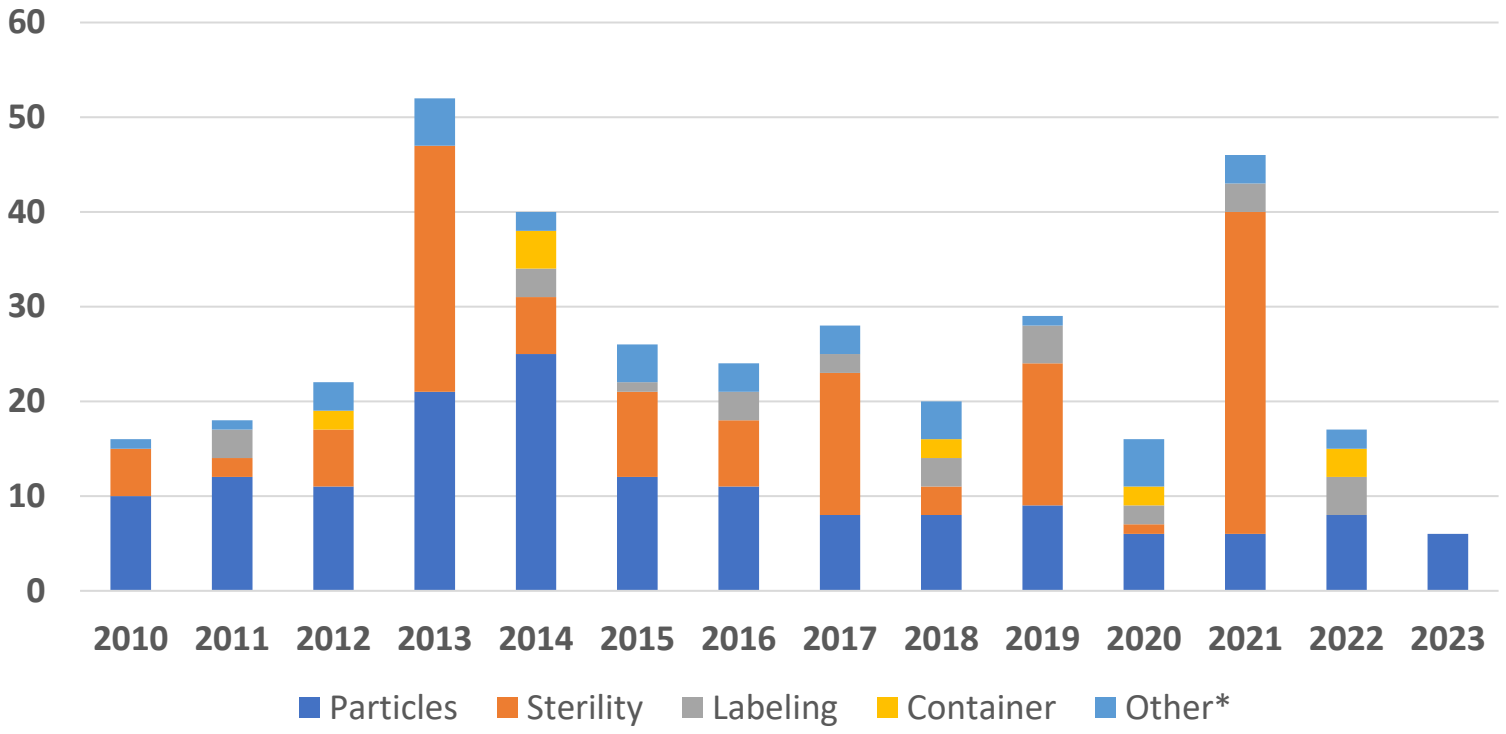
- FDA Recalls and Guidance
- Recent Revisions to Relevant USP Chapters
- PDA VI Benchmarking Survey
- Outstanding Issues
- Q&A

FDA Drug Product Recall Notices



Data obtained from the FDA Recall and Safety Alerts Archive, https://www.fda.gov/Safety/Recalls/default.htm

FDA Injectable Drug Product Recall Notices



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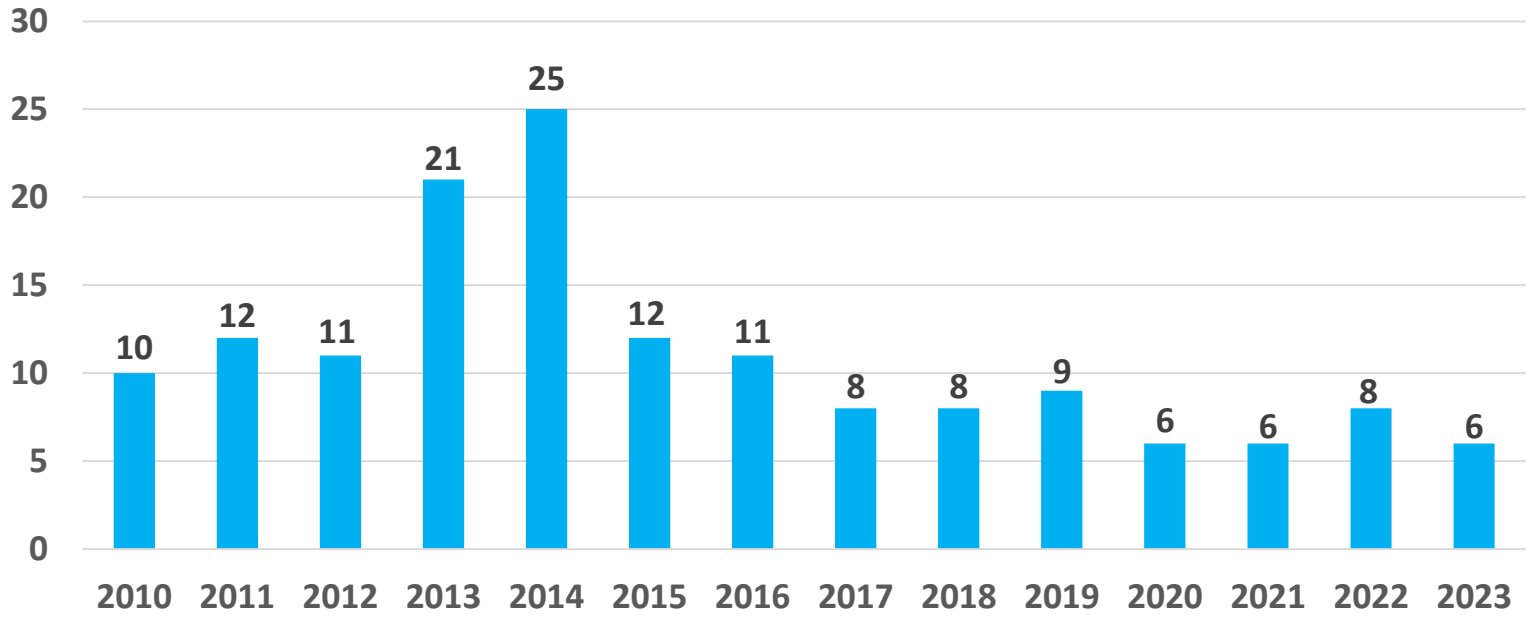
FDA Particle Recall Notices



Data obtained from the FDA Recall and Safety Alerts Archive, https://www.fda.gov/Safety/Recalls/default.htm

FDA Particle Guidance

- **Inspection of Injectable Products for Visible Particulates: Guidance for Industry**
  - Draft published 14 Dec 2021
  - Rumored for >5 years
- Issued jointly by CDER, CBER, CVM
- Scope limited to visible particles
- Comments submitted 1Q2022 from PDA, USP, many others

USP <1790> Visual Inspection of Injections

- Information Chapter
- 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
- Originally published in USP 40 1st Supplement
  - Official Aug 2017, Revision Official May 2022

USP <1790>, What's New

- Expanded discussion of inspector training and qualification methods
  - Fixed acceptance criteria and RZE based method(s)
- References to alternative sampling plans
  - RK Burdick, et al, USP PF 44(5) 2018
- References use of AI in AVI
- Expanded discussion of Difficult to Inspect Products (DIP)
  - Flexible bags
  - Cell/Gene therapy or ATMP products

USP <771> Ophthalmic Products

- Expanded description and discussion of routes of administration
- Table added to identify specific USP particle chapters required for various routes of administration
  - USP <790> required for all
  - USP <788> or <789> required for all but topical

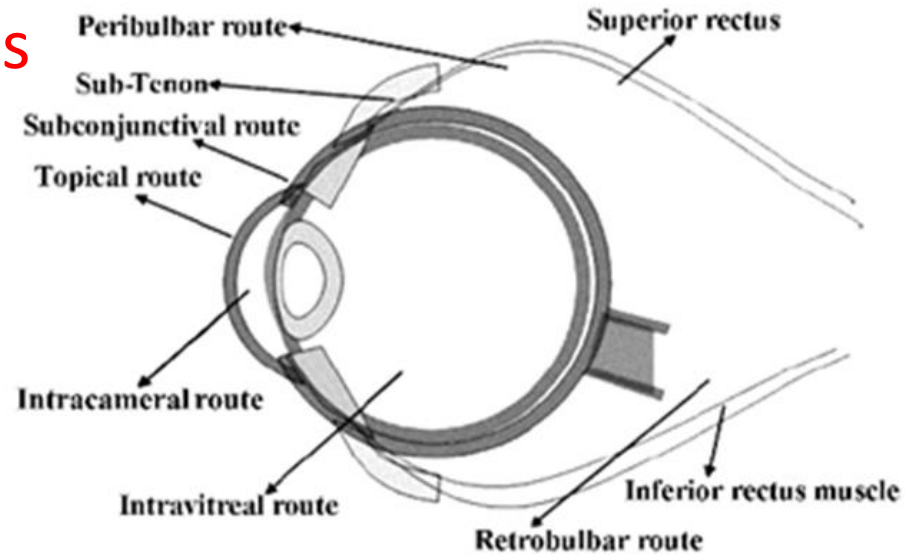


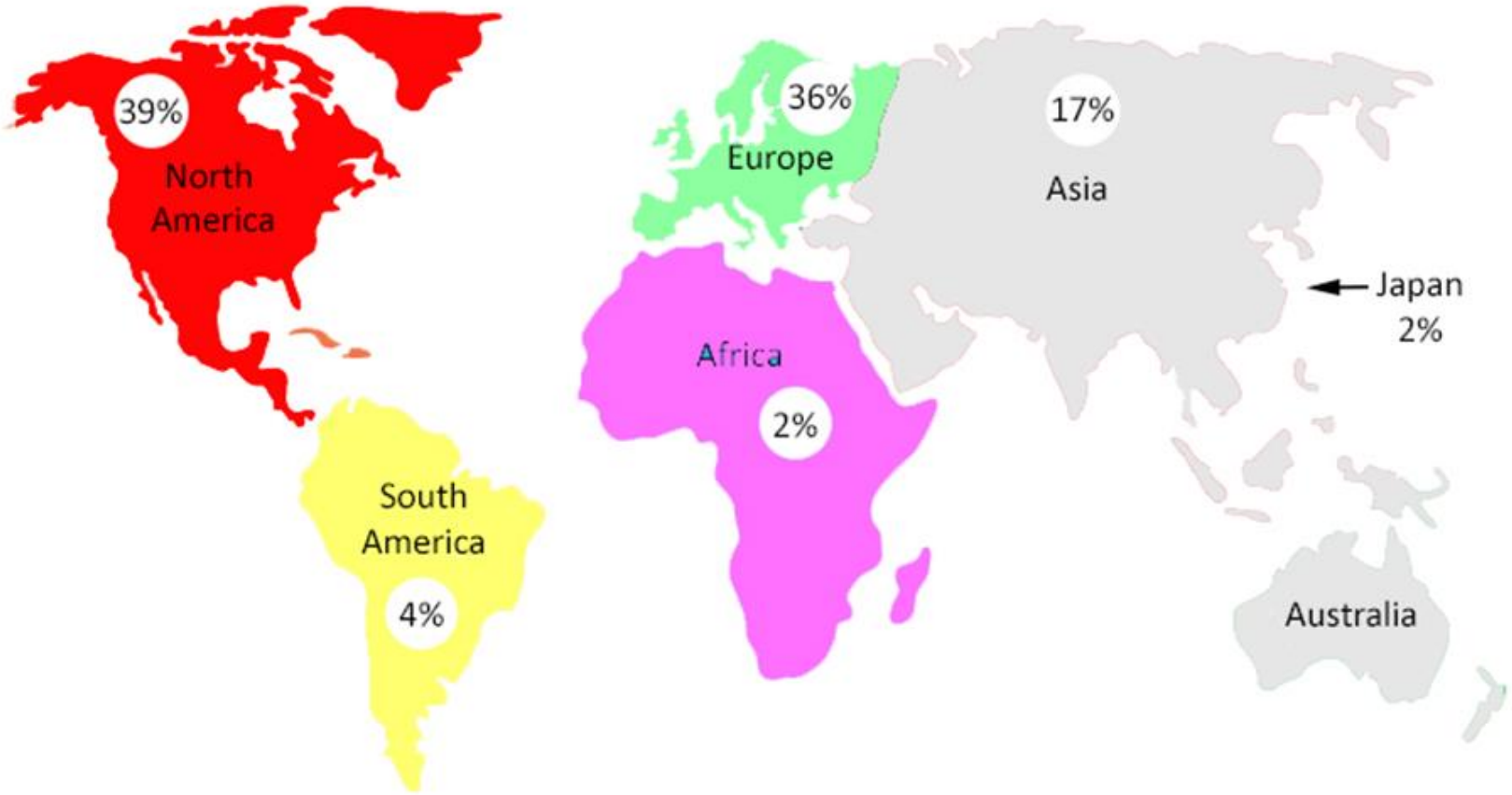
Figure 1 from USP <771>

PDA 2023 VI Benchmarking Survey

- Conducted Nov 2022 through Jan 2023
- 68 questions
- 187 responses, Responses blinded
- Sent to PDA members but non-members could respond
- A coordinated response per site was requested
- 2023 results compared to past surveys in 1996, 2004, 2008 and 2014.
  - Caution when assessing trends
- Results indicate current practice but not necessarily best practice

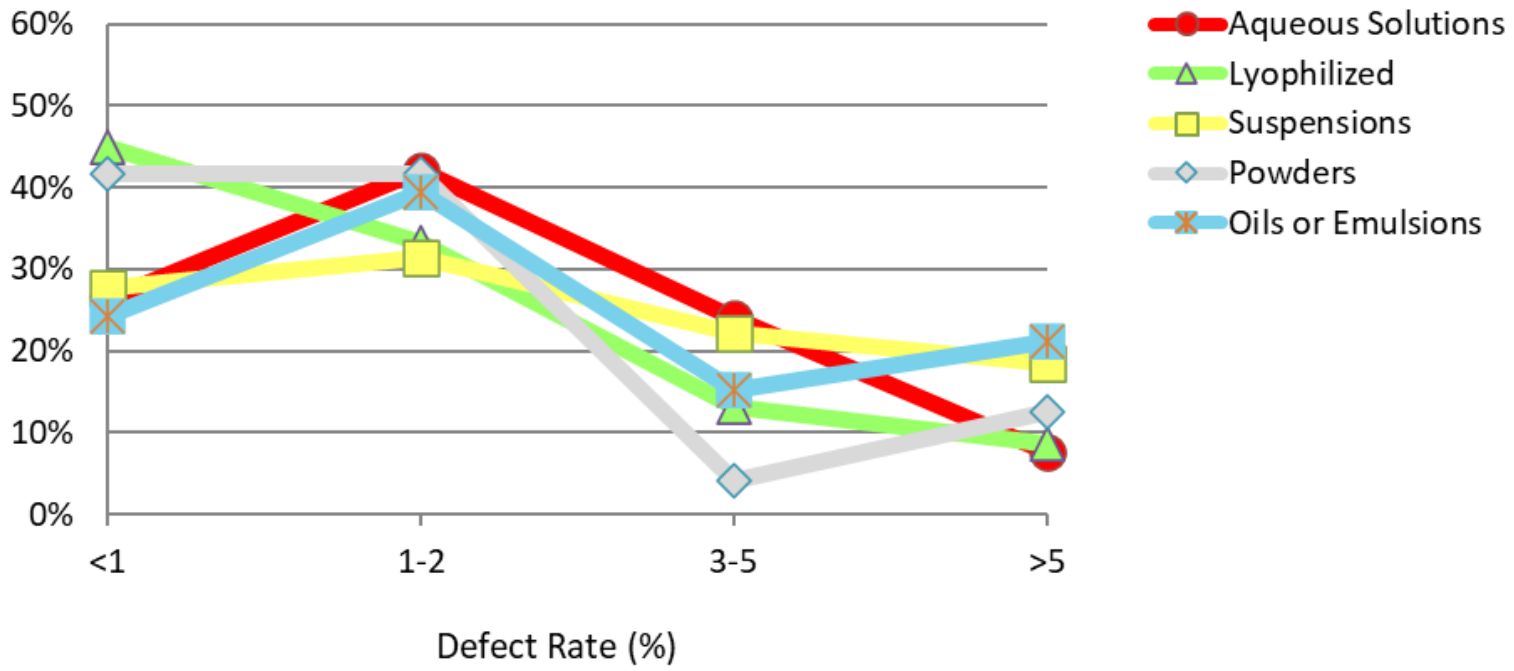
PDA 2023 VI Benchmarking Survey

1.1 In what geographic region is this facility located?



PDA 2023 VI Benchmarking Survey

4.1 What is the average reject rate for this product formulation?



PDA 2023 VI Benchmarking Survey

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

	2023	2014	2008	2003	1996
Particles	**1**	1	1	1	1
Scratches	**2**	2	2	4	4
Crimp Seal	**3**	3	3	3	2
Cracks/Chips	**3**	4	5	2	3
Cap	**4**	5	6	7	9
Stopper/Plug	**5**	7	8	9	8
High/Low Fill	**6**	6	4	5	5
Cake	**7**	8	8	6	6
Leaks	**7**	9	7	8	7

PDA 2023 VI Benchmarking Survey

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

	2023	2014	2008	2003	1996
Lint/Fiber	**1**	1	1	1	1
Product Related	**2**	3	3	4	3
Glass	**3**	2	2	2	2
Rubber/Elastomer	**4**	4	4	5	5
Metal	**5**	5	5	3	4

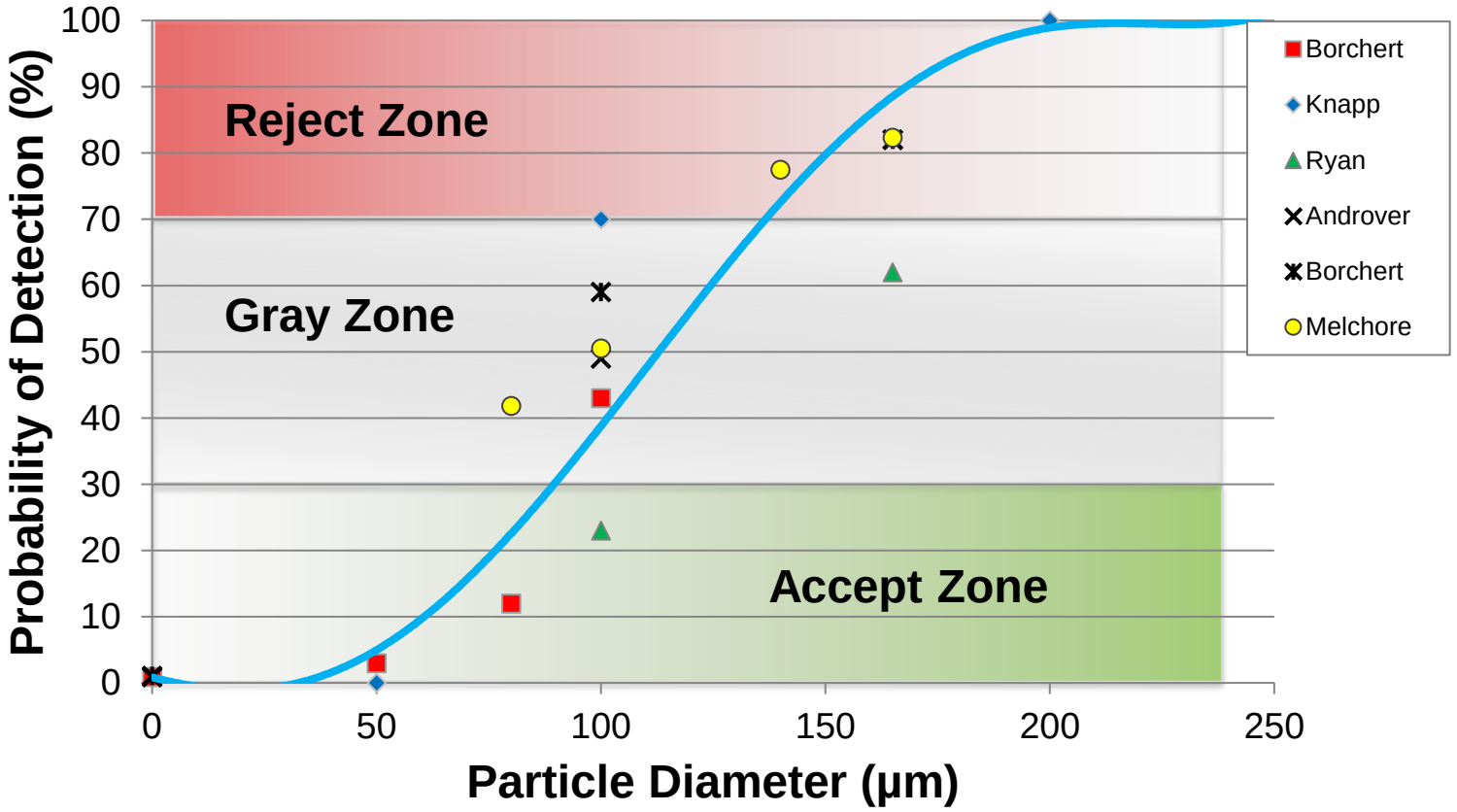
What are Current VI Issues?

- Probabilistic Nature of VI and the Gray Zone
- Lack of Definitive Clinical Patient Risk Data
- Challenges of Difficult to Inspect Products (DIP)
- Limitations of Commonly Used Sampling Plans for Acceptance Sampling

VI Detection Probability

- Human inspectors, and automated inspection systems, cannot detect all visible particles with 100% probability.
- Particle size, shape, color, density, as well as product and package characteristics affect detection.
- This results in a small number (but not zero) of visible particles in product released for use.
- The resulting “Gray Zone” (PoD <70%) results in much confusion and uncertainty in setting specs.
- Therefore, prevention, and not inspection alone, is a critical element of particle control.

Human Inspection Performance



From Shabushnig, Melchore, Geiger, Chrai and Gerger, PDA Annual Meeting 1995

Clinical Risk Assessment

- No controlled clinical studies have been performed to assess the risk of single visible particles.
- All available data is based on anecdotal information or animal studies, often with much higher particle loads.
- Visible particles provide a good measure of process control and cGMP compliance but not a good measure of product safety or patient risk.

Difficult to Inspect Products (DIP)

- Single particle detection near the visible threshold (~100μm) can often be achieved with a high PoD for clear solution in clear vials.
- Products with increasing color, opacity, turbidity, and viscosity decrease the PoD that can be achieved.
- Colored or non-transparent containers or those of very large or small size will also reduce the PoD possible.
- These limitations are addressed with additional supplemental (destructive) testing for product release.

Acceptance Sampling Plans

- The widely used acceptance sampling plans (ANSI/ASQ Z1.4, ISO 2859) are useful but have limited sensitivity.
- They must be used after qualified/validated 100% inspection as a second performance check.
- They were optimized for large batch sizes and do not work well for small clinical batches and CGT/ATMP products.
- For small batches, 200% inspection and pre-inspection of materials and components may be needed for particle control.

Acknowledgements

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  - Robert Miller, Pfizer
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  - Jessie Lindner, PDA
  - Glenn Wright, PDA

  - and all who responded to the survey!

Questions?