From Blur to Clarity: Definition of Particle Visibility Threshold in Parenteral Drug Products

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On behalf of the EFPIA Global Visible Particles Workstream

Introduction

Control of visible particles is an important aspect of the control strategy for injectable products to reduce potential risks to patients

A major technical hurdle for visual inspection stems from different degrees of visibility of particles, rendering particle detection a probabilistic process

To gather new data on particle visibility and shed light on this decade-old challenge, a multi-company blinded visual inspection study was conducted by 10 independent global companies

A major goal of the study was visibility assessment of several particle types of different sizes in small volume vials, as a challenging configuration for visual inspection.

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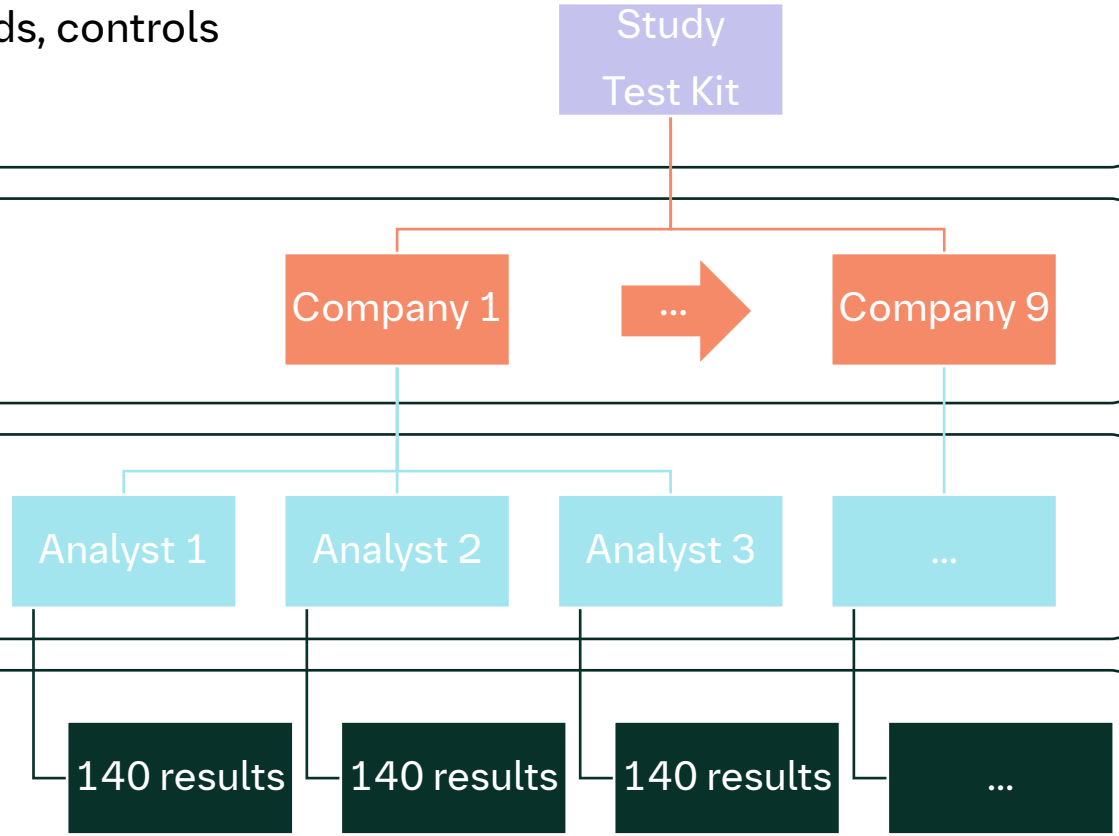
Study Design

Protein surrogate (SU-8), fibers, glass, metal, rubber, PS beads, controls
1 or 5 per container, 50 – 400 µm, 1 ml in 2ml glass vials

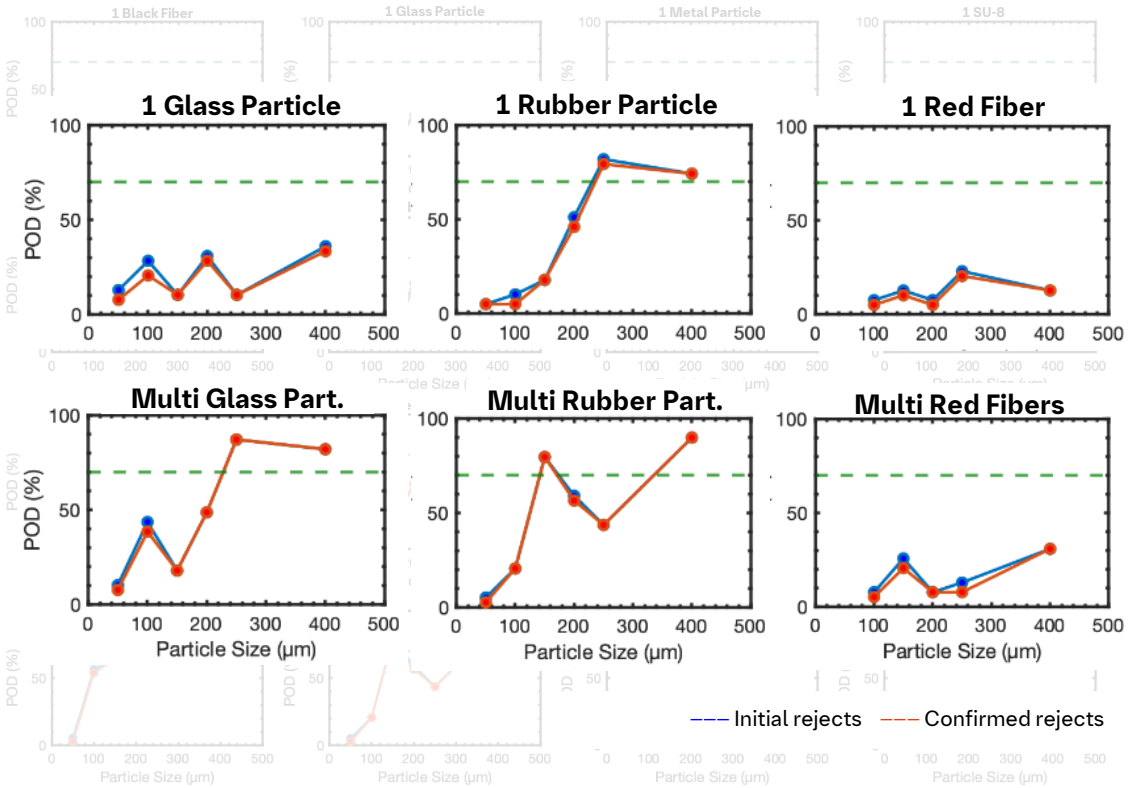
Randomized and blinded particle test kit
shipped sequentially to individual companies

Kit was individually inspected according to
EP 02.9.20 by at least 3 qualified analysts per company

Readout: Particle presence (y/n) + additional observations
→ 5460 individual results from 39 analysts



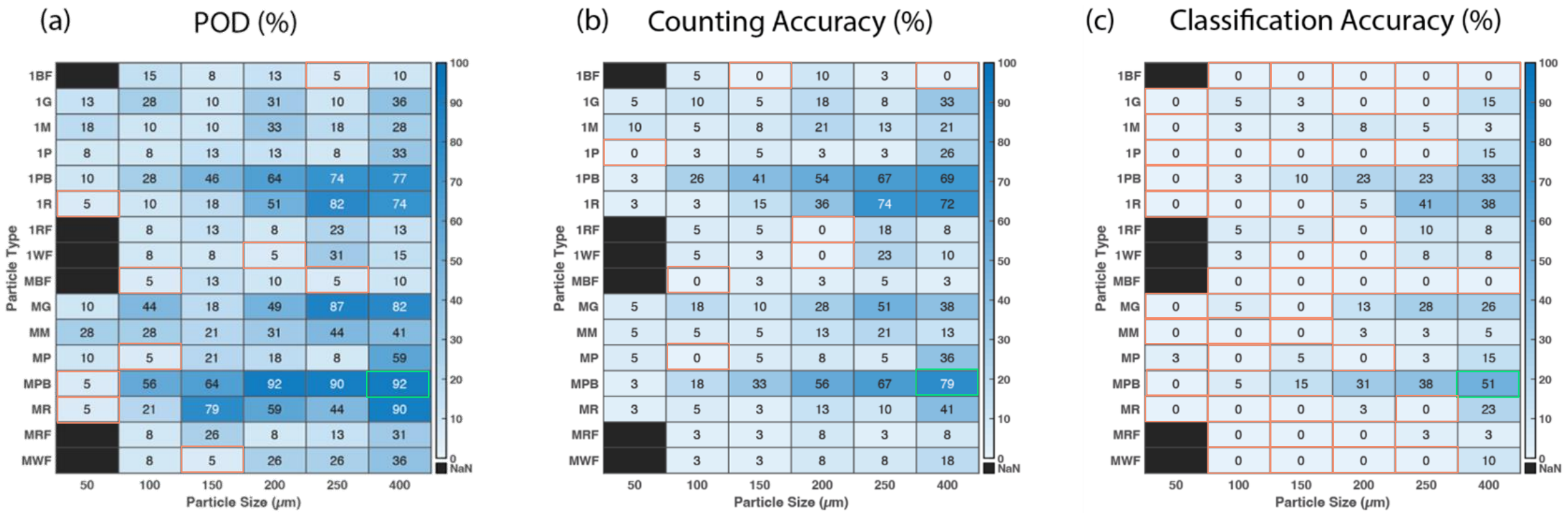
Probability Of Detection (PoD) As Function Of Particle Type And Size



- General trend: presence of multiple particles resulted in higher PoD than single particle per unit
- Detectability of particles smaller than 250 µm has been shown to be unreliable in this study
- Certain particle types, (e.g., PS beads) or multiple particles per unit, have a higher PoD
- PoD >70% reached/exceeded for some particle types between 200 µm and 250 µm, but PoD of fibers did not reach 70% even at 400 µm

Mazaheri et al 2023, J Pharm Sci

Heatmap Overview Of The Multi-Company Threshold Study Outcome



- Average PoD values across companies ranged 5 to 92%, only certain particle types detected with PoD >70%
- PoD increases with increasing number and size, but only for certain particle types
- Counting accuracy was found to be between 0 to 79% (with only 2 instances above 70%)
- Classification accuracy was overall low (with only PS beads and rubber reaching medium values)

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Summary

Setting a generic low threshold for visibility of particles (50 µm, 100 µm or any other exact size) is not practical, and likely not achievable, as it will strongly depend on a variety of factors

Under the conditions of the study classification of particle identity and counting of particles by visual inspection alone is very challenging

Study findings underscore the necessity of robust procedures for analyst training and qualification, setting realistic expectations on size-based visibility limits, and harmonization of guidelines globally

Multiple particle control strategy layers are required to provide assurance for a consistent quality of manufactured parenteral products

All graphs were derived from Mazaheri et al, 2023, J Pharm Sci (DOI: 10.1016/j.xphs.2023.10.002)

Meet The Team
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Mazaheri et al, 2023, J Pharm Sci (DOI: 10.1016/j.xphs.2023.10.002)

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From Blur to Clarity:

Definition of Particle Visibility Threshold in Parenteral Drug Products

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Question

Can we define a universal particle size “visibility” threshold?

"Visibility" limit from a physiological perspective

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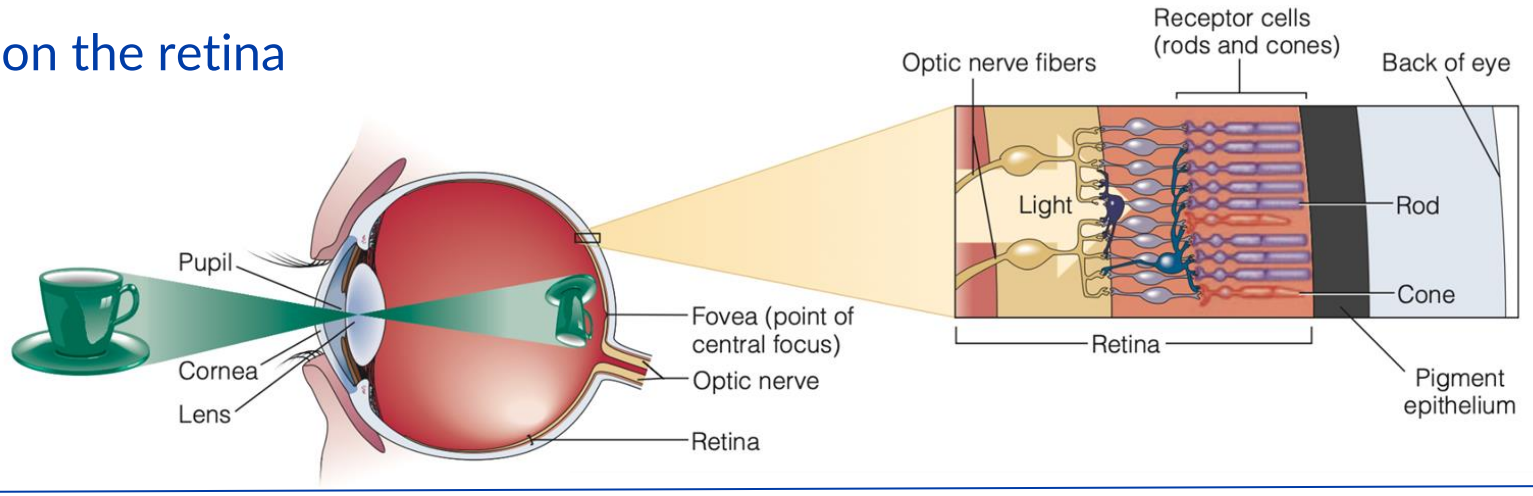
Physiology of human visual perception: detection of objects in the retina of the human eye

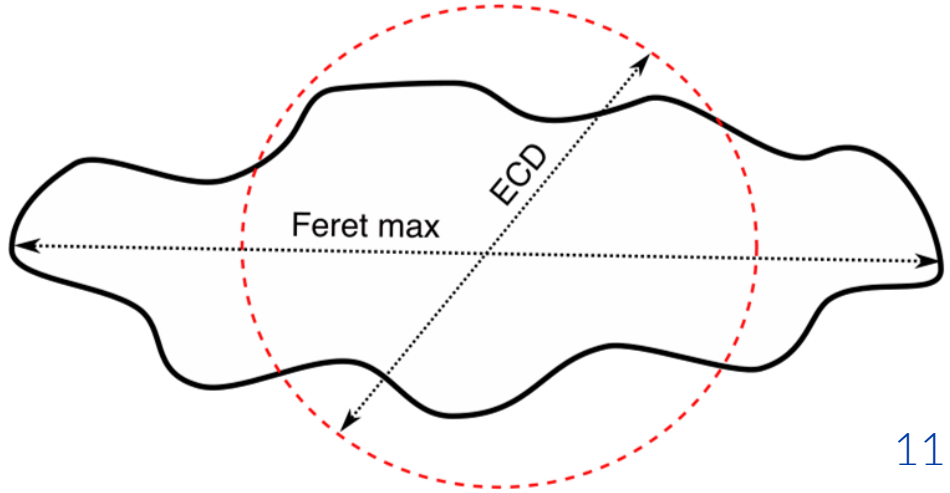
Is based on **2D projections of 3D objects on the retina**



Goldstein, B. E.
Sensation and Perception, 2009

Hypothesis:

2D, area-based particle measurements (e.g. ECD) may be better suited to define particle "visibility" than uni-dimensional measurements



Experimental hypothesis test - threshold study (Knapp test)

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- Inspection panel:
  - 10 qualified operators, 3 inspection rounds each
- Defect test set:
  - 2 different containers - 2R and 20R vial
  - Defect and defect-free units
  - 5 different particle types (metal, glass, rubber, white fibers, black fibers)
  - Gradient of particle sizes in each particle class
- Inspection conditions - according to USP <790>/ Ph. Eur 2.9.20:
  - B&W inspection board with a non-glare white panel base
  - illumination 2’000 - 3’750 lux;
  - 5s/ 5s inspection duration

Results (2R vial)

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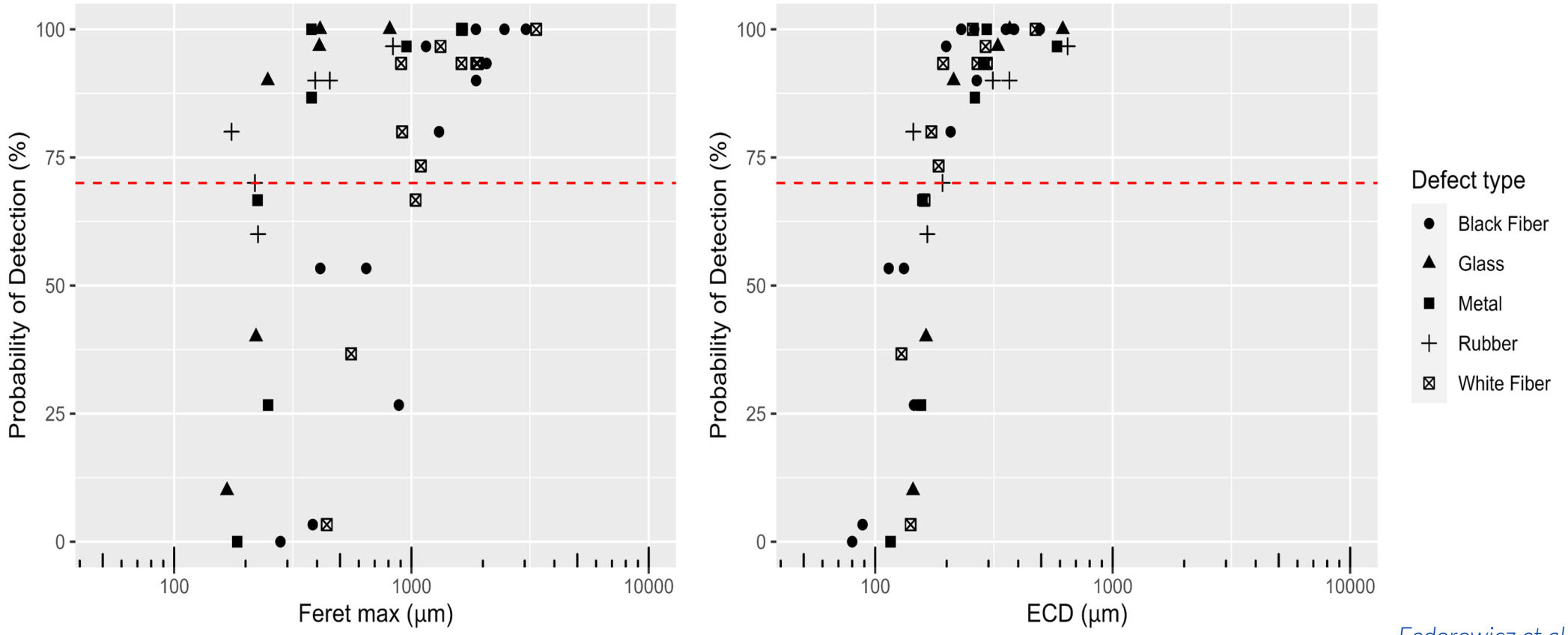
1D size parameter (Feret max)

2D size parameter (ECD)



Fedorowicz et al, (in review)

- If 1D parameter (Feret max) is used - the "visibility" limit varies per particle type
- If 2D/ area-based parameter (ECD) is used - **PoD of 70% (visibility limit) is ca. 200 µm for all particles**

Results (2R vial 20R vial)

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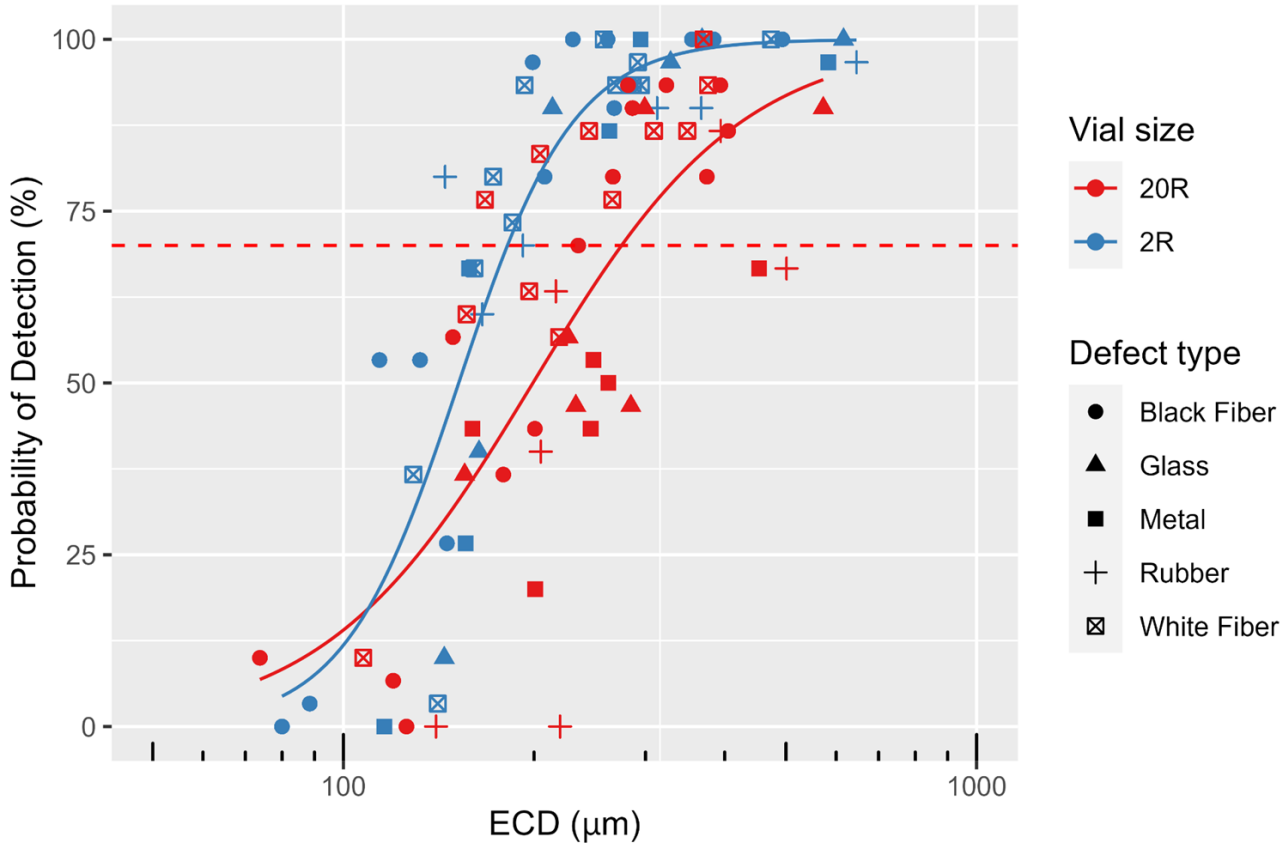

Fedorowicz et al, (in review)

Container dimensions affect the particle “visibility limit”:

Larger container sizes results in a larger particle threshold of detectability (“visibility”)

Conclusions

- Using the area-based size-parameter ECD allows for definition of a single “visibility” limit for particle defects of various types and morphologies. This finding presents exciting opportunities for standardization.

- The “visibility” threshold is not absolute. Changes in container dimensions and other product attributes (data not shown) result in shifts of the “visibility” limit.

expertise. insight. agility.

Thank you!

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