Mastering Particle Size Analysis: A Step-By-Step Illustration of Techniques and Best Practices

Opening

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Examples of Particles in Pharmaceuticals

- Drug substance powder (micron-, nano-)
- Excipient powder
- Granules (wet- or dry- process)
- Suspension, for i.v. injection (really small), or more commonly ophthalmic and oral routes
- Emulsions (oil globules) for i.v., ophthalmic, oral
- Aerosols, nasal spray, metered dose inhalers (MDI), dry powder inhalers (DPI)
- Liposomes, micelles, protein-drug complex, lipid nanoparticles (covid-vaccine)
- Iron colloids
- *Particulates (both visible and sub-visible)*
- *Glass fragments (a unique undesired particulate)*
- *Protein or peptide aggregates (undesired)*

Particle sizing is a poorly posed problem.

The apparent simplicity of particle size analysis is deceptive.

Burgess, D.J., Duffy, E., Etzler, F. et al. AAPS J (2004) 6: 23. https://doi.org/10.1208/aapsj060320

Particle Sizing: the PURPOSE

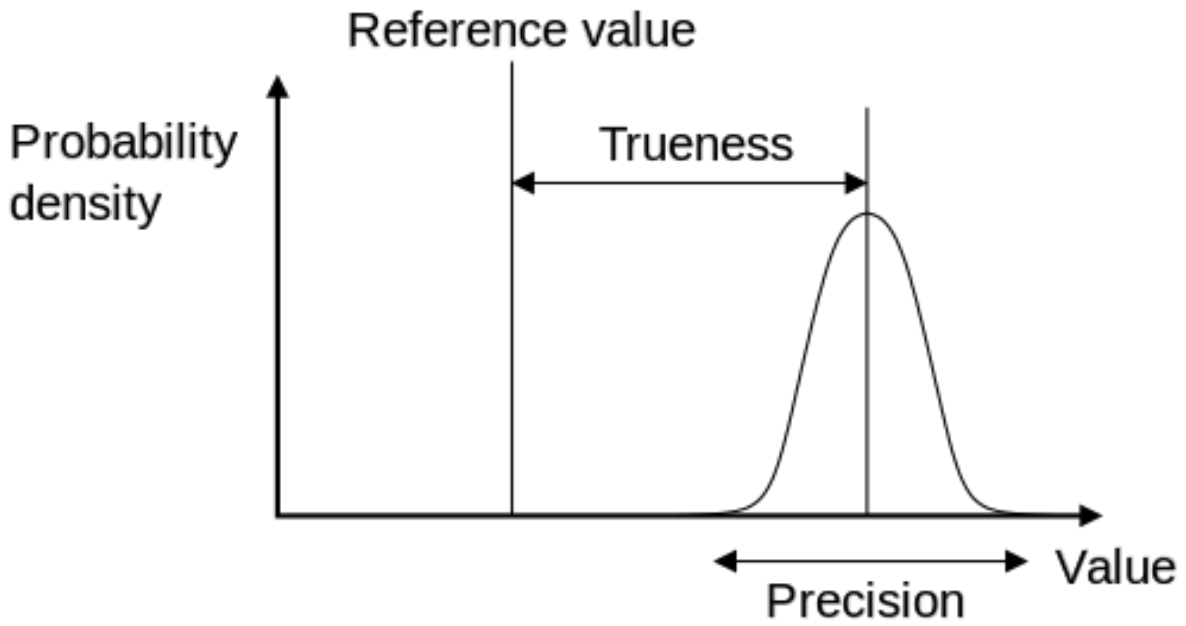
The analysis of the particle size is not an objective in itself but is a means to an end.

- Physical stability (e.g., dispersion sedimentation, agglomeration)
- Dissolution/drug release (e.g., due to surface area differences)
- Bioavailability
- Manufacturability (e.g., power flow, packing density)
- Bioequivalence (e.g., sameness or difference)
- Safety (e.g., particulate matter)

Depending on the purpose of the size measurement, the expectations on analysis outcome (i.e., numbers) may vary, e.g., Product A is 10 nm smaller than Product B ($p<0.05$). Are they “different”?

- What we are truly interested is not the “size”
- What we are actually measuring may not be the “size”

Particle Size Concepts: Trueness and Precision



- "Trueness" refers to the closeness of agreement between the arithmetic mean of a large number of test results and the true or accepted reference value.
- "Precision" refers to the closeness of agreement between test results.

*ISO 5725

Particle Size Concepts: What is “Trueness” in Size?

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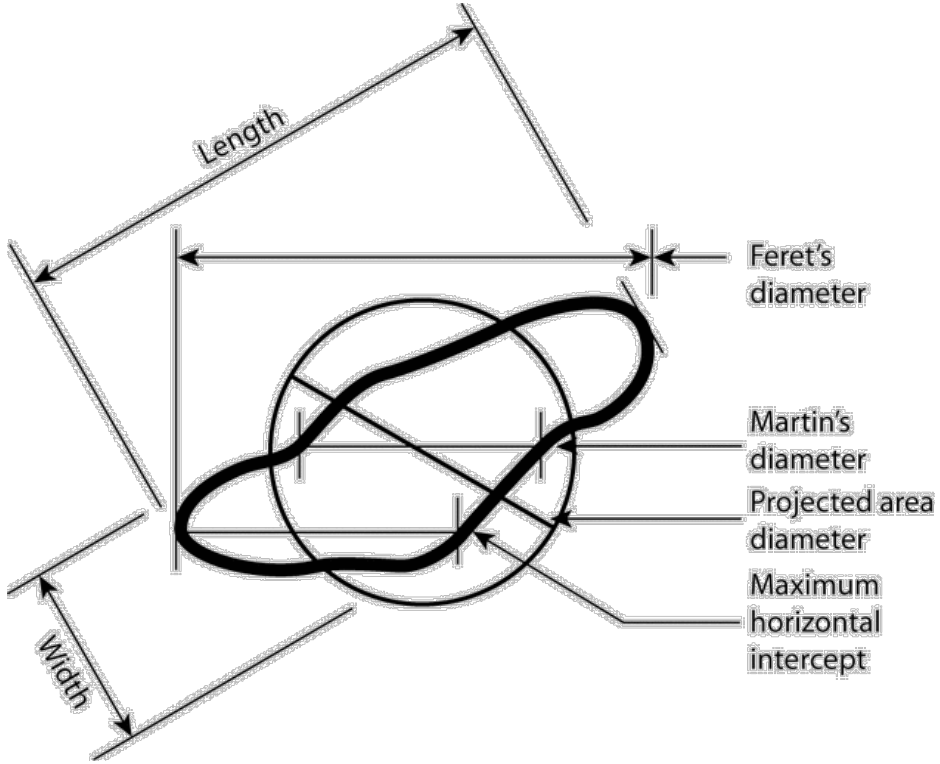

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Feret's Diameter—The distance between imaginary parallel lines tangent to a randomly oriented particle and perpendicular to the ocular scale.

Martin's Diameter—The diameter of the particle at the point that divides a randomly oriented particle into two equal projected areas.

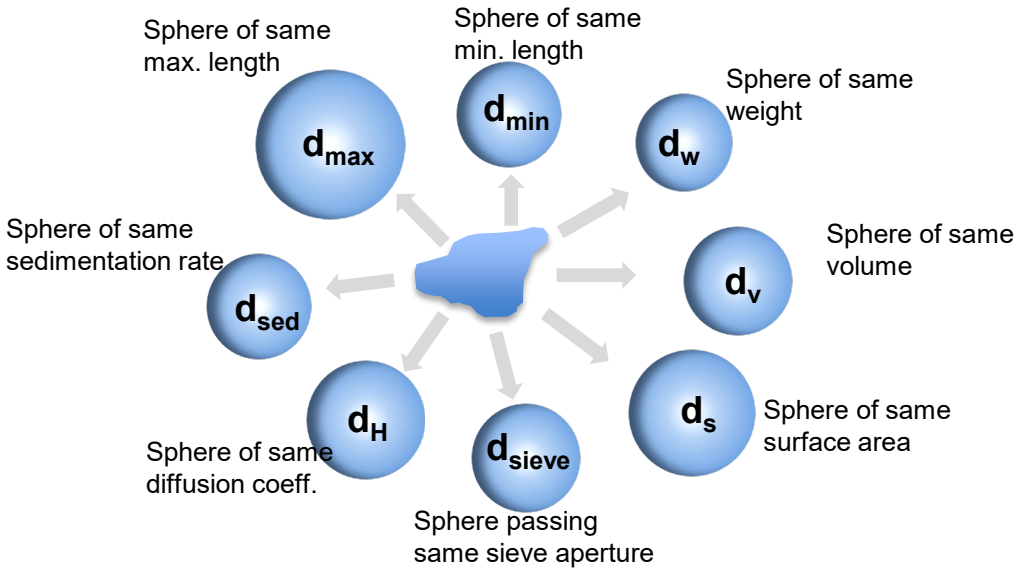
Projected Area Diameter—The diameter of a circle that has the same projected area as the particle.

Length—The longest dimension from edge to edge of a particle oriented parallel to the ocular scale.

Width—The longest dimension of the particle measured at right angles to the length

Particle Size Concepts: Equivalent Spheres

- Particles are 3-dimensional objects, and unless they are perfect spheres (e.g., oil globules, liposome vesicles, micelles, or air bubbles), they cannot be fully described by a single dimension such as a radius or diameter
- Concept of equivalent spheres (may not always be the most appropriate, e.g., for needle shaped particles)



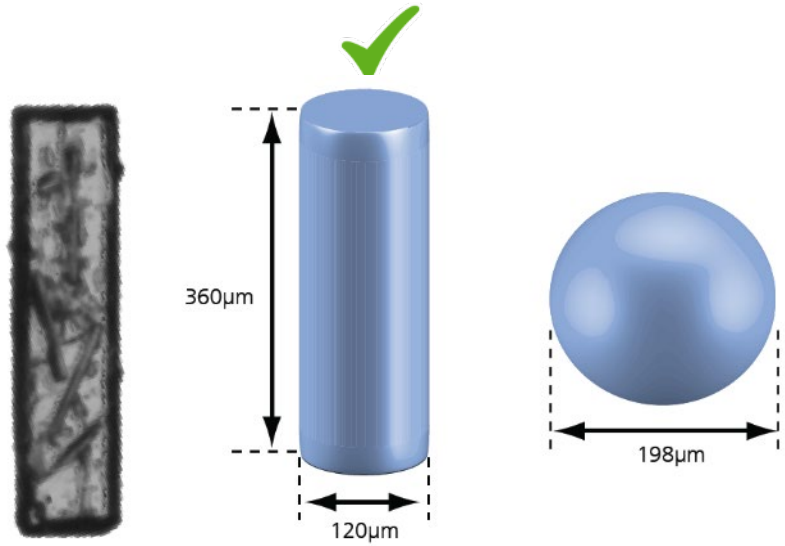
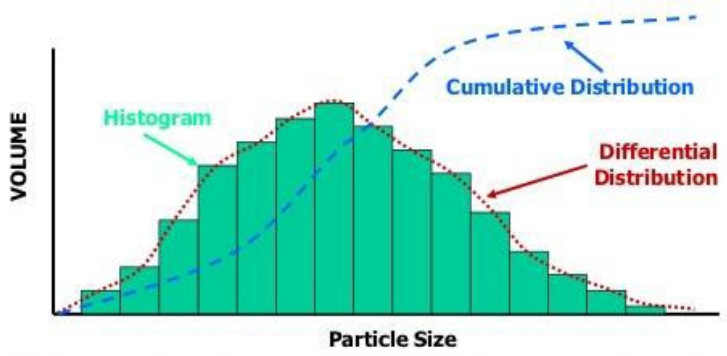


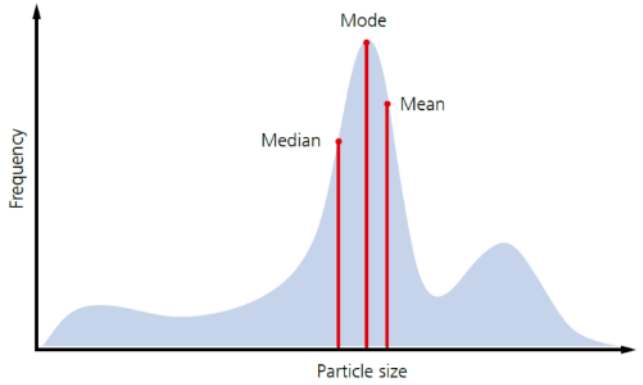
Illustration of the volume equivalent rod and sphere of a needle shaped particle.

- Different measurement technique assumes different equivalent sphere models, and hence may not necessarily give exactly the same results

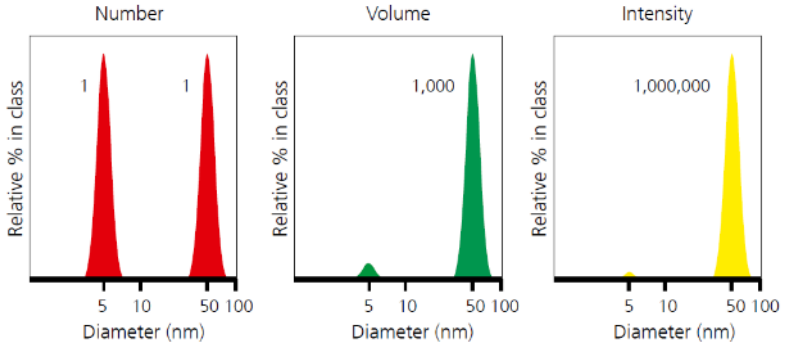
Particle Size Concepts: Distribution and Mean

- Unless the sample is perfectly mono-disperse, it will consist of a statistical distribution of particles of different sizes
- Most commonly shown as a frequency (histogram) or cumulative (undersize) distribution curve



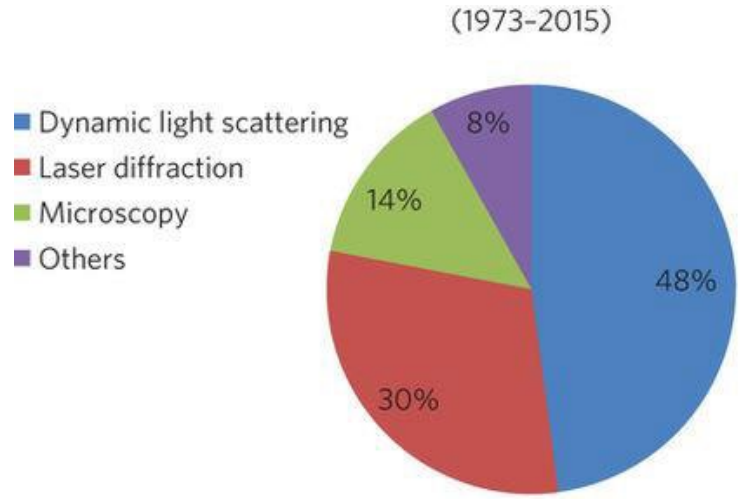


- Average: Median, Mode, Means (e.g., D[1,0], D[3,2], D[4,3])
- Distribution: Percentiles (e.g., Dv90), Poly-dispersity index, SPAN
- Weighted distributions
  - Number-weighted (image analysis, SEM)
  - Volume-weighted (static light scattering)
  - Intensity-weighted (dynamic light scattering)



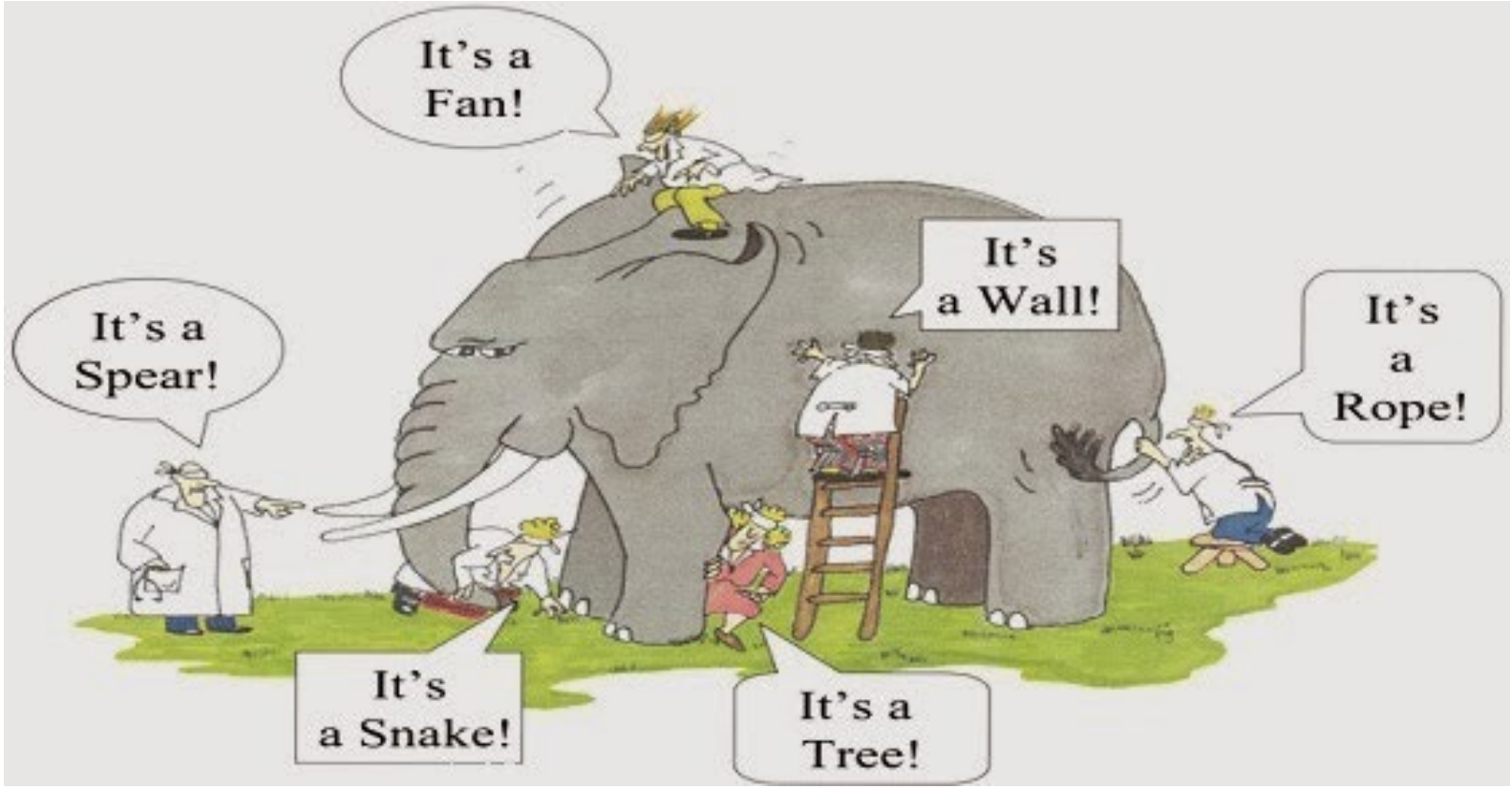
Techniques to Determine Particle Size Distribution

Technique	Size range	Principle
Dynamic light scattering (DLS)	1 nm to 1 µm	Brownian motion + light scattering
Laser diffraction (LD)	30 nm to 3000 µm	Static light scattering (Mie or Fraunhofer)
Electron microscopy (EM)	0.1 nm to a few micron	Electron density contrast
Image analysis	1 µm to a few hundred micron	Image analysis
Light obscuration	Subvisible particles (0.5 µm to 400 µm)	Single particle light blockage
Nanoparticle tracking analysis (NTA)	20 nm to 1 µm	Brownian motion + image analysis
Field flow fractionation (FFF) + multi-angle light scattering (MALS) + DLS	1 nm to a few micron	Brownian motion + flow based separation + light scattering
Resonant mass measurement (RMM)	50 nm to 5 µm	Buoyant mass
Focused Beam Reflectance Measurement	1 µm to 1000 µm	Chord length



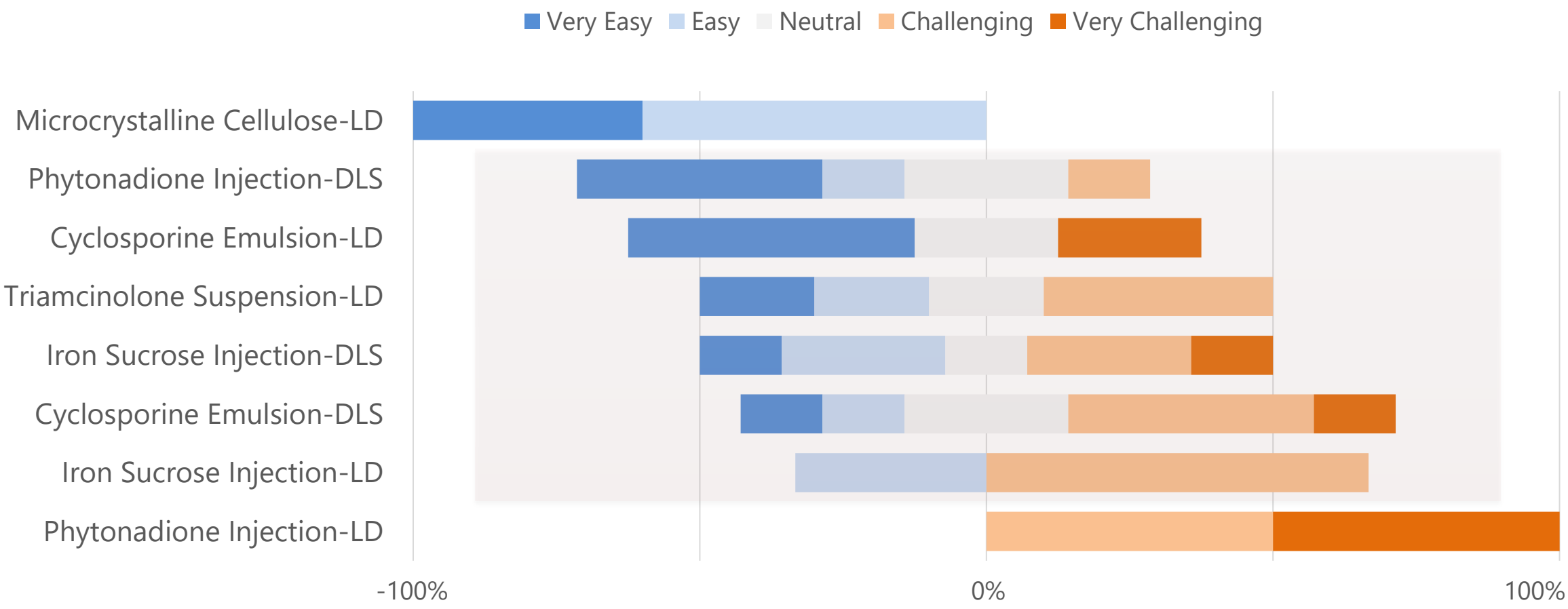
S. D'Mello, et al. *Nature Nanotechnology*, 2017, 12, p.523-529

What Is The Right Answer?



https://medium.com/betterism/the-blind-men-and-the-elephant-596ec8a72a7d

Difficulties: In the View of the Experts



* Pre-workshop Sample Measurement Survey Results: seven vendors participated, two techniques (DLS, LD), five materials, 19 survey responses

Workshop Agenda: Day 1

Session 1	8:55 – 9:55 am	DLS Theory, Practice and Regulatory Perspective	In-person & Online
Session 2	9:55 – 12:15 pm	Vendor Perspective (7 vendors) and Q&A	In-person & Online
Lunch Break			
Session 3	1:10 – 2:40 pm	DLS Equipment Demonstration (3 materials, 7 vendors)	In-person
Session 4	2:50 – 5:30 pm	Small Group Work Sessions	In-person

Workshop Agenda: Day 2

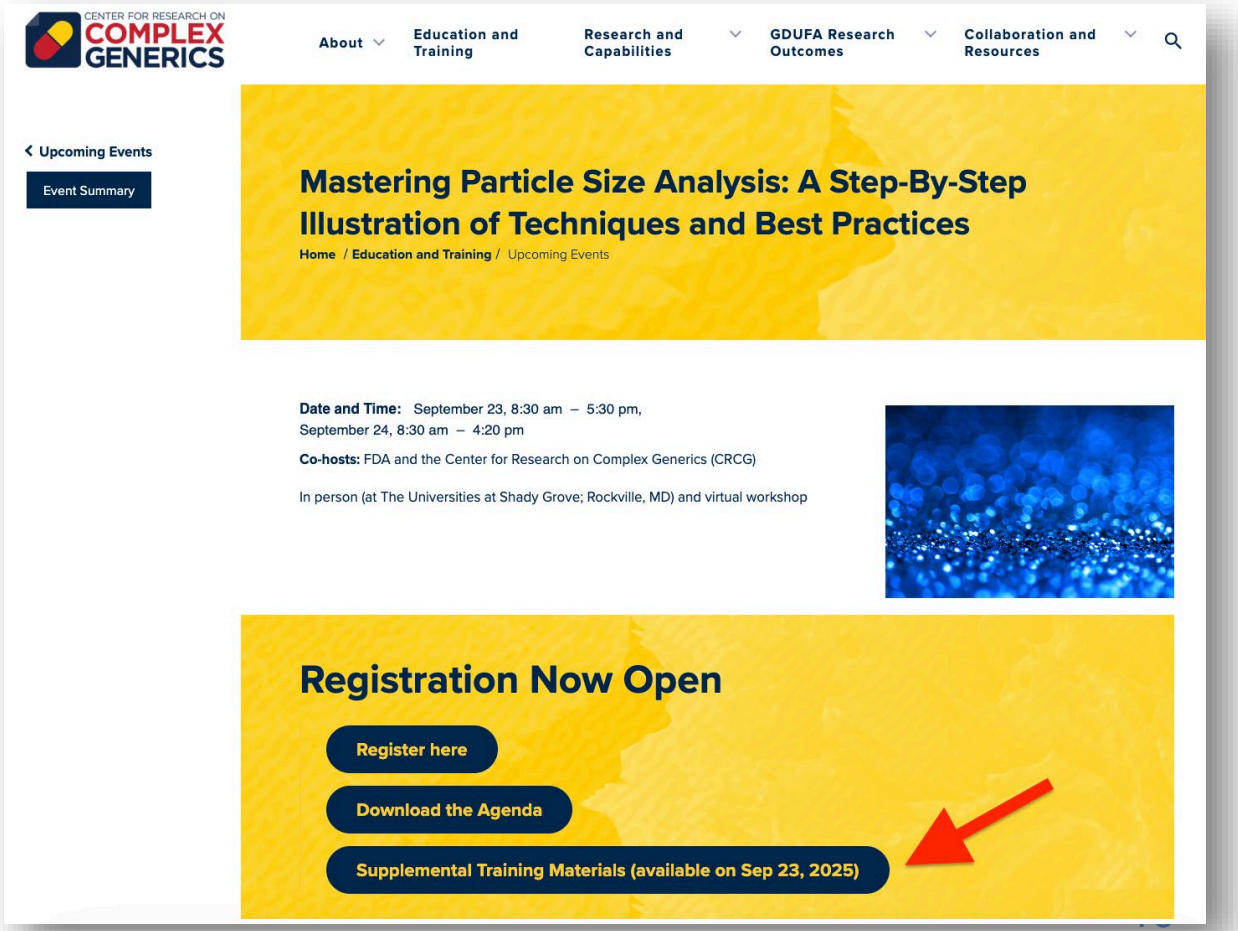
Session 5	8:40 – 9:30 am	LD Theory and Practice	In-person & Online
Session 6	9:30 – 10:30 am	Industry Perspective (challenges and hurdles)	In-person & Online
Session 7	10:45 – 12:15 pm	Vendor Perspective (4 vendors) and Q&A	In-person & Online
Lunch Break			
Session 8	1:25 – 2:10 pm	LD Equipment Demonstration (3 materials, 4 vendors)	In-person
Session 9	2:10 – 3:10 pm	Small Group Work Sessions	In-person
Session 10	3:20 – 4:10 pm	Waypoint Exercise	In-person

Training Materials on Particle Sizing

A comprehensive particle size training course will be made available on CRCG website, effective today 9/23/25.

The training course include the following topics:

1. Particle size concept and light scattering phenomenon
2. Dynamic light scattering
3. Laser diffraction
4. Asymmetrical Flow Field Flow Fractionation
5. Sub-visible particle analysis
6. Method validation and common deficiencies



https://www.complexgenerics.org/education-training/mastering-particle-size-analysis-a-step-by-step-illustration-of-techniques-and-best-practices/

Session 1: DLS Theory, Practice and Regulatory Perspective

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Dynamic Light Scattering Theory and Practice

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Regulatory Perspectives: Method Validation and Common Deficiencies