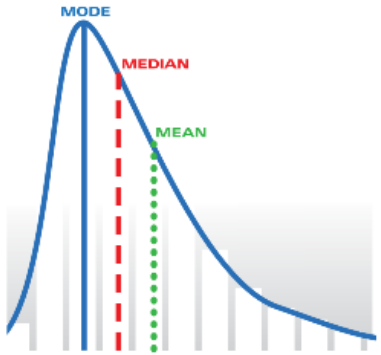
Interpreting Your PSA Results

Decoding the Acronyms and Finding Insights



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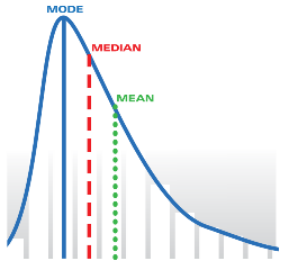
Outline

- The Basics
- Define Parameters
- Choose Parameters
- Interpret Results



The Workflow

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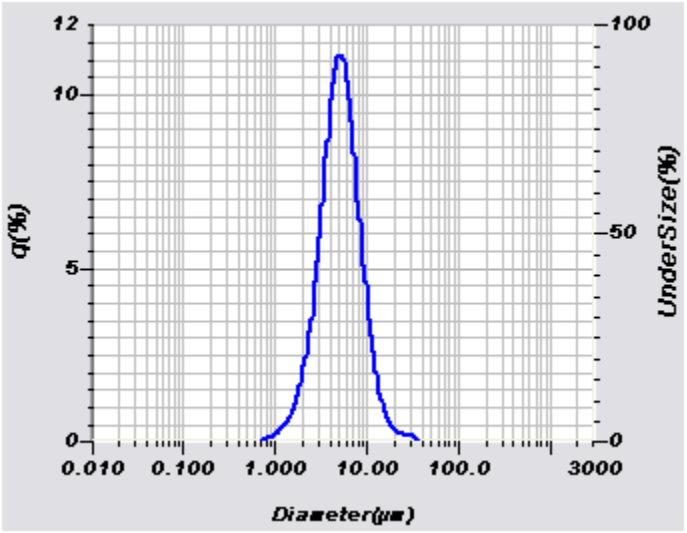
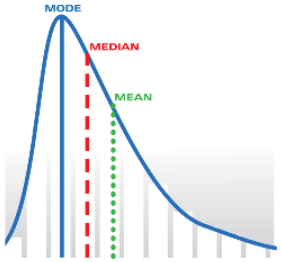
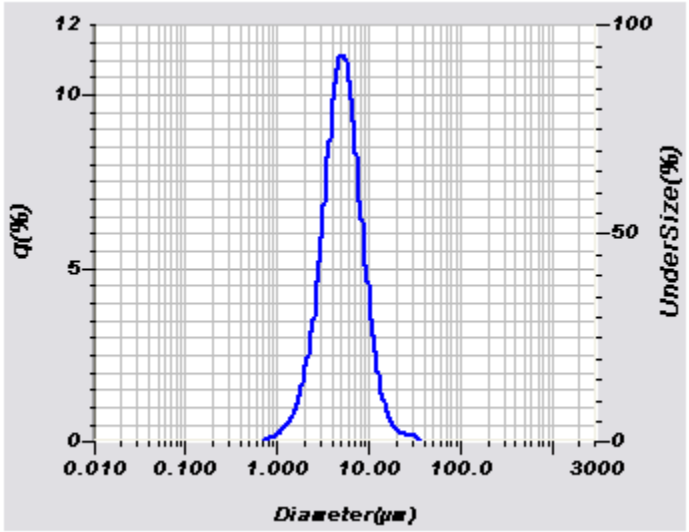




The Problem



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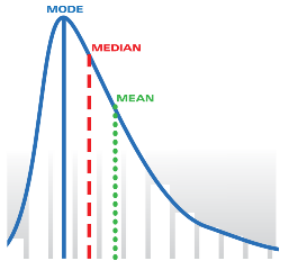
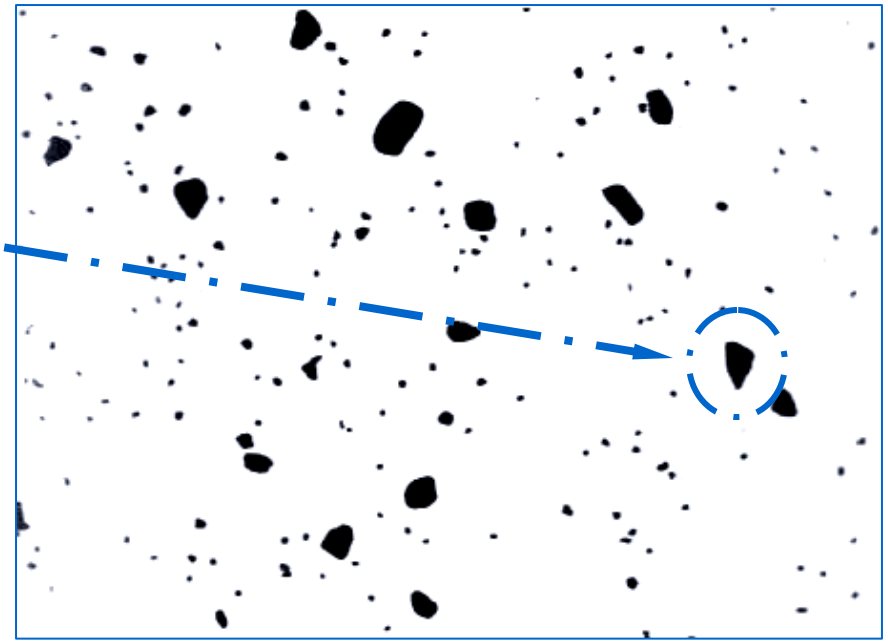
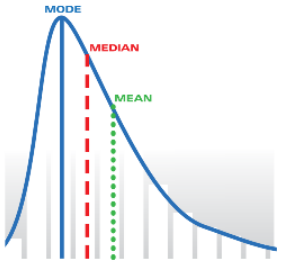


The Basics

Particle

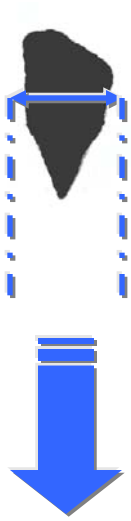
Particle Distribution





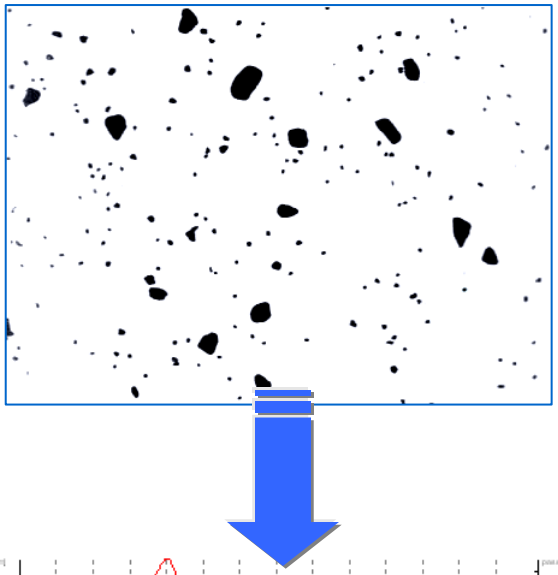
The Basics

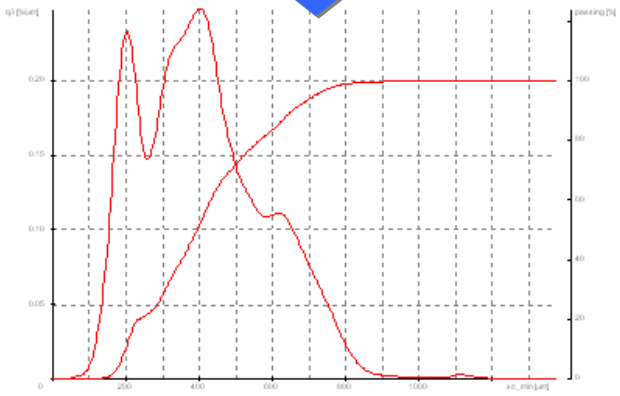
Particle Size

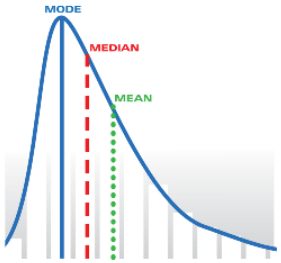


4 µm

Particle Size Distribution

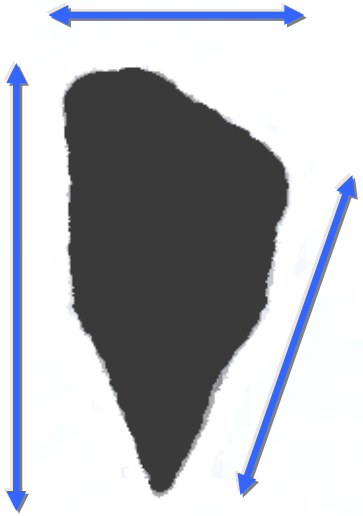




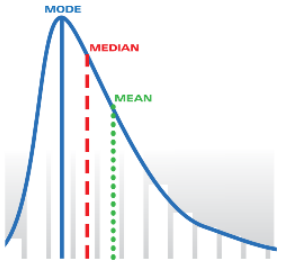


The Basics

Which is the most meaningful size?

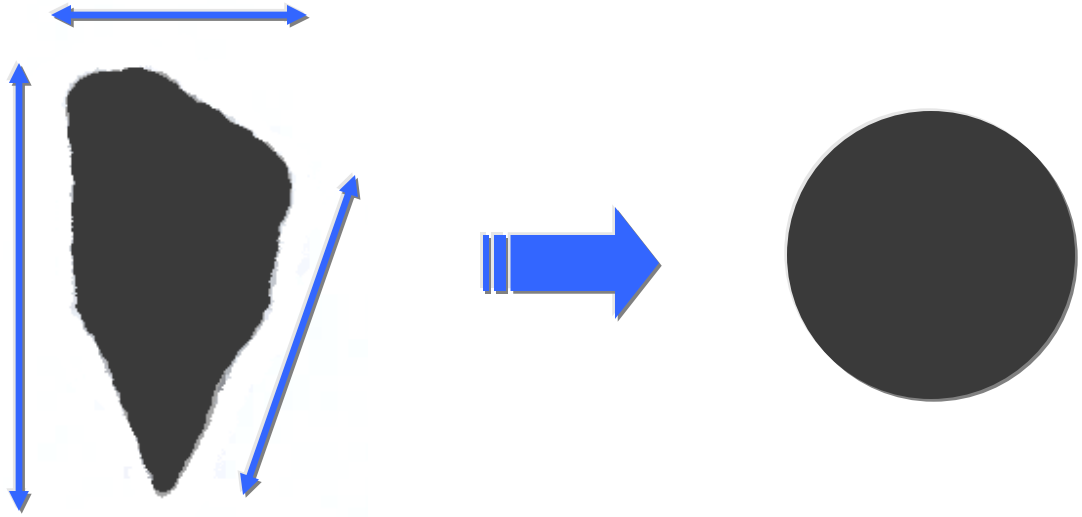


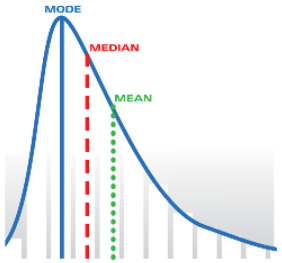
different size definitions → different results



The Basics

What sizes can be measured?

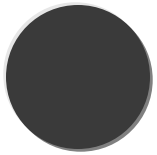




The Basics

Laser Diffraction

Equivalent Spherical Diameter



Dynamic Light Scattering

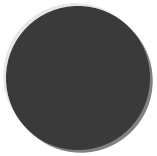
Hydrodynamic Radius

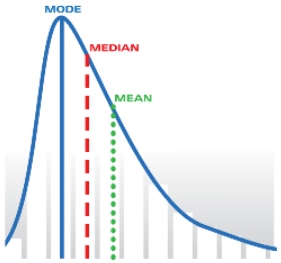
Image Analysis

Lengths, Widths, Equivalent Spherical

Acoustic Spectroscopy

Equivalent Spherical Diameter



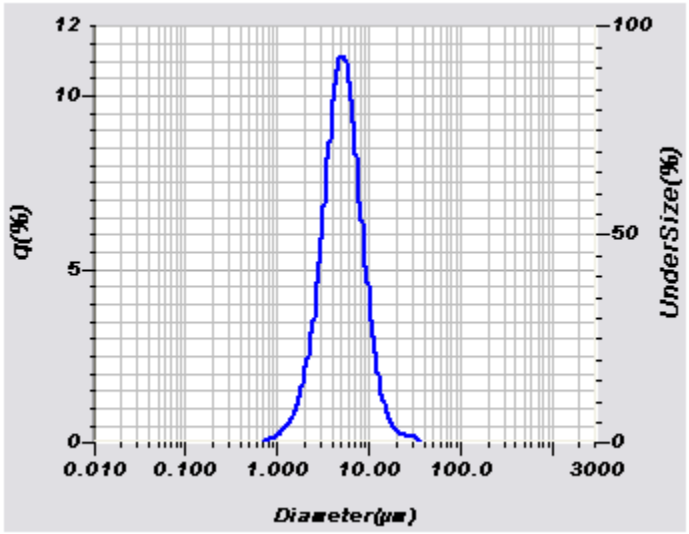


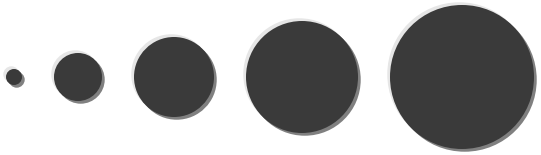
The Basics

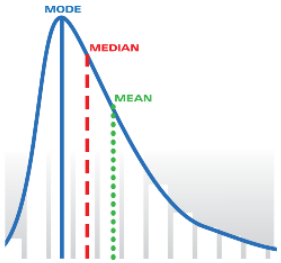
Laser Diffraction

Assumes hard, spherical shape model

q% = amount of each size by volume





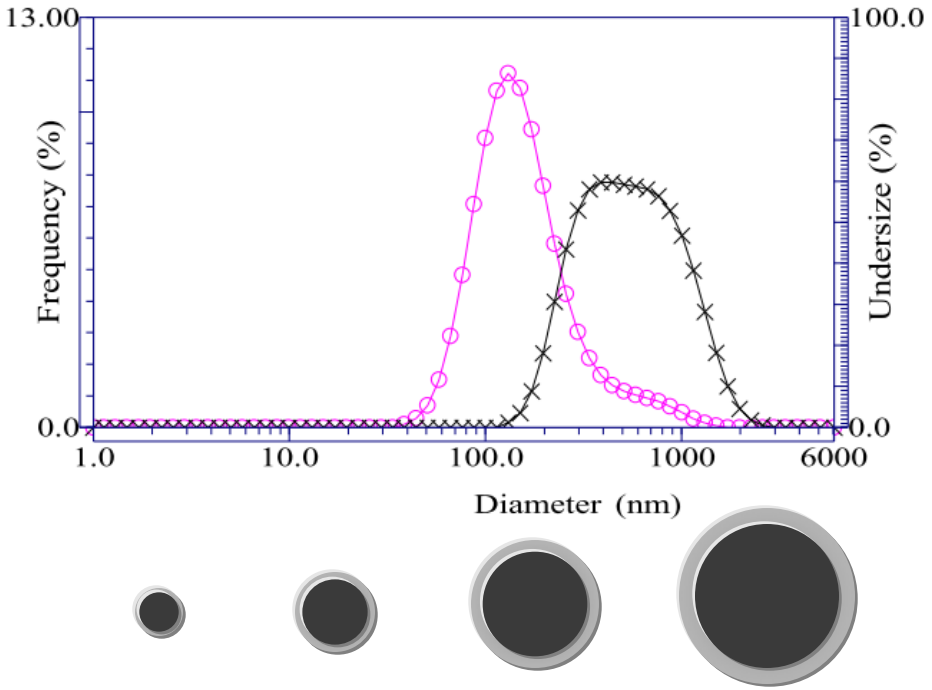


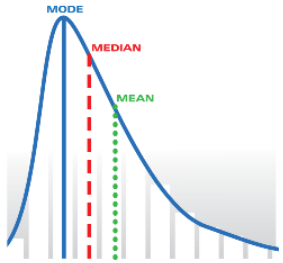
The Basics

Dynamic Light Scattering

Assumes hard, spherical shape model

Frequency %
= amount
of each size
by volume

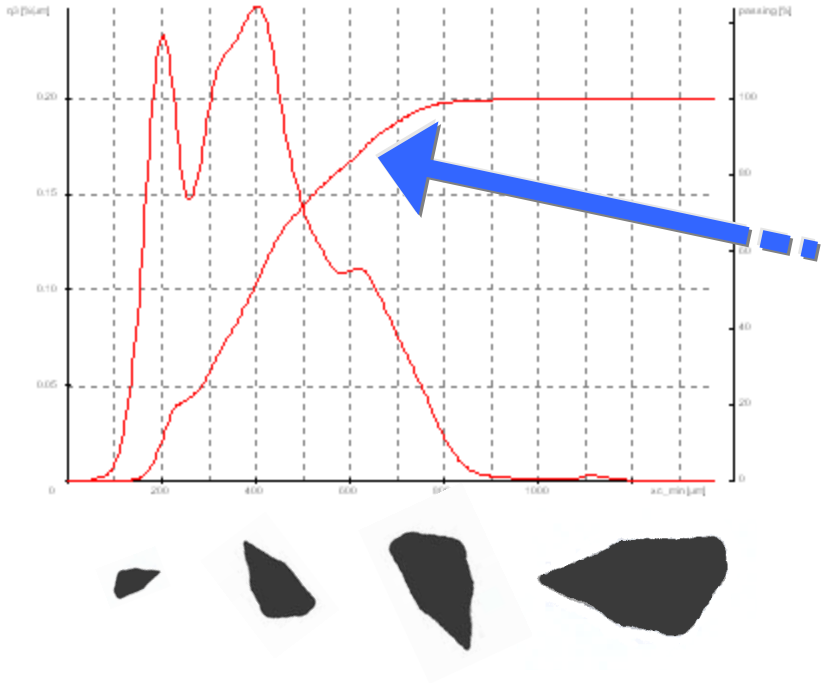




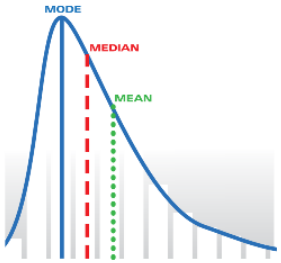
The Basics

Image Analysis

Measures particle projection → no shape assumption



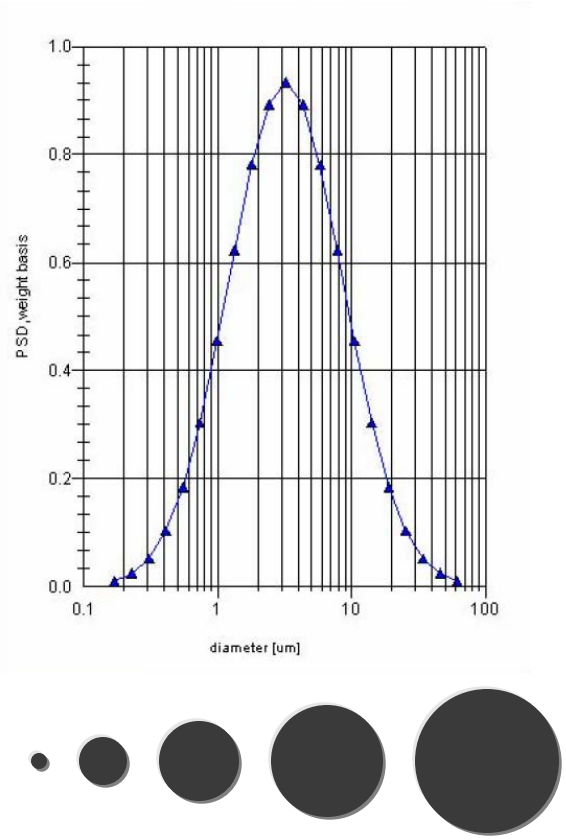
Undersize
Passing
Q3

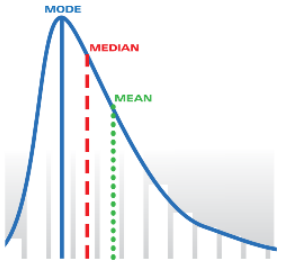


The Basics

Acoustic Spectroscopy

Assumes hard, spherical shape model

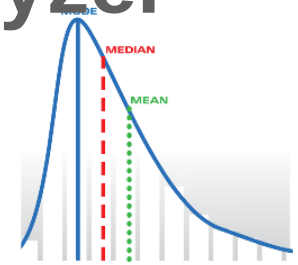




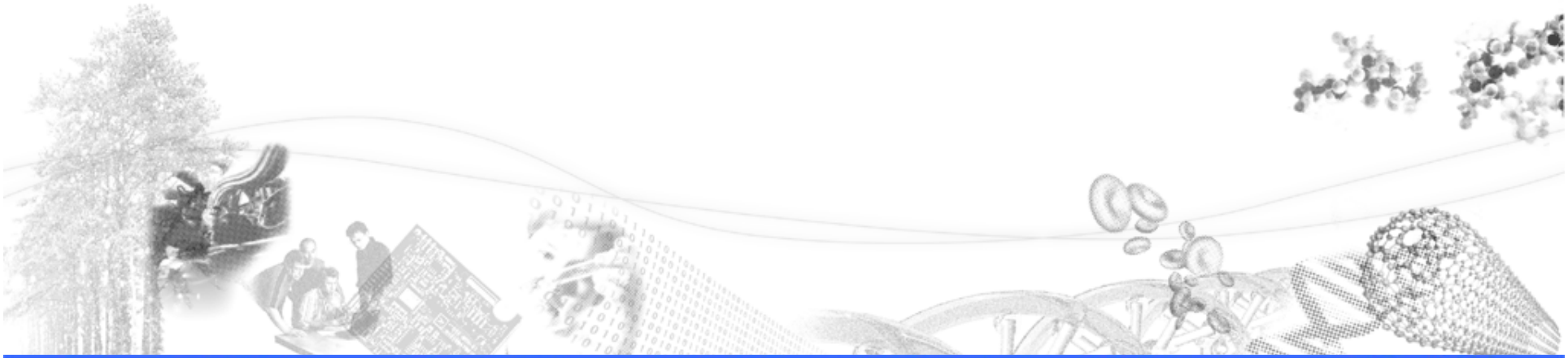
Quiz!

Conclusions

- **Understand the data**
  - **A little goes a long way!**
- **Know something about the particles in your sample**
- **Particles have multiple dimensions, know which dimension your analyzer measures!**



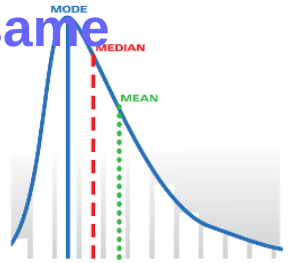
Defining Parameters



Terms, Terms, and more Terms

Particle Size

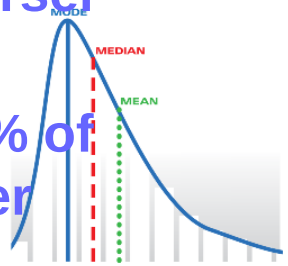
Monomodal:	**One Peak**
Bimodal:	**Two Peaks**
Multimodal:	**Multiple Peaks**
Monodisperse:	**All particles have same size**
Polydisperse:	**Particles have many sizes**
Volume diameter:	**Diameter of a sphere having the same volume as the particle**
Surface diameter:	**Diameter of a sphere having the same surface as the particle**



Terms, Terms, and more Terms

Particle Size

Frequency% / q% / p3 / Retained / Sph Vol%	Amount of each size by volume
Volume-based diameter	Calculated from vol. distribution emphasizes coarse particles (larger volume)
Number-based diameter	Calculated from number dist. (individual particles) emphasizes fine particles
Cumulative% on diameter	% of distribution finer/coarser than specified size
Diameter on cumulative%	Size at which a specified % of distribution is finer/coarser

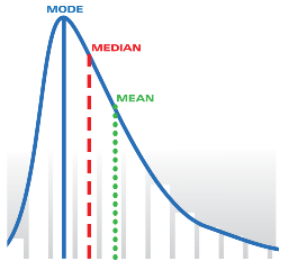


Terms, Terms, and more Terms

Particle Shape

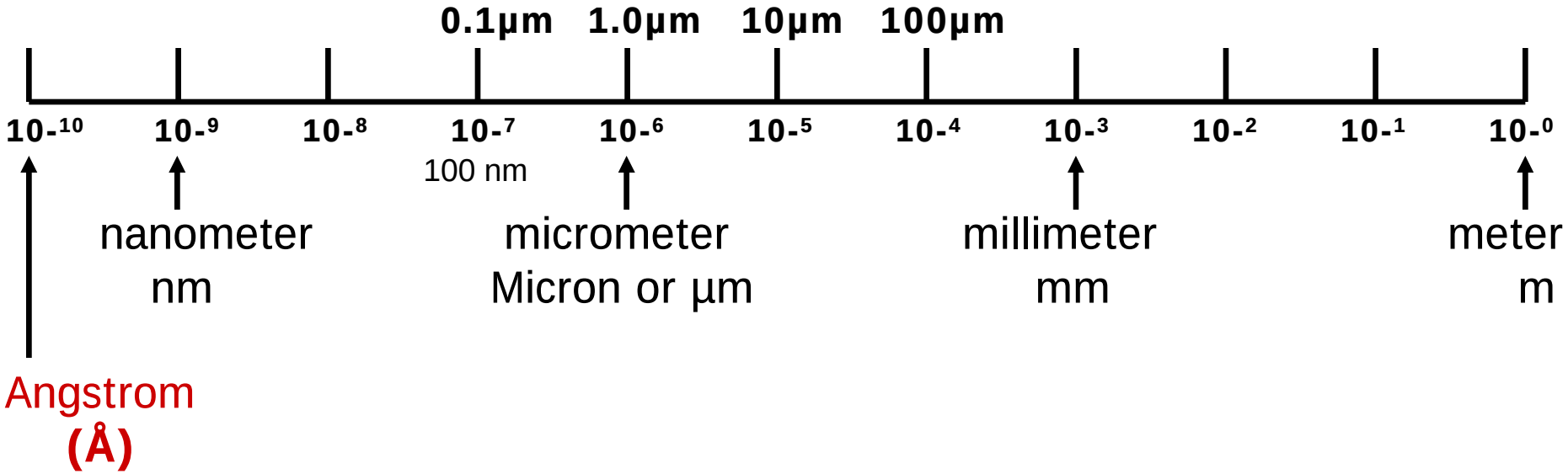
Acicular:	**Needle-shaped, rigid**
Angular:	**Edgy, hard angles**
Fibrous:	**Thread-like, non-rigid**
Granular/Blocky:	**Irregular-shaped, low aspect-ratio**
Spherical:	**Regular-shaped, unity aspect ratio**

Aspect ratio:	**Breadth / length OR Length / breadth**
Sphericity:	**How spherical is the particle?**
Roundness:	**How round is the particle?**

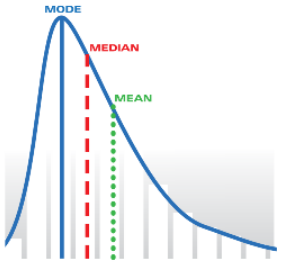


Quiz!

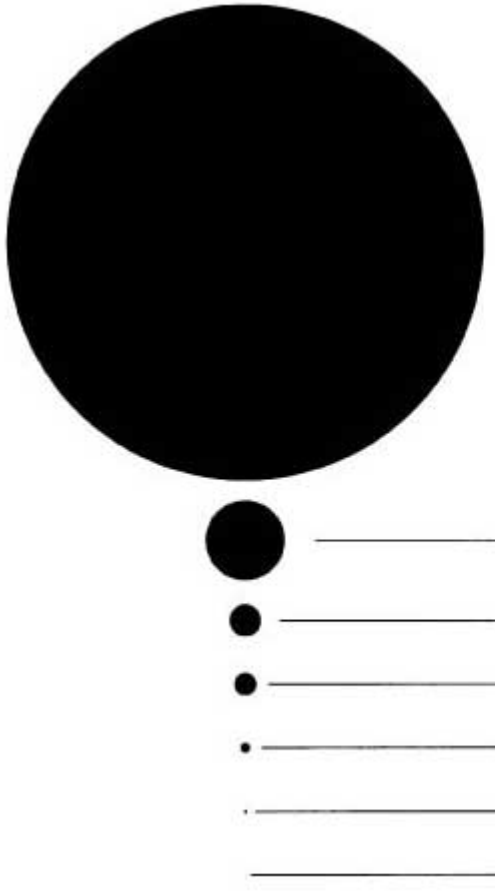
Size Terminology



The most common designation is micrometers or microns. When very small, in colloid region, measured in nanometers, with electron microscopes or by dynamic light scattering.

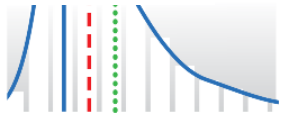


Relative Size



- Human Hair

- Visible Particles: Lint, Dust, width of the **ridges of fingertips**.
- Dust and free flowing powders
- Suspensions and fine powders
- Suspensions and fine powders
- Emulsions and Colloids
- Proteins, Viruses, and Macro-Molecules



Quiz!

Central Values

Mean

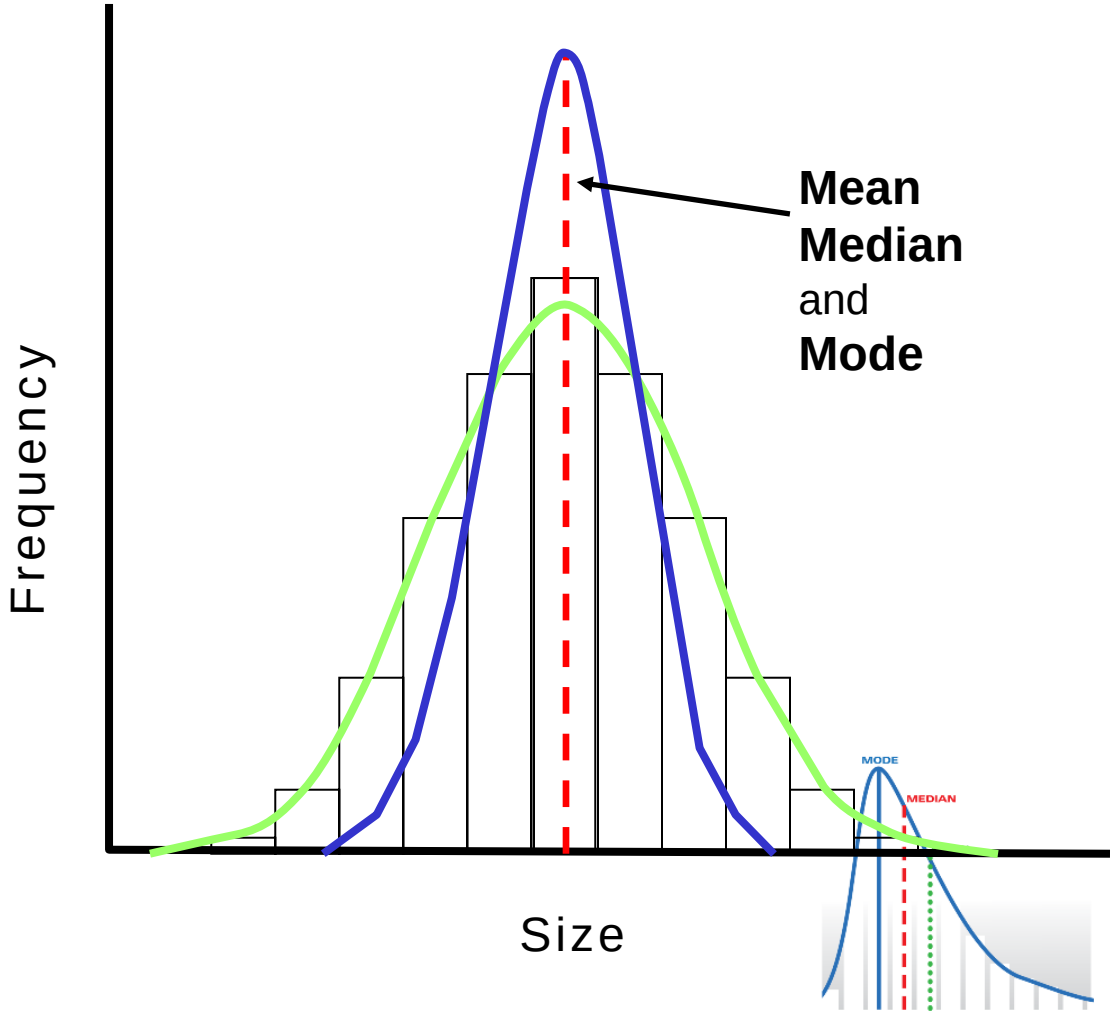
- Weighted Average
- Center of Gravity

Median

- 50% Point

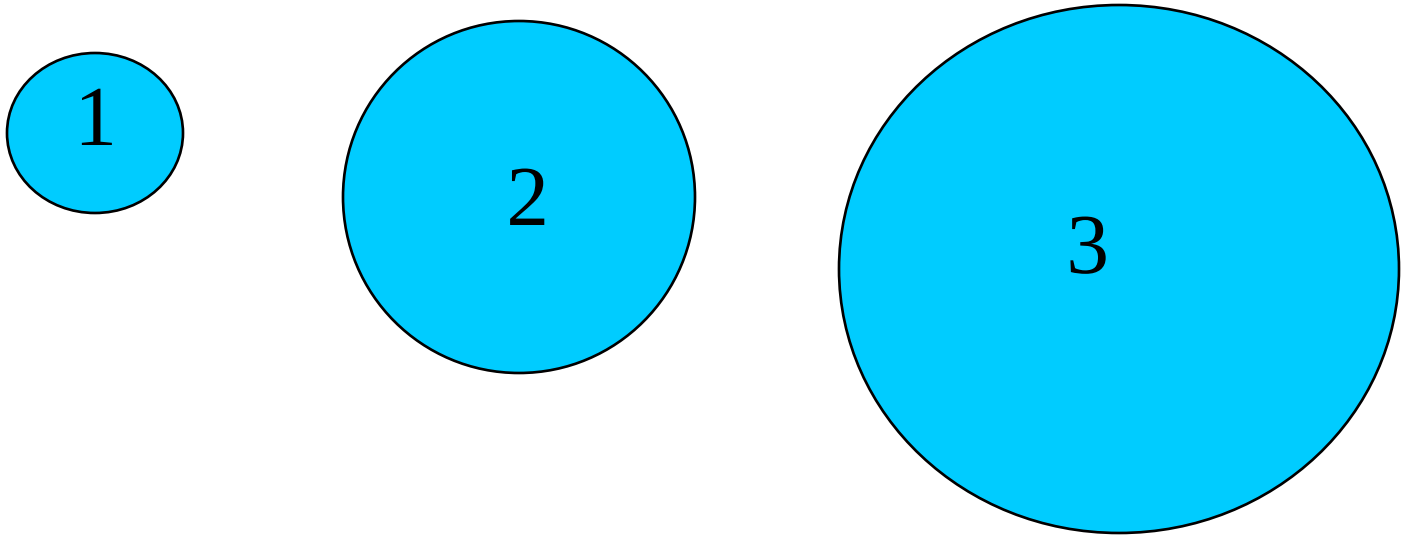
Mode

- Peak of the distribution
- Most common value



What does “Mean” mean?

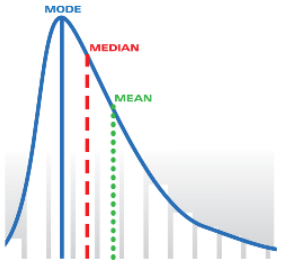
Three spheres of diameters 1,2,3 units



What is the average size of these spheres?

Average size = (1+2+3) ÷ 3 =2.00

This is called the D[1,0] - the number mean



Many possible Mean values

$$X_{nl} = D[1,0] = \frac{1+2+3}{3} = 2.00$$

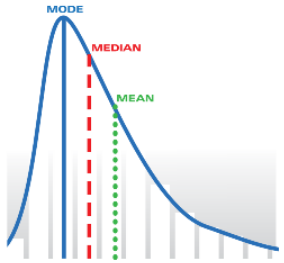
$$X_{ns} = D[2,0] = \sqrt{\frac{1+4+9}{3}} = 2.16$$

$$X_{nv} = D[3,0] = \sqrt[3]{\frac{1+8+27}{3}} = 2.29$$

$$X_{sv} = D[3,2] = \frac{1+8+27}{1+2+3} = 2.57$$

$$X_{vm} = D[4,3] = \frac{1+16+81}{1+8+27} = 2.72$$

None of the answers are wrong they have just been calculated using different techniques



Volume-based Mean diameter

D[4,3] which is often referred to as the Volume Mean Diameter [VMD]

$$D[4,3] = \frac{\sum D_i^4 n_i}{\sum D_i^3 n_i}$$

Monitoring the D[4,3] value in your specification will emphasize the detection of large particles

Mean Size

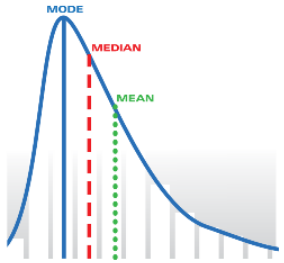
The frequency distribution is found using the arithmetical mean diameter, as shown in the formula below.

Mean Diameter = $\Sigma\{q(J) \times X(J)\} / \Sigma\{q(J)\}$

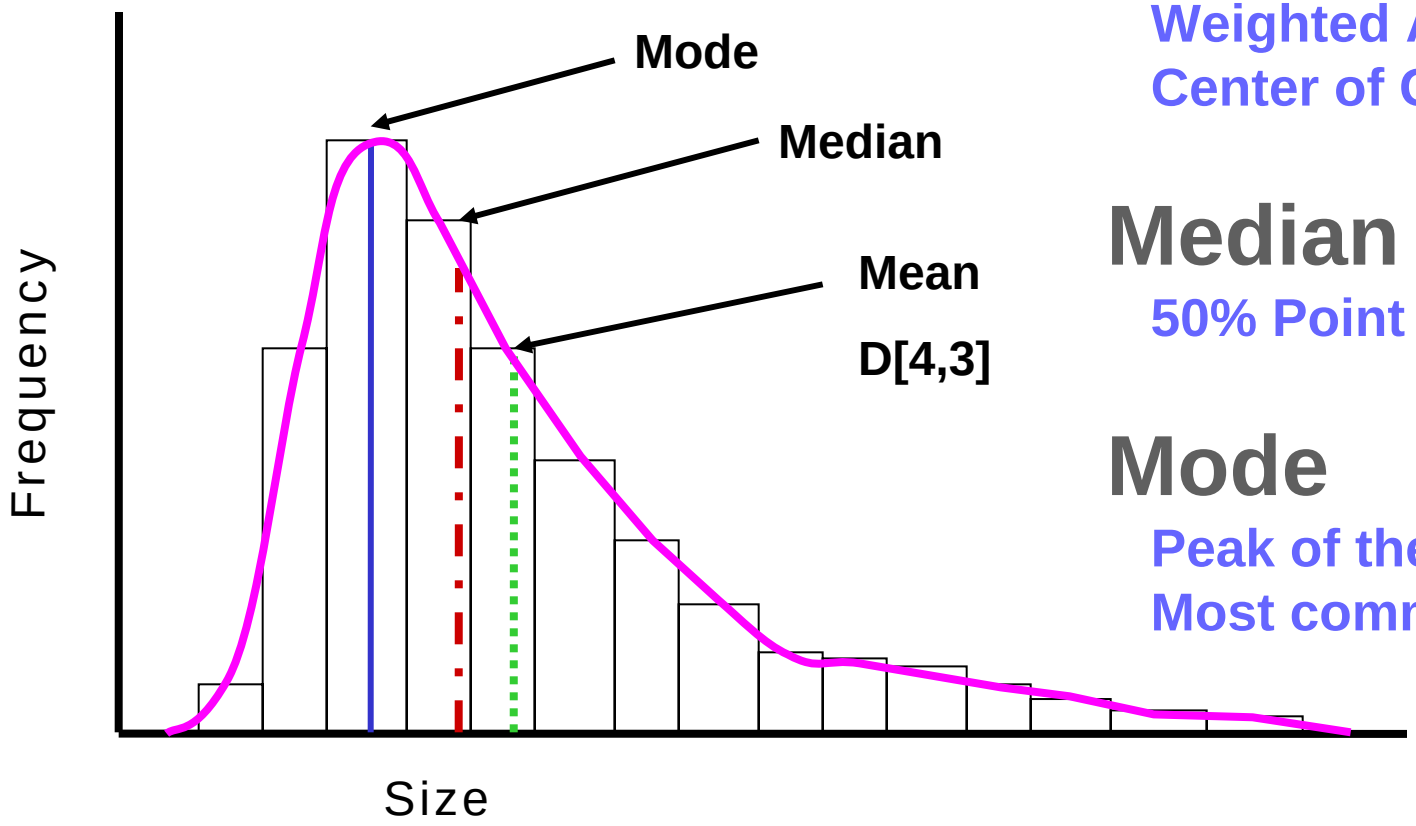
J : Particle Diameter Division Number

q(J) : Frequency Distribution Value (%)

X(J) : Jth Particle Diameter Range's Representative Diameter (μm).



Central Values revisited



Mean

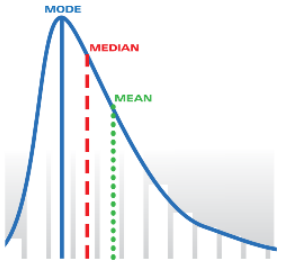
Weighted Average
Center of Gravity

Median

50% Point

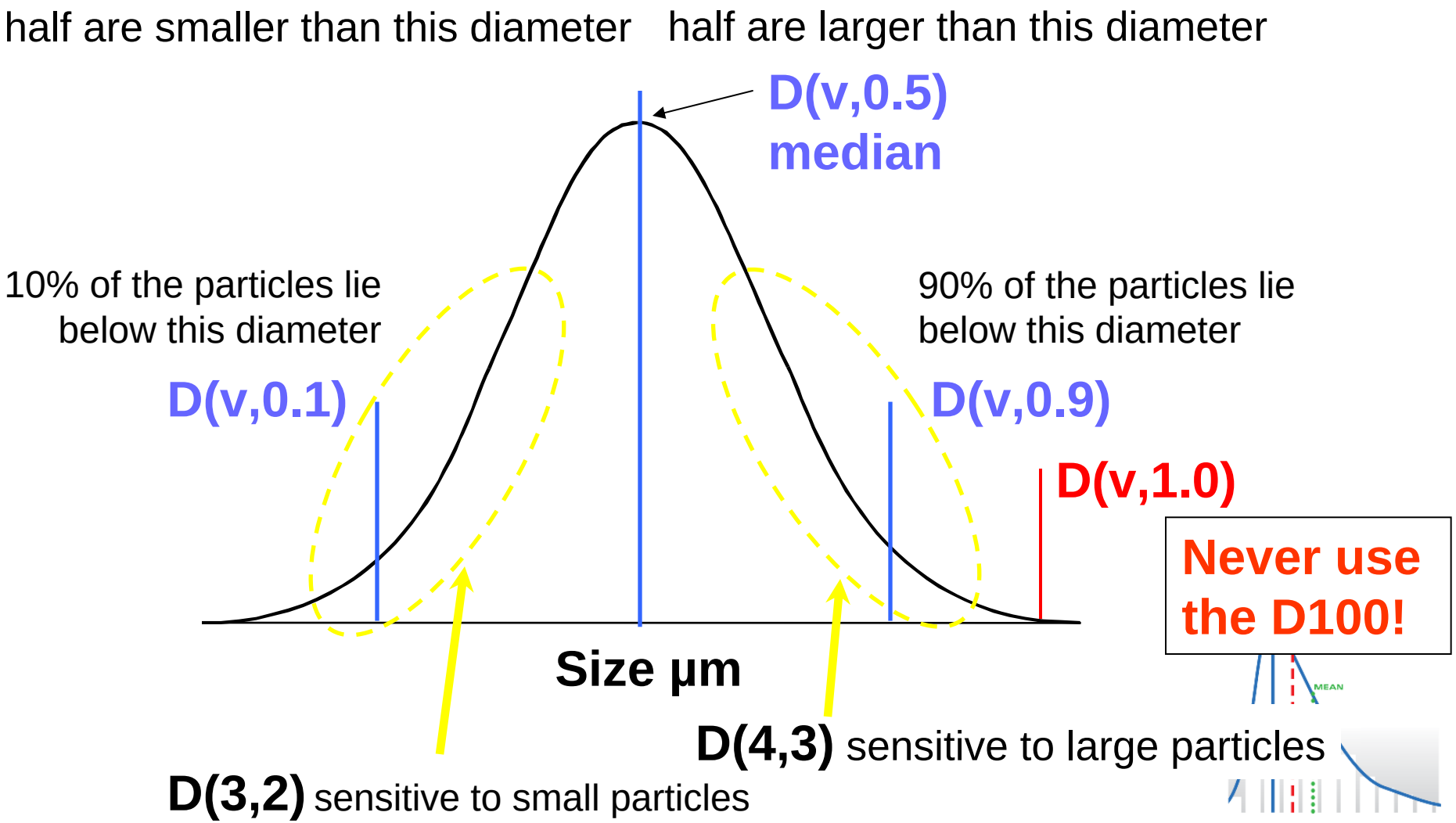
Mode

Peak of the distribution
Most common value

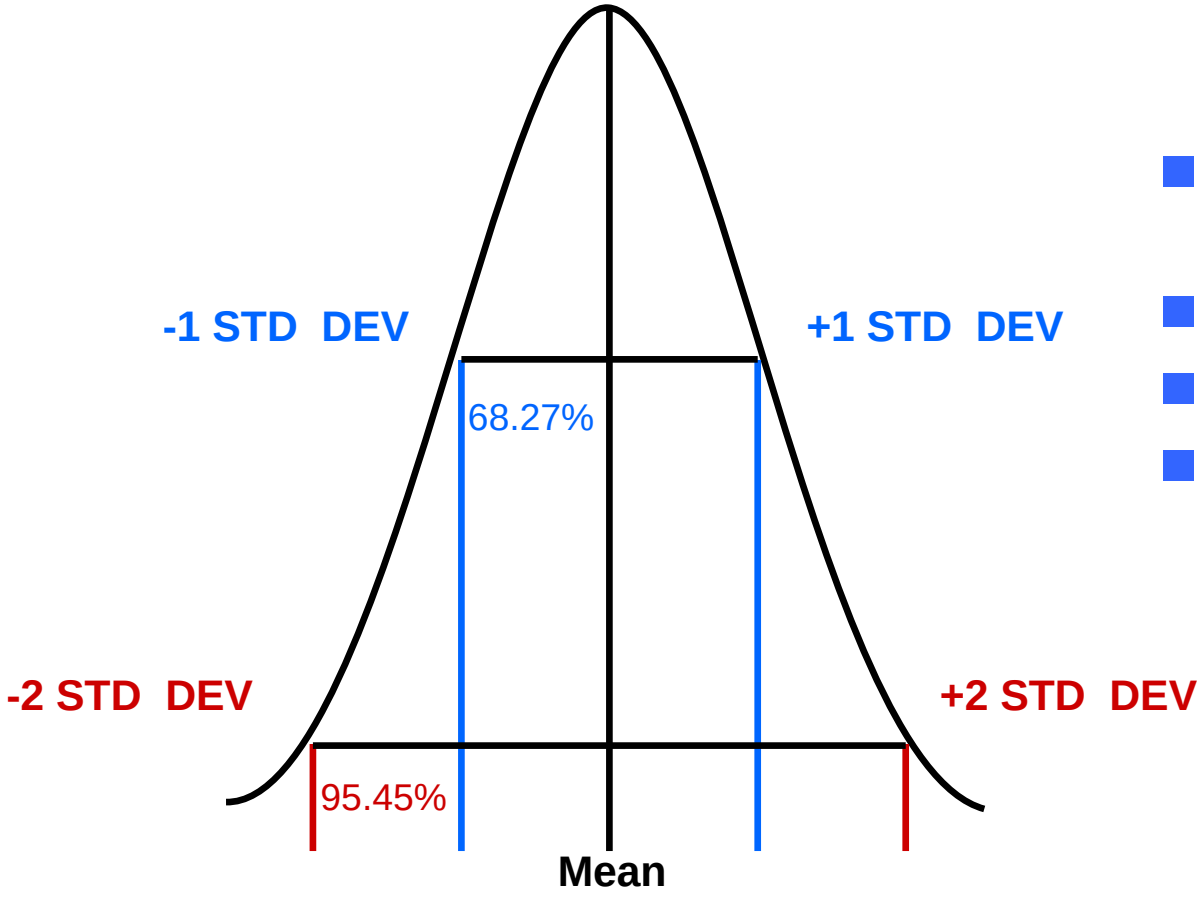


Remember: D[4,3] is sensitive to large particles

Most Common Statistics

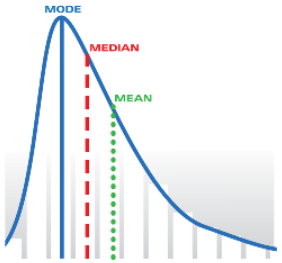


Standard Deviation

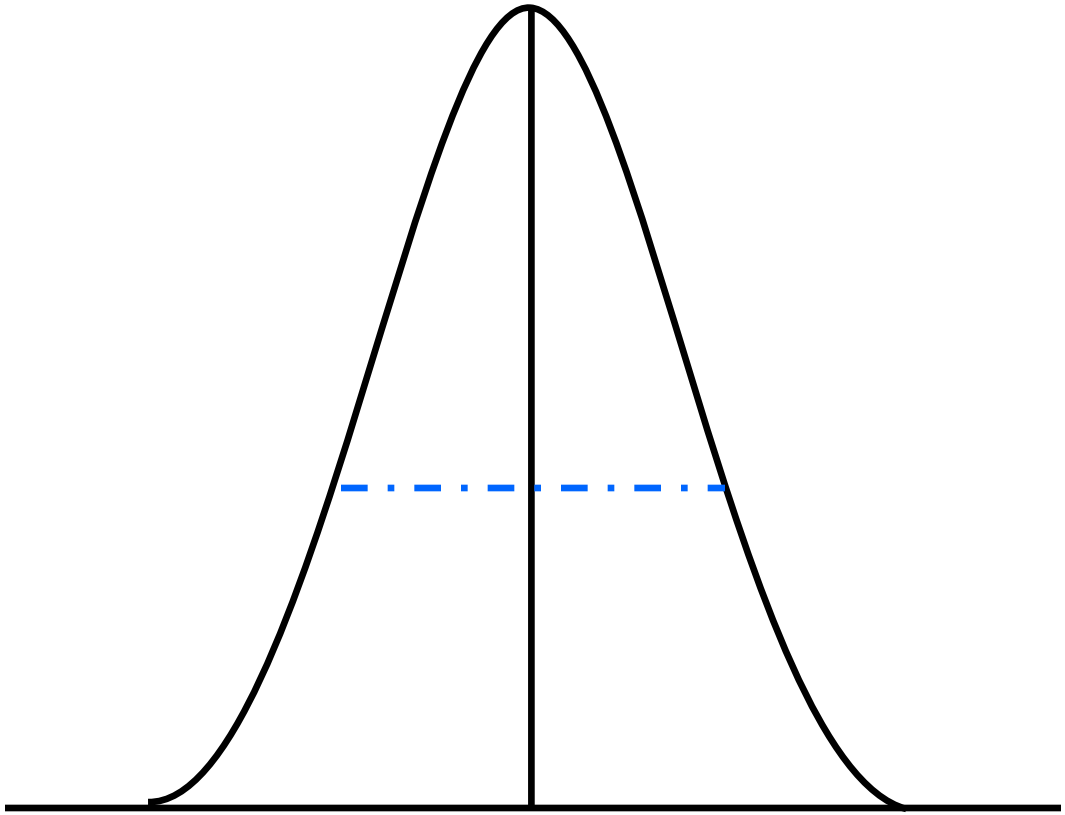


- Normal (Gaussian) Distribution Curve
- μ = distribution mean
- σ = standard deviation
- Exp = base of natural logarithms

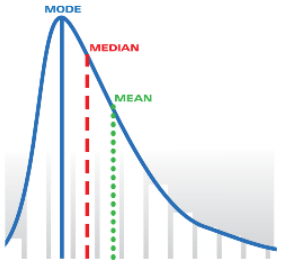
$$Y = \frac{1}{\sigma\sqrt{2\sigma}} \; Exp\left[\frac{-(x-\mu)^2}{2\sigma^2}\right]$$



Distribution Width



- Polydispersity Index (PI, PDI)
- Span
- Geometric Std. Dev.
- Variance
- Etc…

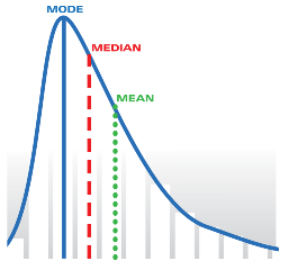


Quiz!

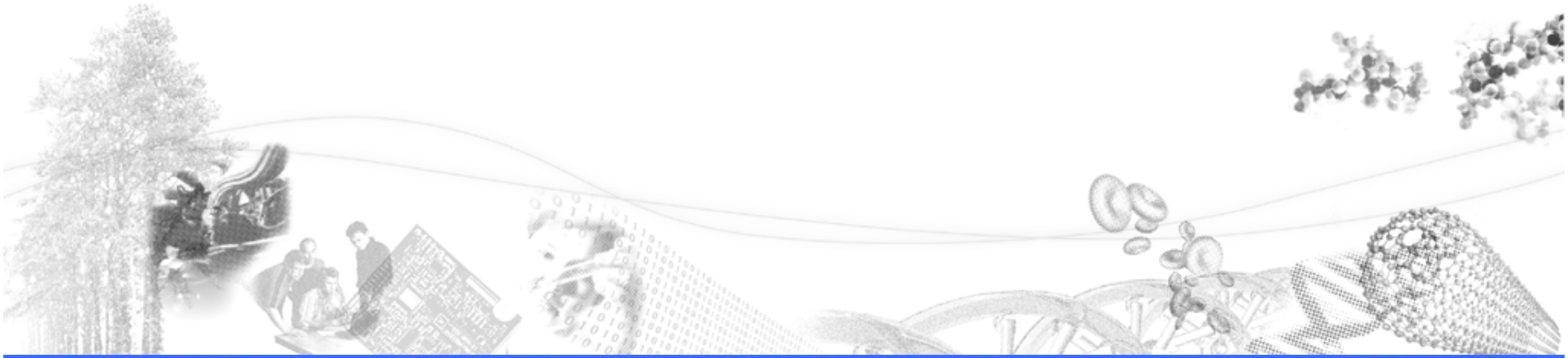
Conclusions

- **Be familiar with the nomenclature**
- **Many parameters can describe distribution**

  D50, D10, D90 commonly used
- **Which Mean do you mean?**



Choosing Parameters

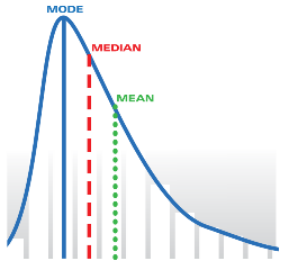


Choosing good statistics

Statistics describing the distribution must…

- Tell us about our process
- Must be relevant
- Must be controlled well
- Be reproducible!

Poor precision is the result of either a poor method or poor statistical choices



The Basis for Reliable Data

Reproducibility!

Prepare, measure, empty, repeat

What would be good reproducibility?

Look at the accepted standards

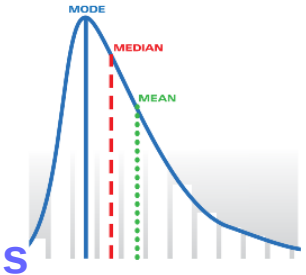
ISO 13320

- **COV < 3% at Median (D50)**
- **COV < 5% at D10 and D90**

USP <429>

- **COV < 10% at Median (D50)**
- **COV < 15% at D10 and D90**

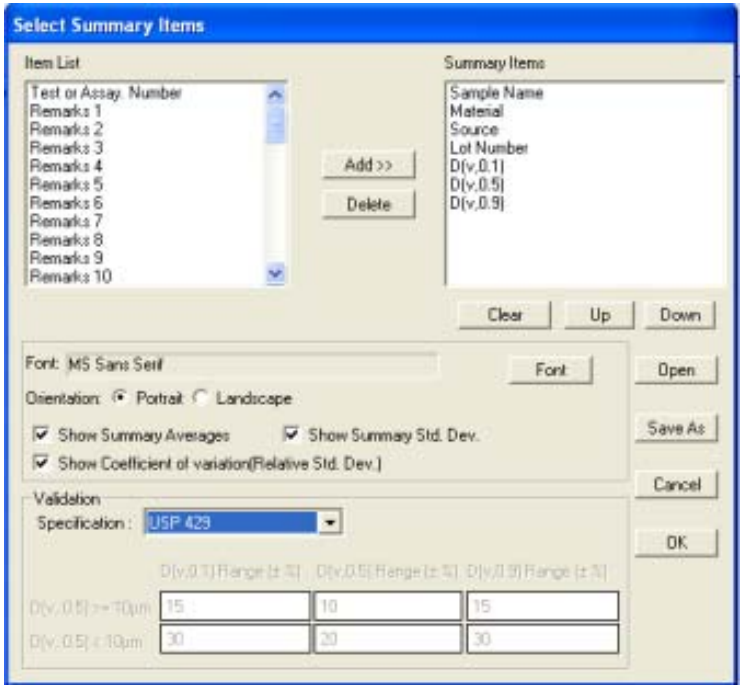
COV = 100 * (StDev / Mean)

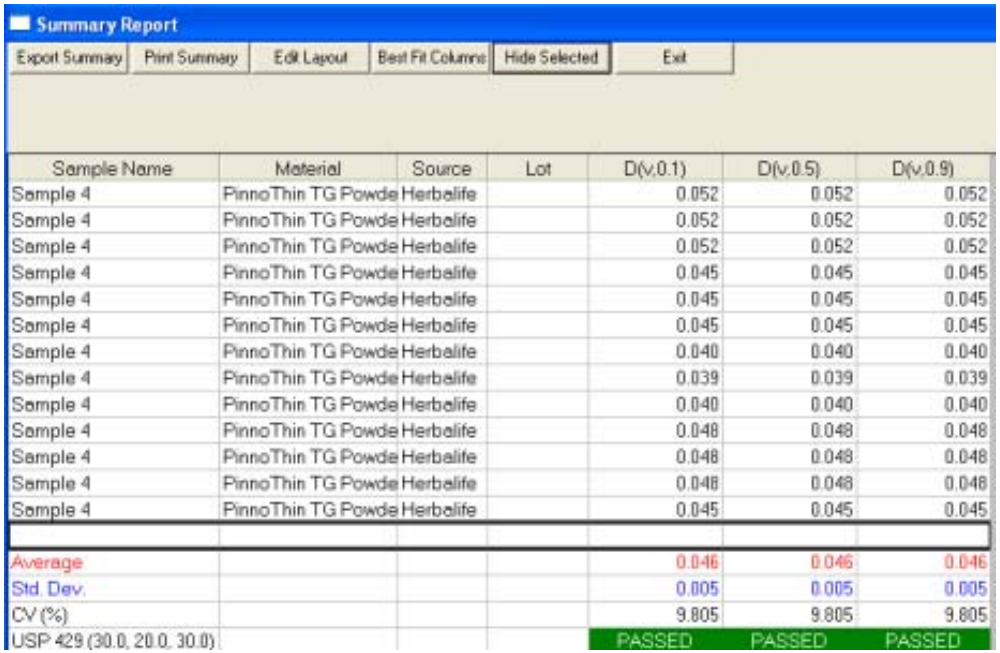


Note: All limits double when D50 < 10 µm

Note: Must acquire at least 3 measurements from unique samplings

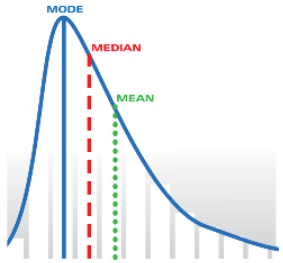
Calculation Automation





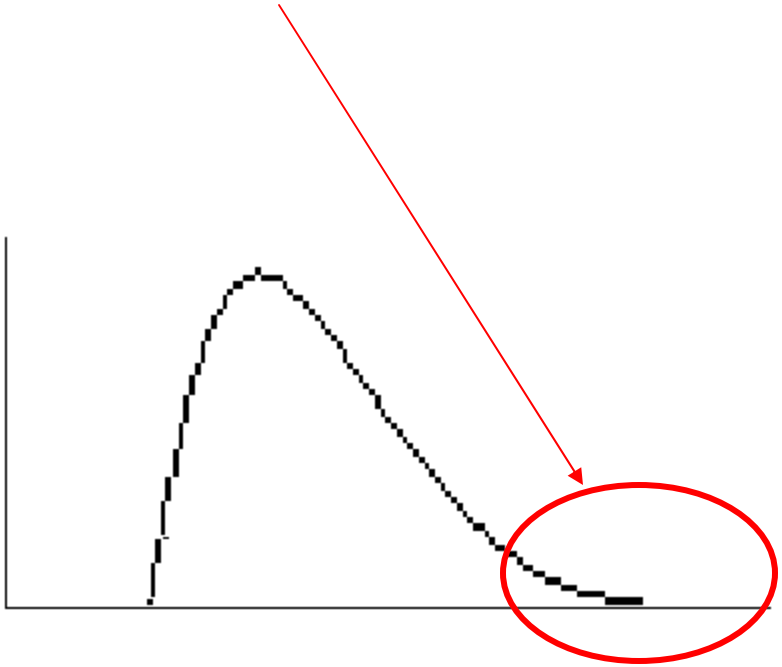
Sample Name	Material	Source	Lot	D(v,0.1)	D(v,0.5)	D(v,0.9)
Sample 4	PinnoThin TG Powde	Herbalife		0.052	0.052	0.052
Sample 4	PinnoThin TG Powde	Herbalife		0.052	0.052	0.052
Sample 4	PinnoThin TG Powde	Herbalife		0.052	0.052	0.052
Sample 4	PinnoThin TG Powde	Herbalife		0.045	0.045	0.045
Sample 4	PinnoThin TG Powde	Herbalife		0.045	0.045	0.045
Sample 4	PinnoThin TG Powde	Herbalife		0.045	0.045	0.045
Sample 4	PinnoThin TG Powde	Herbalife		0.040	0.040	0.040
Sample 4	PinnoThin TG Powde	Herbalife		0.039	0.039	0.039
Sample 4	PinnoThin TG Powde	Herbalife		0.040	0.040	0.040
Sample 4	PinnoThin TG Powde	Herbalife		0.048	0.048	0.048
Sample 4	PinnoThin TG Powde	Herbalife		0.048	0.048	0.048
Sample 4	PinnoThin TG Powde	Herbalife		0.048	0.048	0.048
Sample 4	PinnoThin TG Powde	Herbalife		0.045	0.045	0.045
Average				0.046	0.046	0.046
Std. Dev.				0.005	0.005	0.005
CV (%)				9.805	9.805	9.805
USP 429 (30.0, 20.0, 30.0)				PASSED	PASSED	PASSED

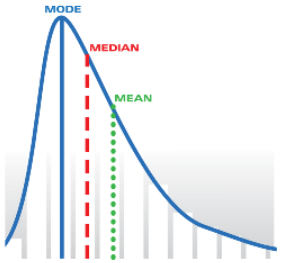
Unique, automatic feature in LA-950 software



Distribution Extremes

- At a distance of a few standard deviations, non-instrumental errors can dominate



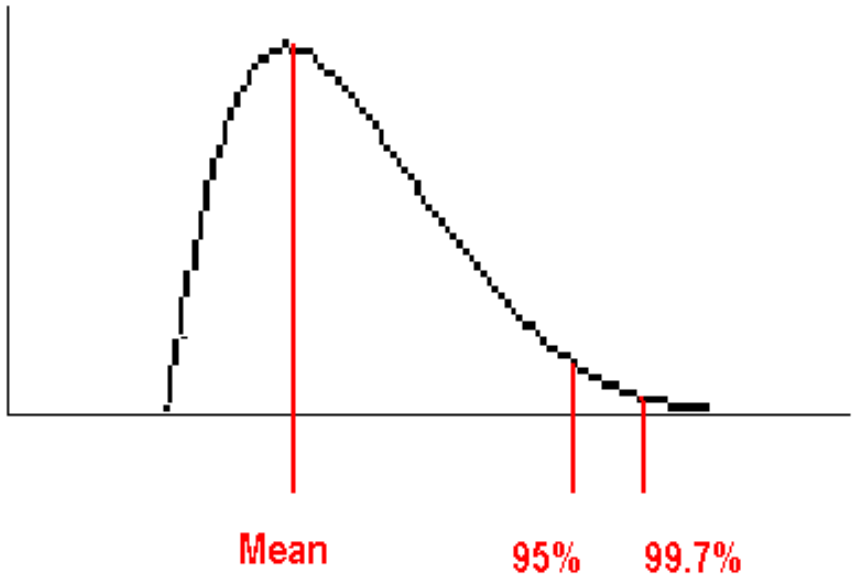


2 and 3 Standard Deviations

- 95% of the distribution is within 2 standard deviations from the Mean
- 99.7% of the distribution is within 3 standard

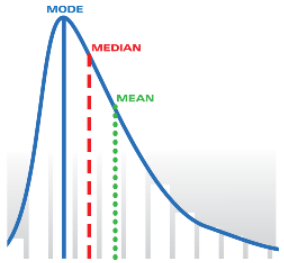
  deviations

  from the mean



Reproducibility at the Extremes

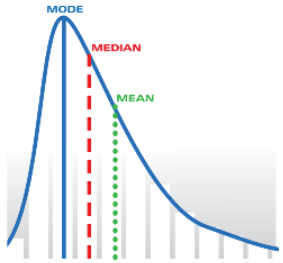
- If we want the same level of reproducibility at the D99 value as the D50, we need to analyze similar amounts of material in the D99 histogram band



Better Method to Monitor Extremes

- Instead of specifying the D95, D99, D99.99, D100, DMax

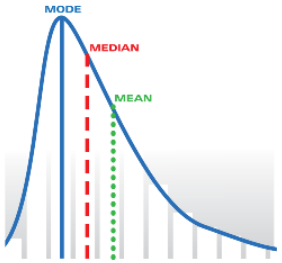
- Specify the % of material greater than a certain size



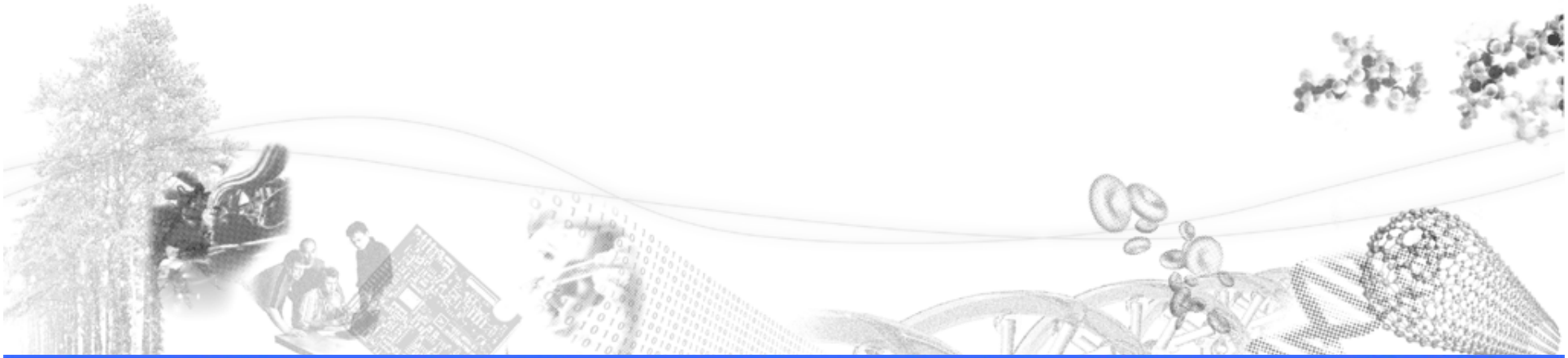
Quiz!

Conclusions

- **Parameters should reflect product performance**
  - But don't make your life more difficult than it needs to be!
- **Look to appropriate standards**
  - ISO 13320, USP <429> can provide guidance
- **Avoid monitoring the extremes whenever possible**
  - Better to use D(4,3) when you want spec. to be sensitive to presence of large particles



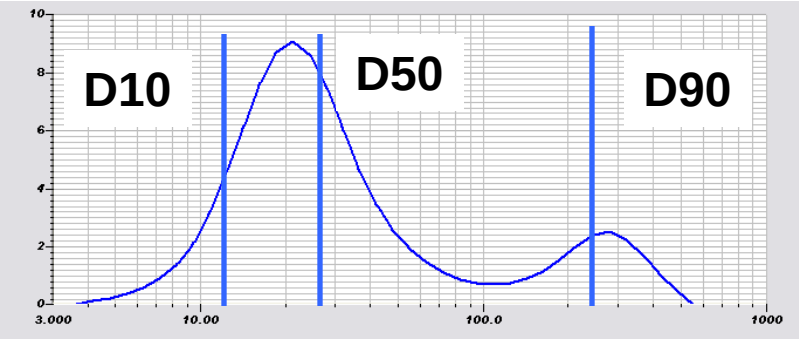
Advanced Result Interpretation

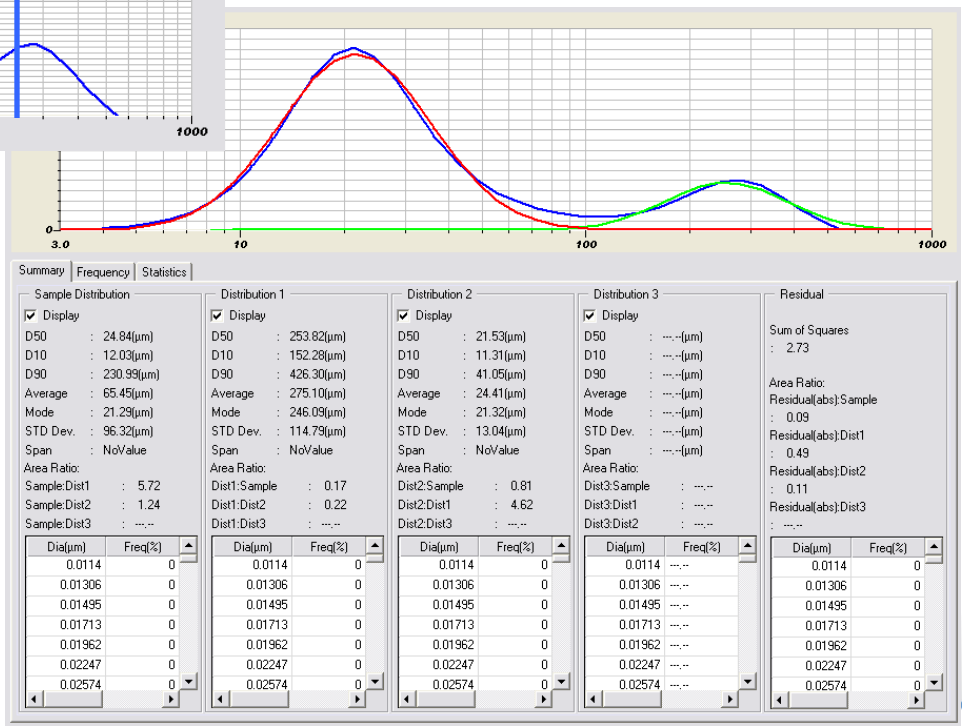


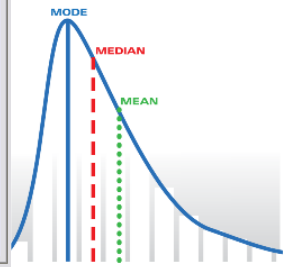
General

Multiple Modes

Multiple peaks can be better described individually



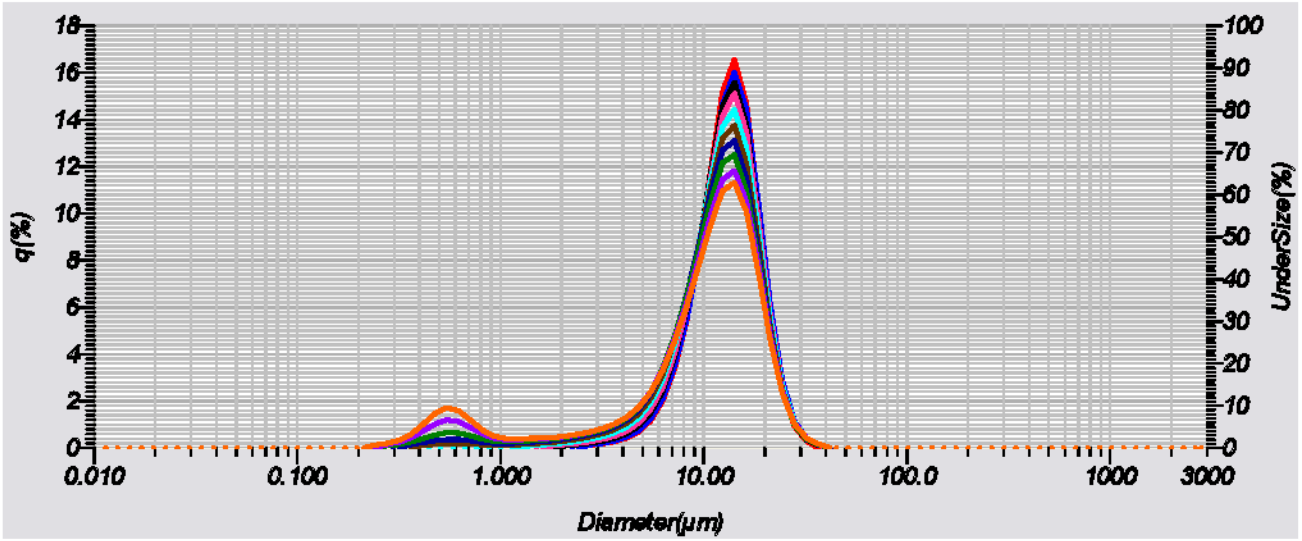




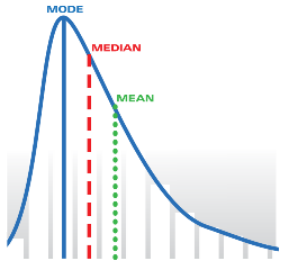
Laser Diffraction

Multiple Scattering

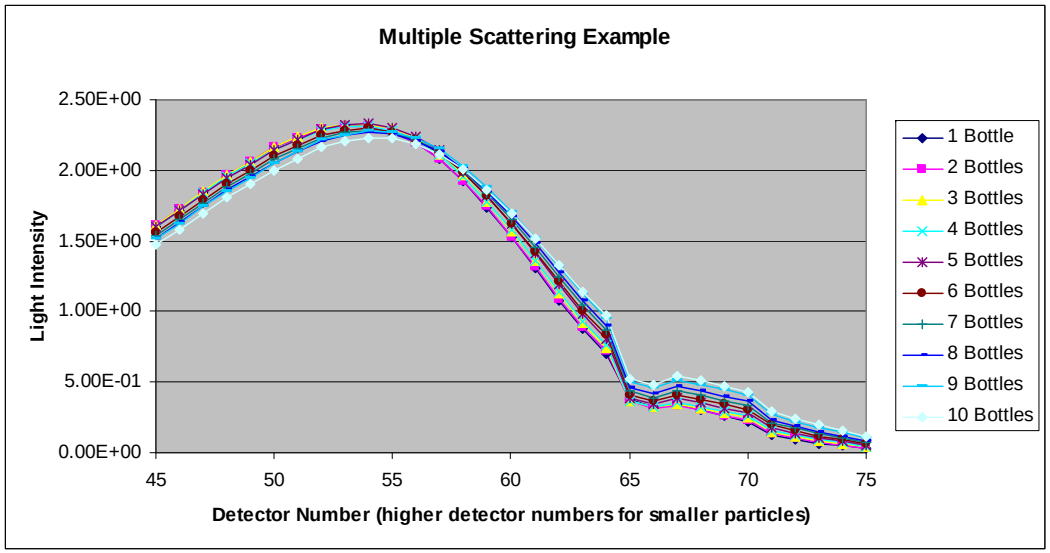
Watch for finer “particles” appearing with increasing concentration

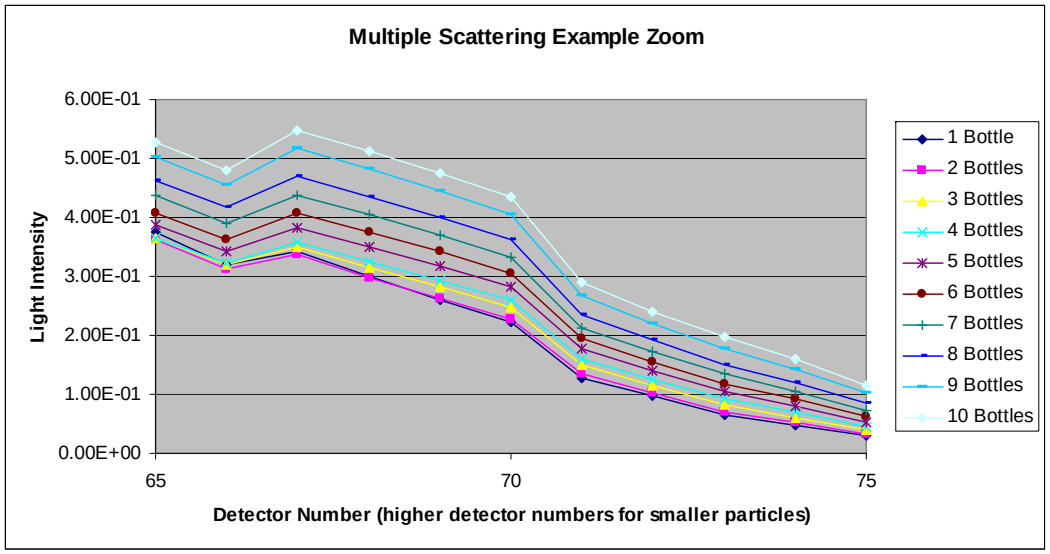


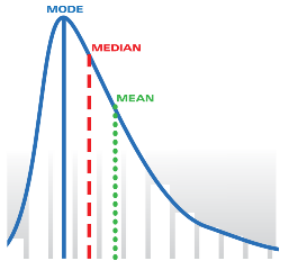
Graph Type	Test or Assay. Number	Transmittance(R)	Transmittance(B)	Verification
	1 bottle	85.4(%)	85.2(%)	1.OK 2.OK 3.OK
	2 bottles	70.7(%)	71.8(%)	1.OK 2.OK 3.OK
	3 bottles	58.1(%)	60.2(%)	1.NG 2.OK 3.OK
	4 bottles	48.1(%)	51.9(%)	1.NG 2.OK 3.OK
	5 bottles	39.4(%)	44.7(%)	1.NG 2.OK 3.OK
	6 bottles	32.4(%)	38.6(%)	1.NG 2.OK 3.OK
	7 bottles	27.7(%)	34.1(%)	1.NG 2.NG 3.OK
	8 bottles	23.4(%)	29.9(%)	1.NG 2.NG 3.OK
	9 bottles	18.9(%)	25.9(%)	1.NG 2.NG 3.OK
	10 bottles	15.9(%)	22.7(%)	1.NG 2.NG 3.OK



Multiple Scattering



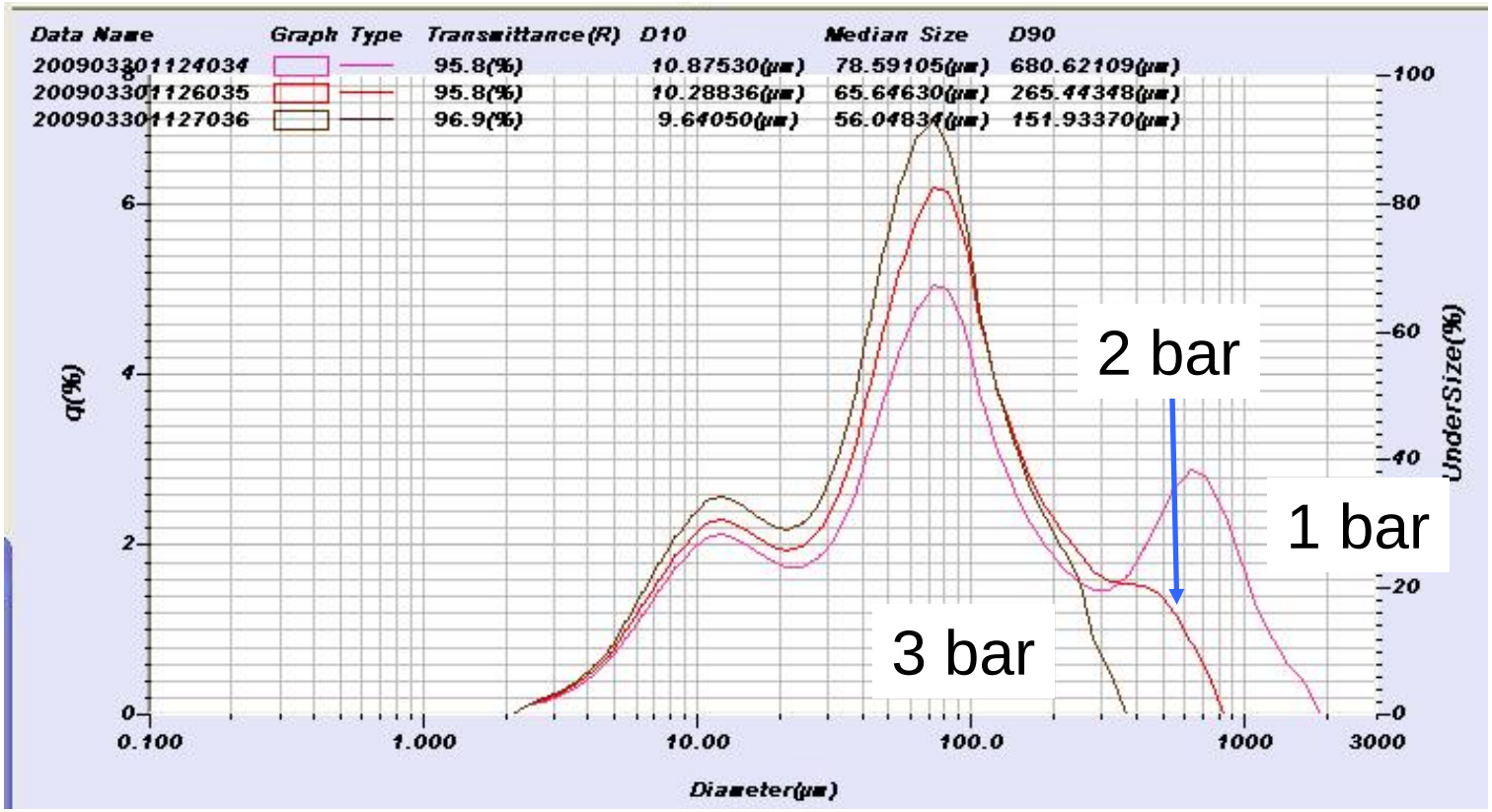


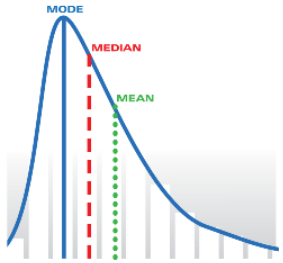


Laser Diffraction

Dispersing Agglomerates

Watch for no change in coarsest particles with changing energy

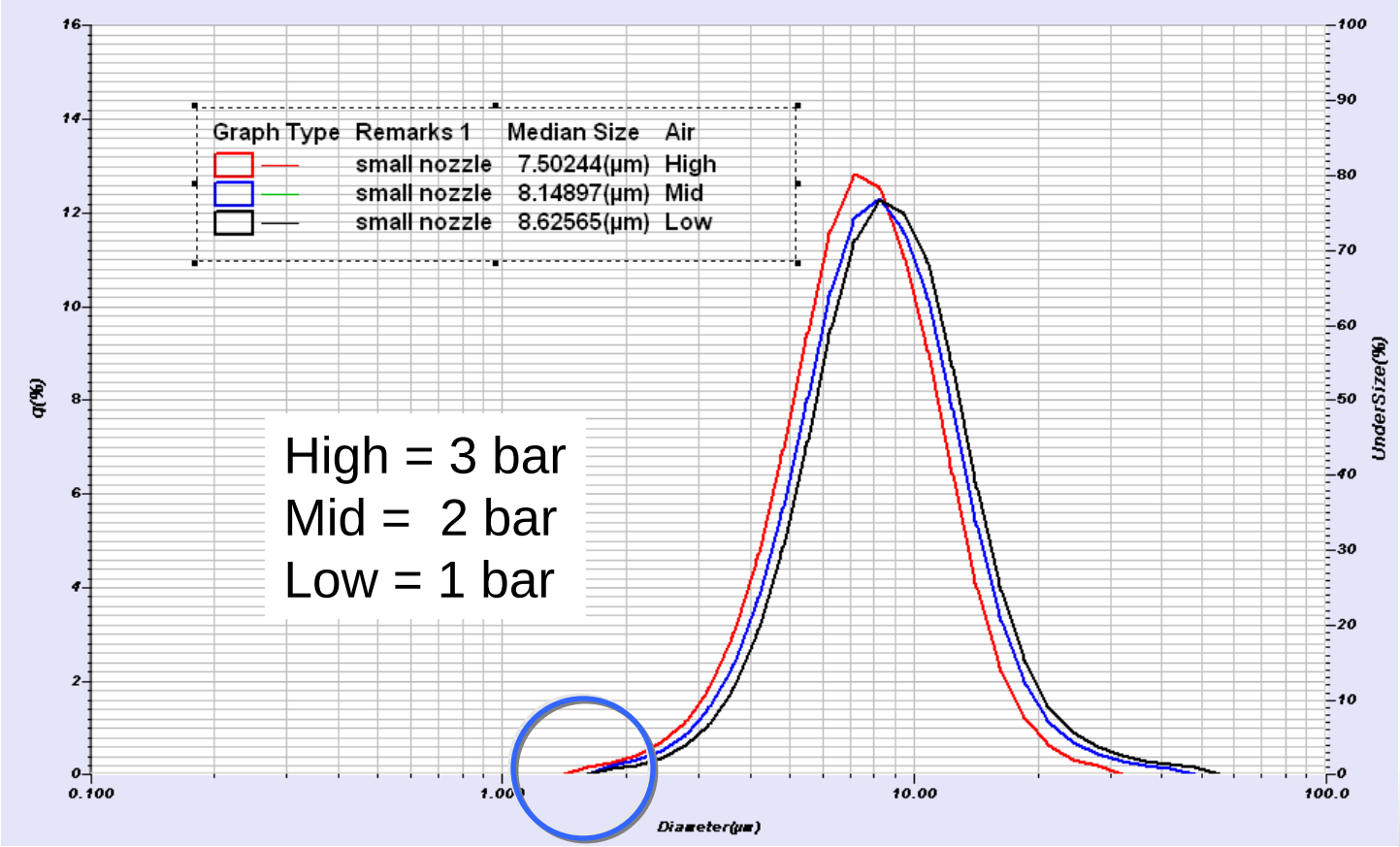


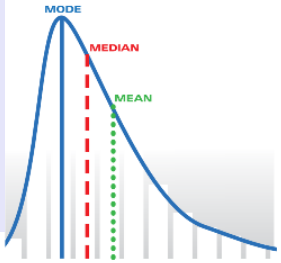


Laser Diffraction

Breaking Particles

Watch for finer particles being created with increasing energy





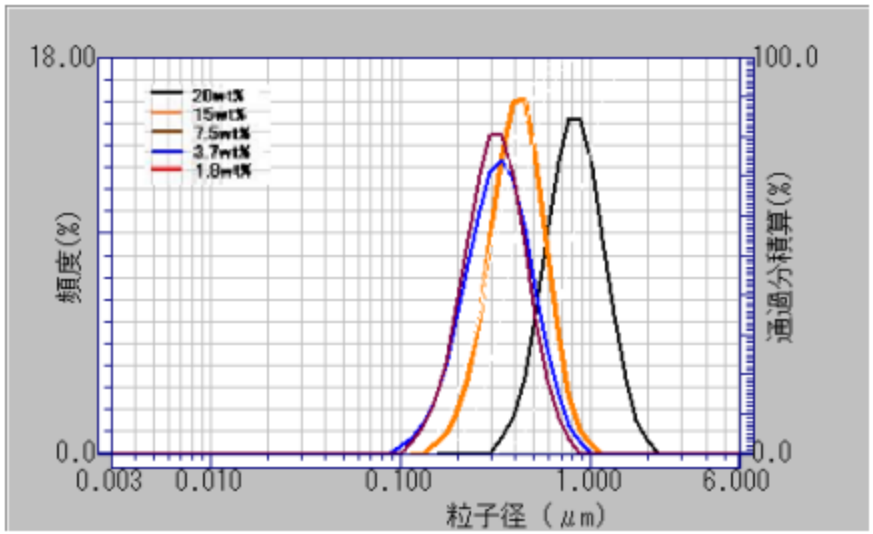
Dynamic Light Scattering

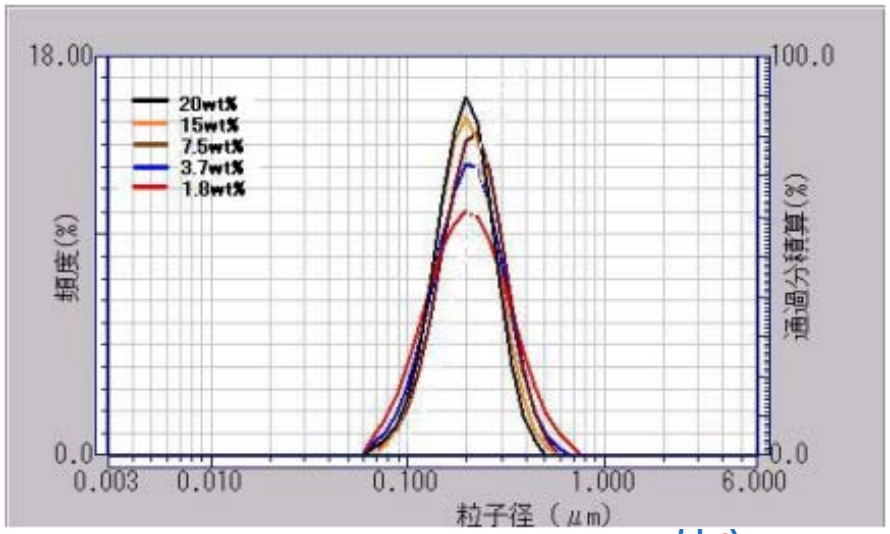
Restricted Diffusion

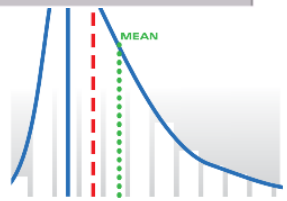
Use *bulk viscosity* for concentrated sample

Apparent size shifts larger with increasing concentration

Polydispersity (distribution width) remains a constant







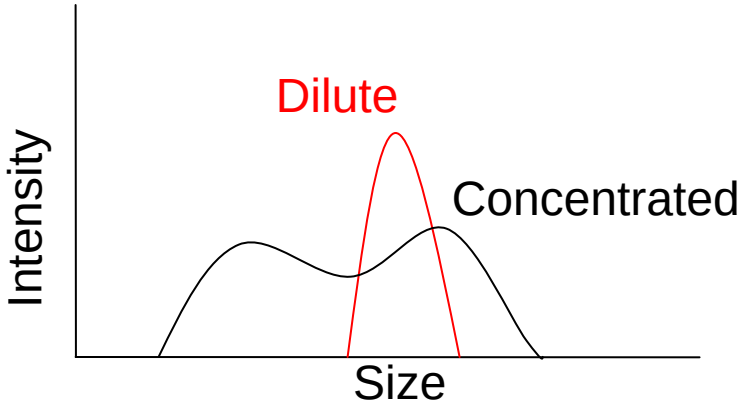
Dynamic Light Scattering

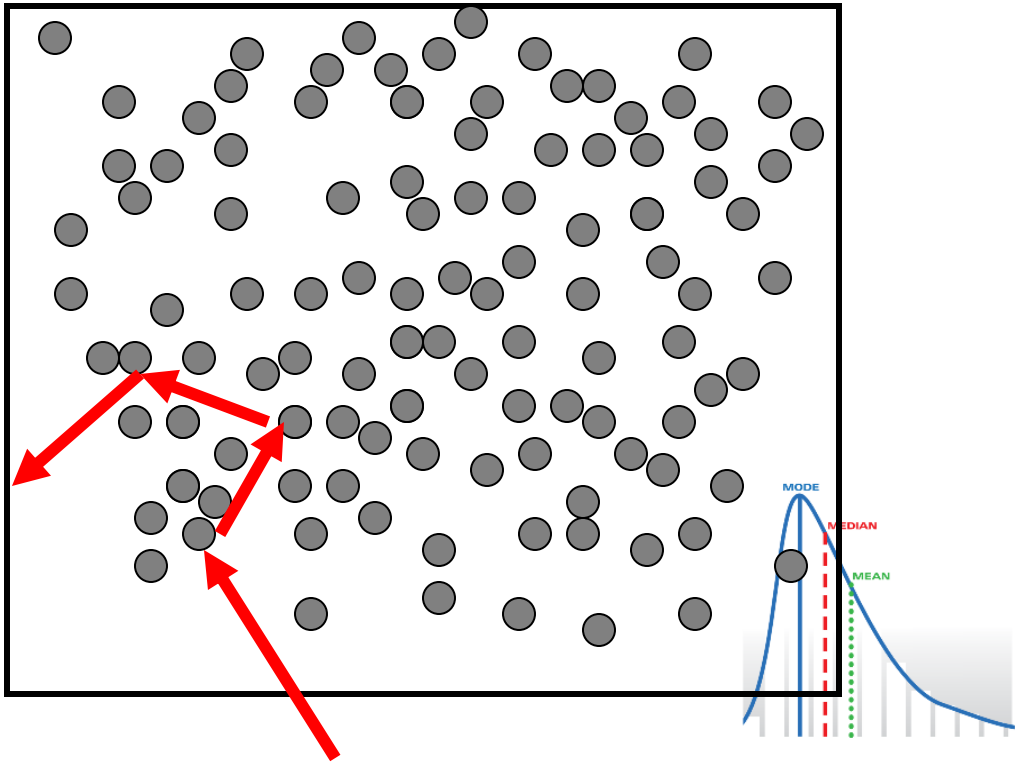
Multiple Scattering

Incident light scatters off of multiple particles

Particles appear smaller, distribution shifts finer

Distribution broadens in comparison to dilute analysis





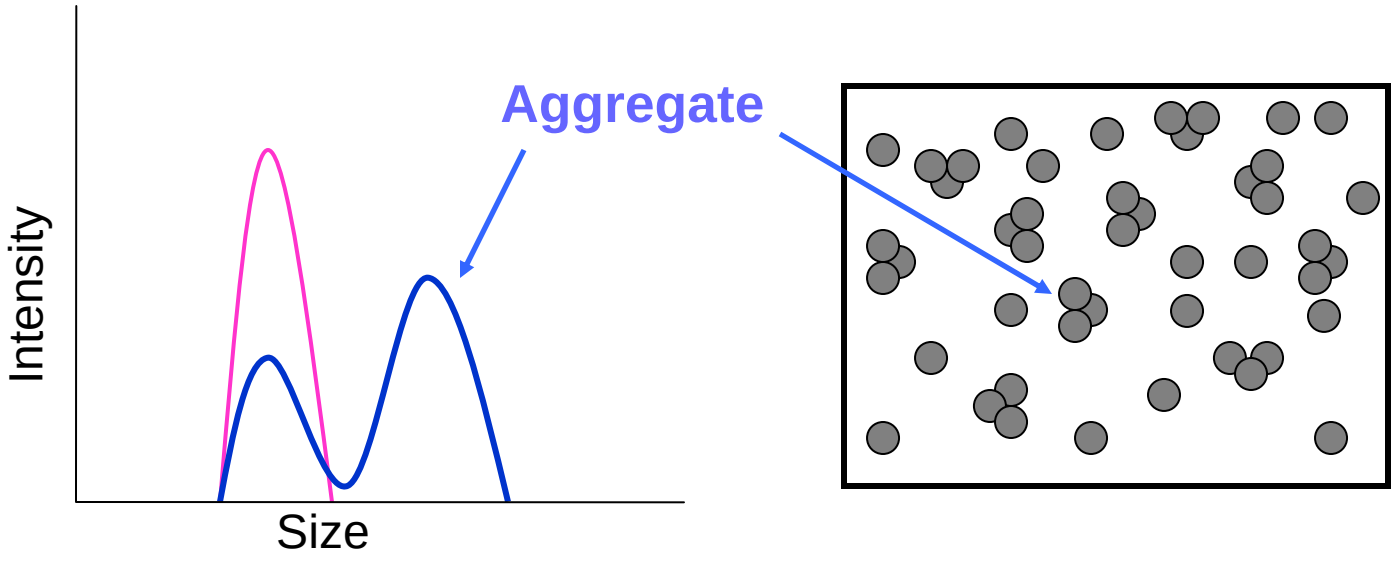
Dynamic Light Scattering

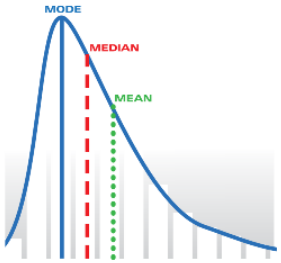
Aggregation Equilibrium

Cannot remove aggregates when created by equilibrium

Filtration will only remove already-formed aggregates

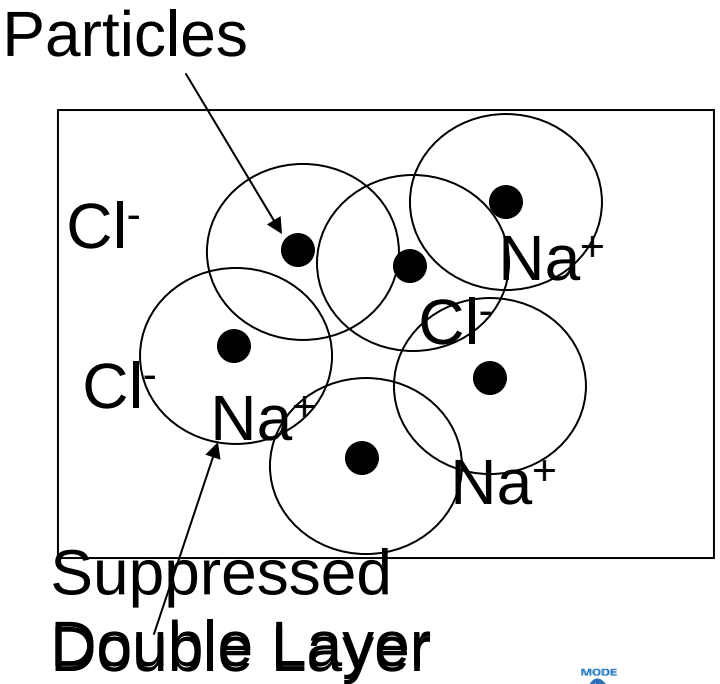
Important test for understanding formulation stability





Electrostatic Effects

- The electrostatic interaction of particles
- Overlapping double layers give larger size values
- Salt will suppress the double layer



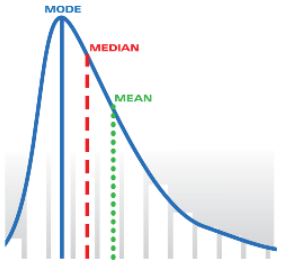
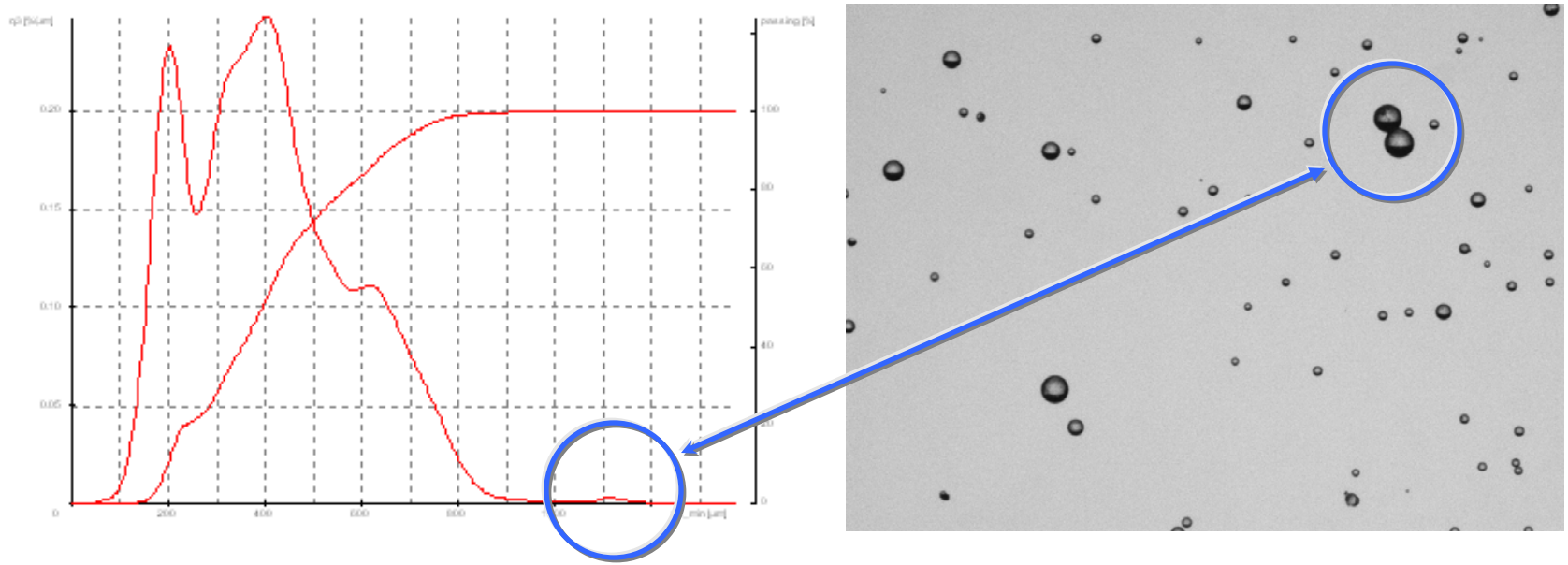


Image Analysis

Overlapping Particles

Check images of coarsest particles to verify



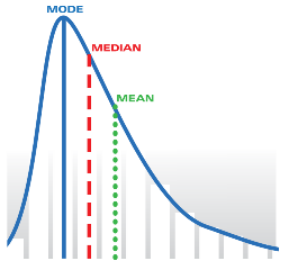
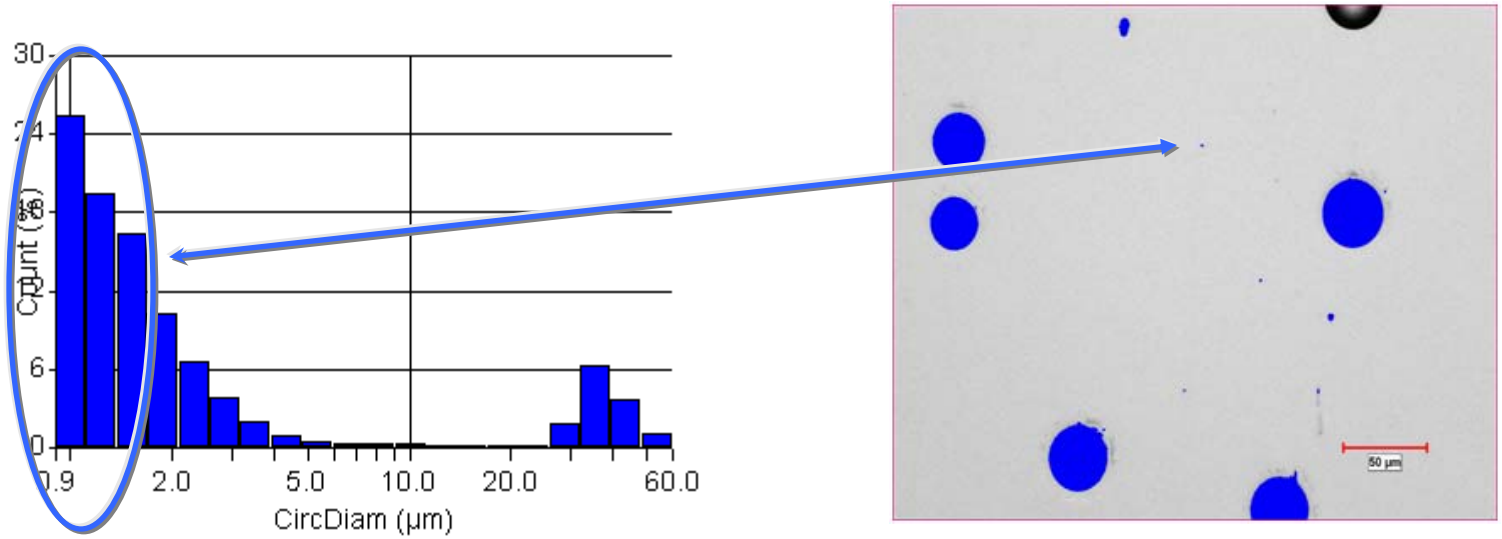


Image Analysis

Noise Detection as Particles

Check images of finest particles to verify



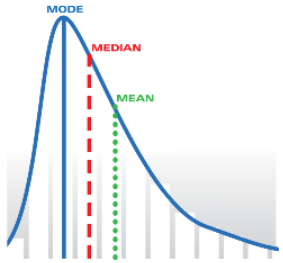
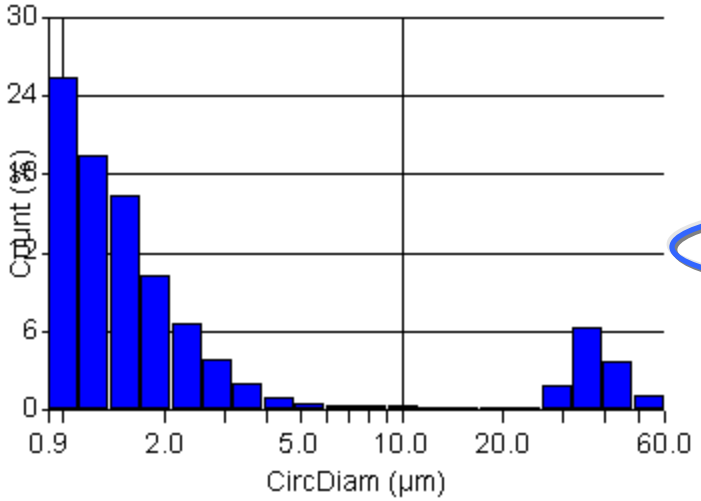


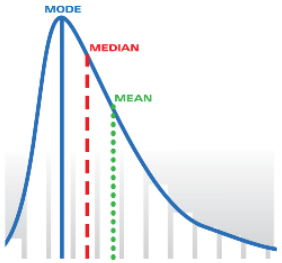
Image Analysis

Insufficient Particle Count

Vary number of particles detected/analyzed

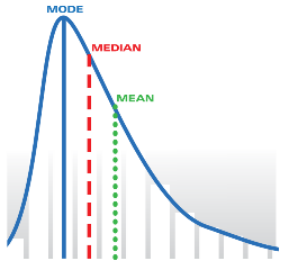


Statistics		
Minimum:	0.9	µm
Maximum:	56.8	µm
Mean:	68	µm
Std Dev.:	12.8	µm
[illegible]	[illegible]	µm
Count:	26765	
[illegible]	[illegible]	
Over:	0	
Accepted:	100	%
Field Count:	2400	
Field Area:	93197.5	µm²
Total Area:	2E+08	µm²
D10:	1.0	µm
D50:	1.4	µm
D90:	33.4	µm



Conclusions

- **Look at the distribution graph**
  - See the forest AND the trees
- **Precision != Accuracy**
  - Vary measurement and calculation parameters



For More Details

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Thank-you