

# Particulate Sensors

Particle Characterization Solutions

## **Particle characterization in formulation:**

### **Pharmaceutical particulate material quality control**

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Chair Royal Society of Chemistry Particle Characterisation Group (PCIG)

Chair of BSI LBI/37 (Particle Characterization)

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- In the Pharmaceutical industry:
  - Raw material are not truly raw,
    - Pre-screened, pre-processed, pre-characterised
  - Measurement of inputs
    - Conforms to requirement specification
    - Confirms CoA
    - Not changed during transport
      - Physically
      - Morphologically
      - Contaminants
      - Homogeneity
  - Increasing complexity of supply chains will increase the need to ensure inputs meet specifications

# But Why Particles



**In the Chemical Industry 60% of Products involve particles**

**But in the Pharmaceutical Industry it is more than 80%**

**Beyond Pharmaceutical new industries also need particles**

- Pharmaceuticals
- Additive Manufacturing
- Nano technology
- Advanced materials
- Battery technology

# Why Characterize Particles?

## Particle Characterization

“.....it must be realized that particle size analysis is not an objective in itself but is a means to an end, the end being the correlation of powder properties with some process of manufacture, usage or preparation”

H Heywood Proc. 1st Particle Size Anal. Conf.  
September 1966 p 355 - 359 (Heffer)

- **Number**
- **Zeta Potential**
- **Rheology**
- **Surface Area**
- **Pore Size**
- **Composition**
- **Distribution**
- **Gas absorption**
- **Moisture absorption**
- **Combustion rate**
- **Flowability**
- **Filter-ability**
- **Viscosity**
- **Agglomeration**

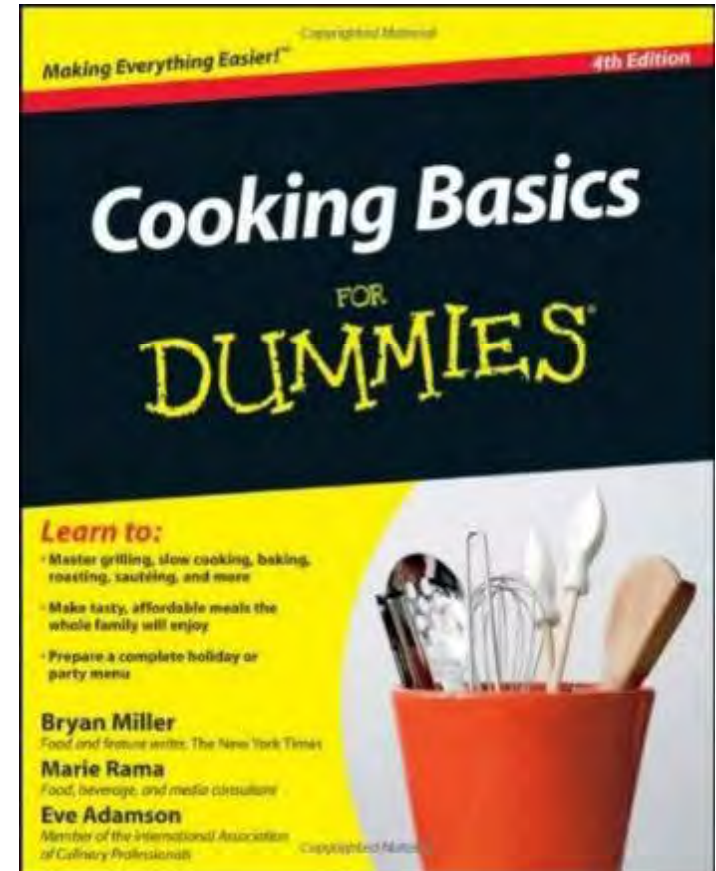
# “Particles Count”

## You Need:

- Understand your ingredients
- Know how to use the equipment
- Know what you want to make

Most particle characterization problems are not the equipment!!

~~Plug and play~~



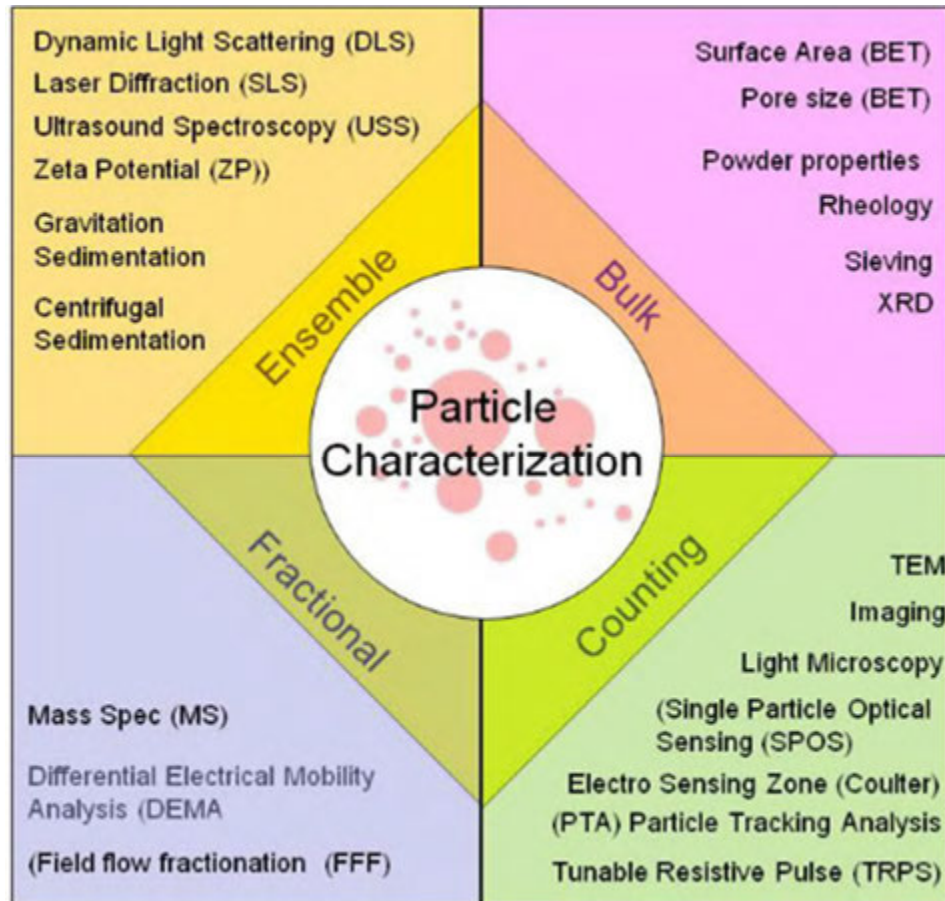
# Particle Sizing methods



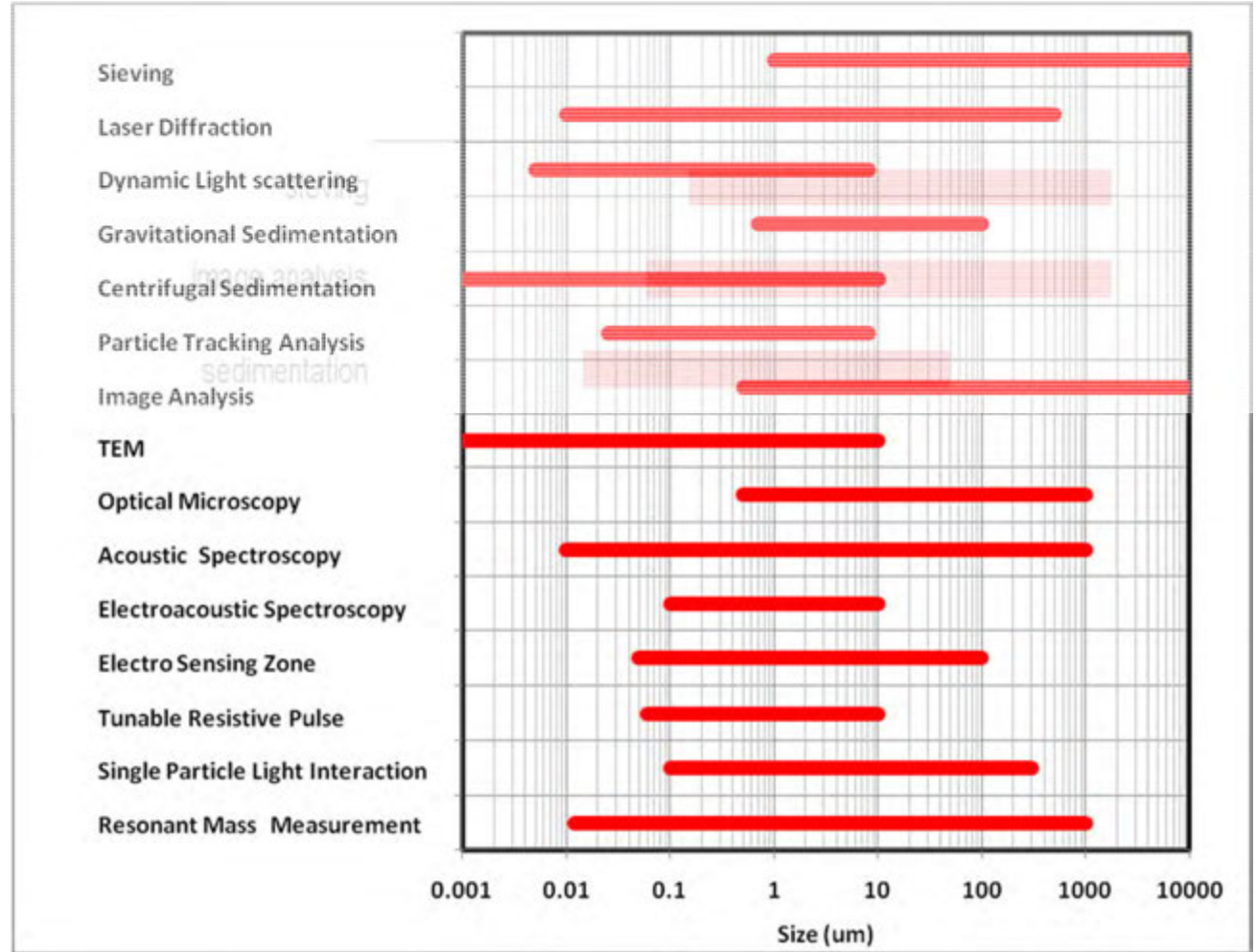
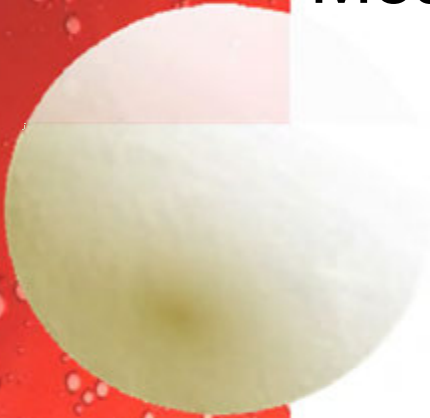
- **Particle characterization is not new**
- **These are the major instrumental techniques used for particle size distribution analysis in the pharmaceutical industry**
  - **Sieves: 5000 years old?**
  - **Sedimentation: 100+ years**
  - **Electrozone Sensing: 70years old**
  - **Light scattering (PCS): 40 years old**
  - **Laser diffraction: 30 years old**
  - **Light Microscopy –130 years**
  - **Electron Microscopy –70 years old**

# Particle Sizing methods

- Counting Methods
- Ensemble Methods
- Fractionation Methods
- Bulk Methods

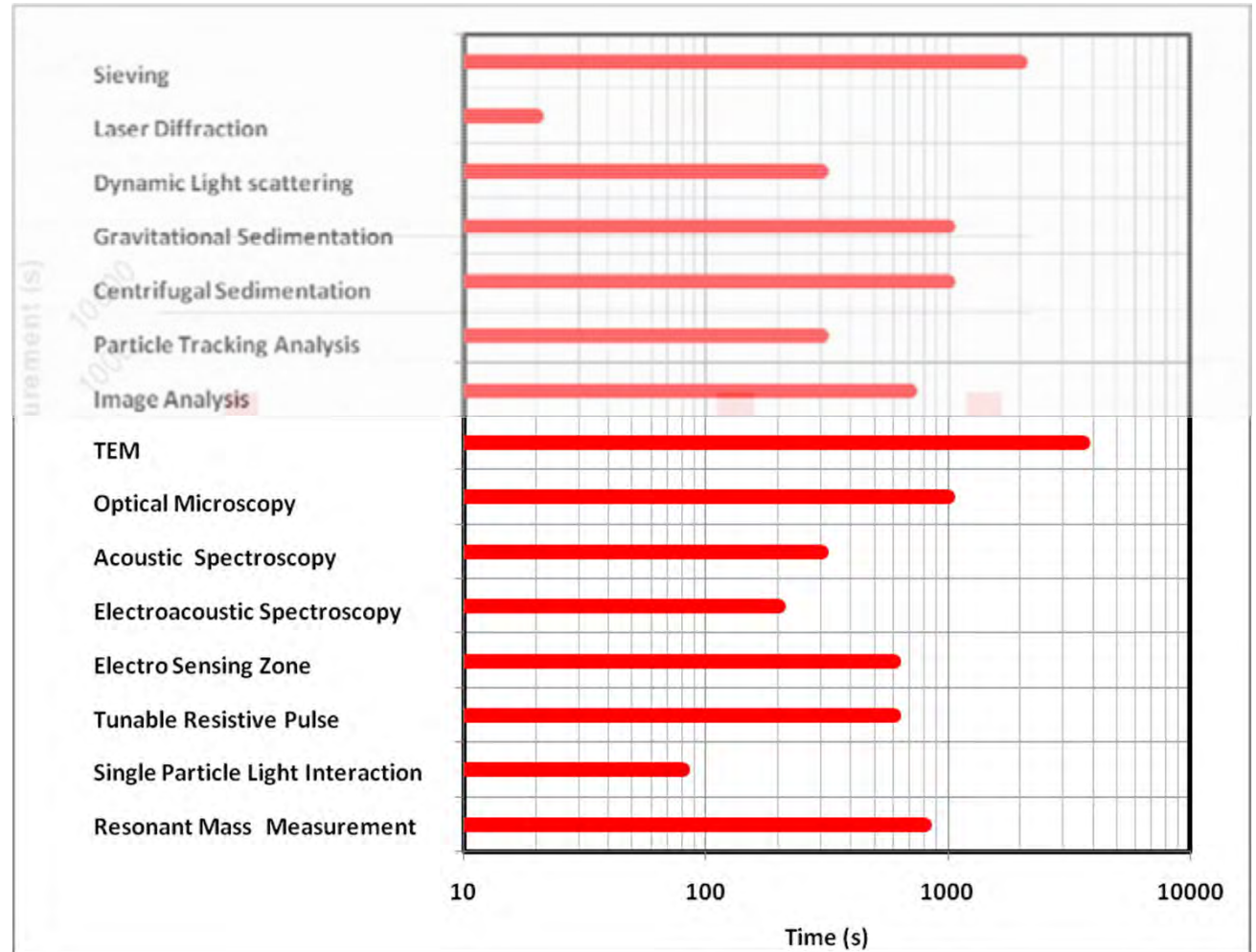


# Analysis Methods Measurement range

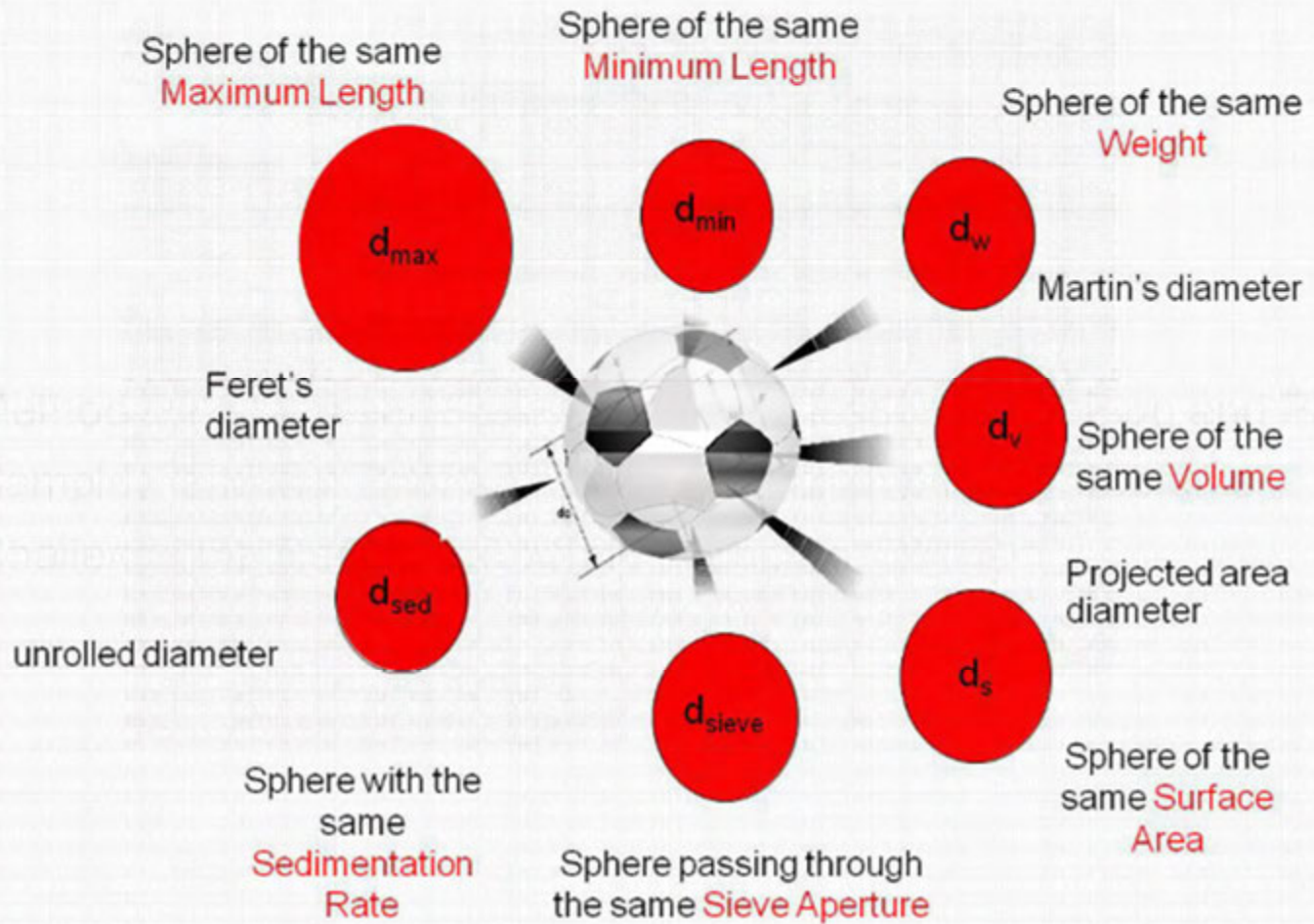




# Analysis Methods Measurement time



## VED: particles and football



# Method Selection

Particles are like football supporters



- Method Development: Particle characterization is not Plug and Play
- Sample Handling: Poor sample presentation 80% of problems
- Challenge the Result: Is it what I expect

# Method selection

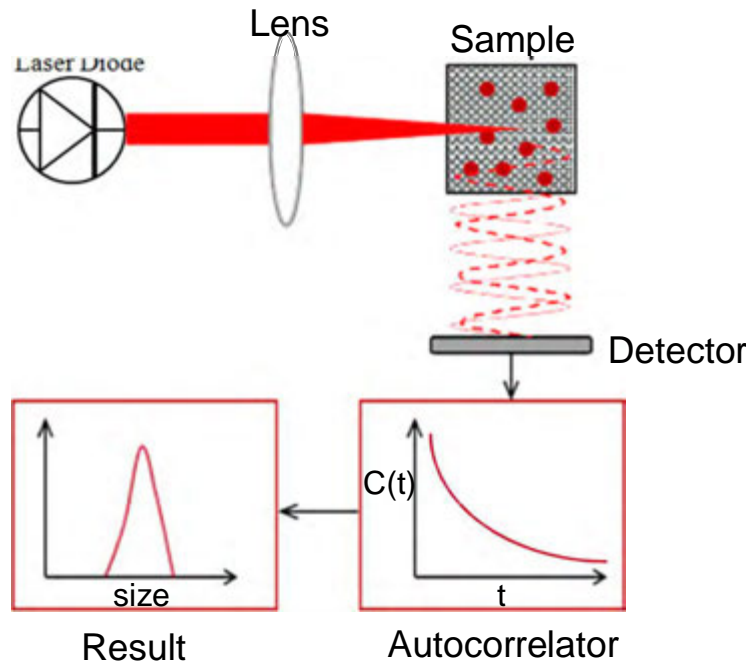
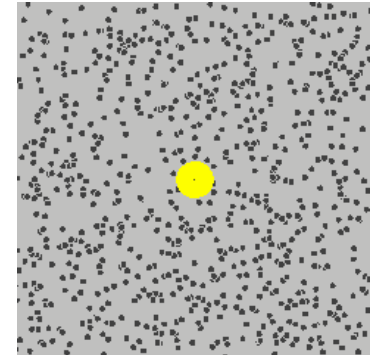
Particles are like football supporters



- Try to understand not only the crowd properties check out the individuals
- Still need a statistically significant number to understand what is going on

# Dynamic Light Scattering (DLS)

- Brownian motion moves particles
- Small particles = faster
- Large particles = slower
- Relatively long measurement times
- Commodity product 20+ manufacturers



$$D = kT/6\pi\eta R$$

D = Diffusion coefficient  
k = Boltzman's constant  
T = Temperature Kelvin  
h = Viscosity of solvent  
R = Radius of particle

PSS Nicomp N3000

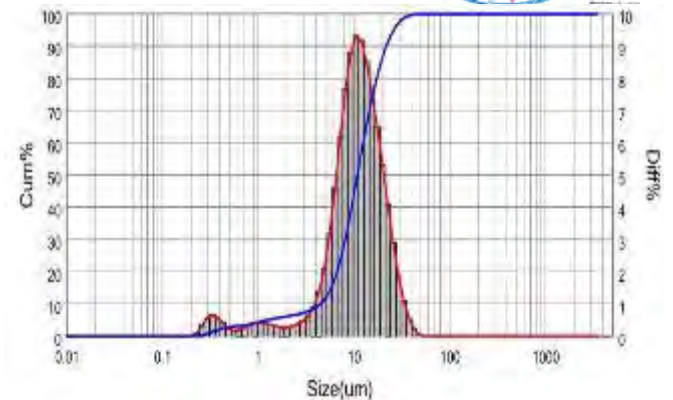
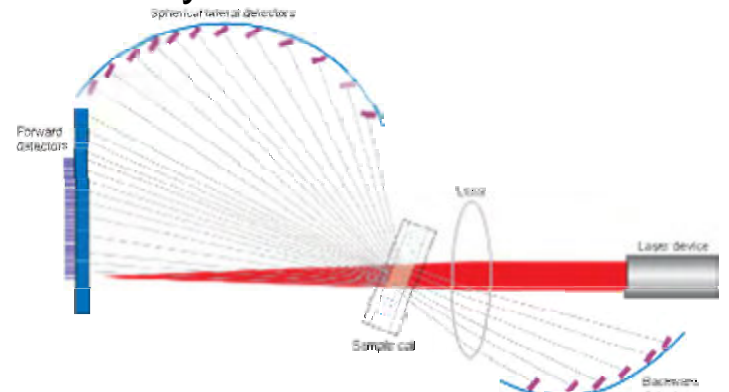
# Laser diffraction (SLS)



- Angular distribution of scattered light
- Fast, wide size range
- Able to measure both wet and dry
- Low concentration



Bettersize S3 plus



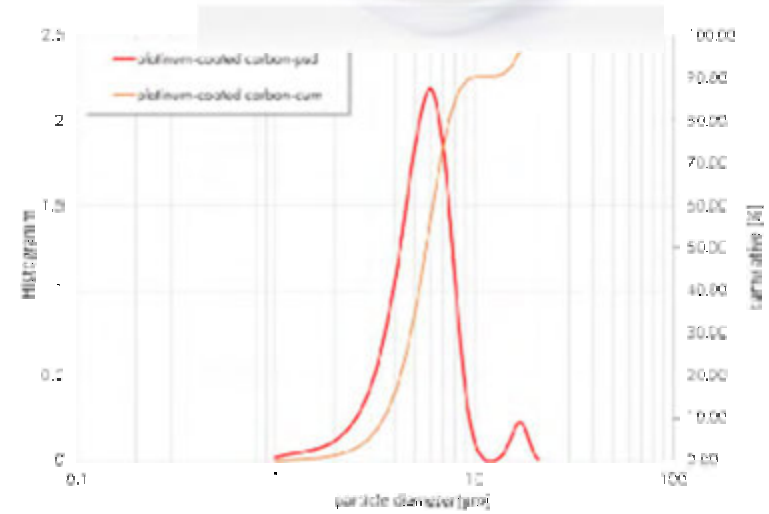
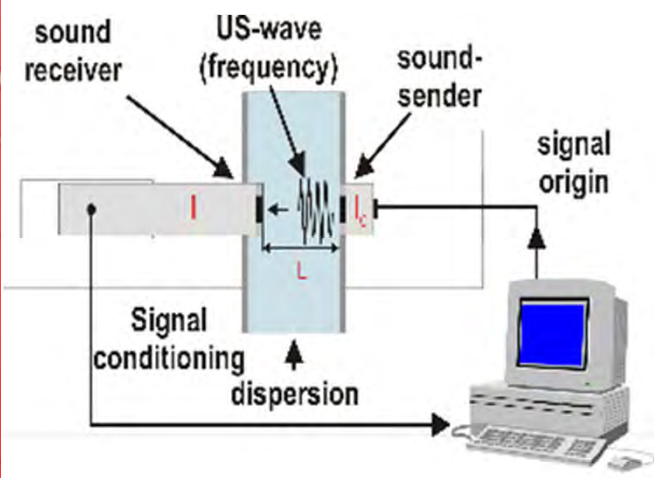
# Acoustic Spectroscopy



- Sample can be in motion (pumping, etc.)
- Sample concentration: 0.1 – 50 vol-%
- Size 10 nm – about 1000 μm



## Dispersion Technology DT1202

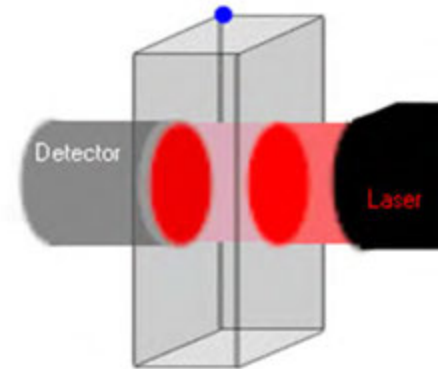


$$\text{attenuation}(dB/cm/MHz) = \frac{10}{fL} \log \frac{I_0}{I}$$

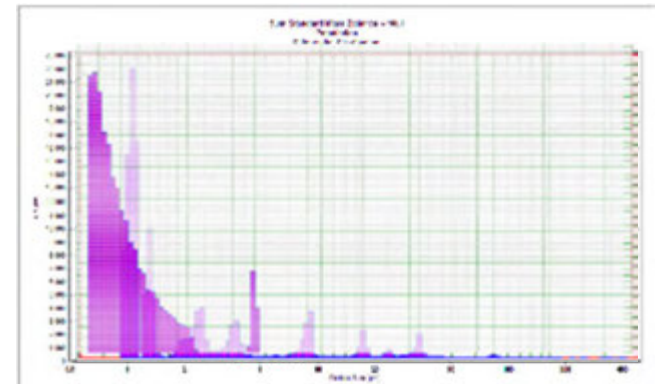
# Single Particle Optical Sensing

- Particles interact with light in measurement zone
- Generates a pulse
- Pulse converted to particle size
- Particle size + concentration

Need to measure below coincidence error limit



PSS Accusizer A7000

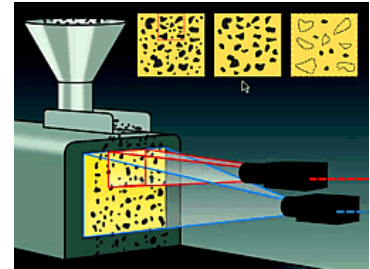
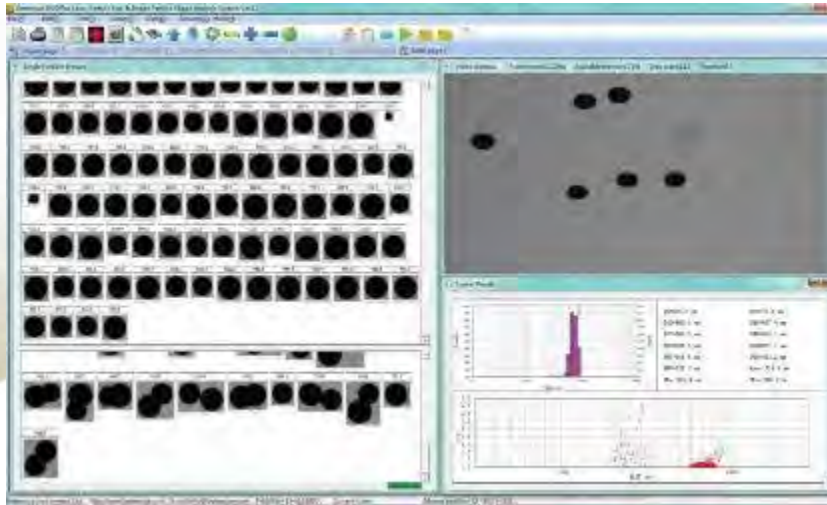


Fat emulsion "tail" with 10 micron latex spike





# Imaging

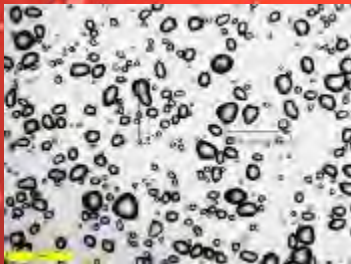
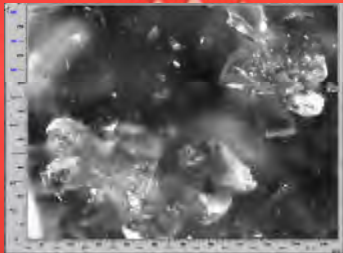


ISO 9276-6 Representation of results of particle size analysis —  
Part 6: The descriptive and quantitative representation of  
particle shape and morphology

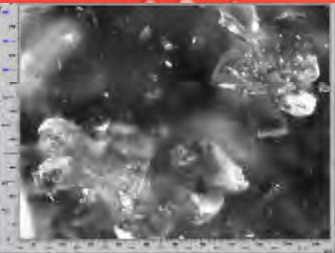
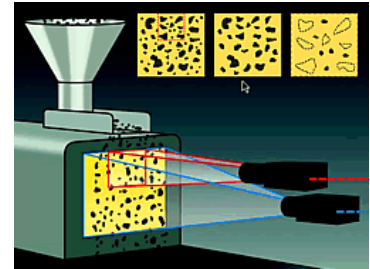
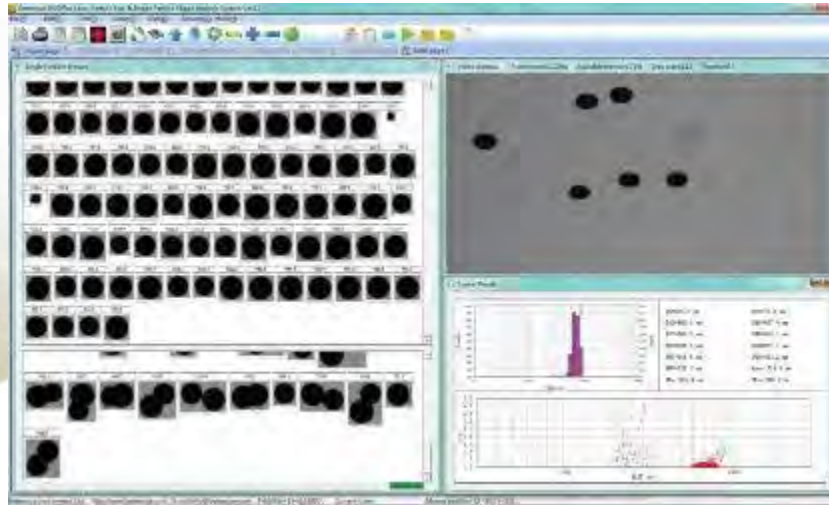
Bettersize BeVision D2

## Shape descriptors

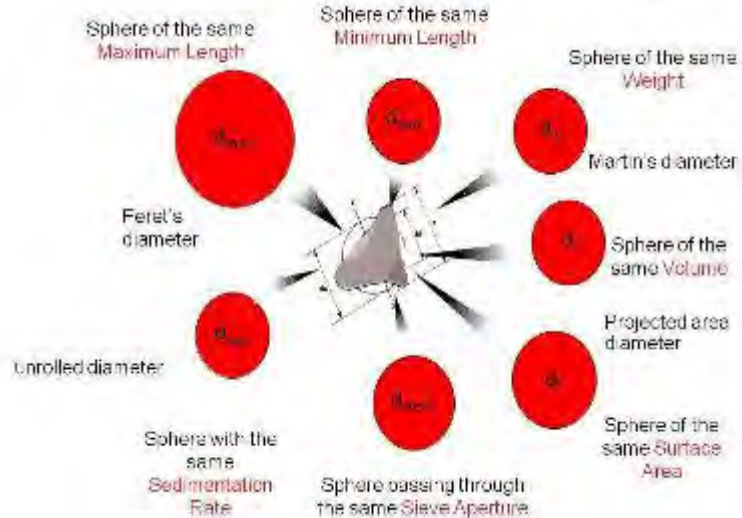
- Macroshape descriptors
  - Geometrical descriptors
  - Proportion descriptors
- Mesoshape descriptors
- Combination of shape descriptors
- Roughness descriptor



# Imaging



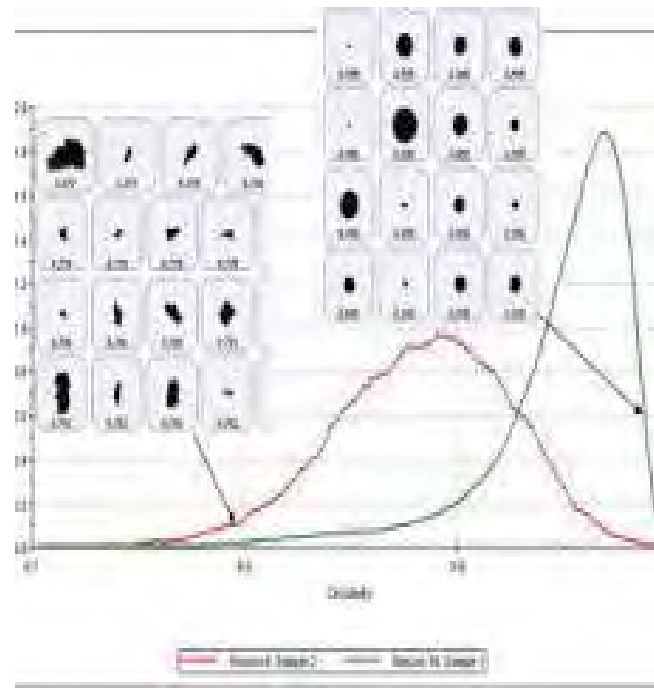
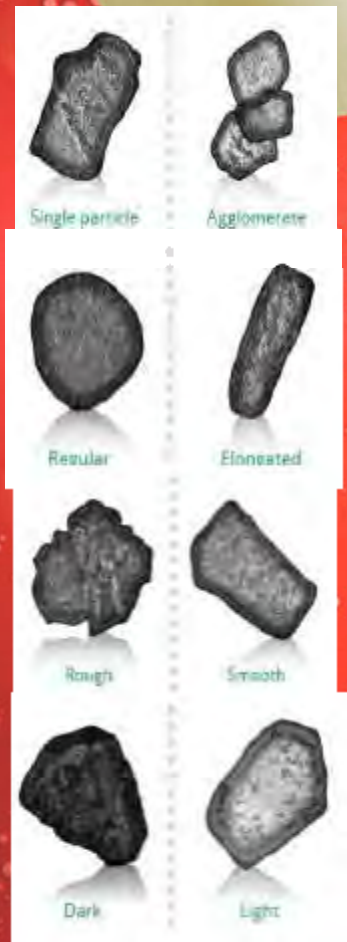
## ISO 9276-6 Representation of results of particle size analysis — Part 6: The descriptive and quantitative representation of particle shape and morphology



## Bettersize Bevision D2



# Particle Shape



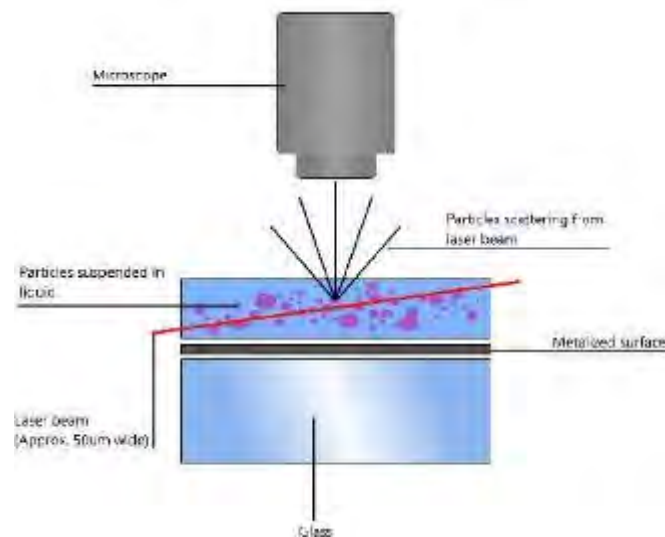
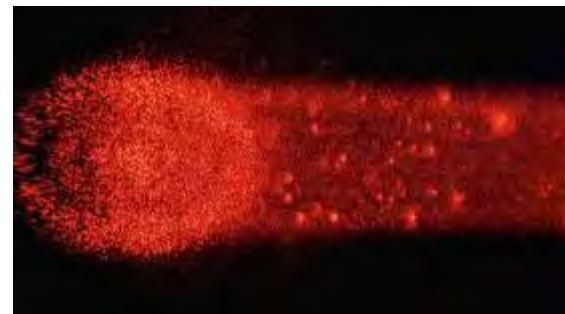
## Particle Shape

- Irregularly shaped particles/agglomerates
- increased likelihood of part porosity
- Cause Inhomogeneities in part
  - balling effects
  - Lack of fusion
- Interact differently with beam
- Jam during spreading

# Particle Tracking Analysis

- Nanoparticle tracking NTA
- Going Full circle
- Brownian Motion (DLS like)
- Individual Particle motion tracking
- Camera based
- Zeta potential capability
- Multiple laser systems provide Multi-wavelength

$$D = kT/6\pi\eta R$$

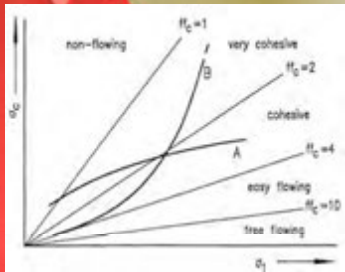


# Bulk Powder Properties

## Dynamic Powder Analyzers

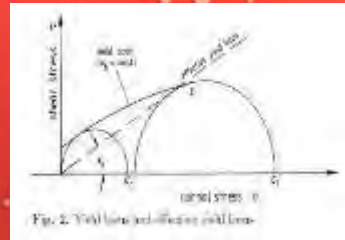
- Static Shear Cells
- Powder Rheometers
- Only one number “flow ene

$$E_{flow} = \int_0^H \left( \frac{T}{R \tan a} + F_{base} \right) dH$$



## Or Individual measures of powder properties

- Angle of repose
- Tap Density
- Voidage
- Cohesiveness



Bettersize Powderpro A1



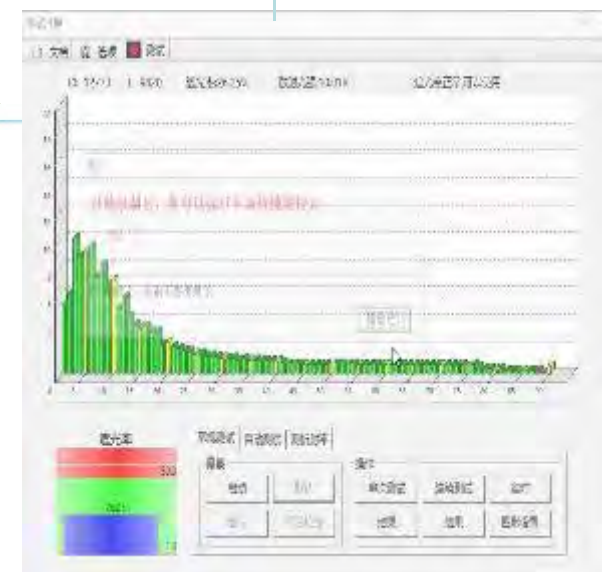
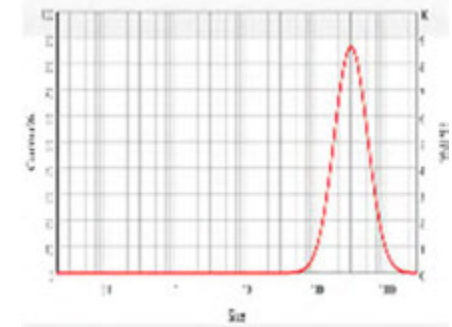
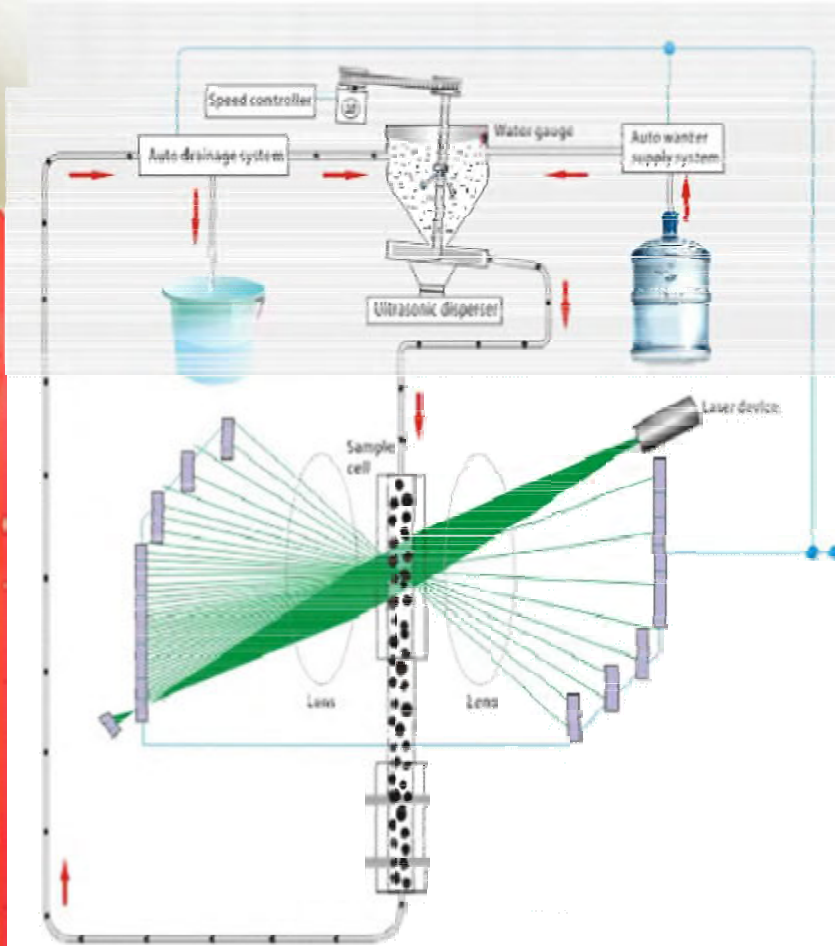
Manual analysis of macroscopic, physical properties of a powder



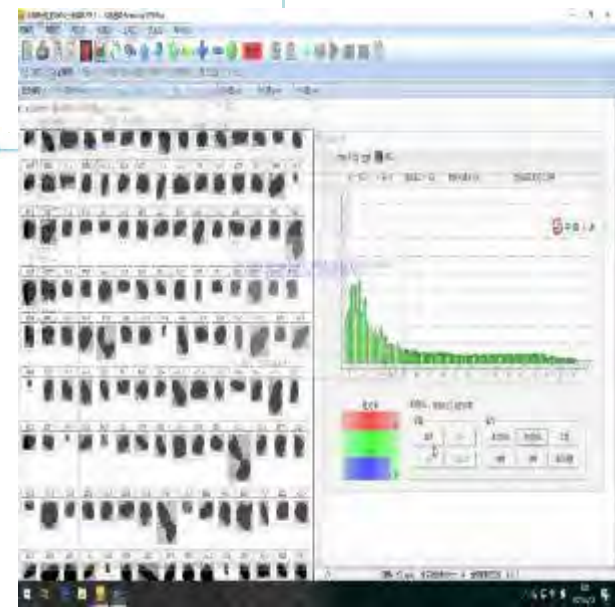
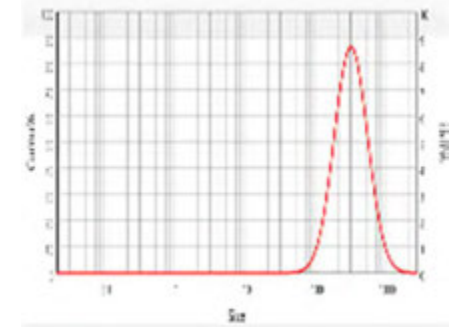
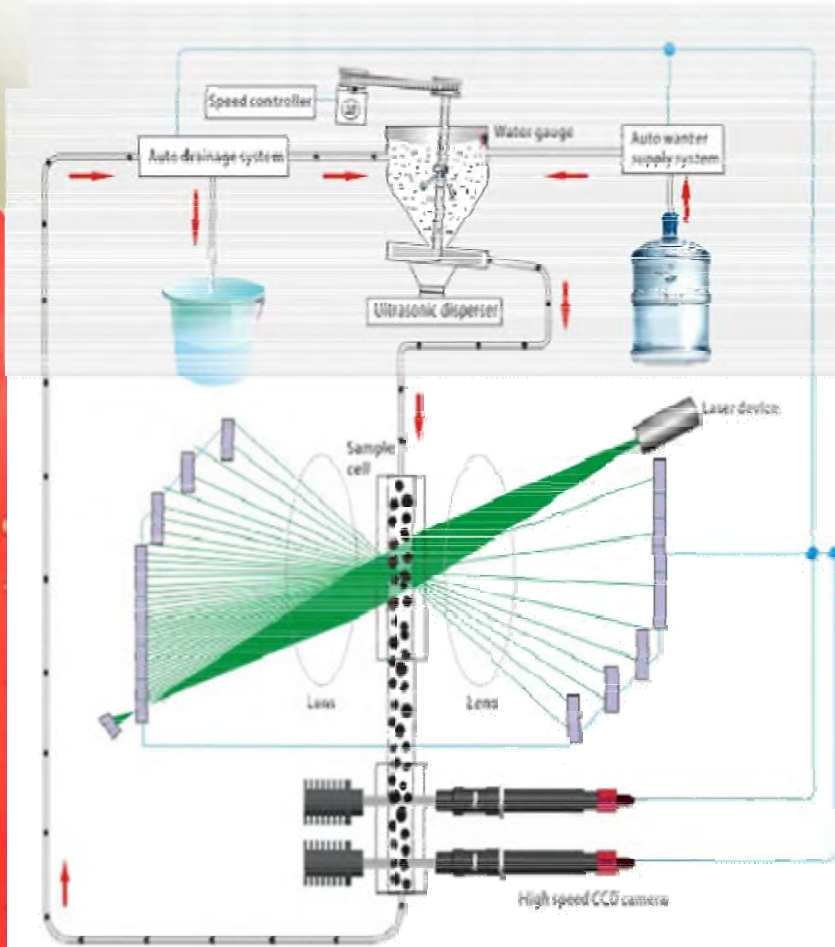
# Combining methods

- Separation and DLS
  - Using a separation technique with DLS as a detection enhances specificity i.e.
    - FFF + DLS
    - MS+ DLS
- Imaging and chemical composition
  - Using Spectroscopy with Imaging enables chemical heterogeneity as well as physical, i.e.
    - IR, Raman, UV-Vis
- Ensemble Measurement and Imaging
  - Provides the fast, large population with the detailed morphological information of Imaging i.e.
    - Laser Diffraction and Imaging

# Laser diffraction and image analysis combined



# Laser diffraction and image analysis combined





# Differences in batches



## Silica-1

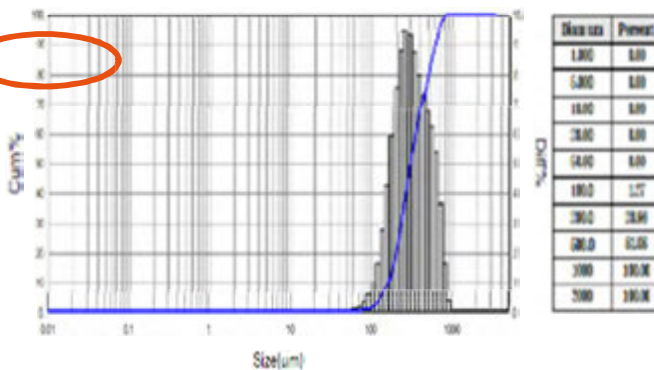
Bettersize™

### Bettersizer S3 Plus Particle Size Analysis Report

Page 1/10 2008

Sample: 11-04-09	Method:	Sample Filter: SP Instruments
Operator: PS	Date: 2009-05-10 15:02:23	Measured By: SP Instruments
Method: Laser	Preparation:	Medium: None
Dispersant: Trisolve	Ultrasonic: 1 min	Stirring: 1000
Appl: 0%	Mode: L3 - Multipeak	Distribution: Volume
Particle ID: 144433	Median D3: 1.220	Count:

D[4,0]: 142.4 um	D[3,0]: 265.0 um	D[2,0]: 280.7 um	D[1,0]: 2.28 %	
D[2,0]: 280.9 um	D[1,0]: 164.5 um	SPIN: 1.65	Residual: 16.96 %	
D0 = 139.6 um	D0 = 140.1 um	D10 = 150.7 um	D10 = 152.0 um	D5 = 213.4 um
D50 = 143.6 um	D50 = 161.8 um	D90 = 123.3 um	D90 = 126.1 um	D90 = 744.0 um



## Silica-2

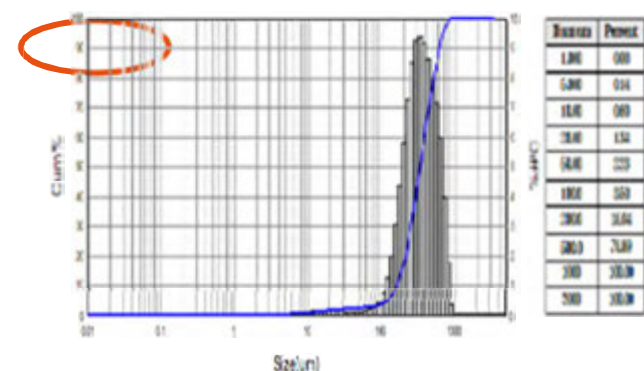
Bettersize™

### Bettersizer S3 Plus Particle Size Analysis Report

Page 1/10 2008

Sample: 09-04-09	Method:	Sample Filter: SP Instruments
Operator: PS	Date: 2009-05-10 12:42:28	Measured By: SP Instruments
Method: Laser	Preparation:	Medium: None
Dispersant: Trisolve	Ultrasonic: 1 min	Stirring: 1000
Appl: 0%	Mode: L3 - Multipeak	Distribution: Volume
Particle ID: 144433	Median D3: 1.220	Count:

D[4,0]: 142.4 um	D[3,0]: 265.0 um	D[2,0]: 280.7 um	D[1,0]: 2.28 %	
D[2,0]: 280.9 um	D[1,0]: 164.5 um	SPIN: 1.65	Residual: 16.96 %	
D0 = 139.6 um	D0 = 140.1 um	D10 = 150.7 um	D10 = 152.0 um	D5 = 213.4 um
D50 = 143.6 um	D50 = 161.8 um	D90 = 123.3 um	D90 = 126.1 um	D90 = 744.0 um



# Differences in batches



## Silica-1

betterson

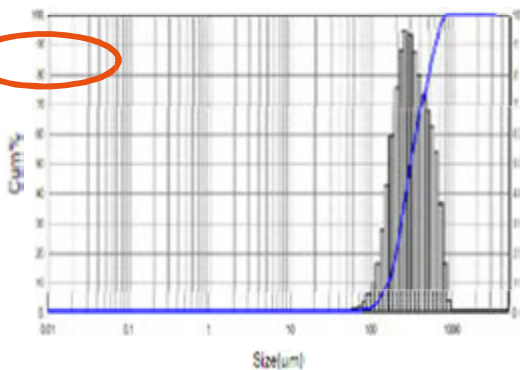
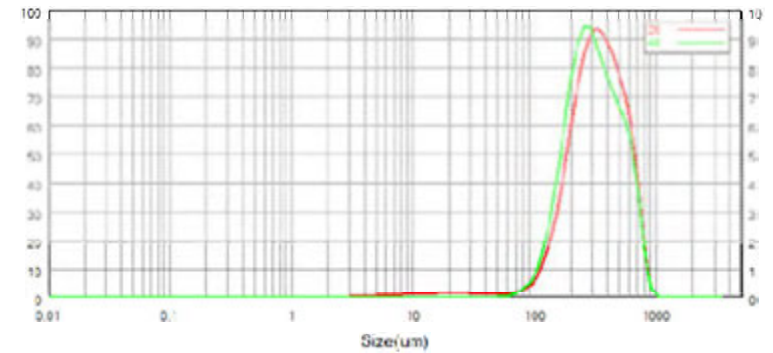
### Betterson S3 Plus Particle Size Analysis Report

Page 3/10x-200x

Sample: 17-Sand-Average	Method: Laser	Sample Owner: SP Instruments
Operator: PNI	Preparation: Wetmount 1 ml	Measured By: SP Instruments
Method: Laser	Wavelength: 633 nm	Medium: Water
Dispersion: Thonick	Mode: 3.0 - Multipeak	Stirring: 1000
Optical: 90°	Median MZ: 1.820	Distribution: Volume
Particle ID: 1.644.815	Median MZ: 1.820	Recount:

D[4,0]: 342.4 nm	D[4,5]: 286.0 nm	D[mode]: 269.7 nm	D[5]: 2.58 %
D[2,0]: 280.9 nm	D[2,5]: 194.6 nm	D[10]: 1.60	Recount: 16.96 %

D00 = 130.0 nm	D01 = 140.0 nm	D02 = 150.0 nm	D03 = 160.0 nm	D04 = 170.0 nm
D05 = 180.0 nm	D06 = 190.0 nm	D07 = 200.0 nm	D08 = 210.0 nm	D09 = 220.0 nm



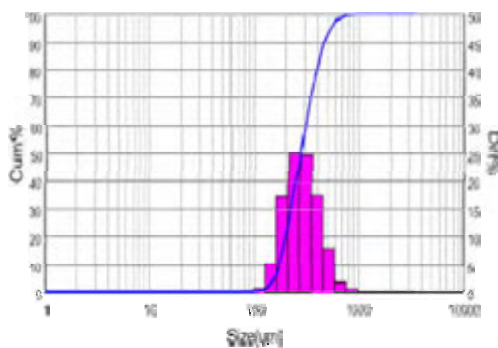
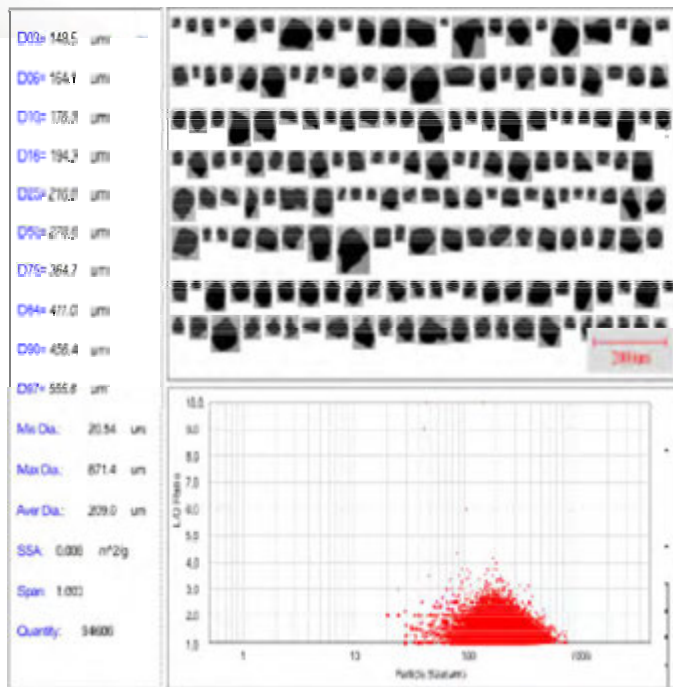
Size (nm)	Percent
1.000	0.00
5.000	0.00
10.000	0.00
15.000	0.00
20.000	0.00
25.000	0.00
30.000	0.00
35.000	0.00
40.000	0.00
45.000	0.00
50.000	0.00
55.000	0.00
60.000	0.00
65.000	0.00
70.000	0.00
75.000	0.00
80.000	0.00
85.000	0.00
90.000	0.00
95.000	0.00
100.000	0.00
105.000	0.00
110.000	0.00
115.000	0.00
120.000	0.00
125.000	0.00
130.000	0.00
135.000	0.00
140.000	0.00
145.000	0.00
150.000	0.00
155.000	0.00
160.000	0.00
165.000	0.00
170.000	0.00
175.000	0.00
180.000	0.00
185.000	0.00
190.000	0.00
195.000	0.00
200.000	0.00
205.000	0.00
210.000	0.00
215.000	0.00
220.000	0.00
225.000	0.00
230.000	0.00
235.000	0.00
240.000	0.00
245.000	0.00
250.000	0.00
255.000	0.00
260.000	0.00
265.000	0.00
270.000	0.00
275.000	0.00
280.000	0.00
285.000	0.00
290.000	0.00
295.000	0.00
300.000	0.00
305.000	0.00
310.000	0.00
315.000	0.00
320.000	0.00
325.000	0.00
330.000	0.00
335.000	0.00
340.000	0.00
345.000	0.00
350.000	0.00
355.000	0.00
360.000	0.00
365.000	0.00
370.000	0.00
375.000	0.00
380.000	0.00
385.000	0.00
390.000	0.00
395.000	0.00
400.000	0.00
405.000	0.00
410.000	0.00
415.000	0.00
420.000	0.00
425.000	0.00
430.000	0.00
435.000	0.00
440.000	0.00
445.000	0.00
450.000	0.00
455.000	0.00
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465.000	0.00
470.000	0.00
475.000	0.00
480.000	0.00
485.000	0.00
490.000	0.00
495.000	0.00
500.000	0.00
505.000	0.00
510.000	0.00
515.000	0.00
520.000	0.00
525.000	0.00
530.000	0.00
535.000	0.00
540.000	0.00
545.000	0.00
550.000	0.00
555.000	0.00
560.000	0.00
565.000	0.00
570.000	0.00
575.000	0.00
580.000	0.00
585.000	0.00
590.000	0.00
595.000	0.00
600.000	0.00
605.000	0.00
610.000	0.00
615.000	0.00
620.000	0.00
625.000	0.00
630.000	0.00
635.000	0.00
640.000	0.00
645.000	0.00
650.000	0.00
655.000	0.00
660.000	0.00
665.000	0.00
670.000	0.00
675.000	0.00
680.000	0.00
685.000	0.00
690.000	0.00
695.000	0.00
700.000	0.00
705.000	0.00
710.000	0.00
715.000	0.00
720.000	0.00
725.000	0.00
730.000	0.00
735.000	0.00
740.000	0.00
745.000	0.00
750.000	0.00
755.000	0.00
760.000	0.00
765.000	0.00
770.000	0.00
775.000	0.00
780.000	0.00
785.000	0.00
790.000	0.00
795.000	0.00
800.000	0.00
805.000	0.00
810.000	0.00
815.000	0.00
820.000	0.00
825.000	0.00
830.000	0.00
835.000	0.00
840.000	0.00
845.000	0.00
850.000	0.00
855.000	0.00
860.000	0.00
865.000	0.00
870.000	0.00
875.000	0.00
880.000	0.00
885.000	0.00
890.000	0.00
895.000	0.00
900.000	0.00
905.000	0.00
910.000	0.00
915.000	0.00
920.000	0.00
925.000	0.00
930.000	0.00
935.000	0.00
940.000	0.00
945.000	0.00
950.000	0.00
955.000	0.00
960.000	0.00
965.000	0.00
970.000	0.00
975.000	0.00
980.000	0.00
985.000	0.00
990.000	0.00
995.000	0.00
1000.000	0.00

Sample Name	D00	D10	D15	D25	D50	D60	D64	D50	D90
20 - Glass	132.1	150.3	151.2	228.4	328.3	370.8	343.3	605.1	730.2
40 - Wet Sand	140.3	159.7	162.9	213.4	301.8	343.6	326.6	595.1	734.6
Peak	4.20%	5.40%	3.14%	4.80%	5.55%	5.48%	1.51%	1.17%	0.23%

# Differences in batches

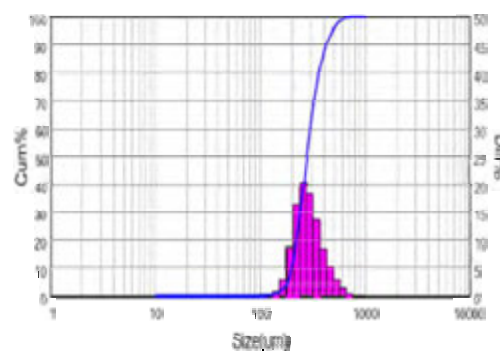
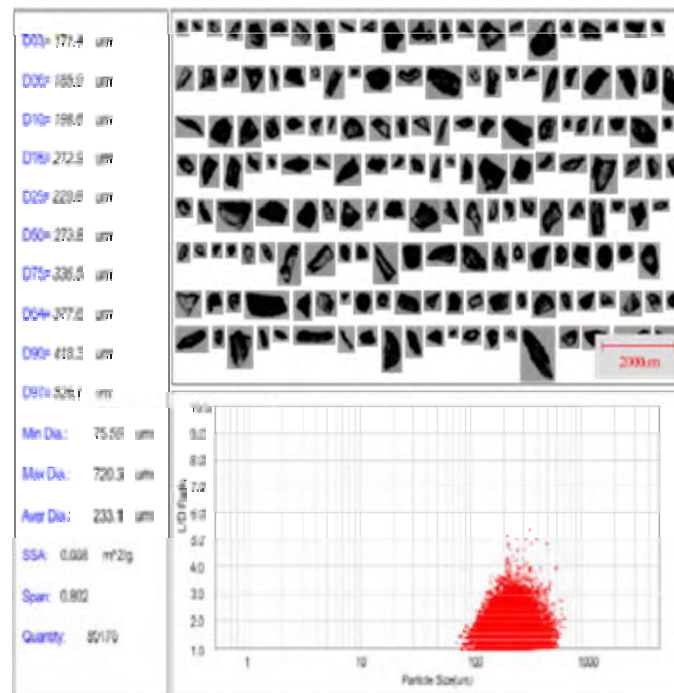


## Silica-1



Diam µm	Percent
1.000	0.00
5.000	0.00
10.00	0.00
20.00	0.00
50.00	0.00
100.0	0.07
200.0	18.29
500.0	93.77
1000	100.00
2000	100.00

## Silica-2



Diam µm	Percent
1.000	0.00
5.000	0.00
10.00	0.00
20.00	0.00
50.00	0.00
100.0	0.02
200.0	19.57
500.0	95.87
1000	100.00
2000	100.00

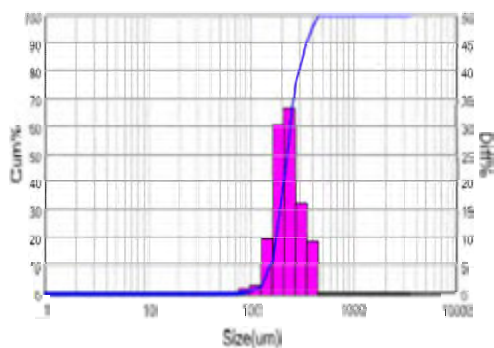
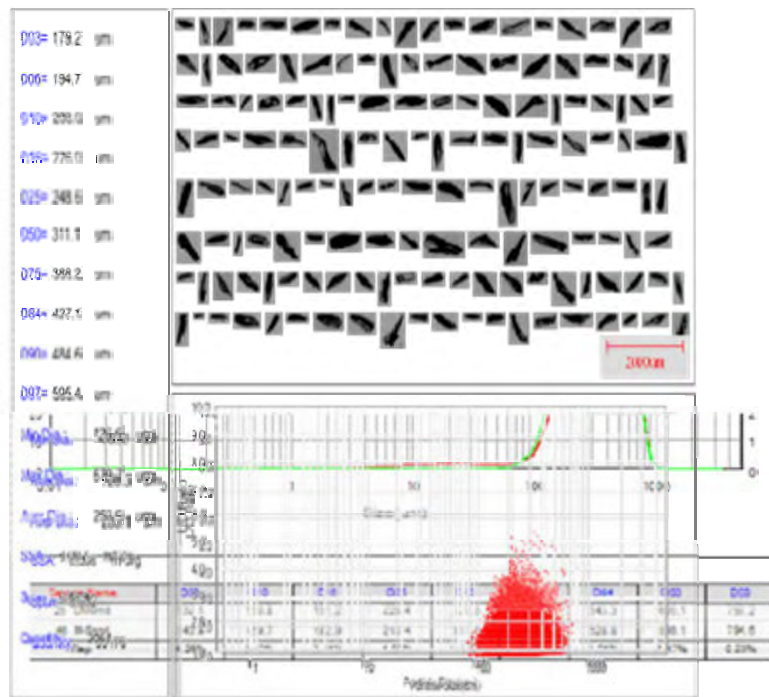
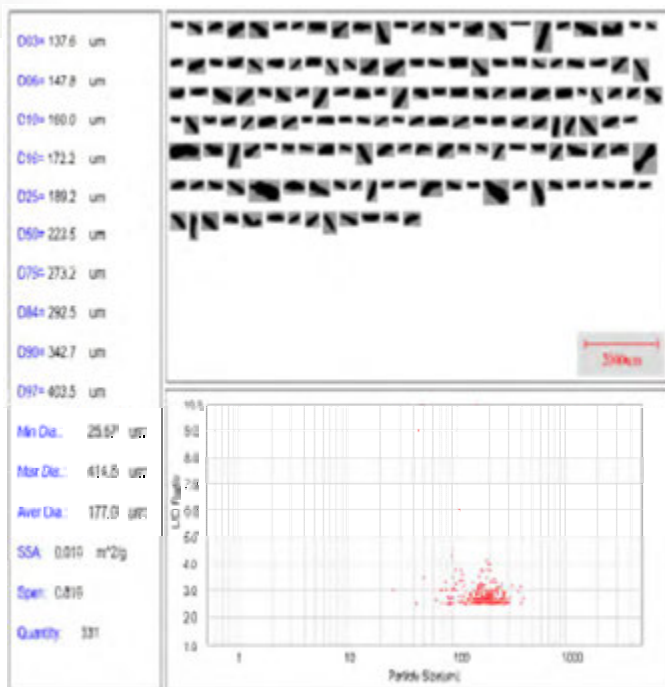
# Differences in batches



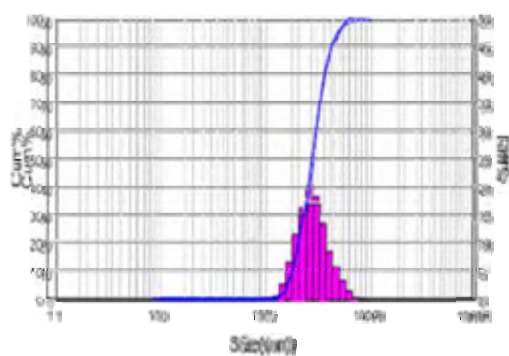
L/D > 2.5

Silica-1

Silica-2



Diam (µm)	Percent
1.000	0.00
5.000	0.00
10.00	0.00
20.00	0.00
50.00	0.01
100.0	0.79
200.0	33.10
500.0	100.00
1000	100.00
2000	100.00

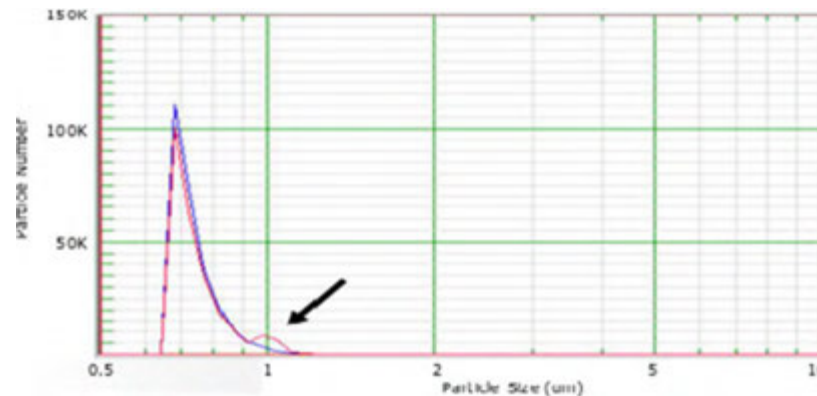
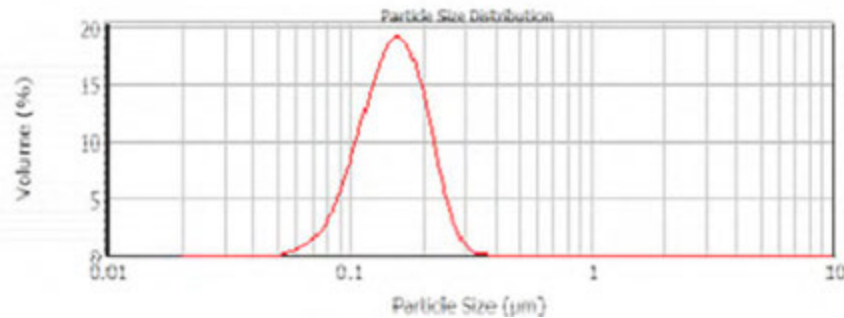


Diam (µm)	Percent
1.000	0.00
5.000	0.00
10.00	0.00
20.00	0.00
50.00	0.00
100.0	0.00
200.0	25.97
300.0	90.37
1000	100.00
2000	100.00

# Contamination Monitoring

Two critical contamination types:

- Small Populations of out of spec homogenous particles
- Presence of heterogeneous particle populations

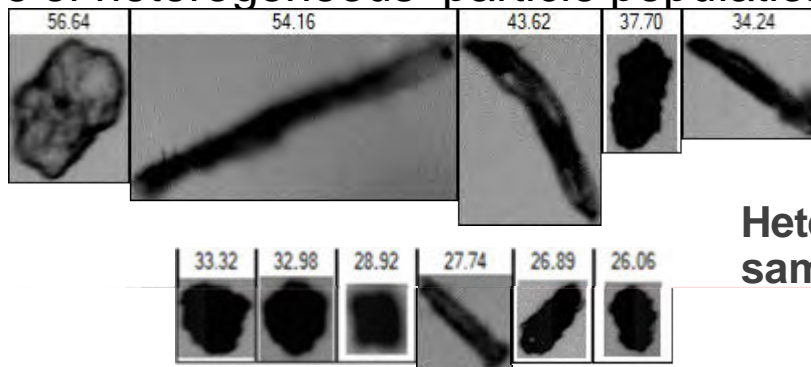


1µm Silica in a CMP slurry, Accusizer can detect at 0.07mg/L while laser Diffraction detection limit is 100mg/L

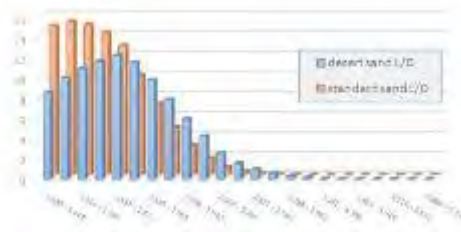
# Contamination Monitoring













Two critical contamination types:

- Small Populations of out of spec homogenous particles
- Presence of heterogeneous particle populations



Heterogeneous samples



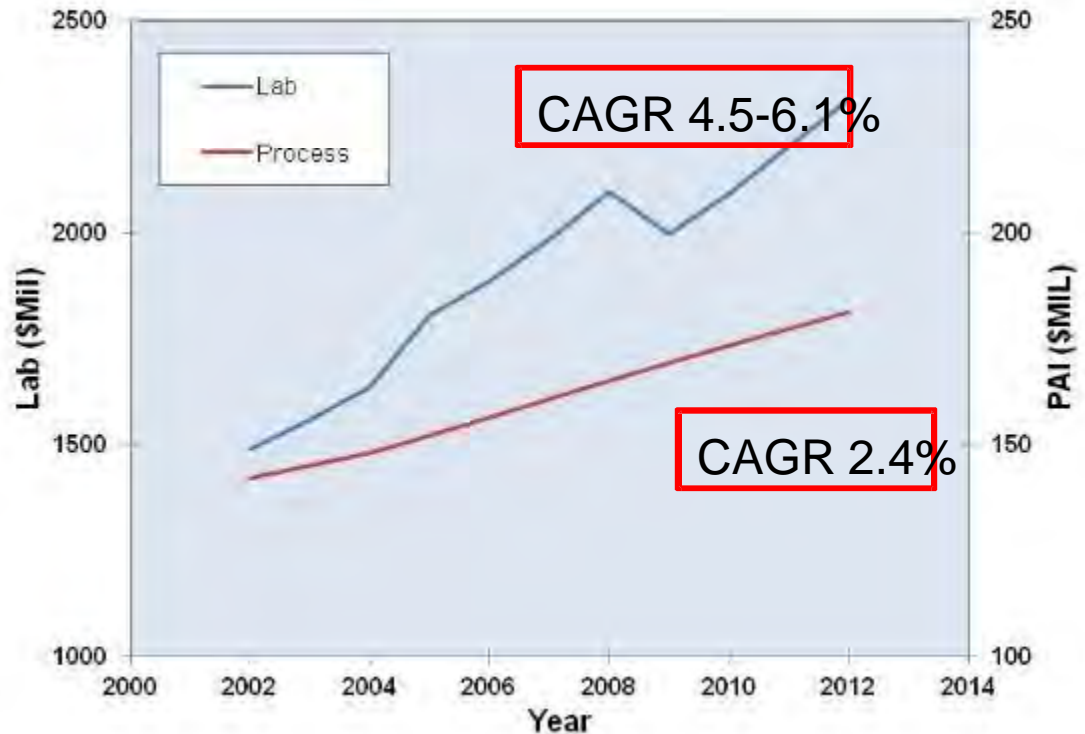
	Desert sand		Standard sand	
				
diameter [µm]	1986	1872	2576	2320
L/D-value	2.554	1.662	1.537	1.255
				
diameter [µm]	1464	1.312	1555	1543
L/D-value	2.13	1.518	1.197	1.47
				
diameter [µm]	994.3	988.2	1032	1028
L/D-value	1.463	1.849	1.014	1.034

\*Nichols, K., et. al., Perturbation Detection Analysis: A Method for Comparing Instruments That Can Measure the Presence of Large Particles in CMP Slurry, report published by BOC Edwards, Chaska, MN

# Why do we still make Laboratory Measurements

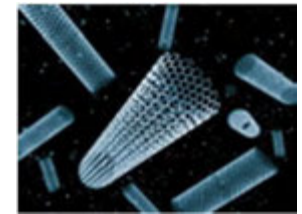


Despite all the claims, the money and all the hopes in the last 15 years the capability to characterise particulate systems in-situ at high concentration has not met the original expectations



# What Next for Particles

- Applications becoming more complex
  - Biotech applications
  - Designer Particles
  - Carbon technology
  - Nano machines
  - Additive Manufacture
- Health and Safety
  - Inhalation: Pollution, nano particles
  - Toxicity: nanotoxicity
  - Biologics:
- Structure formation Functional Properties
- Surface Area measurements becoming more important





Chair Royal Society of Chemistry Particle Characterisation Group (PCIG)

Chair of BSI LBI/37 (Particle Characterization)

Visiting Fellow, School of Chemical and Process Engineering, University of Leeds

Convenor of ISO TC24/SC4/WG14 (Particle Characterization by Acoustic methods)

Convener of ISO/TC 281 WG2 (Fine bubble characterization and measurement)

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