Particulate Sensors

Particle Characterization Solutions

Particle characterization in formulation:

Pharmaceutical particulate material quality control

Dr. Richard J. Tweedie

Chair Royal Society of Chemistry Particle Characterisation Group (PCIG)

Chair of BSI LBI/37 (Particle Characterization)

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RSC INTEREST GROUP PARTICLE CHARACTERISATION

Particles and Raw Materials

- 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"

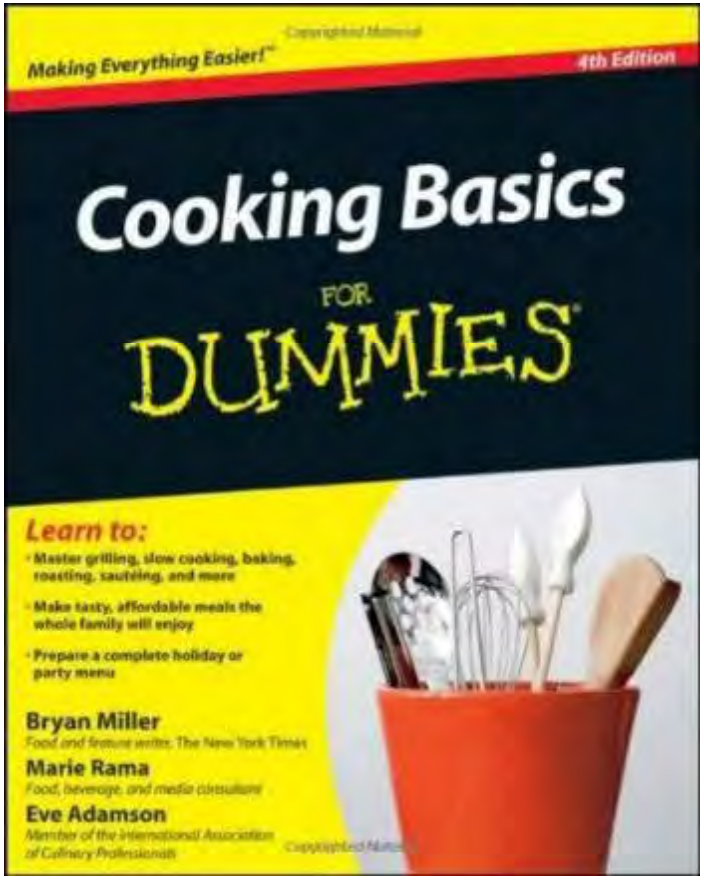
Particulate Sensors
Particle Characterization Solutions

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~~

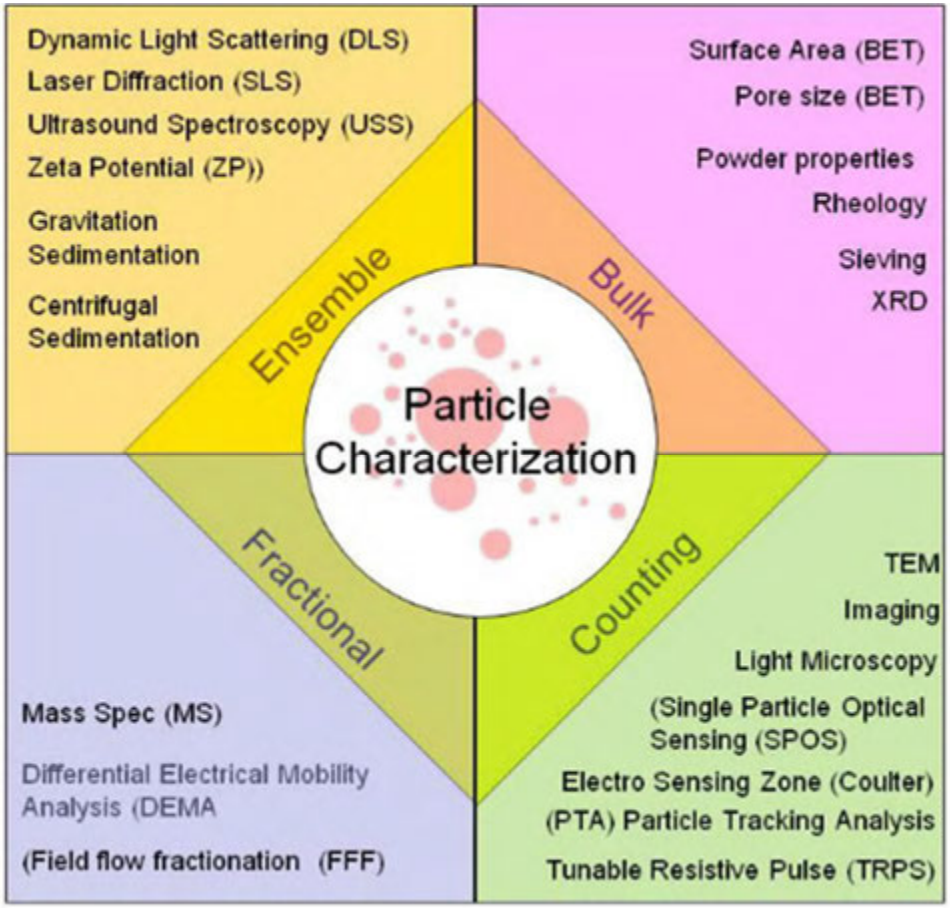


Particle Sizing methods

- **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



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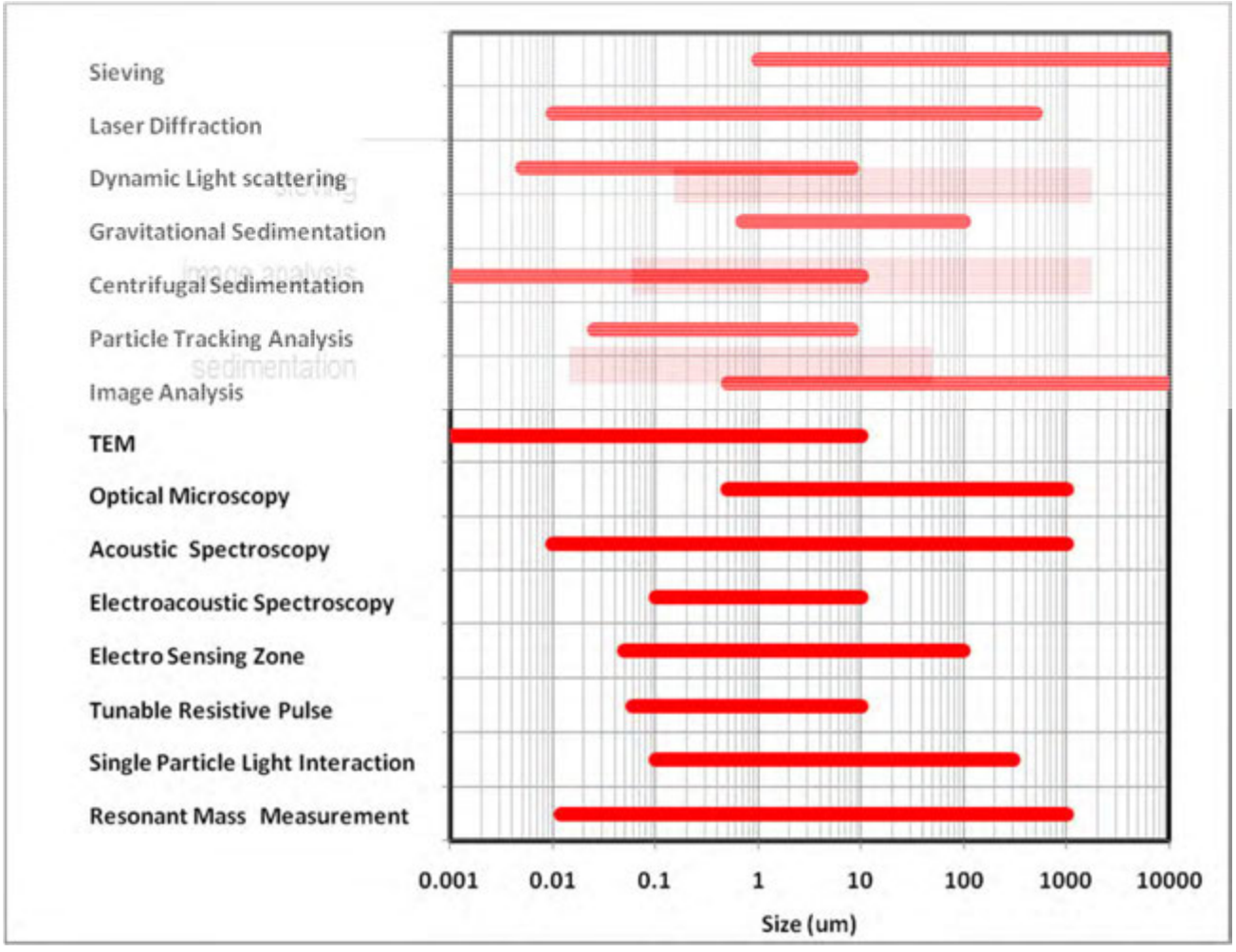
Analysis Methods
Measurement range



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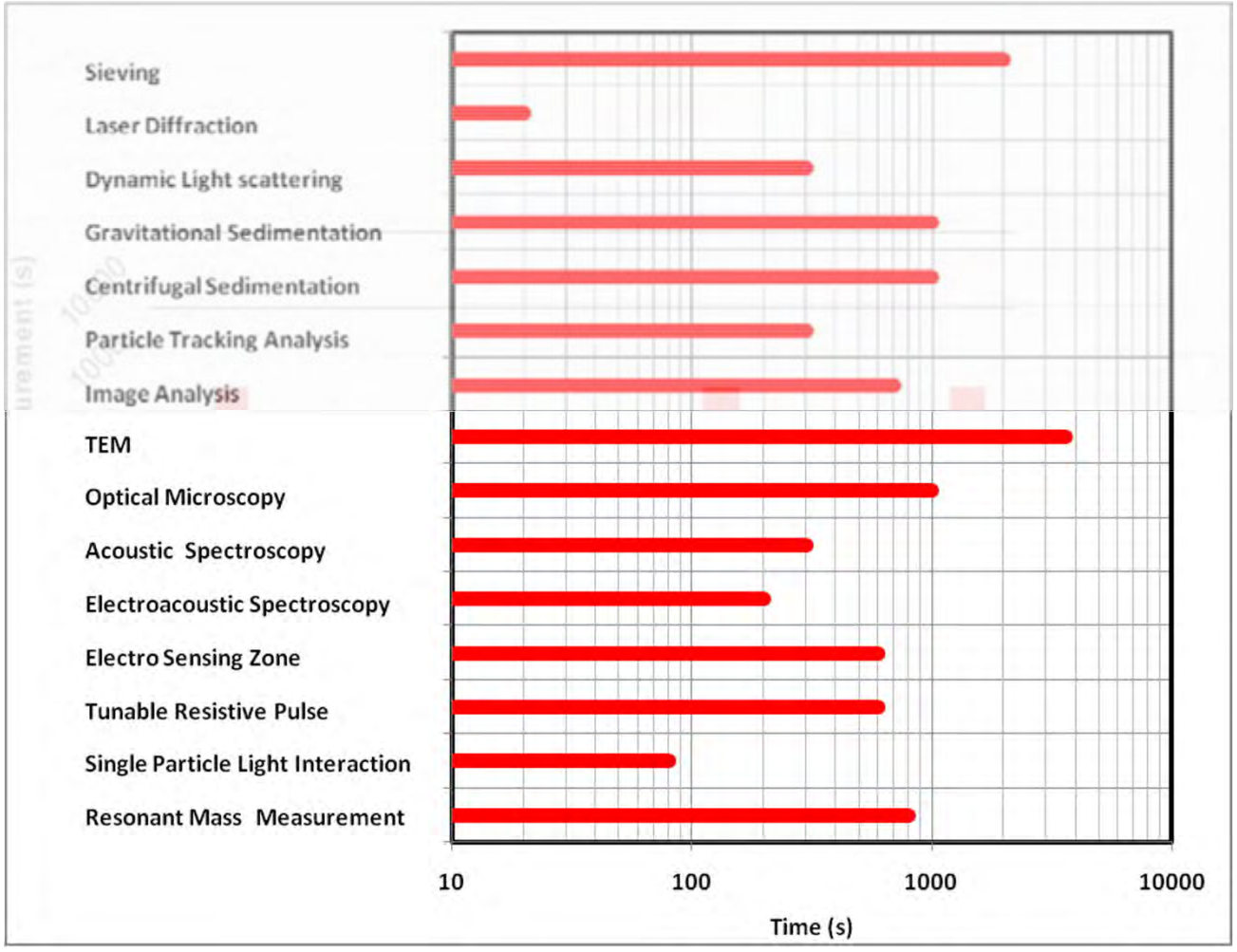
Analysis Methods
Measurement time



Method Selection

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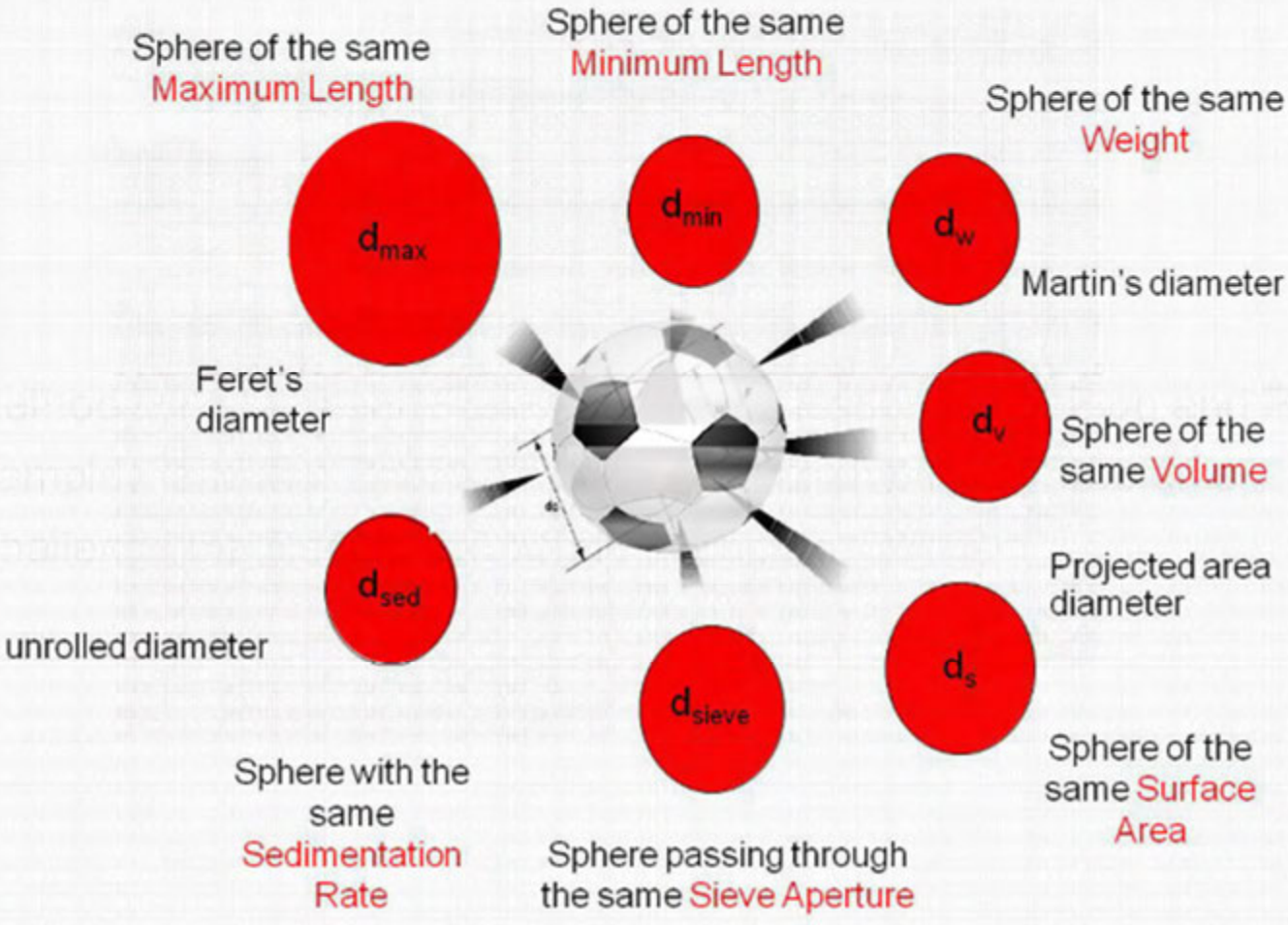
Particle Characterization Solutions

VED: particles and football



Method Selection

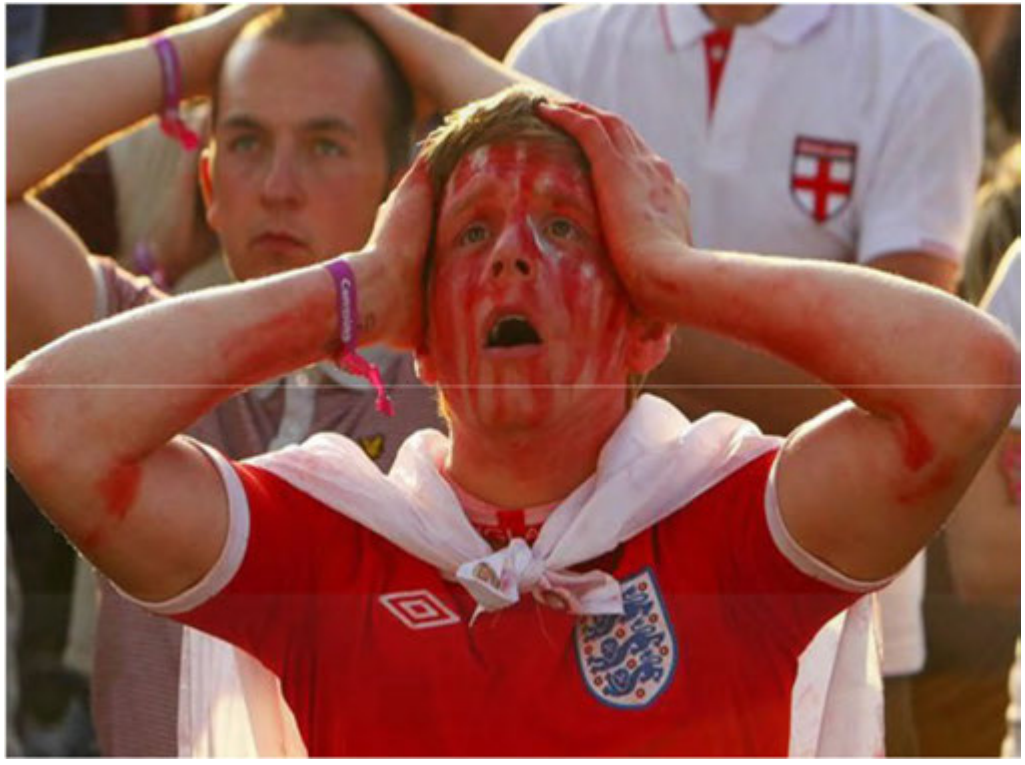
Particles are like football supporters

- 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

Particulate Sensors
Particle Characterization Solutions

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)

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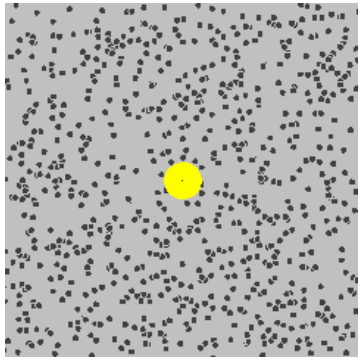
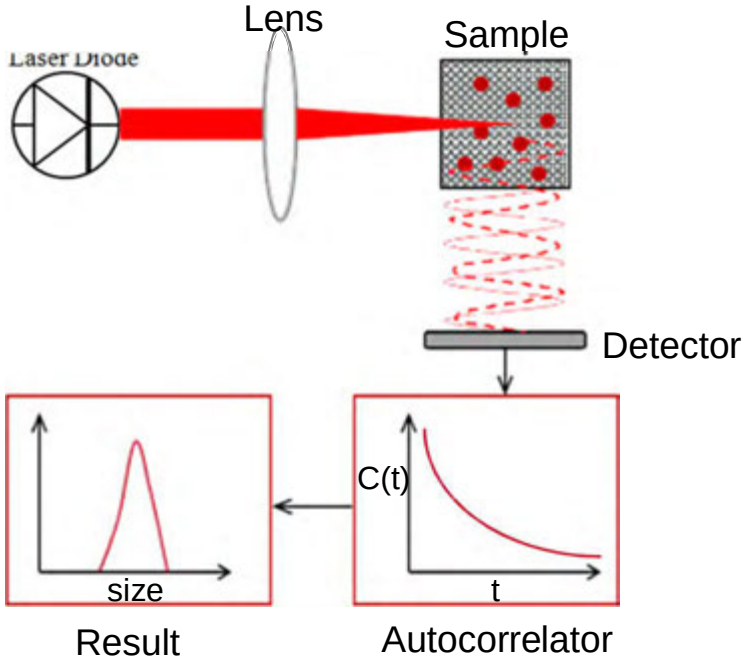
Particle Characterization Solutions

- 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

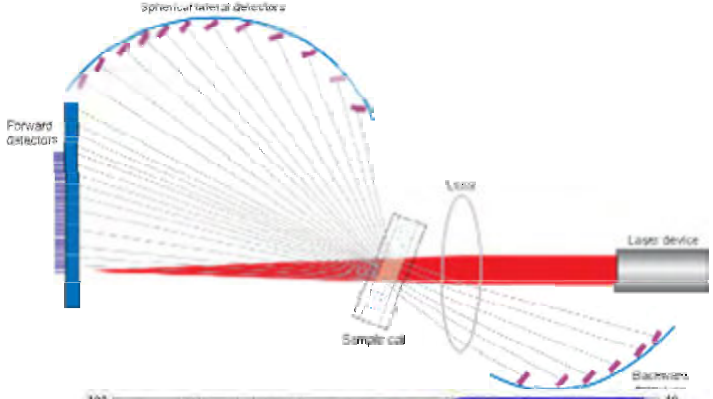
PSS Nicomp N3000

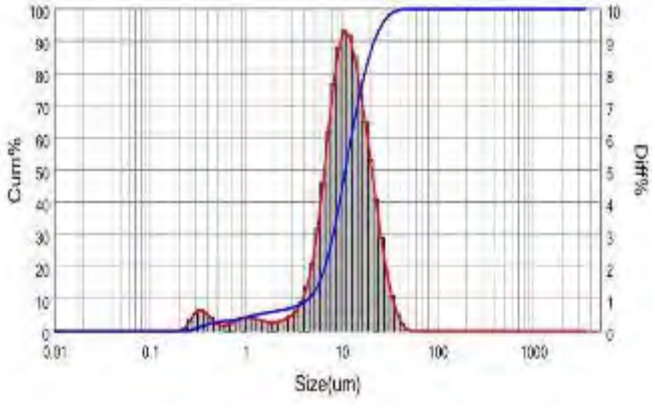
Laser diffraction (SLS)

Particulate Sensors
Particle Characterization Solutions

Bettersize S3 plus

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





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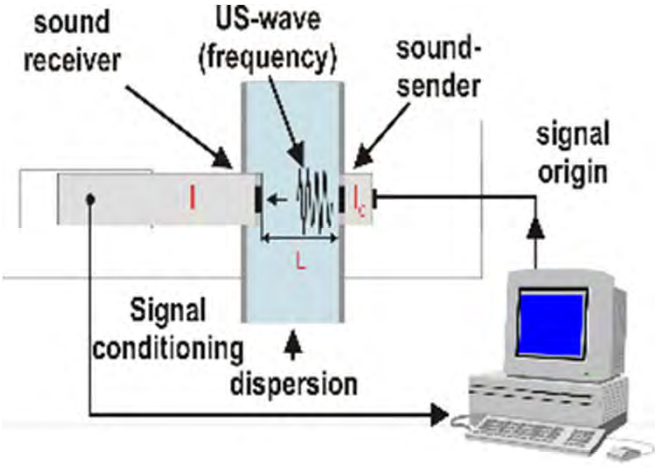
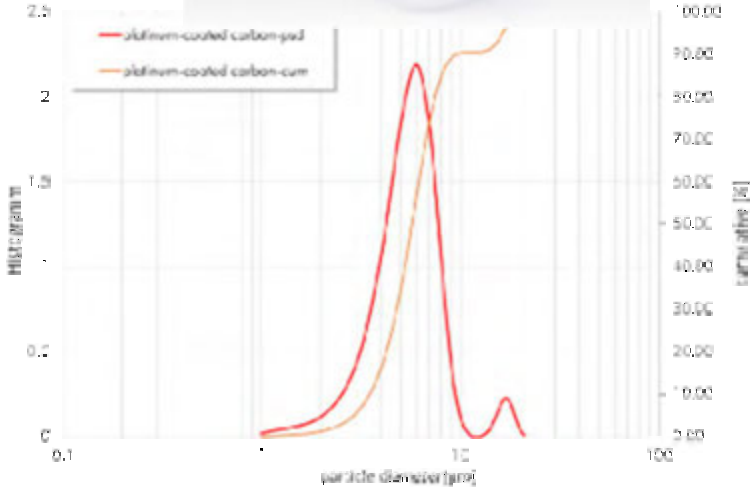
Acoustic Spectroscopy

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

Dispersion Technology DT1202





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

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Single Particle Optical Sensing

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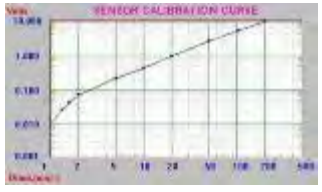
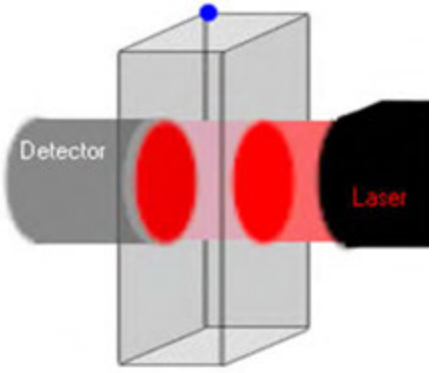
Particle Characterization Solutions

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

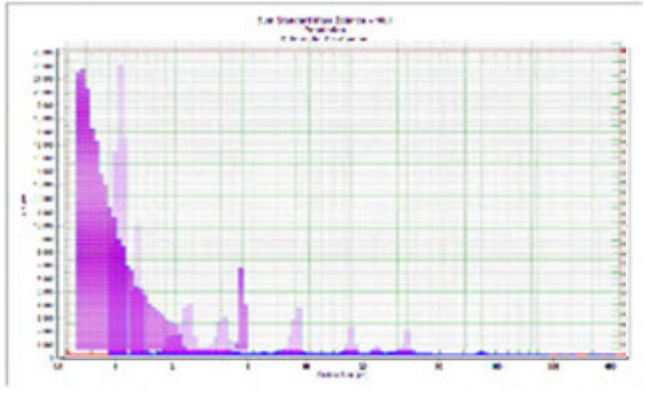
Need to measure below coincidence error limit

PSS Accusizer A7000





Detector Output



Fat emulsion “tail” with 10 micron latex spike

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Imaging

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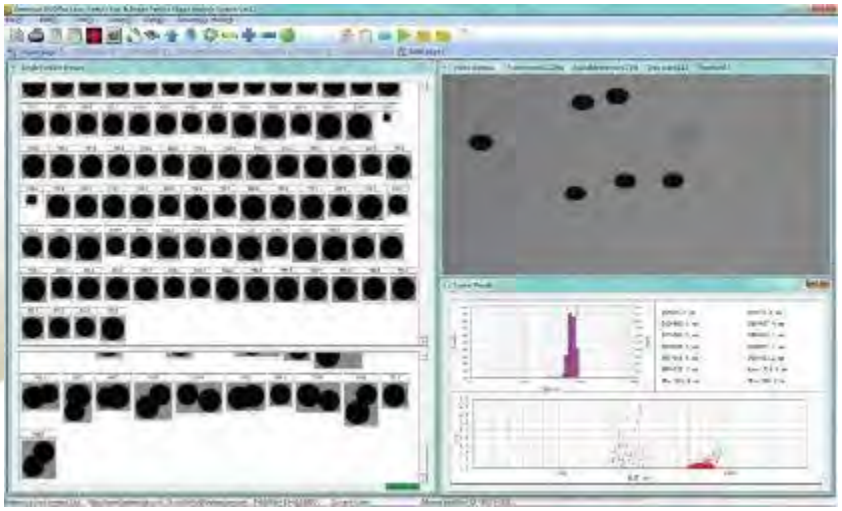
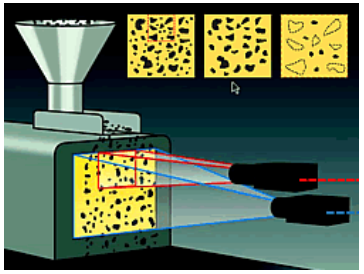
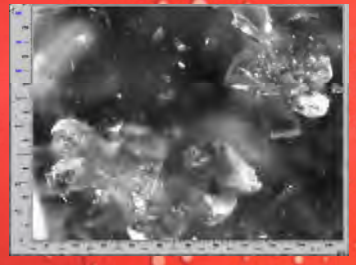
Particle Characterization Solutions







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

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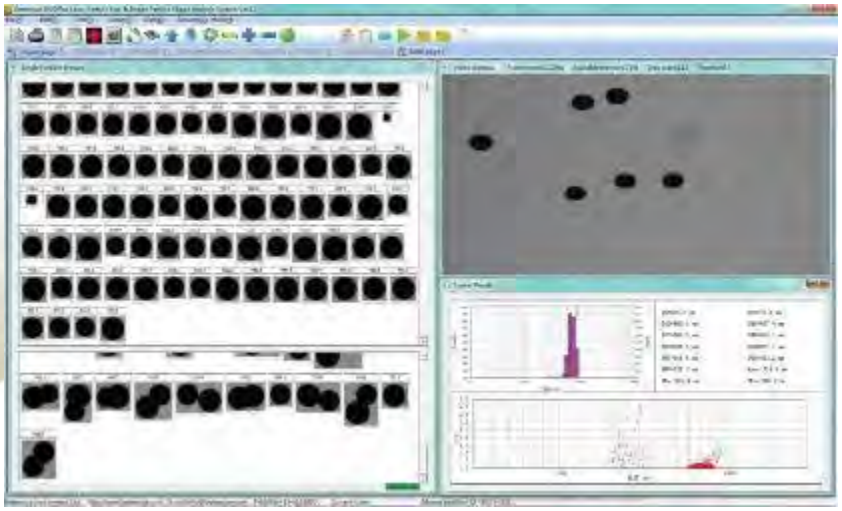

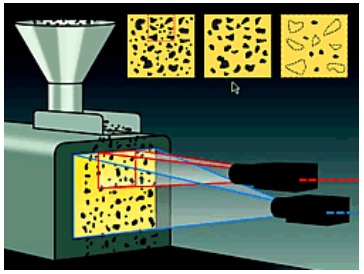

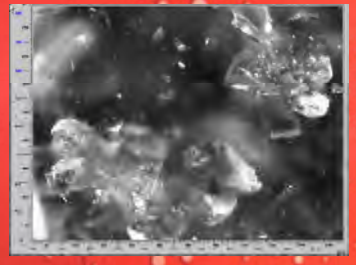

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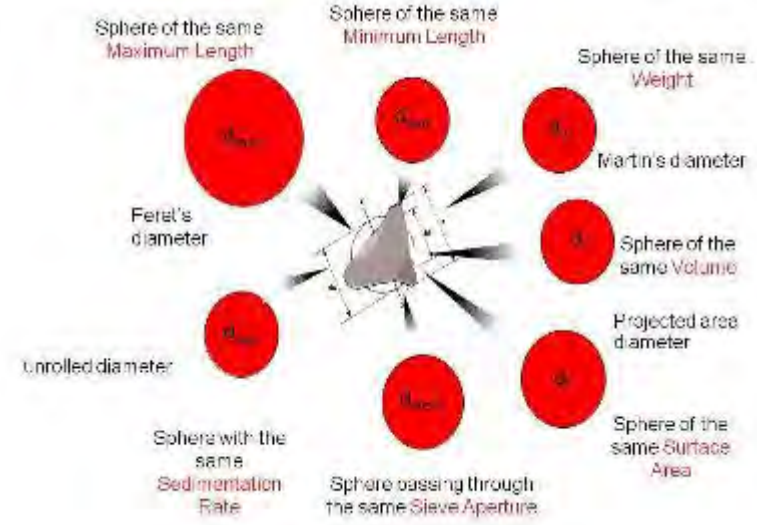

Bettersize Bevision D2

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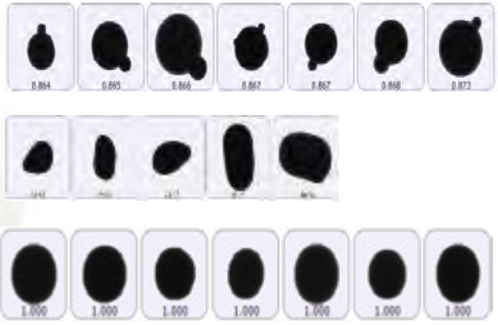
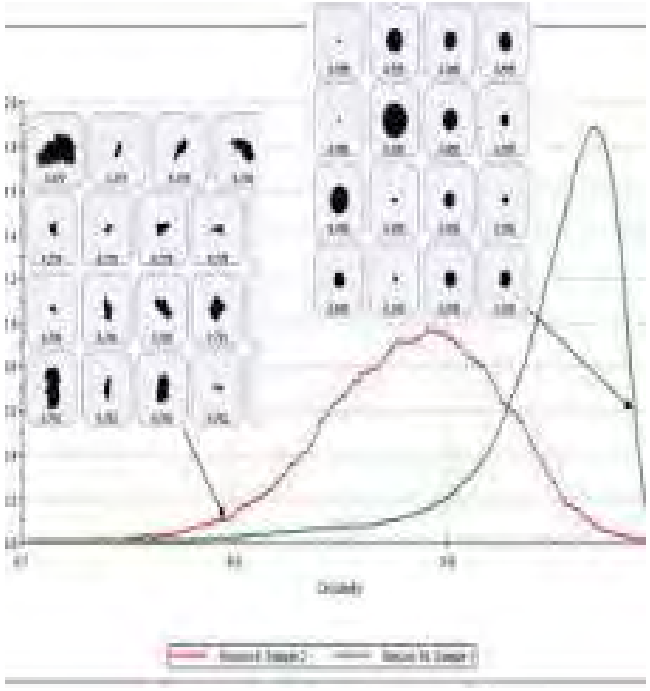
Particle Shape





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

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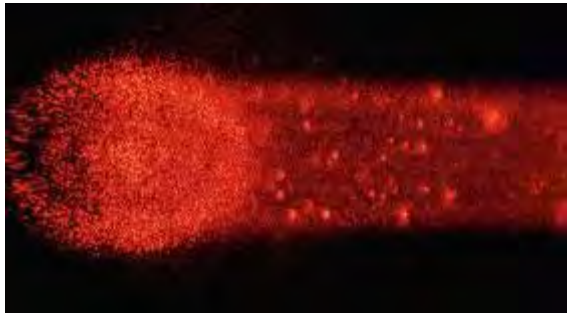
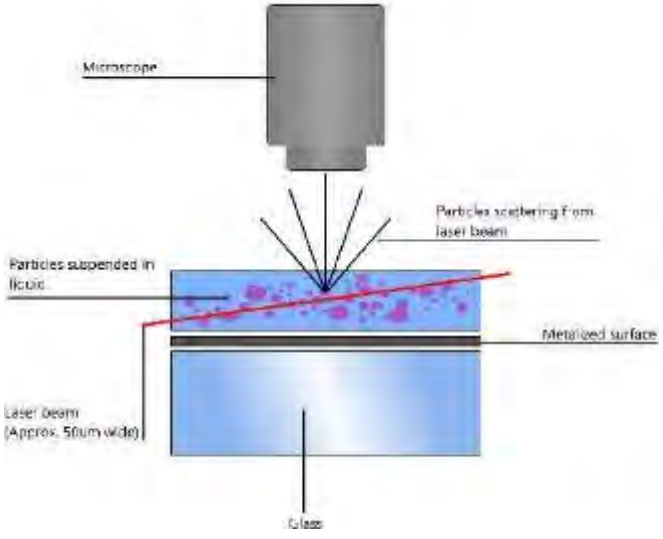
Particle Characterization Solutions

- 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

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





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Bulk Powder Properties

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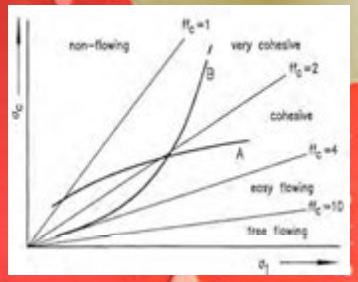
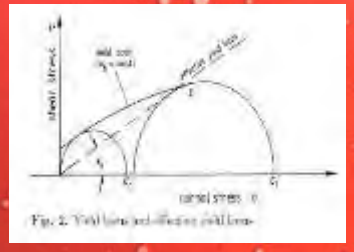
Particle Characterization Solutions

Dynamic Powder Analyers

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

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





Bettersize Powderpro A1

Or Individual measures of powder properties

- Angle of repose
- Tap Density
- Voidage
- Cohesiveness

Manual analysis of macroscopic, physical properties of a powder

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Combining methods

- Separation and DLS
  - Using a separation technique with DLS as a detection enhances specify 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
- Emsemble Measurement and Imaging
  - Provides the fast, large population with the detailed morphlogical information of Imaging i.e
    - Laser Diffraction and Imaging

Laser diffraction

and image analysis combined

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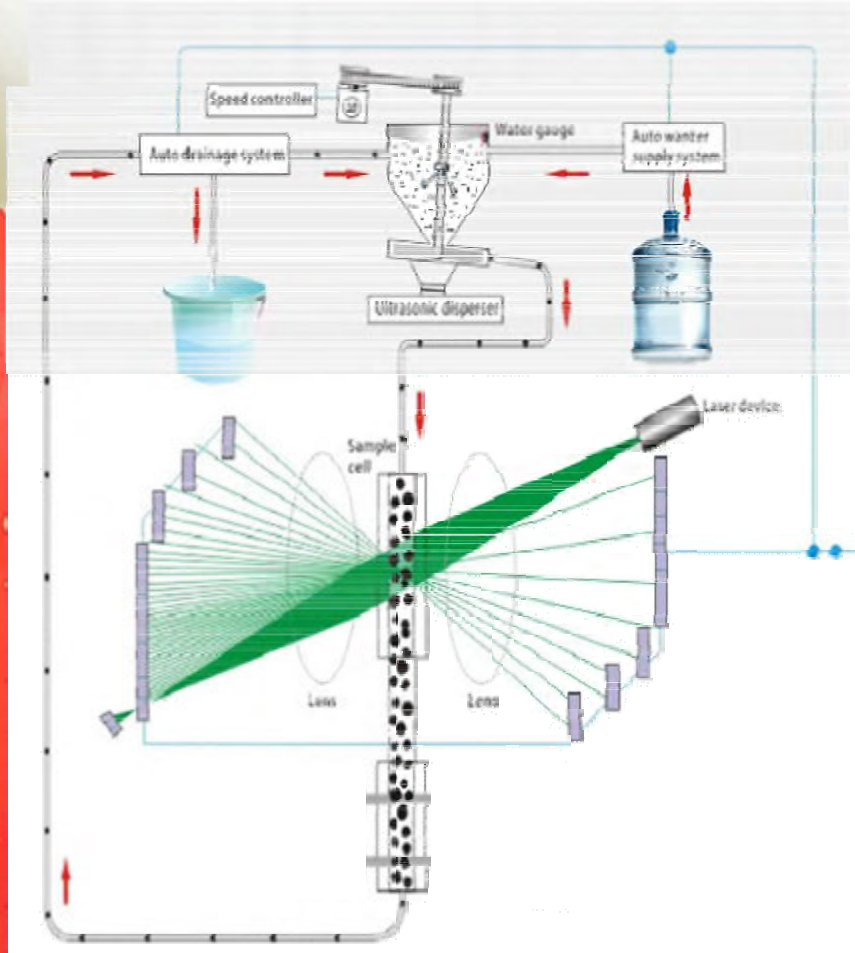
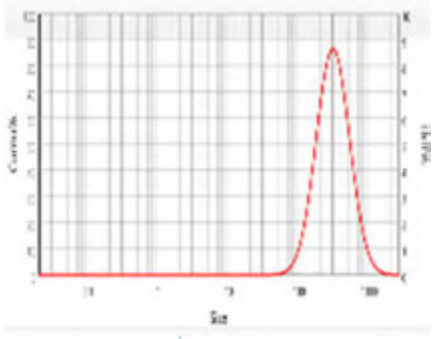
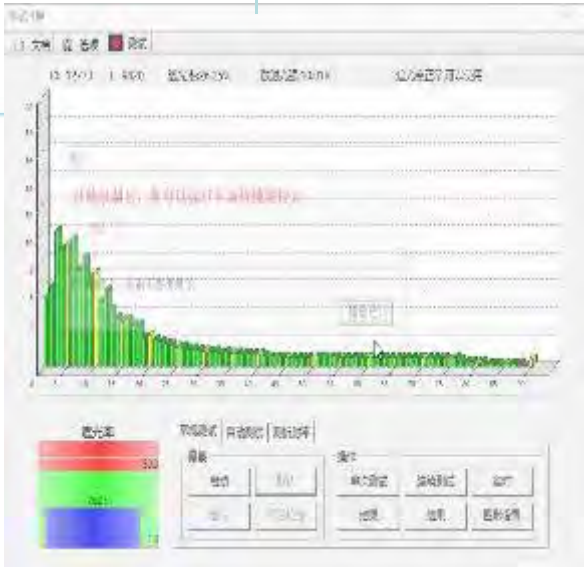
Particle Characterization Solutions







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Laser diffraction

and image analysis combined

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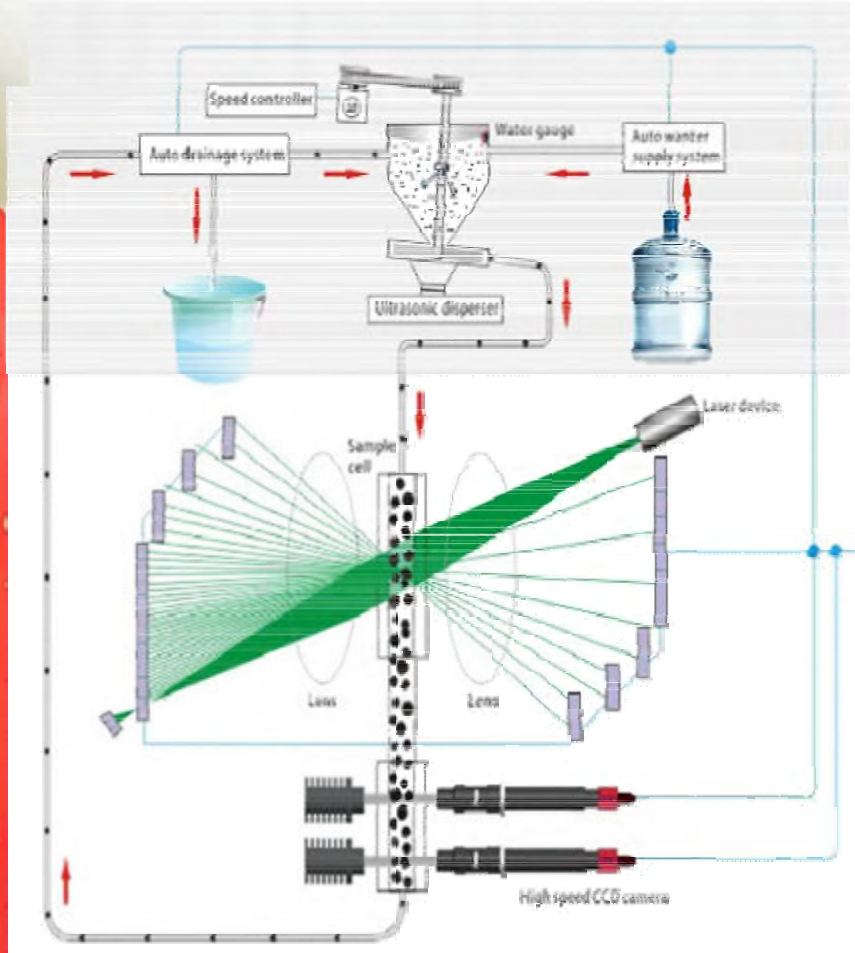
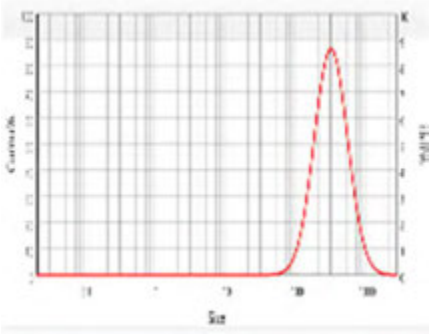
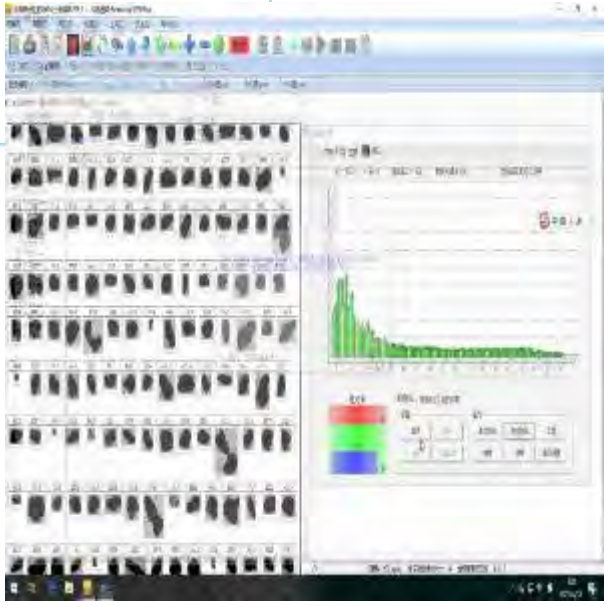
Particle Characterization Solutions







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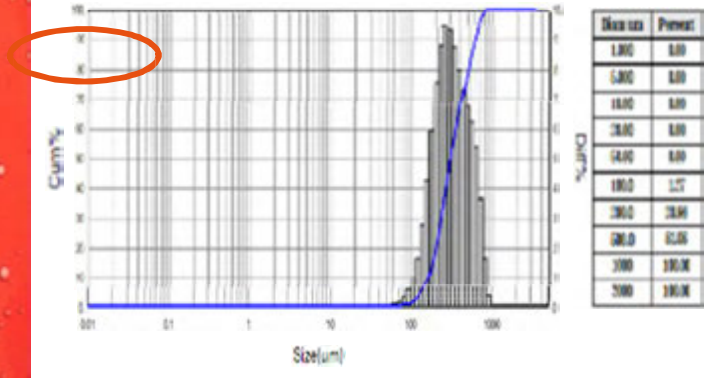
Differences in batches

Silica-1

Bettersizer

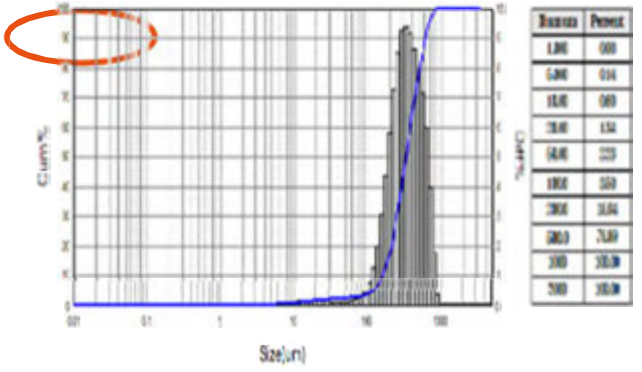
Bettersizer S3 Plus Particle Size Analysis Report



Silica-2

Bettersizer

Bettersizer S3 Plus Particle Size Analysis Report



Differences in batches

Particulate Sensors
Particle Characterization Solutions

Silica-1

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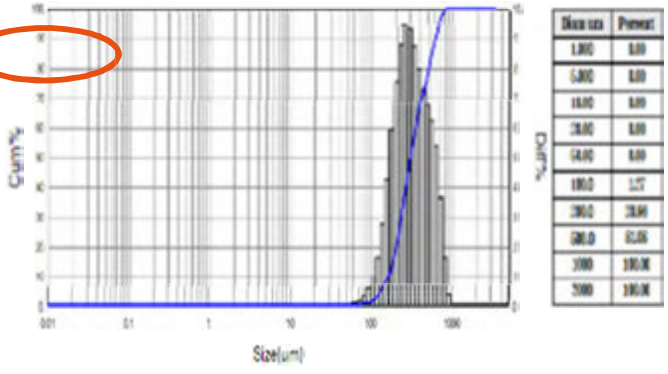
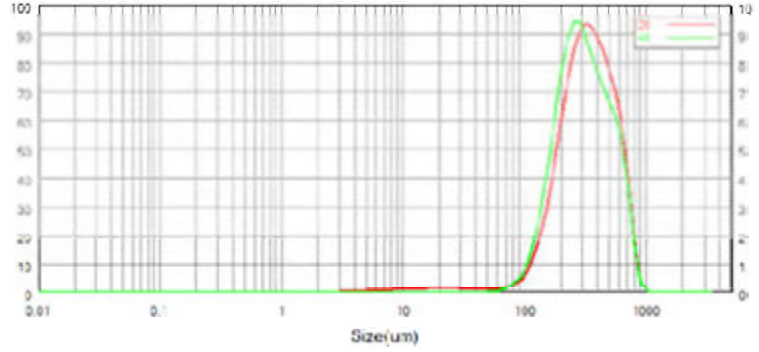


Silica-2



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Differences in batches

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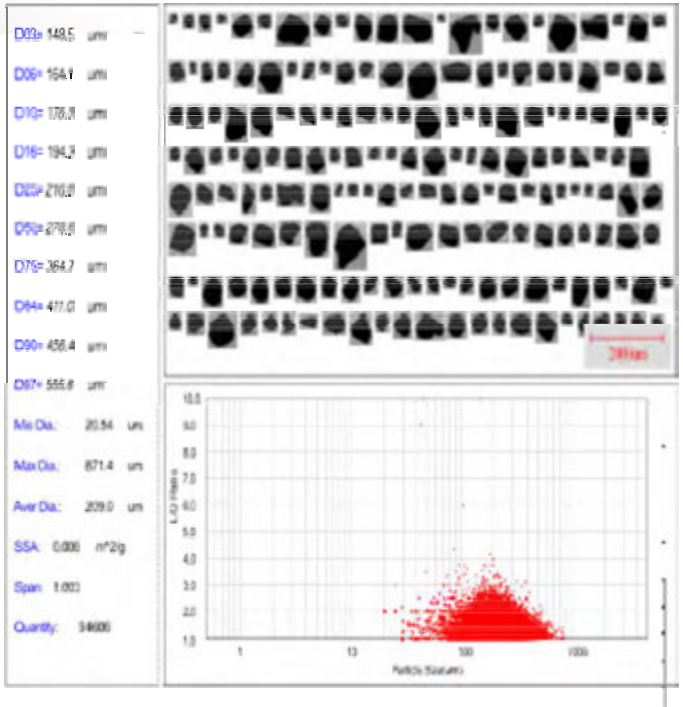
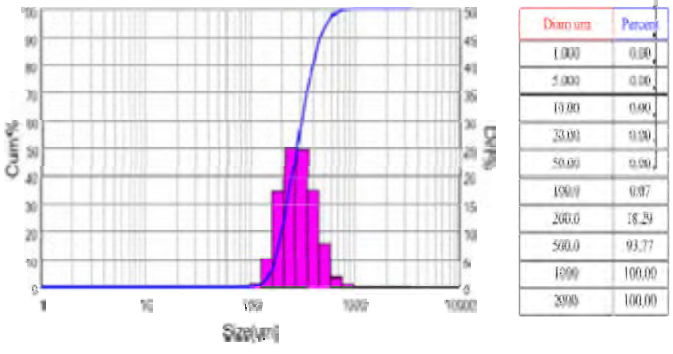
Particle Characterization Solutions

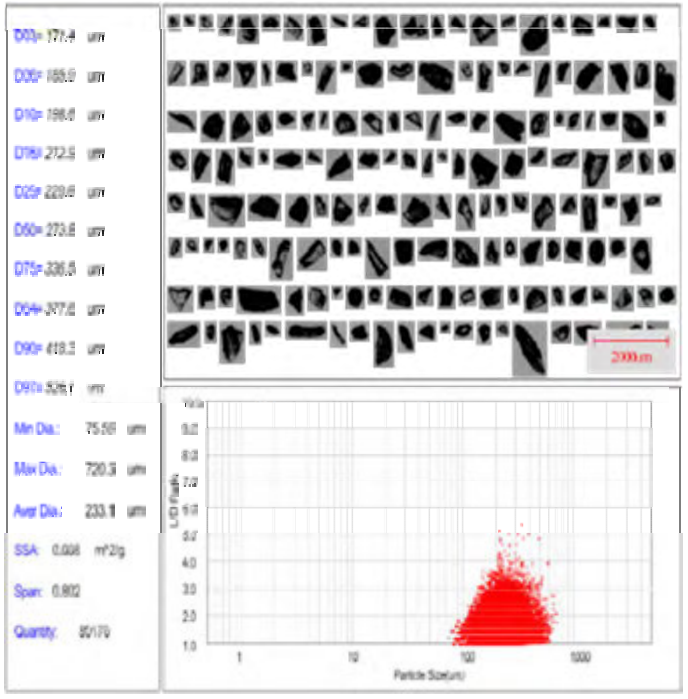
Silica-1

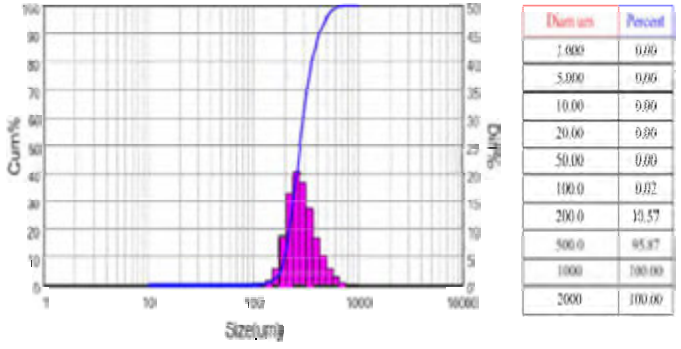




Diam um	Percent
1.000	0.00
5.000	0.00
10.00	0.00
20.00	0.00
50.00	0.00
100.0	0.07
200.0	18.29
500.0	93.77
1000	100.00
2000	100.00

Silica-2





Diam um	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	10.57
500.0	95.87
1000	100.00
2000	100.00

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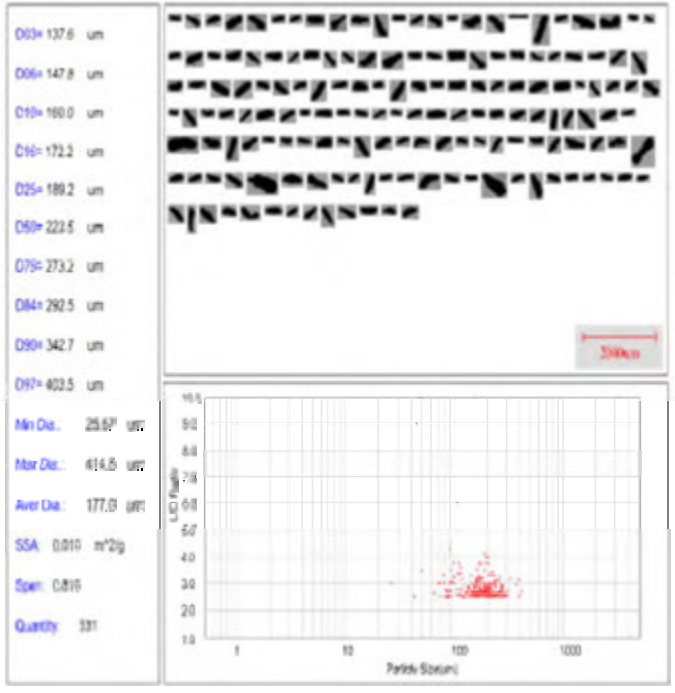
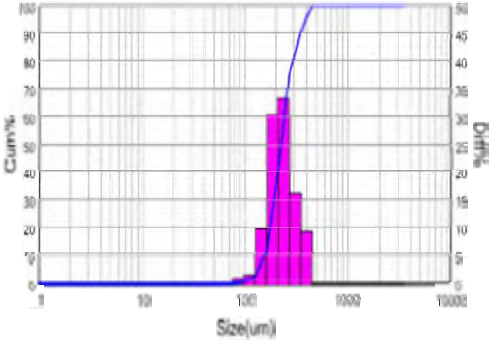
Differences in batches

Particulate Sensors
Particle Characterization Solutions

L/D > 2.5

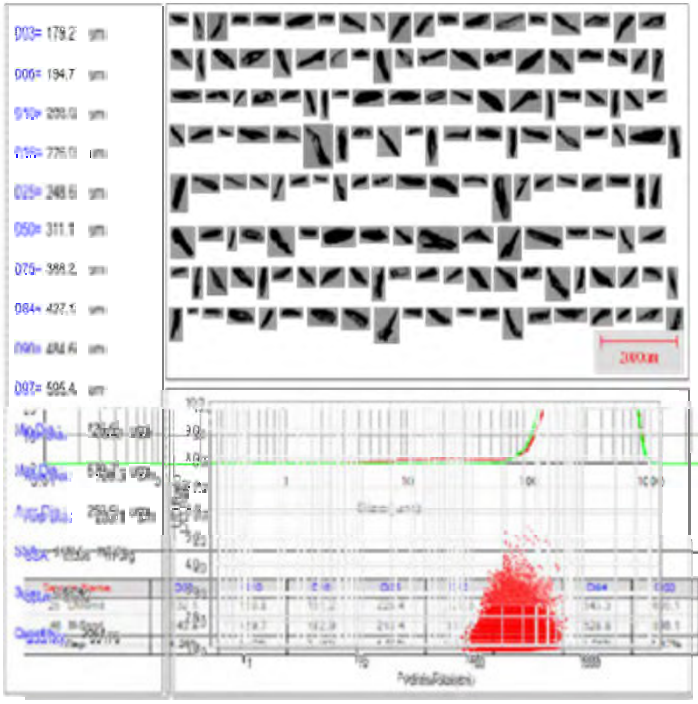
Silica-1

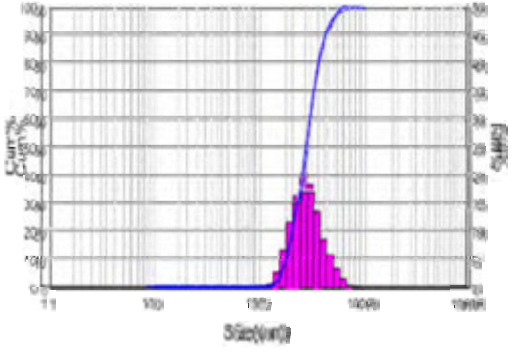




Diam um	Percent
1.000	0.00
5.000	0.00
10.00	0.00
20.00	0.00
50.00	0.01
100.0	0.79
200.0	33.10
500.0	100.00
1000	100.00
2000	100.00

Silica-2





Diam um	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	0.87
500.0	99.20
1000	100.00
2000	100.00

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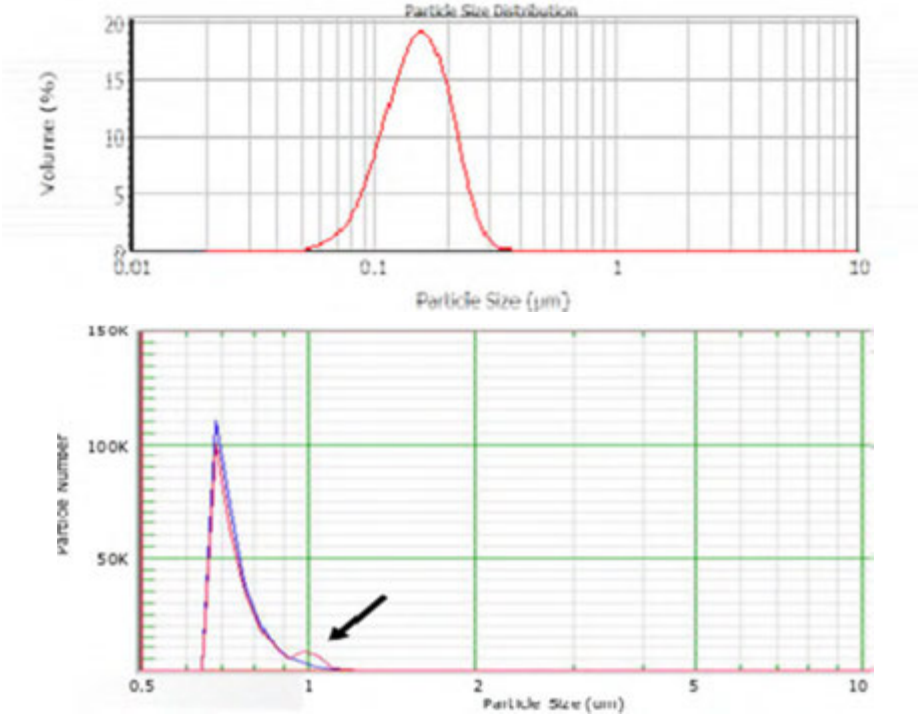
Contamination Monitoring

Particulate Sensors
Particle Characterization Solutions

Two critical contamination types:

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



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

*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

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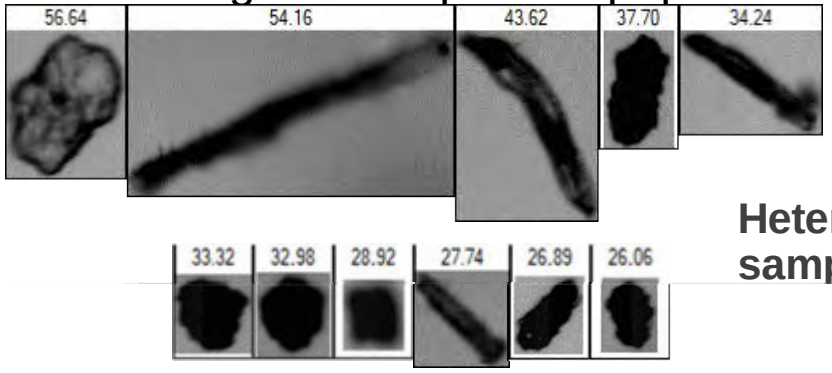
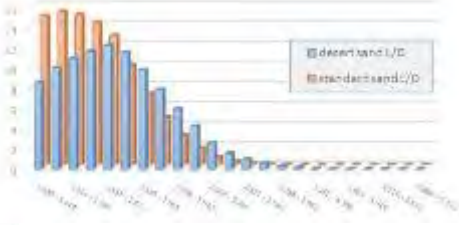


Heterogeneous samples



	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

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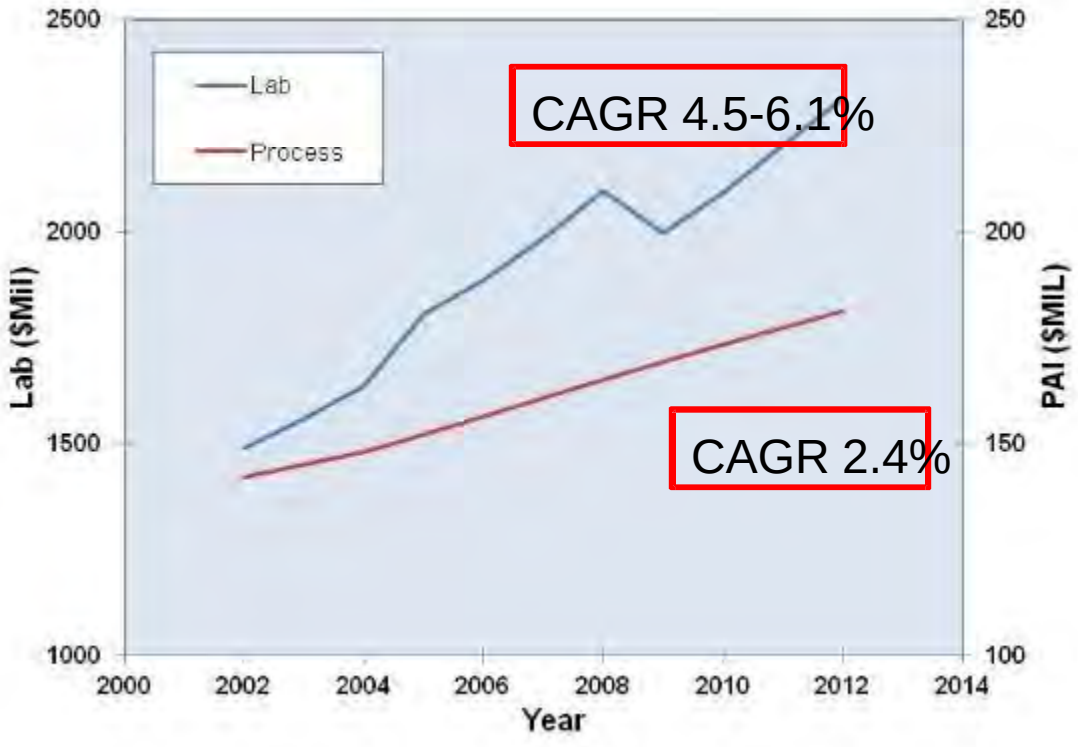
Why do we still make Laboratory Measurements

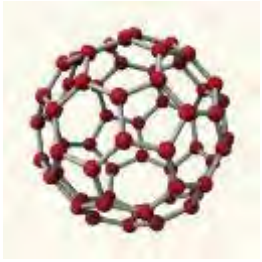
Particulate Sensors
Particle Characterization Solutions

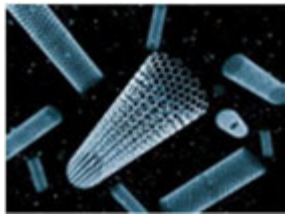
Despite all the claims, the money and all the hopes in the last 15 years the capability to characterise particulate systems in-situ at high concentration has not met the original expectations



What Next for Particles

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





RSC INTEREST GROUP
PARTICLE CHARACTERISATION

Particulate Sensors
Particle Characterization Solutions

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)

Richard J. Tweedie

PhD, MSc, BEng, CEng, CPhys, CSci

Managing Director

Clavering House
Clavering Place,
Newcastle upon Tyne,
NE1 3NG,
United Kingdom
NE1 3NG

Tel: +44 143 467 3096
E-mail: richard.tweedie@particulatesensors.com