Method Development

Creating the Perfect Standard Operating Procedure (SOP)

Explore the future

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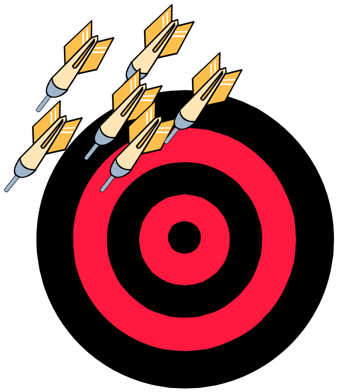
Method Development

- Goal: Reproducible method that tracks product performance
- Choose measurement approach (dry vs. suspension)
- Lock down RI
- Vary measurement settings that can influence result
  - Dry: measurement duration, concentration, air pressure
  - Wet: sampler selection, dispersion, duration, concentration, energy (mixing + ultrasound)
- Test method (reproducibility)
  - Meet ISO, USP or internal guidelines
  - Check COV at d10, d50, d90

Goals

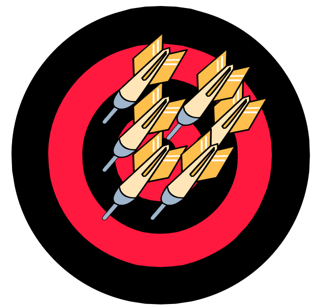
- Reproducible method that tracks product performance
- You might have other goals
  - Accuracy: tricky subject, is it the “real” particle size
  - Repeatability: liquid suspension re-circulating in sampler
  - Reproducibility: prepare, measure, empty, repeat
  - Resolution: optimize to find second populations
  - Match historic data (sieves), but quicker, easier technique
- Use structured approach for any decision/choice that may influence result
- Have data to support selections made
- Document process so others (in future) understand the decisions

Accuracy vs. Precision

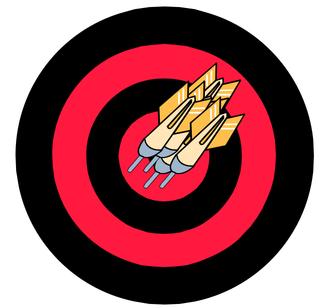


LOW ACCURACY
LOW PRECISION

LOW ACCURACY
HIGH PRECISION



HIGH ACCURACY
LOW PRECISION



HIGH ACCURACY
HIGH PRECISION

- (A) Low accuracy, low precision measurements form a diffuse, off-center cluster; (B) Low accuracy, high precision measurements form a tight off-center cluster; (C) High accuracy, low precision measurements form a cluster that is evenly distributed but distant from the center of the target; (D) High Accuracy, high precision measurements are clustered in the center of the target.

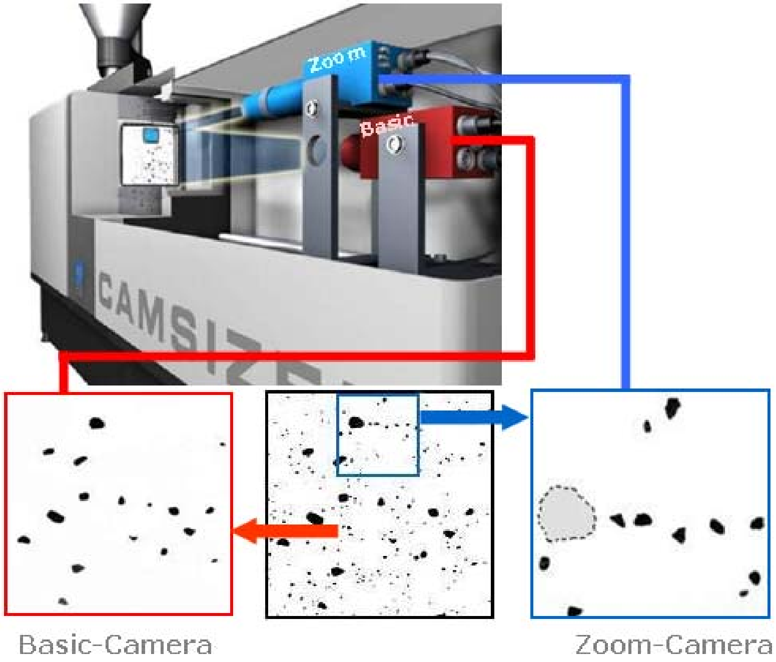
Accuracy

- Is it the “real particle size”?
- Comparison to referee technique
- Microscope (image analysis) is referee technique for particle characterization
- Two kinds of image analysis:
  - Dynamic image analysis; particles flowing
  - Static image analysis; particles sit on slide on automated stage

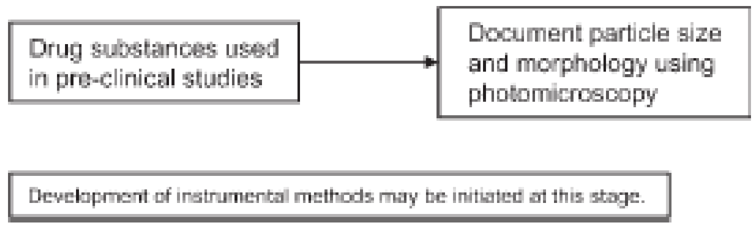
Image Analysis: Two Approaches

Dynamic:
particles flow past camera

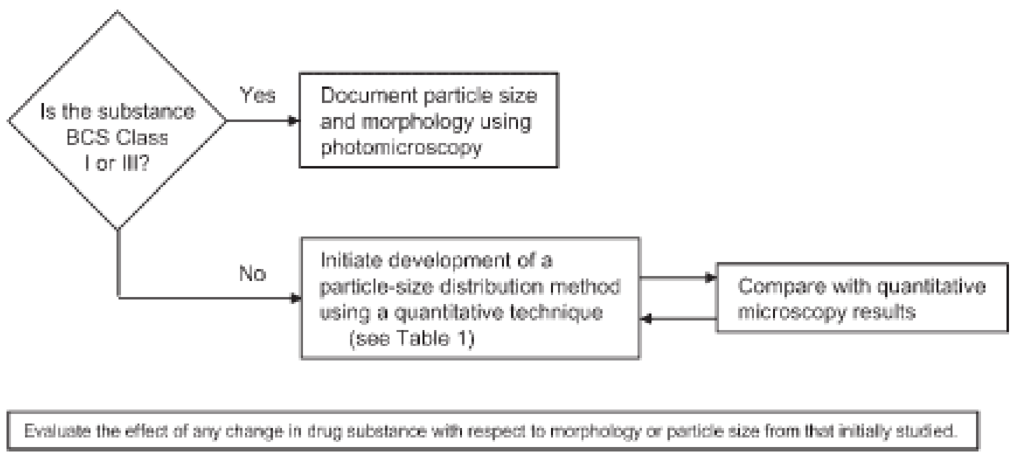
Static:
particles fixed on slide,
stage moves slide



Proposed Pharmaceutical Guidelines

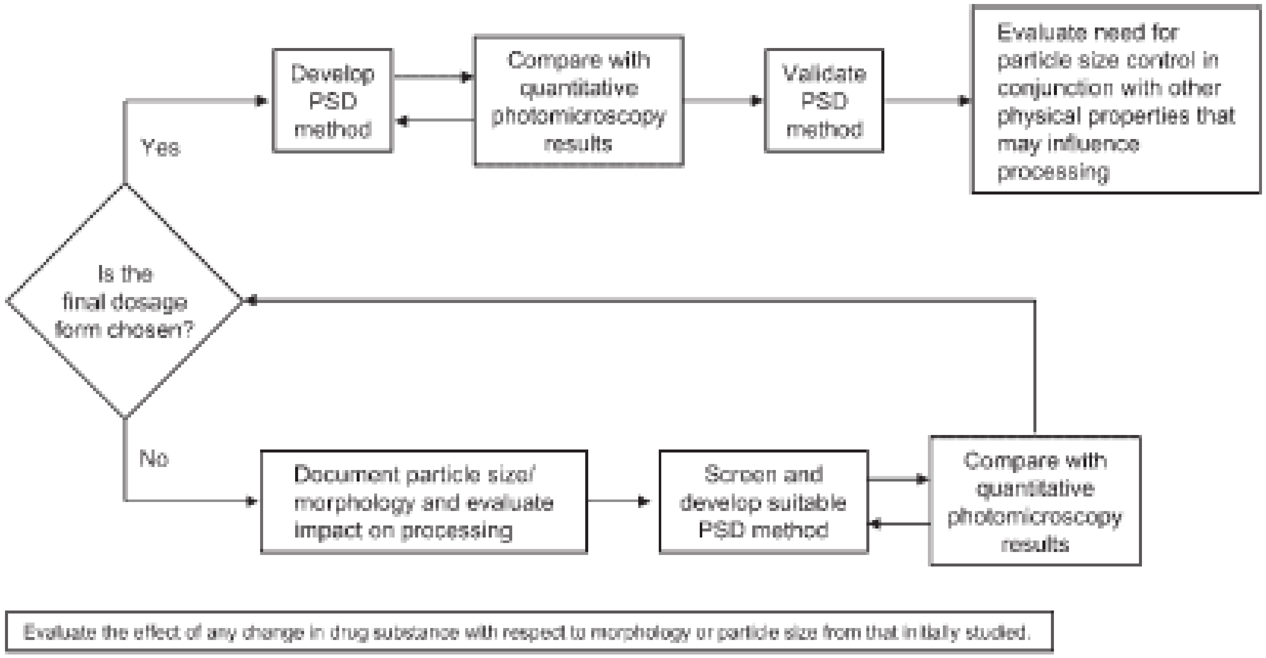


Scheme for outlining particle evaluation for preclinical studies.



Decision tree outlining particle evaluation for Phase I clinical studies

Proposed Pharmaceutical Guidelines

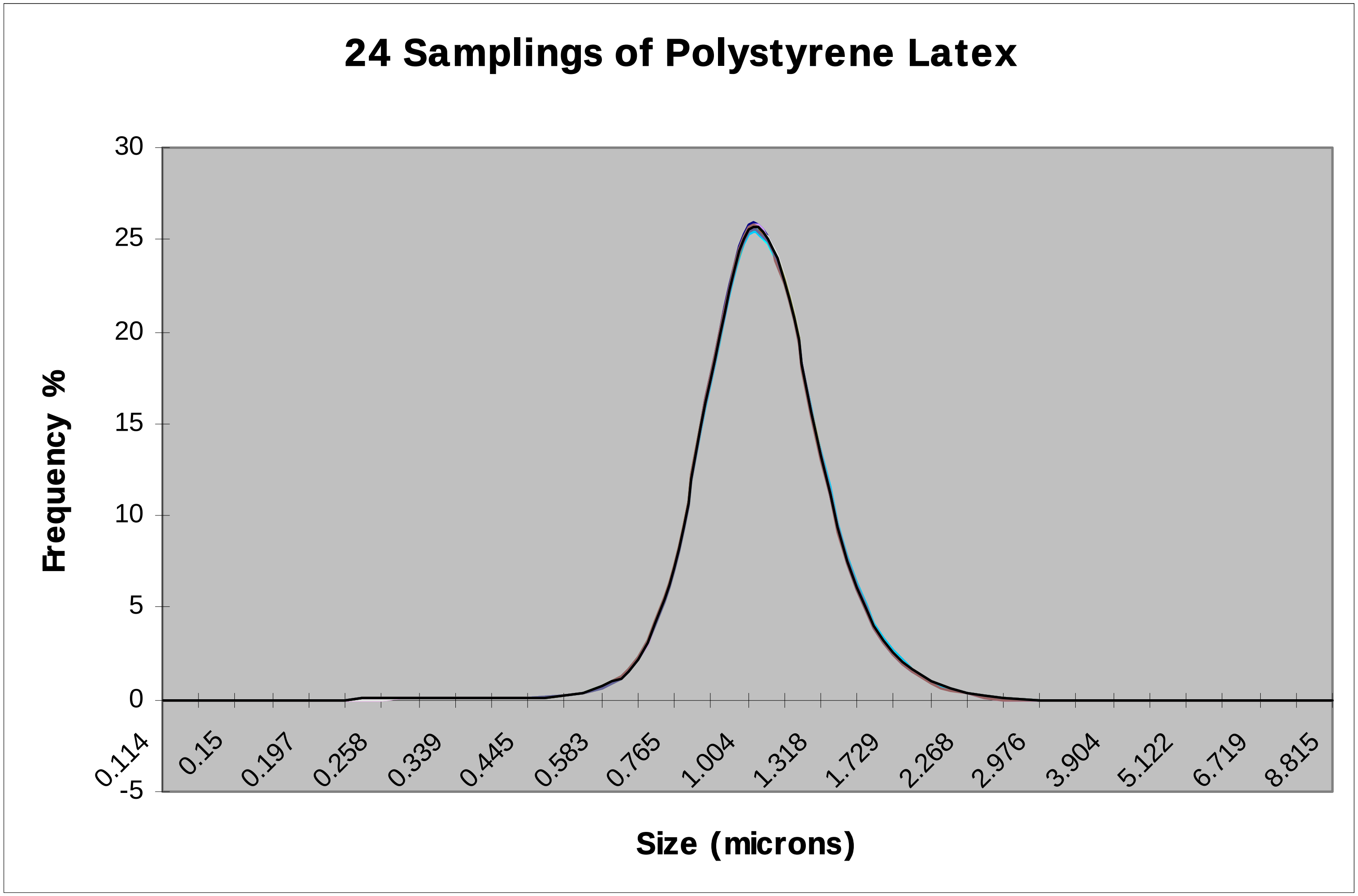


Scheme for outlining particle evaluation for Phase III clinical studies

Repeatability, Reproducibility

- Repeatability: prepare sample, add to wet sampler, re-circulate, measure same multiple times (suspensions only)
- Reproducibility: prepare sample, measure, drain, repeat (suspensions + dry)

Precision (Repeatability)



Explore the future

Reproducibility

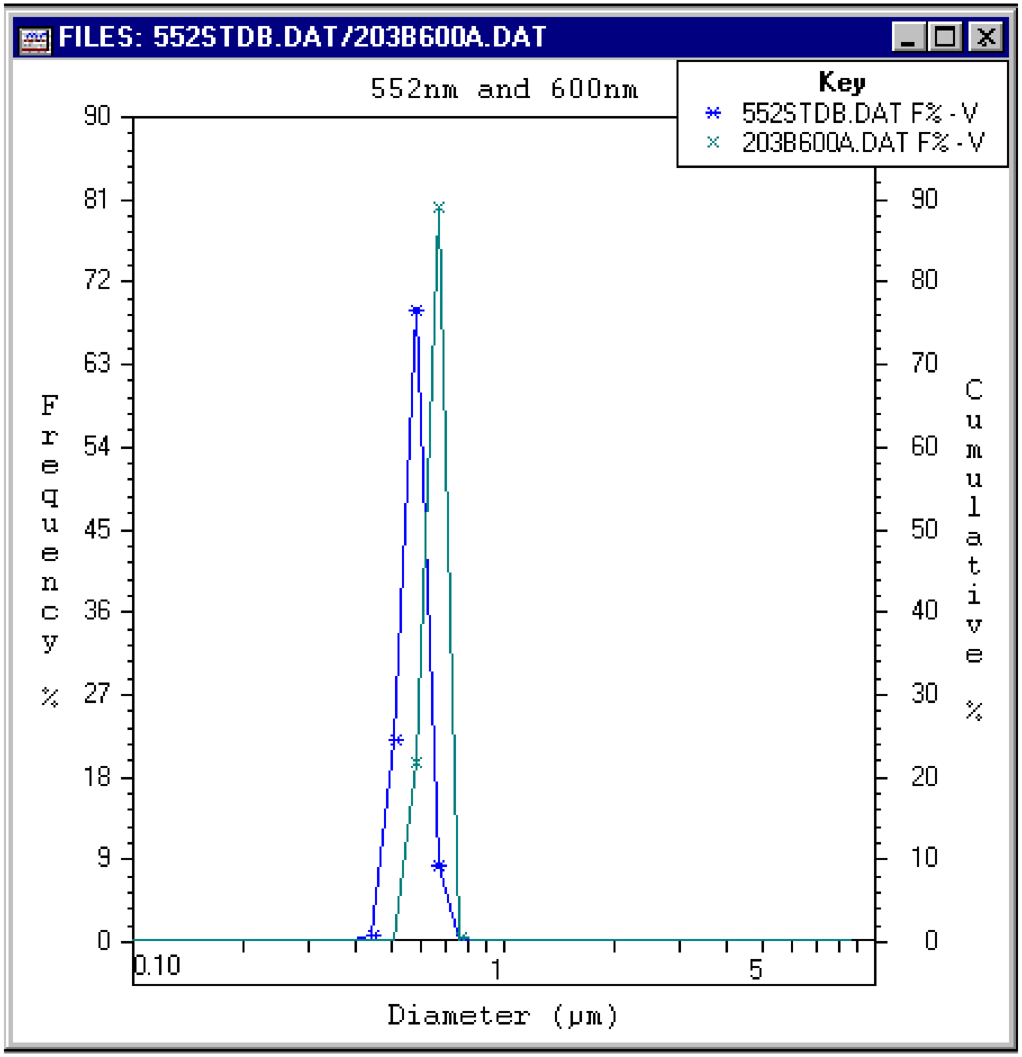
- Reproducibility: prepare, measure, empty, repeat
- What would be good reproducibility?
  - Look at accepted standards
  - Measure 3 times, calculated COV at d_{10}, d_{50}, d_{90}
    - COV (RSD) = st dev/mean * 100
  - ISO13320
    - COV < 3% at median d_{50}
    - COV < 5% at d_{10} & d_{90}
  - USP<429>
    - COV < 10% at median d_{50}
    - COV < 15% at d_{10} & d_{90}

Note: double all limits
When $d_{50} < 10\ \mu m$

Resolution

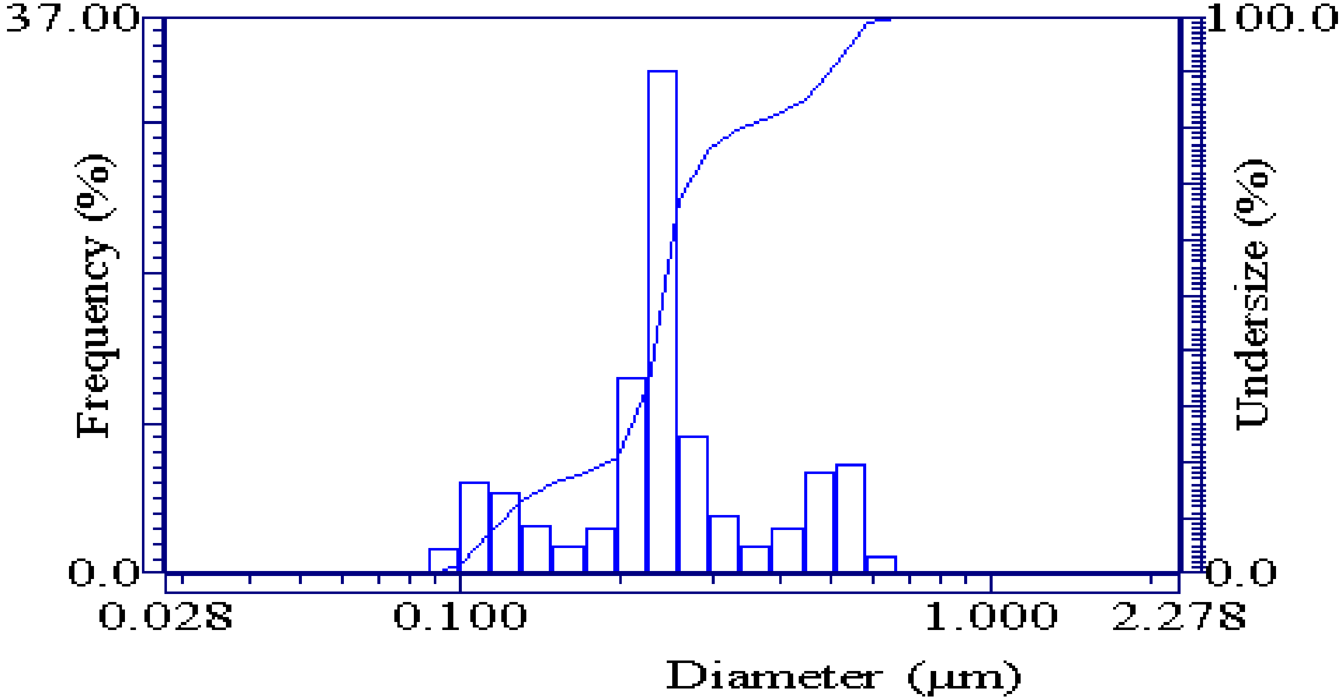
- Ability to measure small differences in particle size
- Small differences between successive samples (different production lots) are most important
- Detection limit of small amount of material outside of main size distribution
- Best defined by user's real-world requirements

Resolution: High or Low Technique?



- Resolve size difference between two materials of similar size
- 552nm and 600nm PSL
- Measured separately: high resolution
- Measure together: low resolution, would blend peaks
- Laser diffraction is a “resolution limited” technique

Resolution Limits

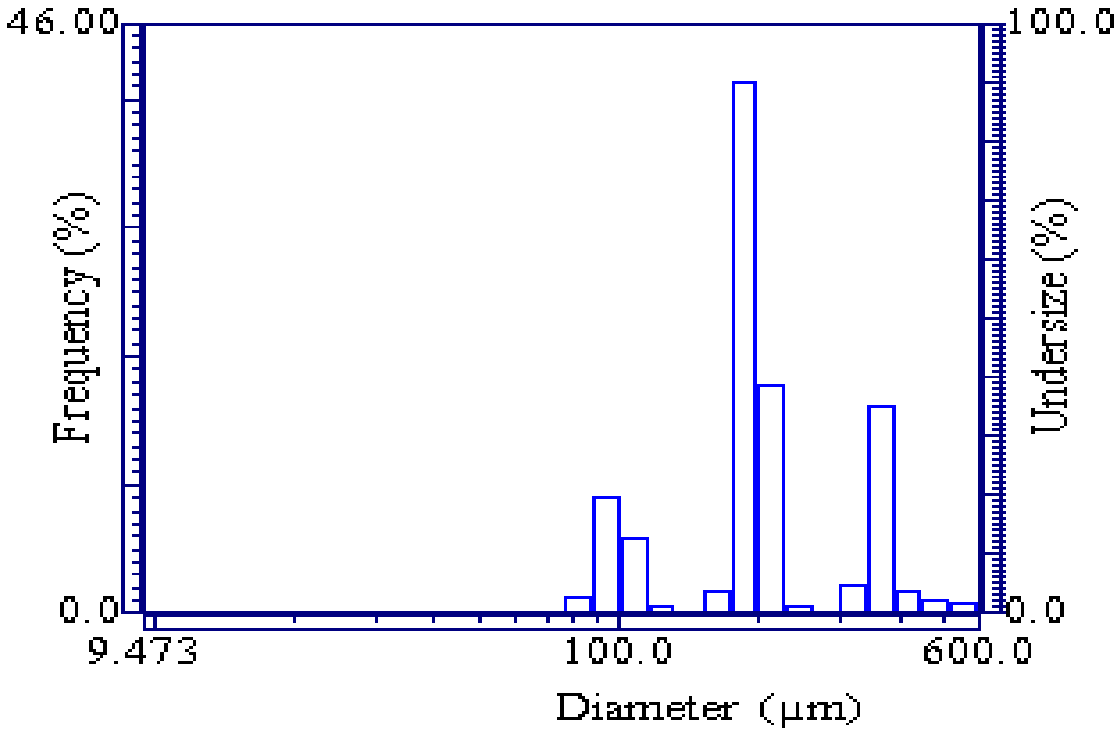


83nm,
204nm,
503nm
PSL

Resolution of multiple modes in a single sample

Next peak 2x of previous size

Resolution Limits

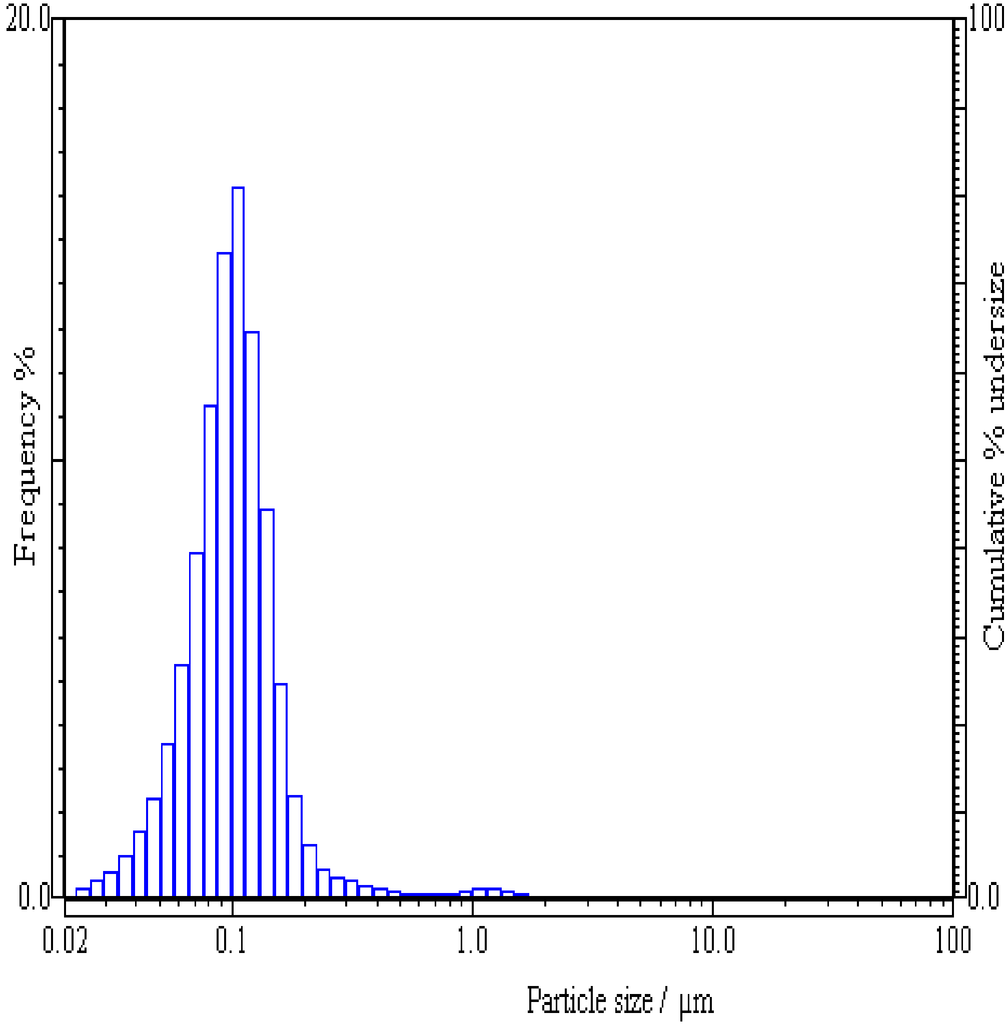


100µm,
200µm,
400µm glass beads

Next peak 2x of previous size

Resolution is independent of where you are on size scale

Resolution: Finding Second Peak



- 0.1 micron silica material
- 2% by weight of ~1 micron quartz standard added
- Original slide showed .25%

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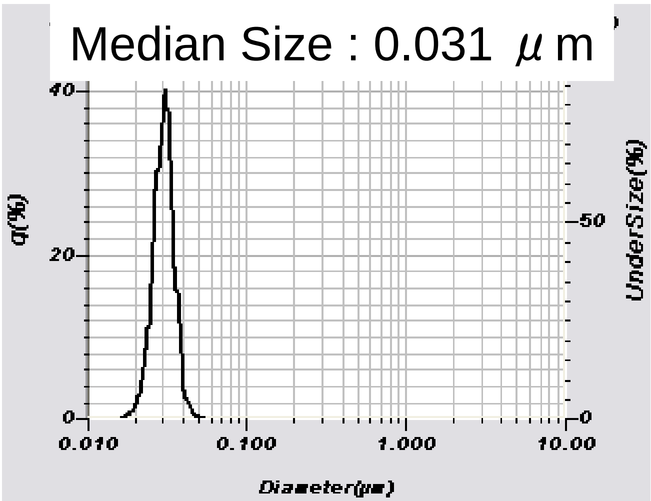
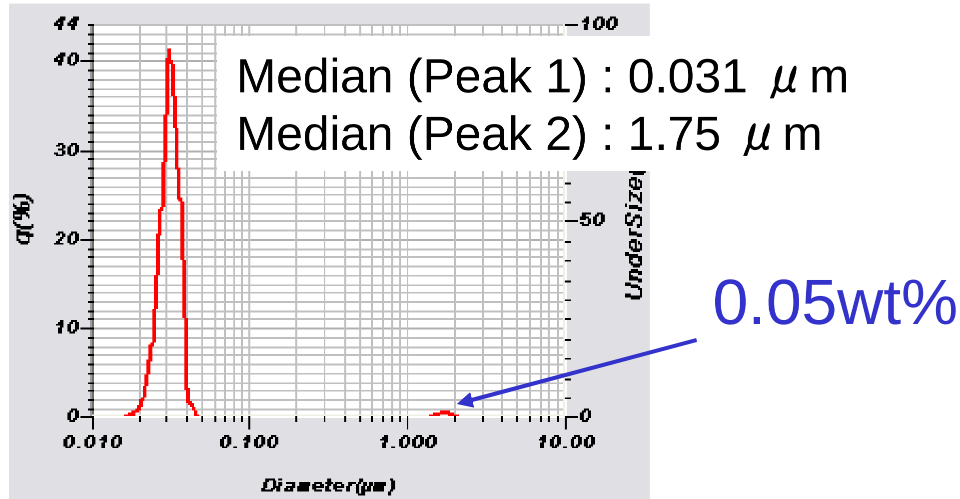
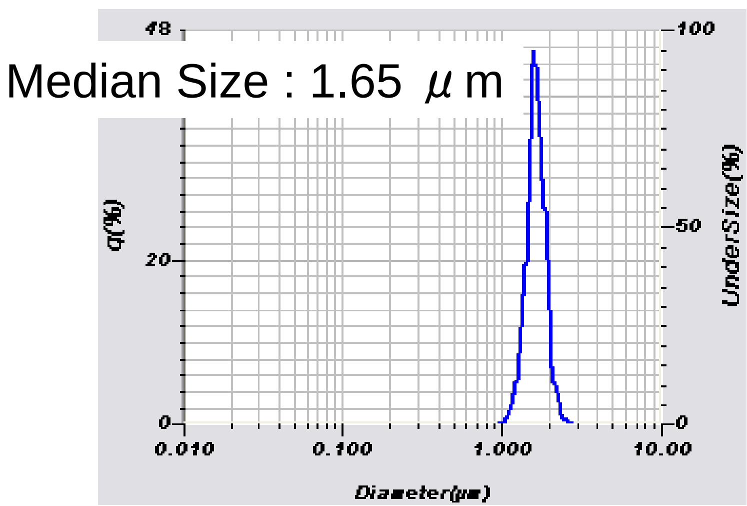
Resolution: Recent LA-950 Data*







Top left: LUDOX™-50 PSD,
Lower left: 0.1wt% Geltech 1.5 PSD
Top right: 0.05wt% Geltech 1.5 in LUDOX
Result shows both oversize particle detection & very good accuracy for both components.

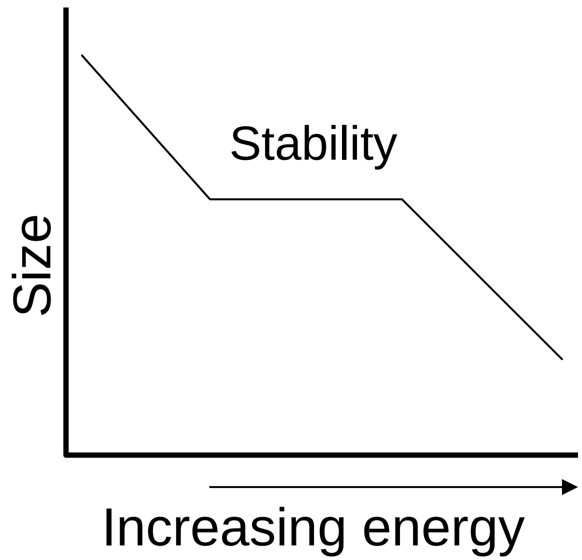
*See AN179 CMP SLURRY MEASUREMENT USING LASER DIFFRACTION

Method Development: Dry

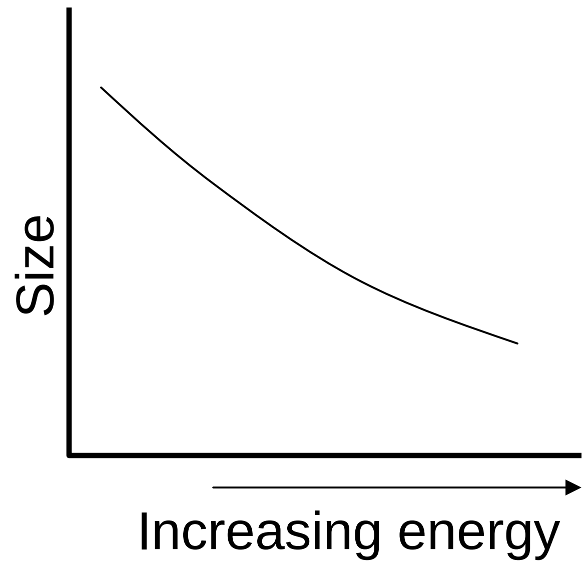
- First get sampling right & determine RI
- Measure at 3 different pressures (low, medium, high)
- Determine optimum pressure based on good dispersion while not breaking particles
- Can also compare dry vs. wet measurements
- Adjust other settings to optimize sample concentration & duration
- Ideally measure all of powder placed into the sampler
  - Segregation can occur on vibrating tray
  - Constant mass flow rate important for stable concentration during measurement
- Once settings chosen, test reproducibility

Size vs. Energy - theoretical vs. actual

Theoretical



Actual



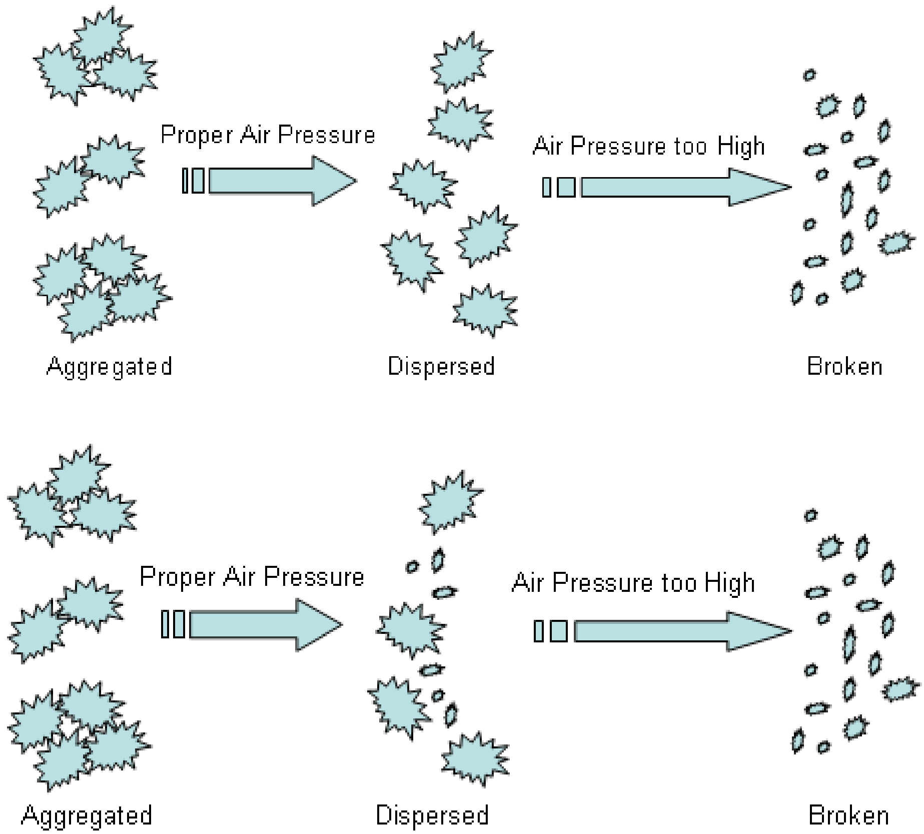
Higher air pressure or longer ultrasound duration

Why is this so?

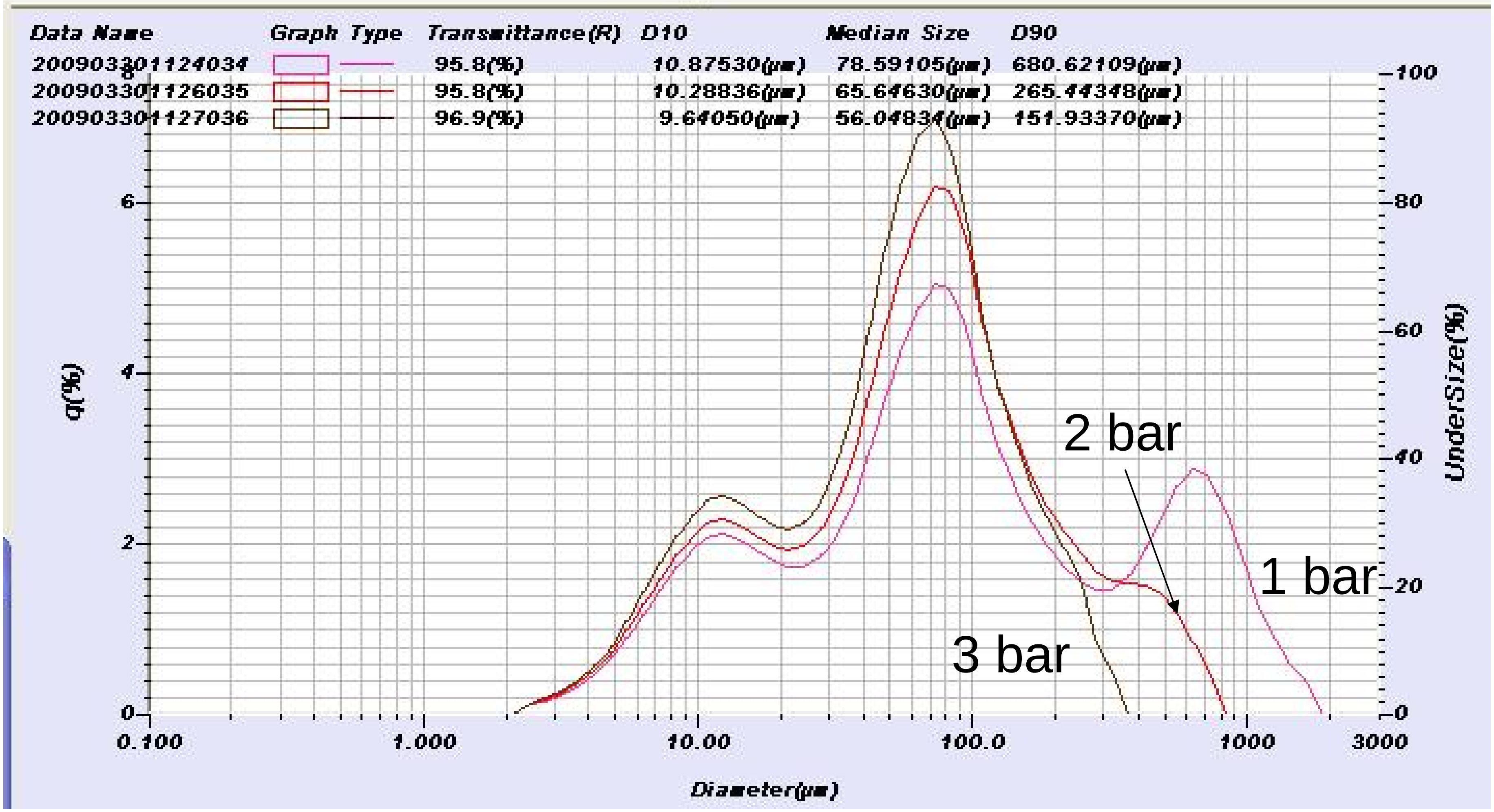
- Dispersion and milling can be parallel rather than sequential processes

Theoretical

Actual



Pressure Titration



Explore the future

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Dry Method Development
Case Studies

Magnesium Stearate

Microcrystalline Cellulose

Explore the future

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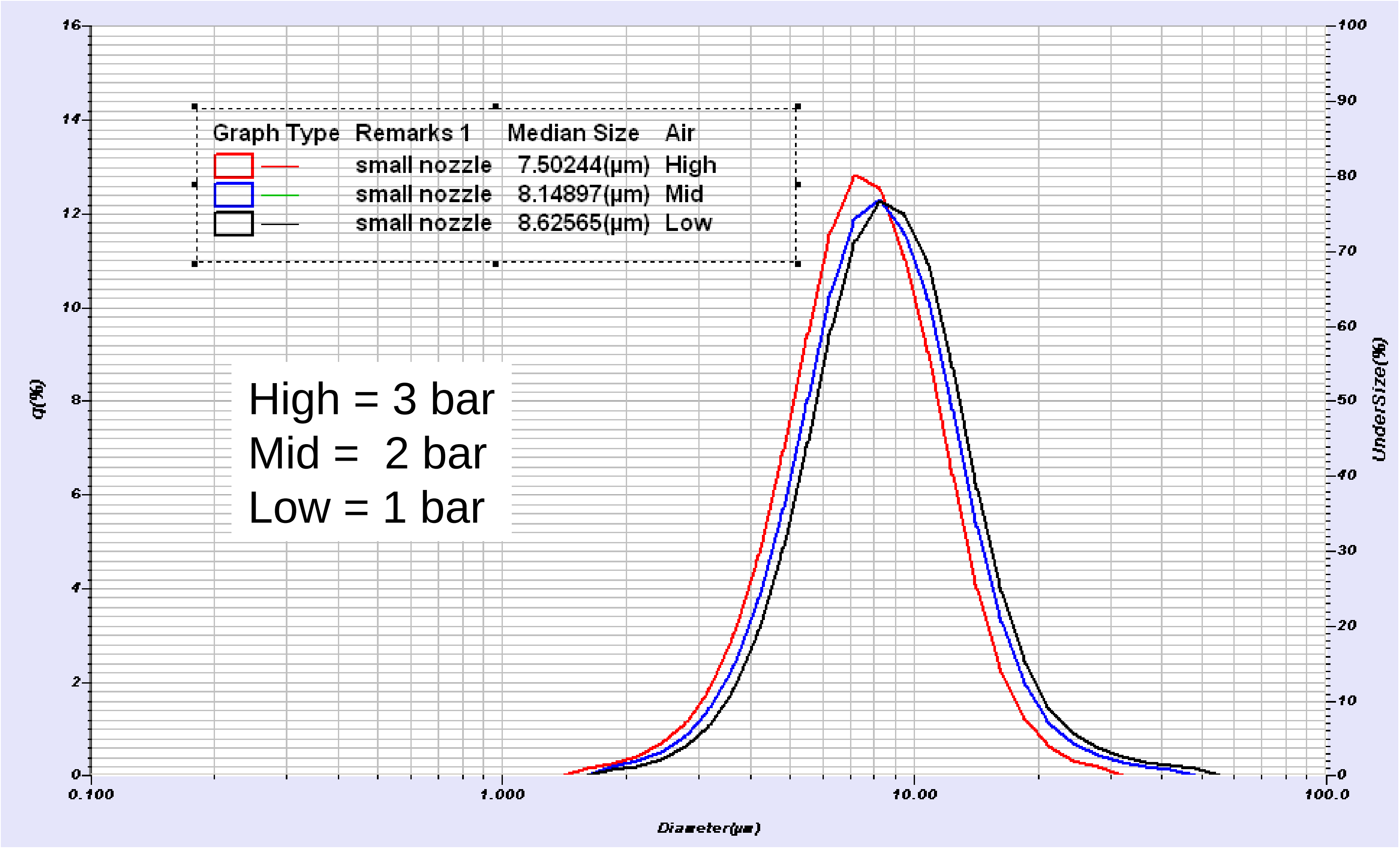
Effect of Air Pressure – Mg Stearate



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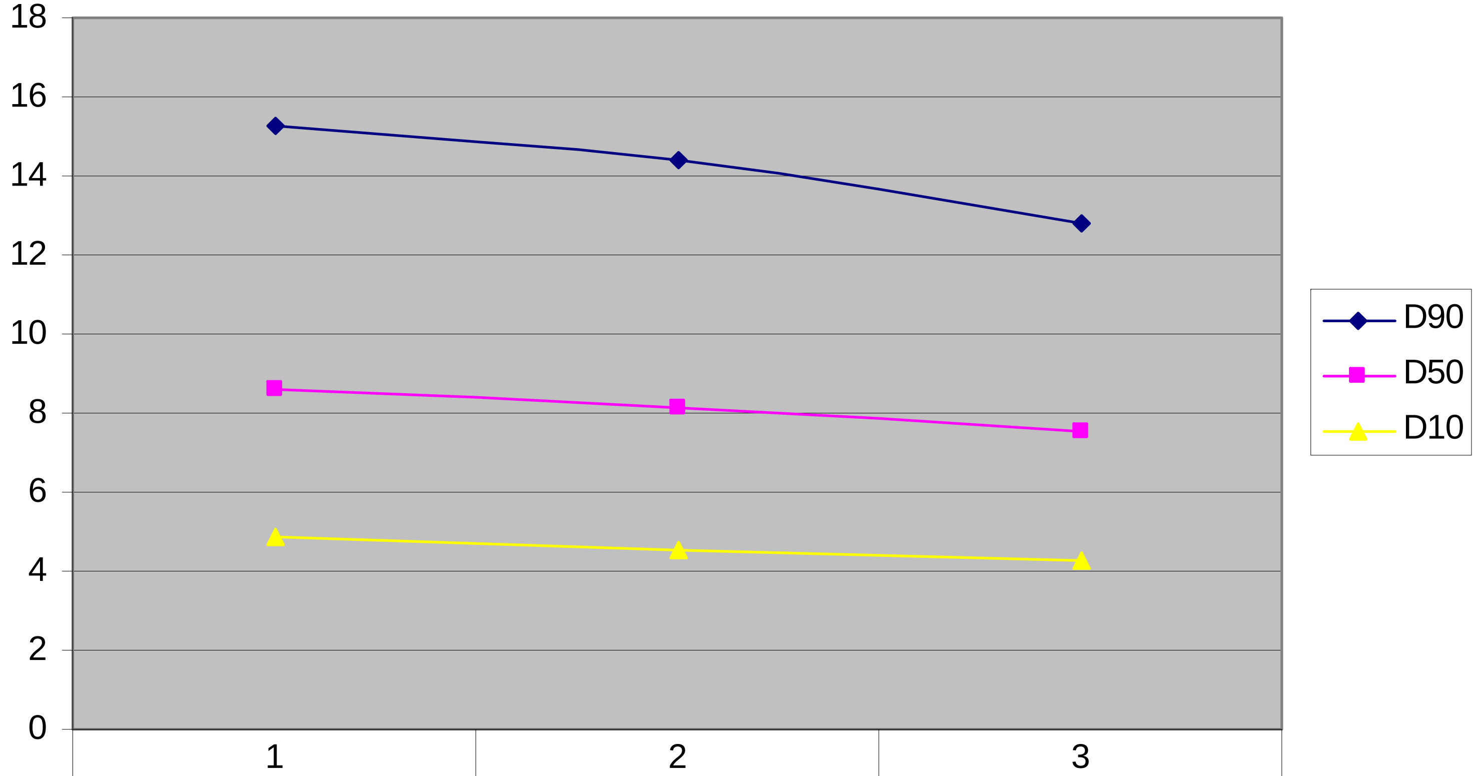
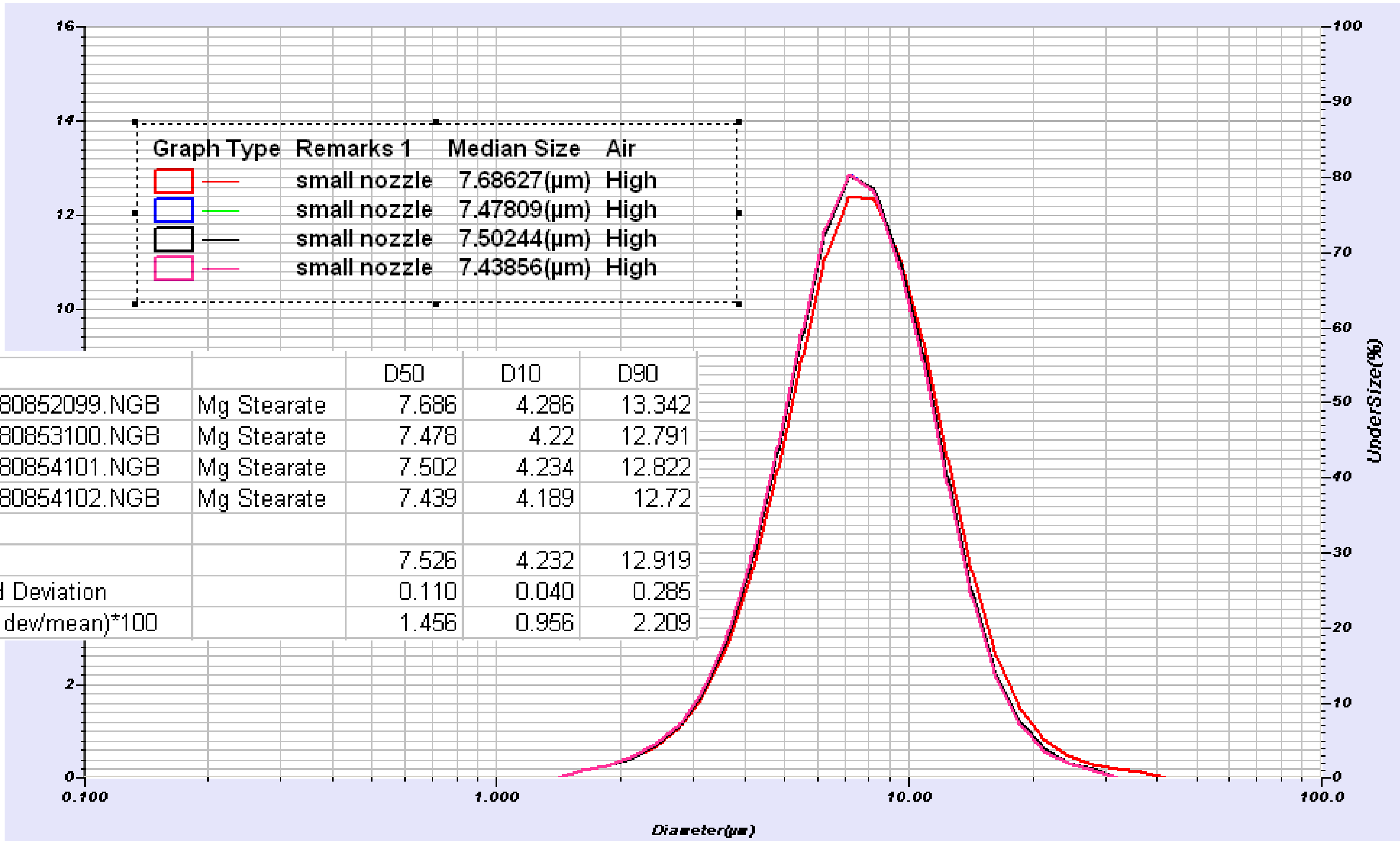
Effect of Air Pressure – Mg Stearate



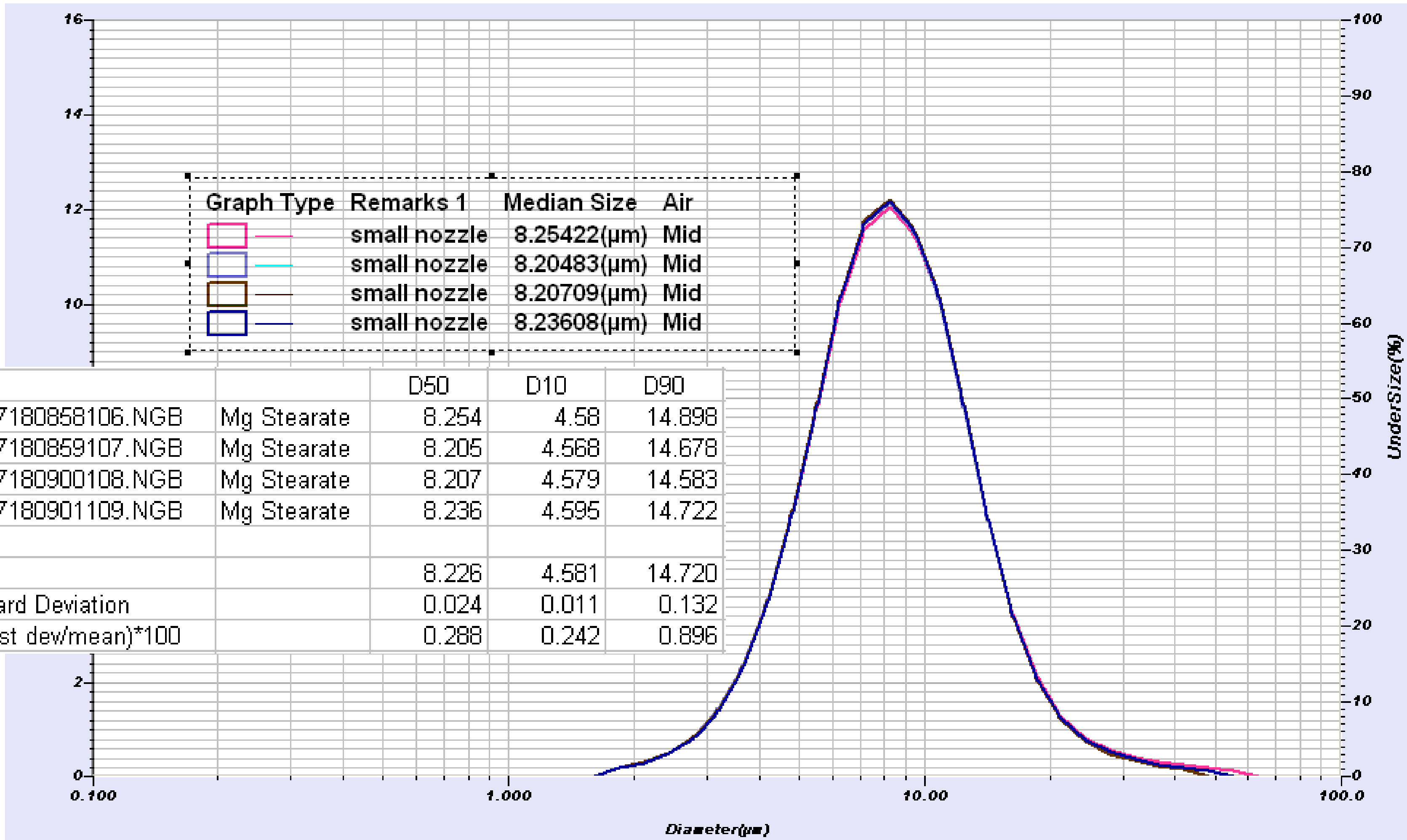
	1	2	3
D90	15.258	14.394	12.822
D50	8.626	8.149	7.502
D10	4.862	4.564	4.234

Reproducibility – Mg Stearate dry, 3 bar



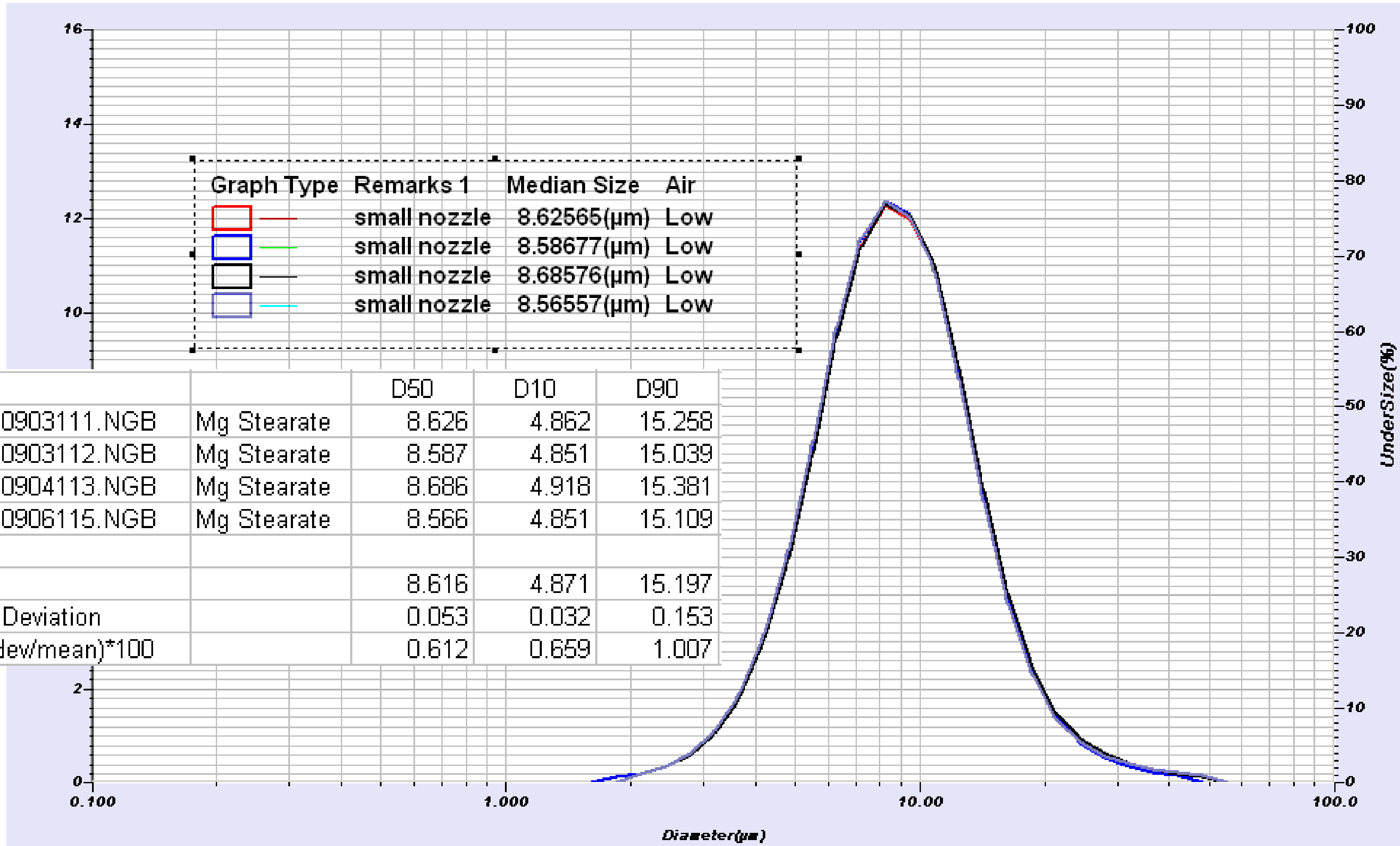
		D50	D10	D90
200707180852099.NGB	Mg Stearate	7.686	4.286	13.342
200707180853100.NGB	Mg Stearate	7.478	4.22	12.791
200707180854101.NGB	Mg Stearate	7.502	4.234	12.822
200707180854102.NGB	Mg Stearate	7.439	4.189	12.72
Mean		7.526	4.232	12.919
Standard Deviation		0.110	0.040	0.285
COV (st dev/mean)*100		1.456	0.956	2.209

Reproducibility – Mg Stearate dry, 2 bar



		D50	D10	D90
200707180858106.NGB	Mg Stearate	8.254	4.58	14.898
200707180859107.NGB	Mg Stearate	8.205	4.568	14.678
200707180900108.NGB	Mg Stearate	8.207	4.579	14.583
200707180901109.NGB	Mg Stearate	8.236	4.595	14.722
Mean		8.226	4.581	14.720
Standard Deviation		0.024	0.011	0.132
COV (st dev/mean)*100		0.288	0.242	0.896

Reproducibility – Mg Stearate dry, 1 bar



		D50	D10	D90
200707180903111.NGB	Mg Stearate	8.626	4.862	15.258
200707180903112.NGB	Mg Stearate	8.587	4.851	15.039
200707180904113.NGB	Mg Stearate	8.686	4.918	15.381
200707180906115.NGB	Mg Stearate	8.566	4.851	15.109
Mean		8.616	4.871	15.197
Standard Deviation		0.053	0.032	0.153
COV (st dev/mean)*100		0.612	0.659	1.007

Explore the future

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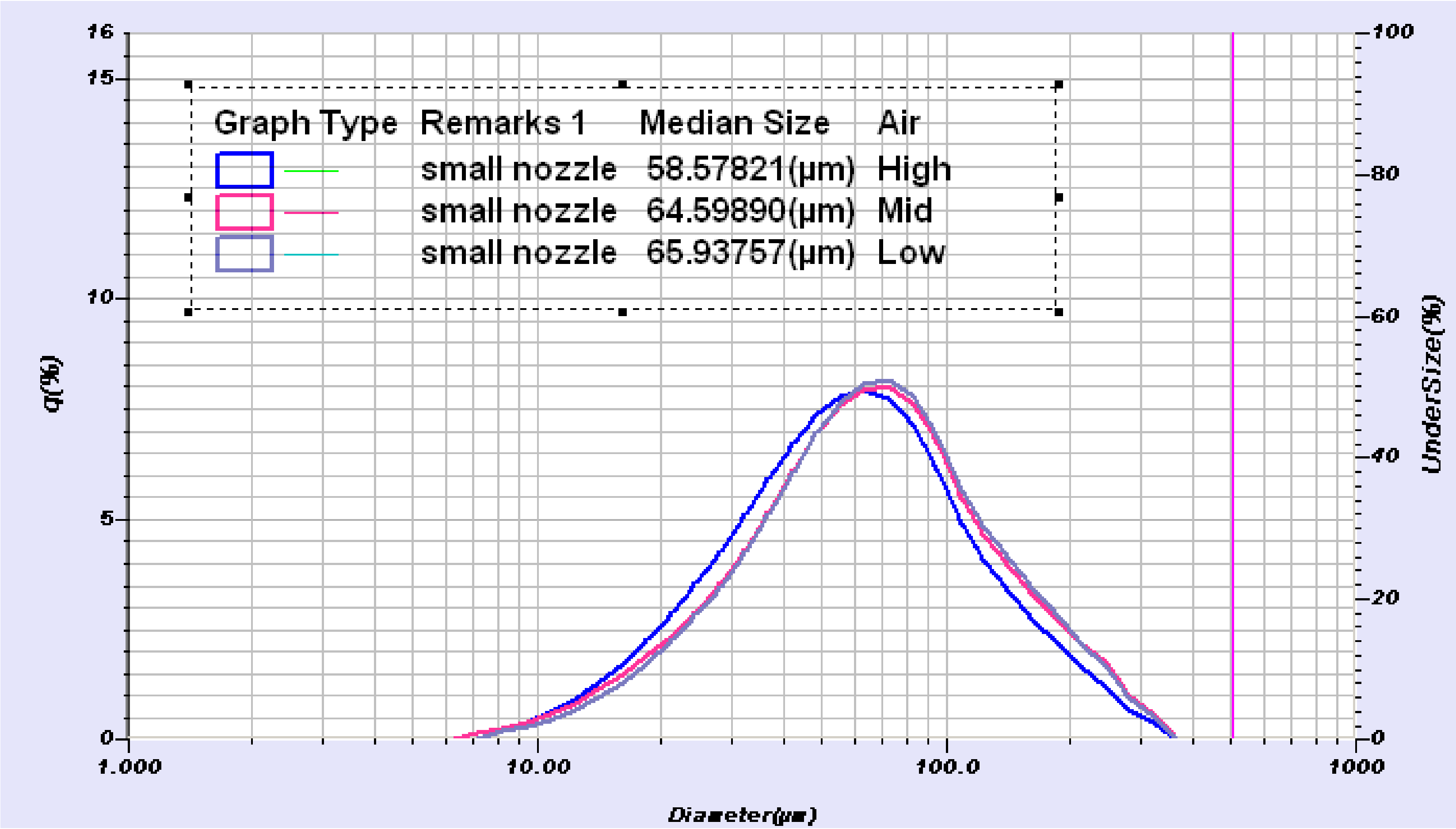
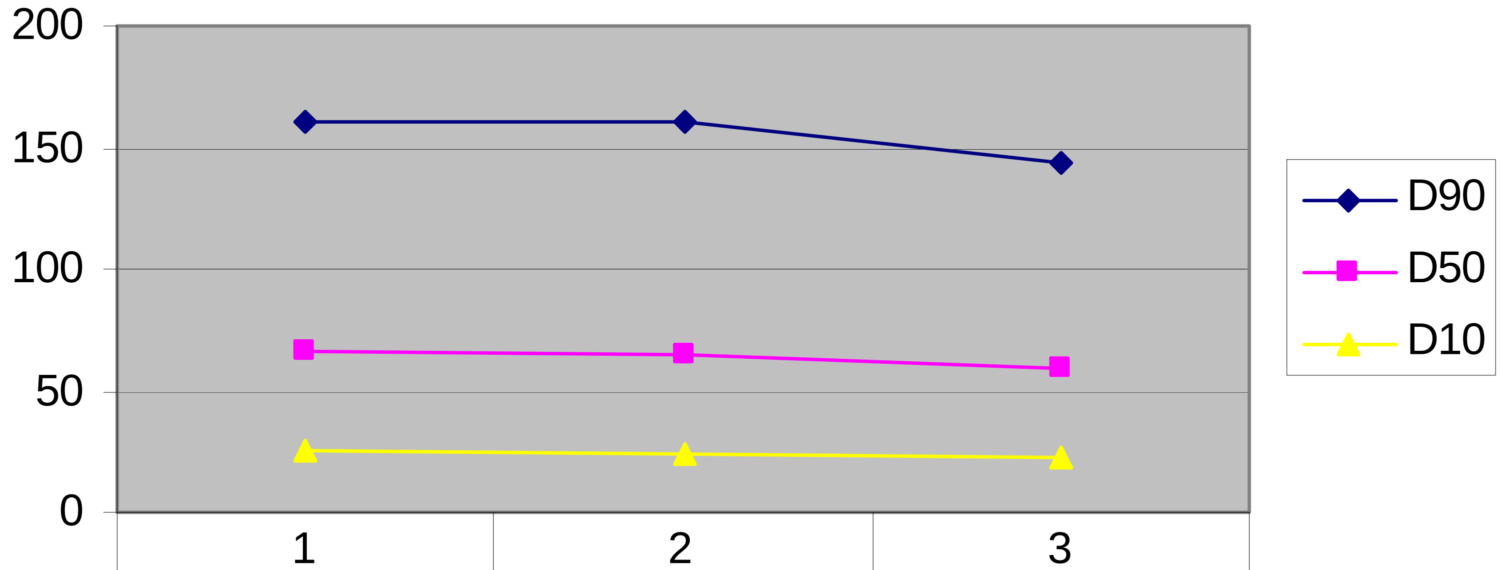
Effect of Air Pressure - MCC

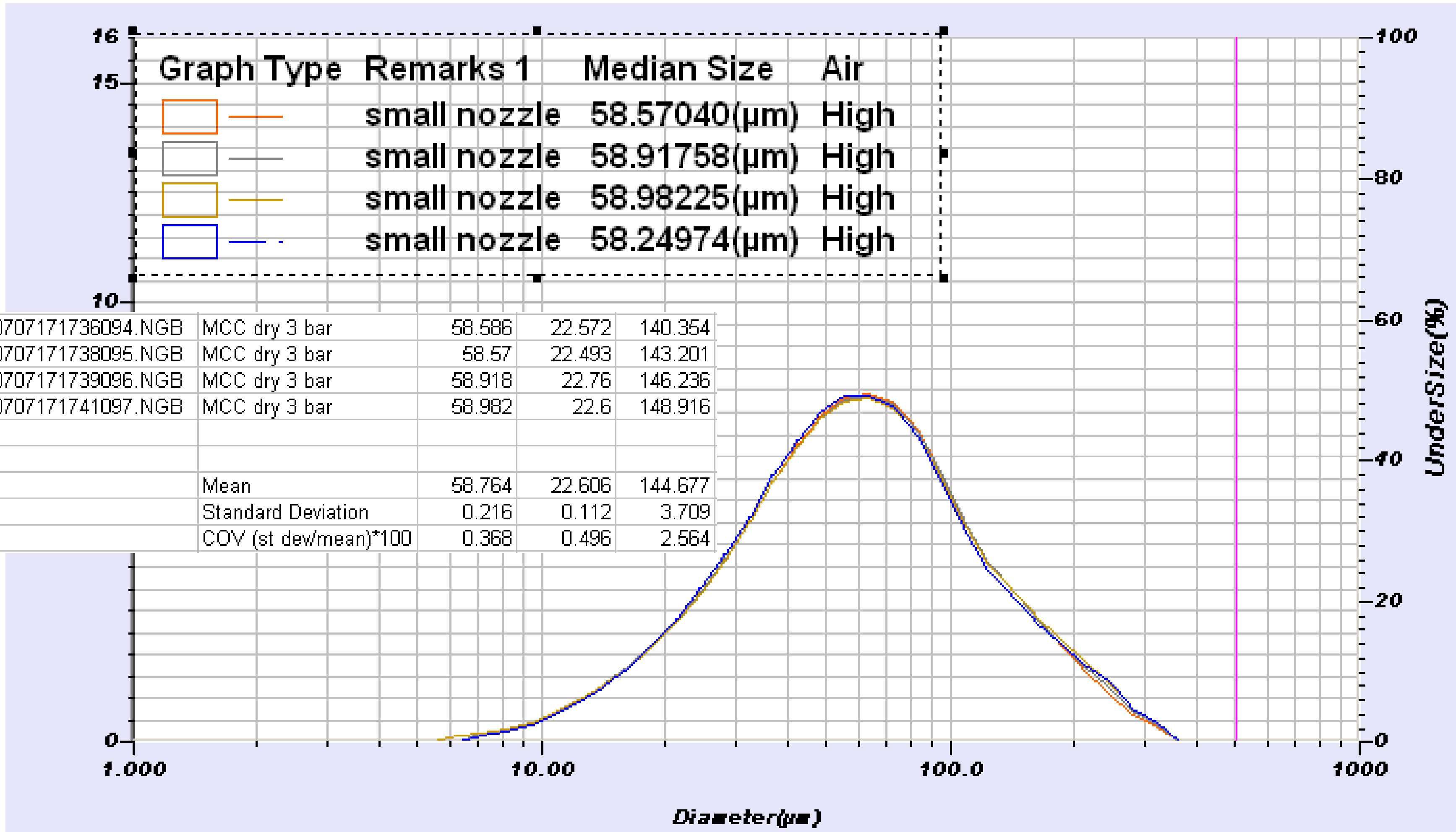


Effect of Air Pressure - MCC



	1	2	3
D90	161.158	160.713	144.259
D50	65.938	64.599	58.578
D10	25.76	24.308	22.655

Reproducibility – MCC dry, 3 bar

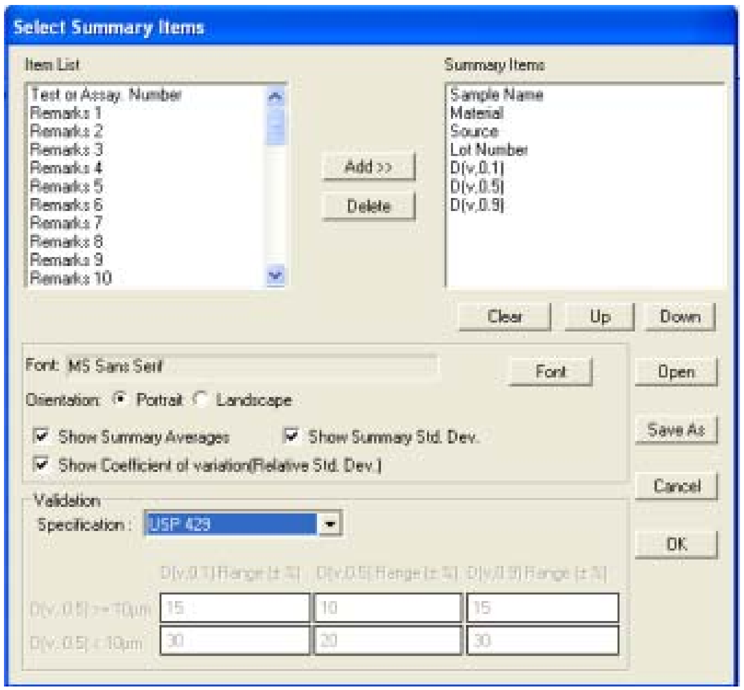


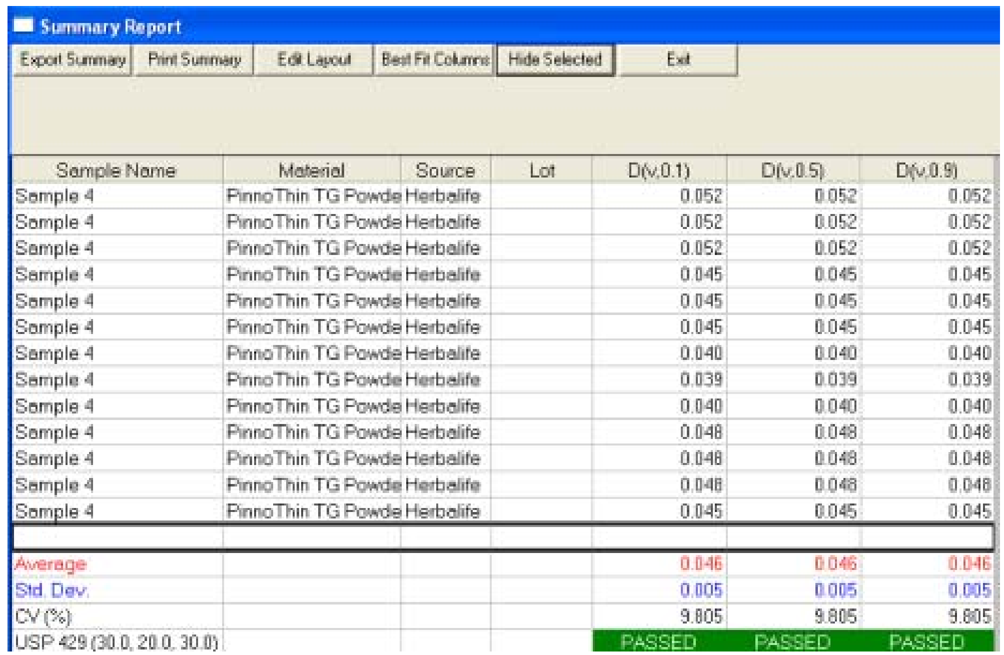
200707171736094.NGB	MCC dry 3 bar	58.586	22.572	140.354
200707171738095.NGB	MCC dry 3 bar	58.57	22.493	143.201
200707171739096.NGB	MCC dry 3 bar	58.918	22.76	146.236
200707171741097.NGB	MCC dry 3 bar	58.982	22.6	148.916
	Mean	58.764	22.606	144.677
	Standard Deviation	0.216	0.112	3.709
	COV (st dev/mean)*100	0.368	0.496	2.564

Explore the future

Calculation Automation

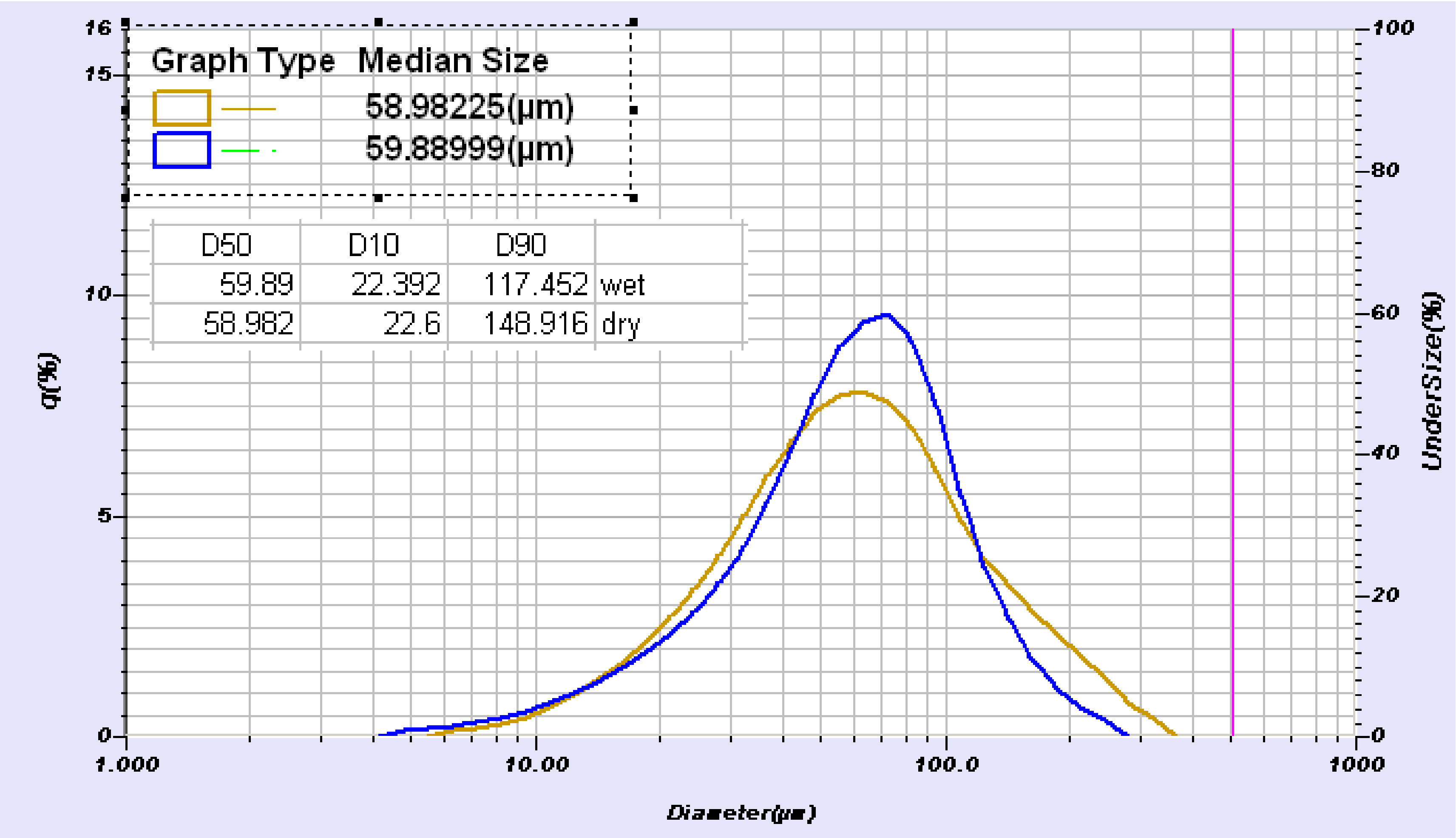
From LA-950 Software





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

MCC Wet vs. Dry

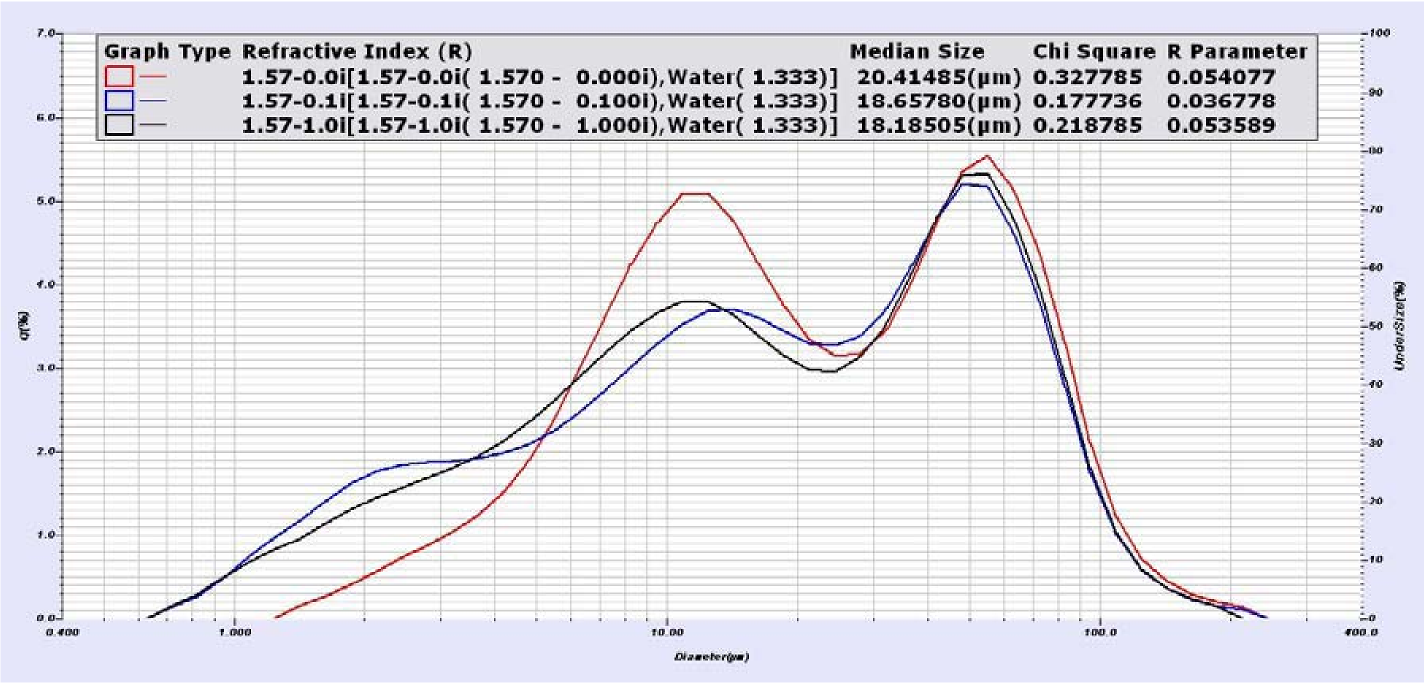


Method Development -Wet

- First determine RI
- Choose solvent (water, surfactants, hexane, etc.)
- Sampler selection: sample volume
- Pump & stirrer settings
- Concentration
- Measurement duration
- Does the sample need ultrasound?
  - Document size-time plot
  - Disperse sample, but don't break particles
  - Check for reproducibility

Determine RI

- Real component via literature or web search, Becke line, etc.
- Measure sample, vary imaginary component to see if/how results change
- Recalculate using different imaginary components, choose value that minimizes R parameter error calculation

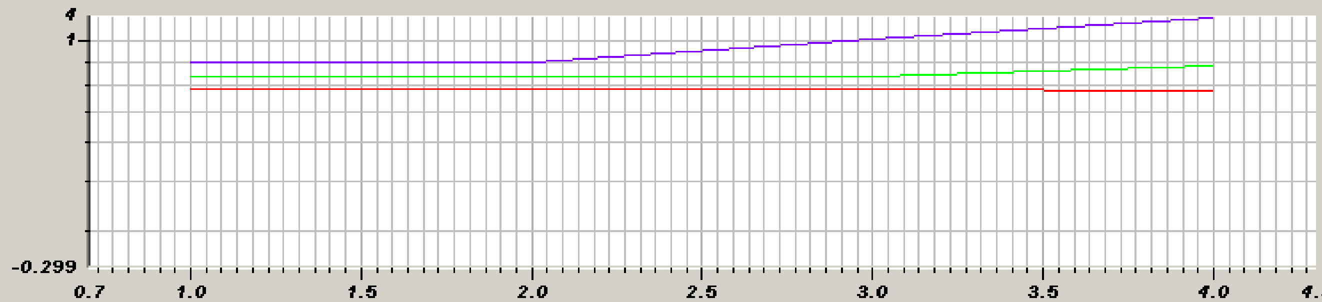


RI Software Automation

Calculation Optimization

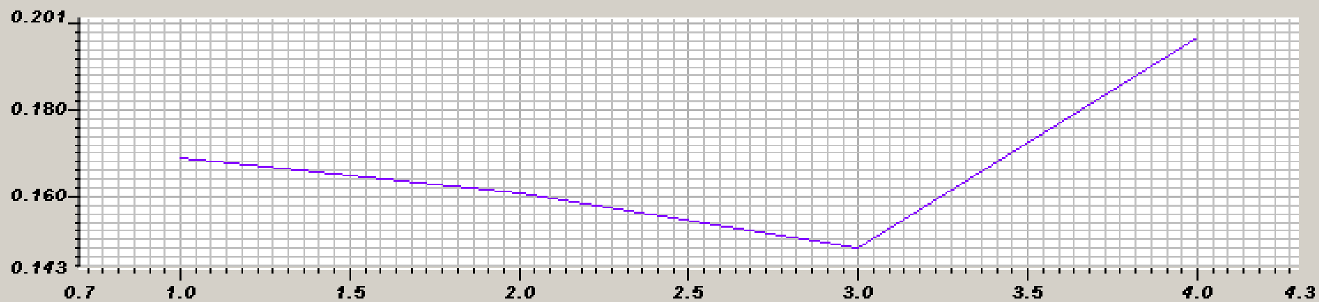
Imaginary Refractive Index Wizard -Result-

Graph Summary | Distributions | D90,D50,D10 | R Value



	Imaginary_RI- 1.48- 0.00i	Imaginary_RI- 1.48- 0.01i	Imaginary_RI- 1.48- 0.10i	Imaginary_RI- 1.48- 1.00i
D90	0.389097	0.400848	1.28502	3.95191
D50	0.187871	0.187613	0.183241	0.325576
D10	0.101424	0.100706	0.0938086	0.0878223

Graph Summary | Distributions | D90,D50,D10 | R Value



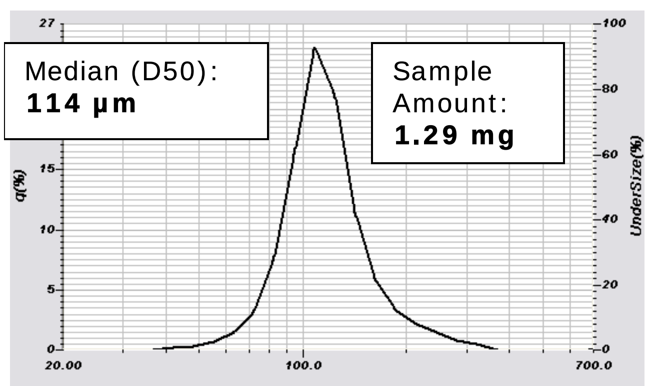
	Imaginary_RI- 1.48- 0.00i	Imaginary_RI- 1.48- 0.01i	Imaginary_RI- 1.48- 0.10i	Imaginary_RI- 1.48- 1.00i
R P	0.168491	0.160476	0.14784	0.196245

Sampler Selection

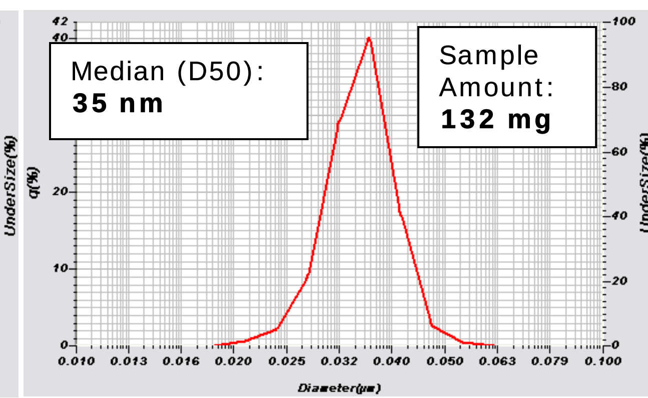
- Larger, broad distributions require larger sample volume
- Lower volume samplers for precious materials or solvents

LA-950 Sample Handlers	Dispersing Volume (mL)
Aqua/SolvoFlow	**180 - 330**
MiniFlow	**35 - 50**
Fraction Cell	**15**
Small Volume Fraction Cell	**10**

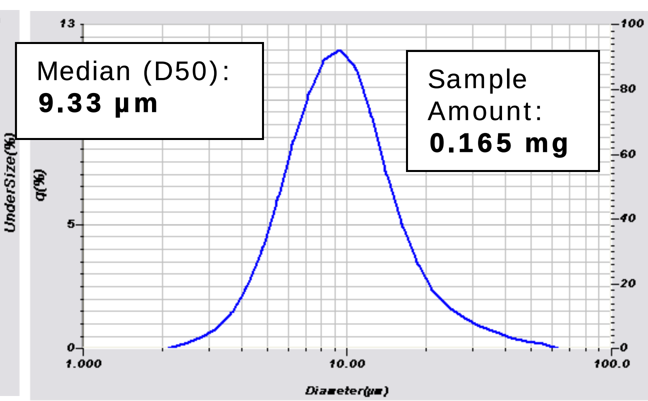
Note: Fraction cell has only magnetic stir bar, not for large or heavy particles



Bio polymer



Colloidal silica

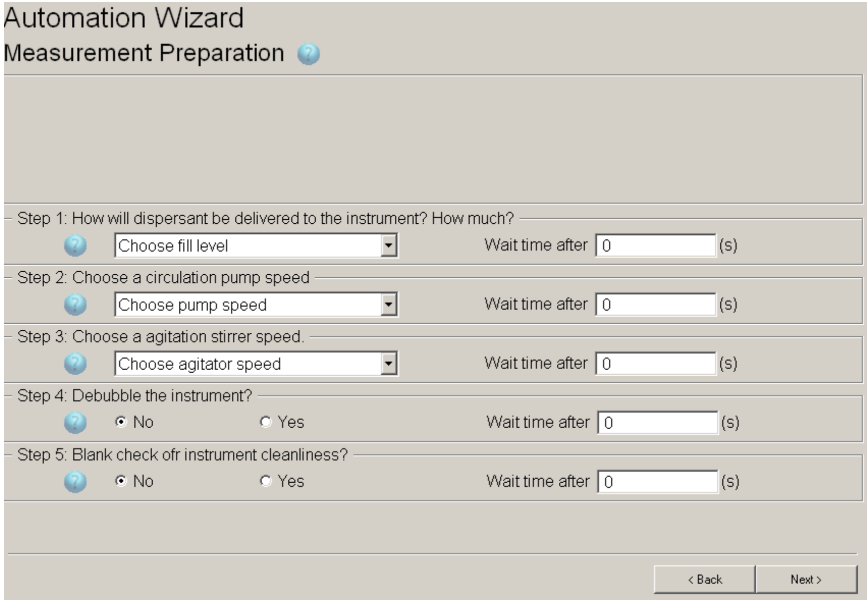


Magnesium stearate

Pump & Stirrer Settings

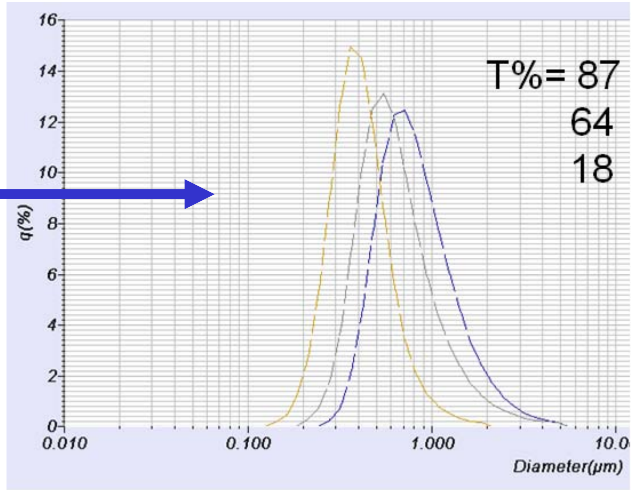
- Must be high enough to suspend & circulate heavy particles
- Not so high that bubbles are introduced
- Adding energy – can disperse loose agglomerates
- Measure at several settings & select optimum
- Can be automated in software (see right)

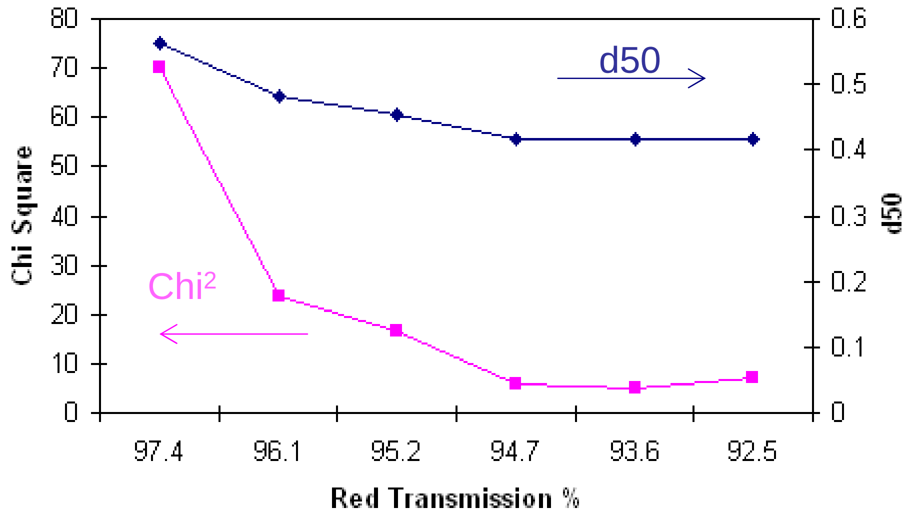
Exp #	Agitation	Circulation	D_{mean} (nm)	D_{10} (nm)	D_{90} (nm)
1	1	1	187.03	137.5	245.7
2	1	3	184.23	135.9	242.1
3	3	1	187.28	137.8	245.8
4	3	3	184.61	136.1	242.5
5	1	1	185.32	136.3	243.7
6	1	3	184.04	135.8	241.8
7	3	1	184.13	135.8	241.9
8	3	3	184.98	136.4	242.9
Parameters Selected: Agitation: 2 Circulation: 2					

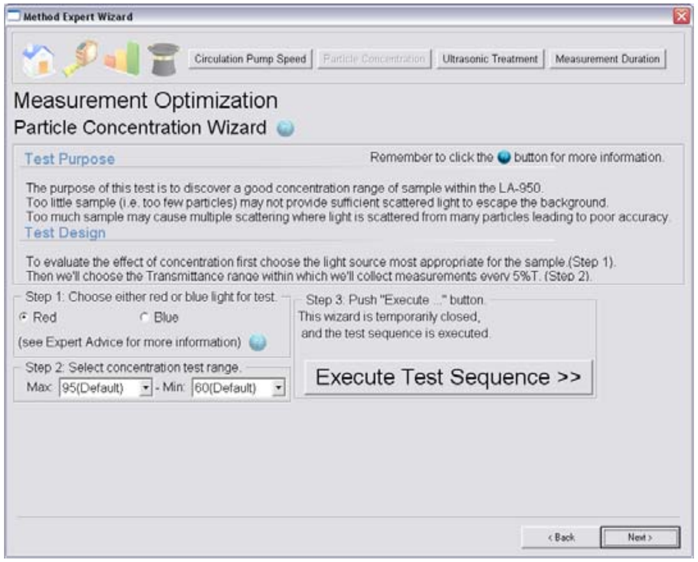


Concentration

- High enough for good S/N ratio
- Low enough to avoid multiple scattering
- Typically 95 – 80 %T
- Measure at different T%, look at Chi Square calculation

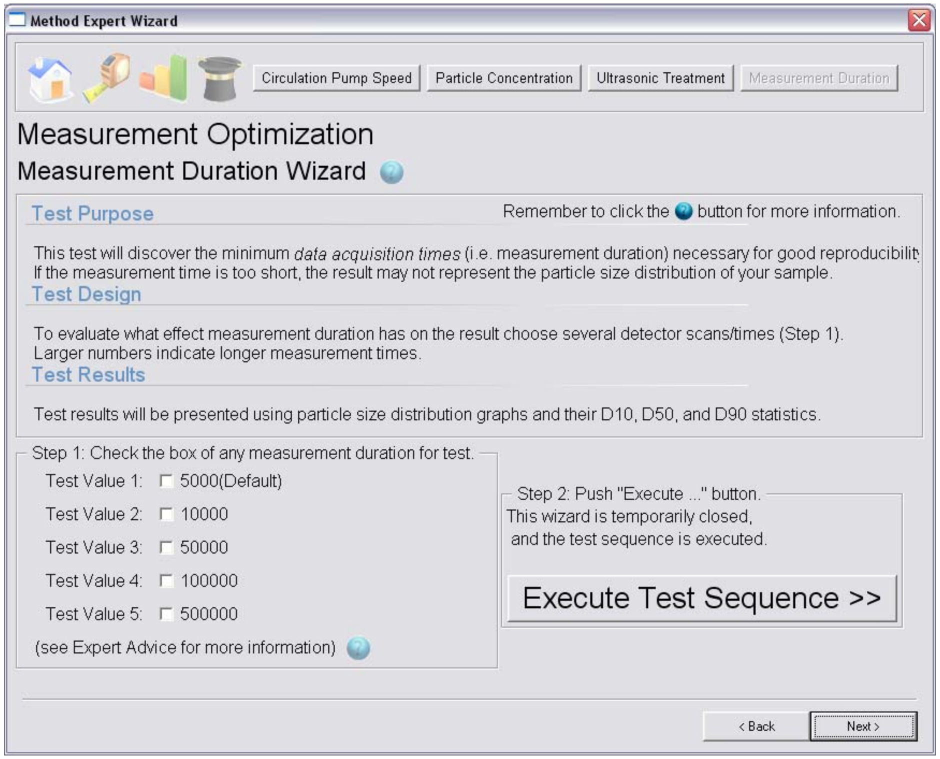






Measurement Duration

- Long enough for reproducibility
- Typically 5 sec, up to several minutes
- Longer time for large, broad distributions
- Can be automated in software
- Could be used for robustness testing during method validation

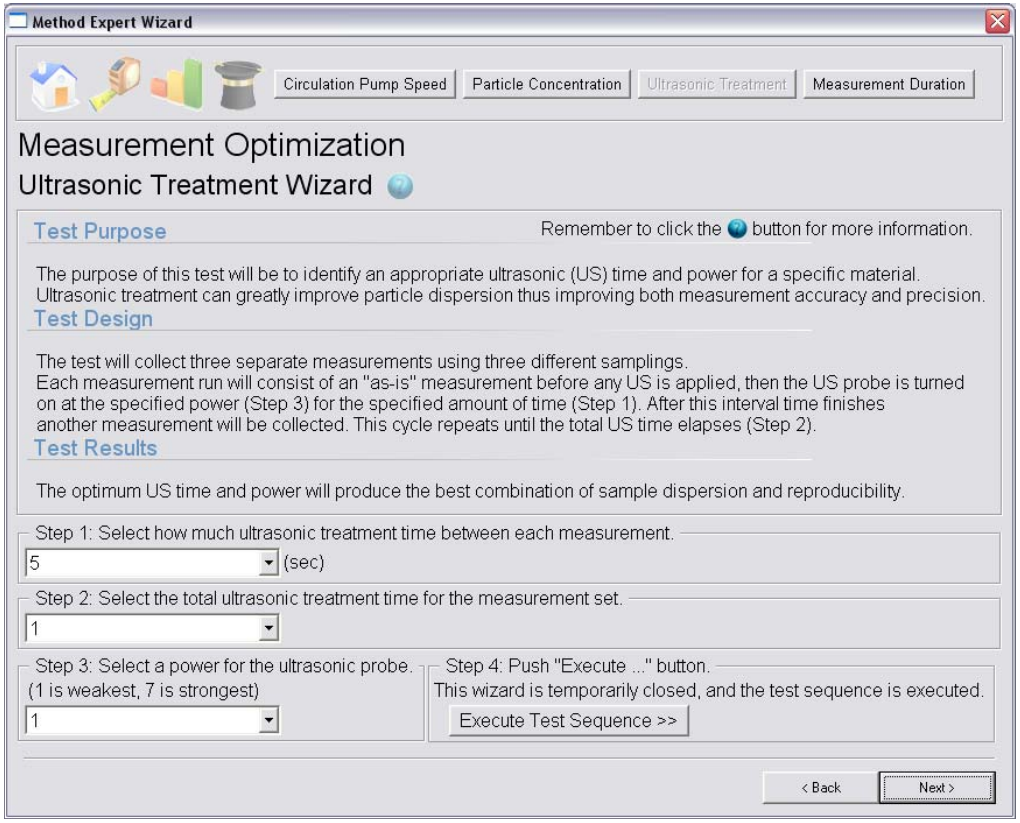


Ultrasound

- Adding energy to break up agglomerates – disperse to primary particles, without breaking particles
- Similar to changing air pressure on dry powder feeder
- Typically set to 100% energy, vary time (sec) on
- Investigate tails of distribution
  - High end to see if agglomerates removed
  - Small end to see if new, smaller particles appear (breakage)
- Test reproducibility, consider robustness
- Note:
  - Do not use on emulsions
  - Can cause thermal mixing trouble w/solvents - wait
  - Use external probe if t> 2-5 minutes

Software Automation

- Level (power)
- Time on
- Iterations
- Delay
- Generate result graphs



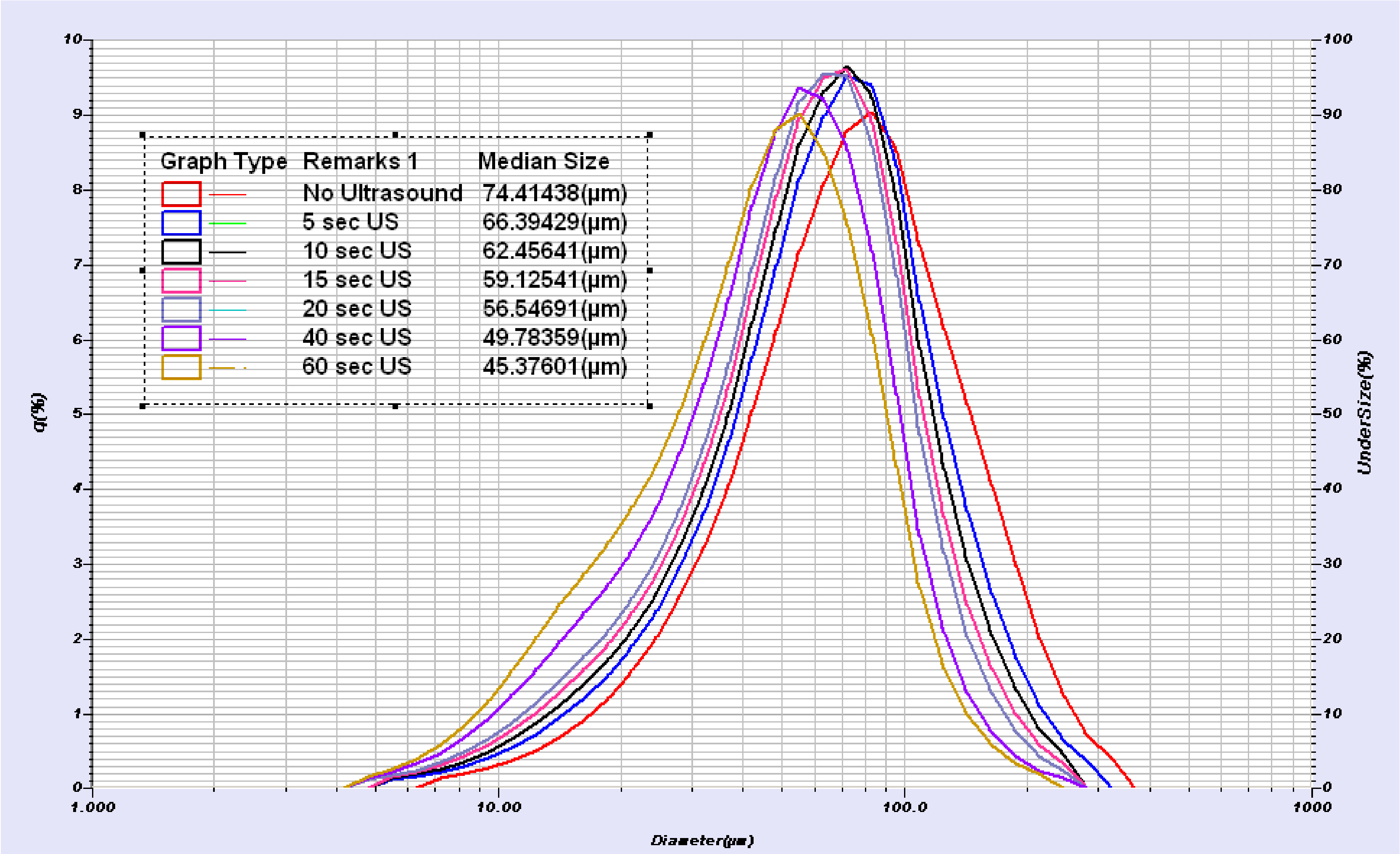
Wet Method Development
Case Study

Microcrystalline Cellulose

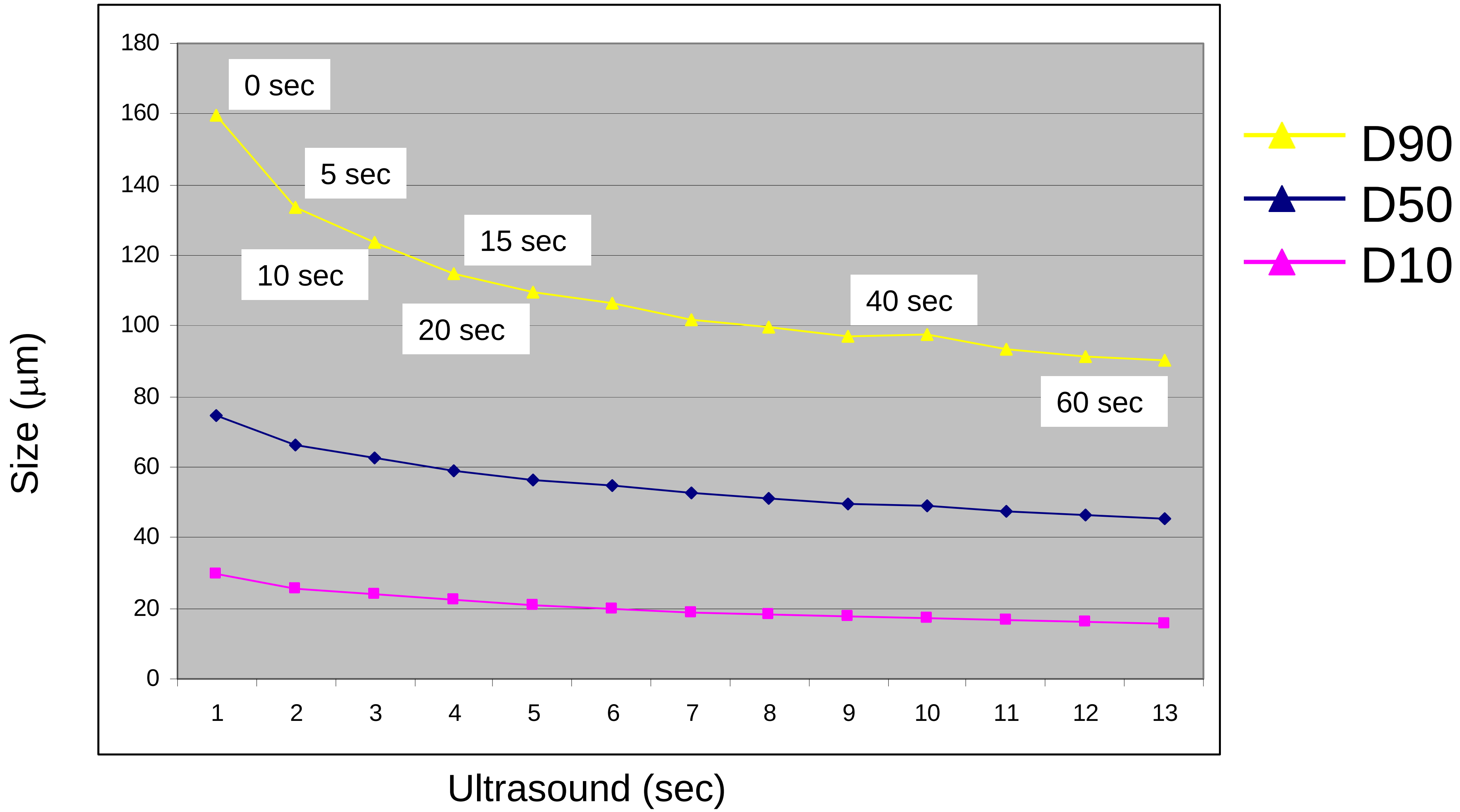
Explore the future

HORIBA

Effect of Ultrasound - MCC



Effect of Ultrasound - MCC



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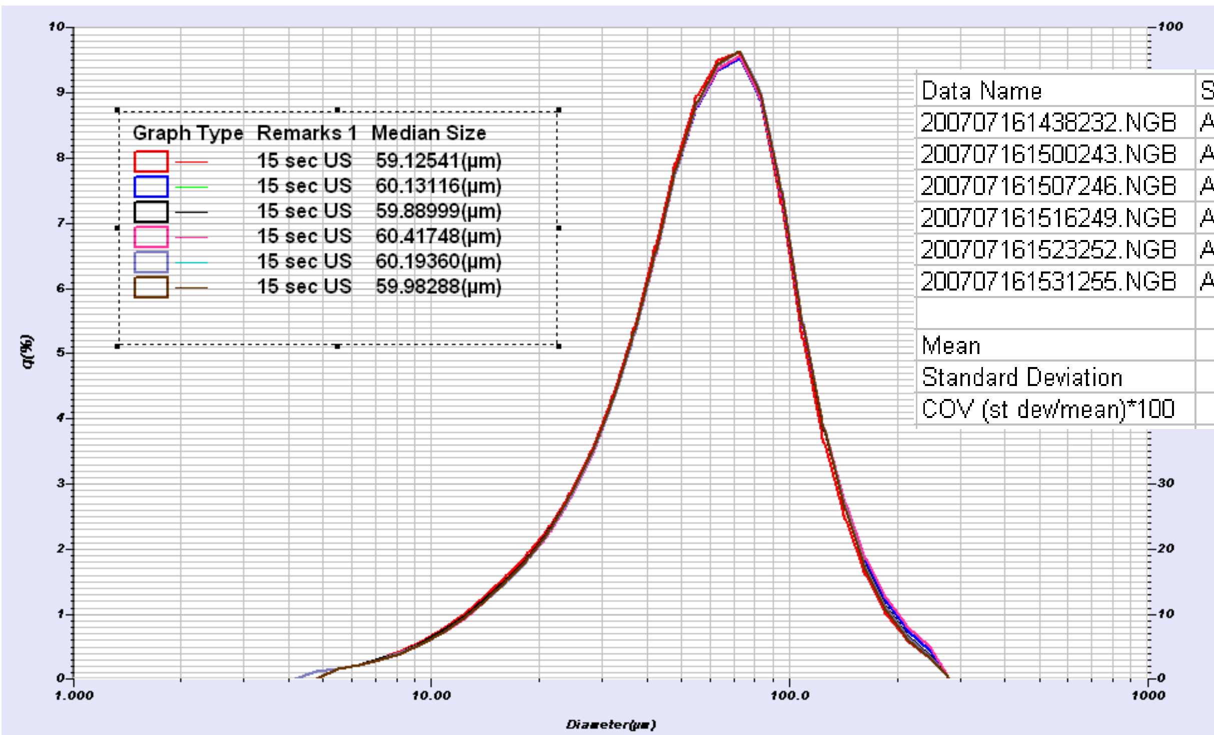
Reproducibility – MCC wet

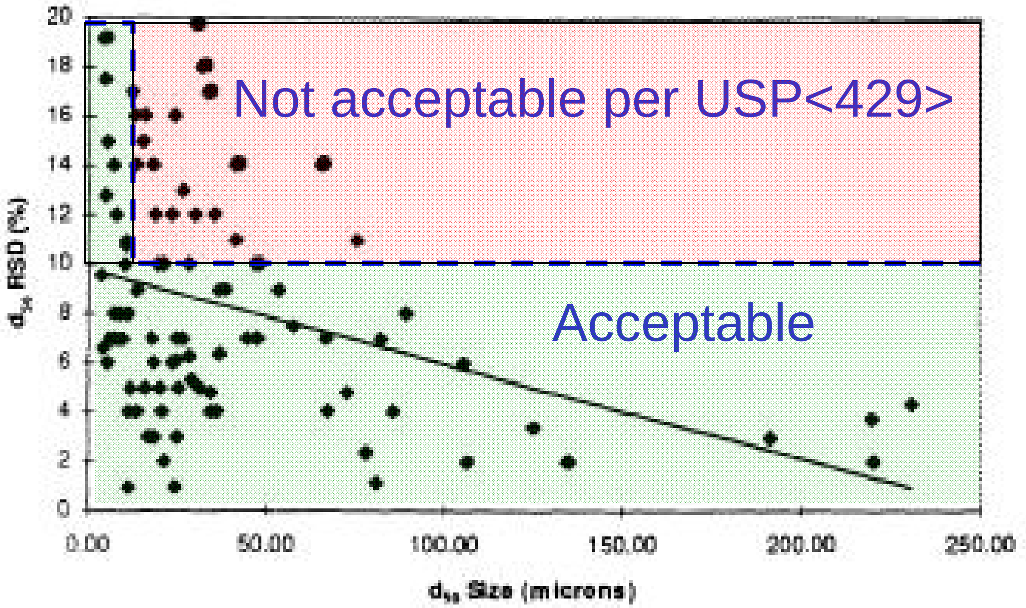
- ISO13320
  - – COV < 3% at median d_{50}
  - – COV < 5% at d_{10} & d_{90}
- USP<429>
  - – COV < 10% at median d_{50}
  - – COV < 15% at d_{10} & d_{90}



Data Name	Sample Name	D50	D10	D90	Comments
200707161438232.NGB	Avicel PH-101	59.125	22.221	114.93	15 sec US
200707161500243.NGB	Avicel PH-101	60.131	22.662	119.116	15 sec US
200707161507246.NGB	Avicel PH-101	59.89	22.392	117.452	15 sec US
200707161516249.NGB	Avicel PH-101	60.417	22.955	119.974	15 sec US
200707161523252.NGB	Avicel PH-101	60.194	22.765	117.289	15 sec US
200707161531255.NGB	Avicel PH-101	59.983	22.829	116.586	15 sec US
Mean		59.95667	22.63733	117.5578	
Standard Deviation		0.446191	0.278596	1.799955	
COV (st dev/mean)*100		0.74419	1.230691	1.531123	

Reproducibility*

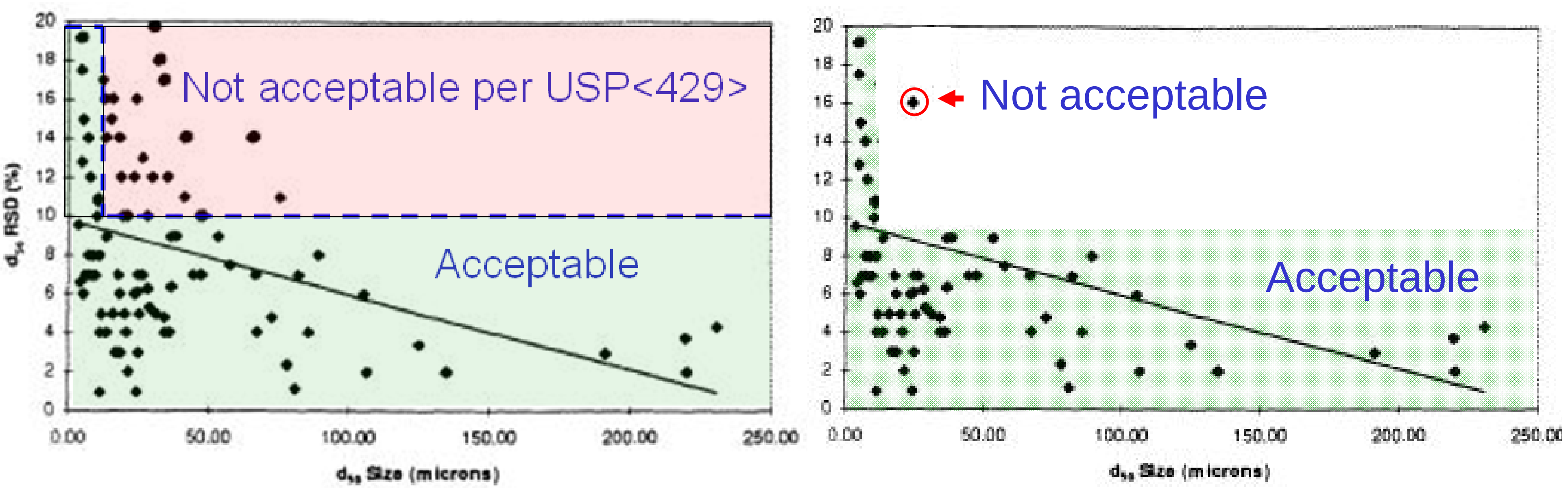
- 58 methods
- Image analysis for morphology
- Laser diffraction for PSD
- If RSD for d50 < 20%, then acceptable for QC environment
- Note: RSD increases with decreasing size



*Barber, Keuter, and Kravig, A Logical Stepwise Approach to Laser Diffraction Particle Size Distribution Analysis Methods Development and Validation Pharmaceutical Development and Technology, 3(2), 153-161 (1998)

Sampler Selection

Remove points from not acceptable region using Fraction Cell



*Barber, Keuter, and Kravig, A Logical Stepwise Approach to Laser Diffraction Particle Size Distribution Analysis Methods Development and Validation Pharmaceutical Development and Technology, 3(2), 153-161 (1998)

Conclusions

- Must have representative sample
- Powders: select air pressure
- Suspensions: wet, disperse
- Check accuracy w/microscope
- Investigate system settings: concentration, agitation, ultrasound
- Design for maximum precision
- Follow guidelines in standards

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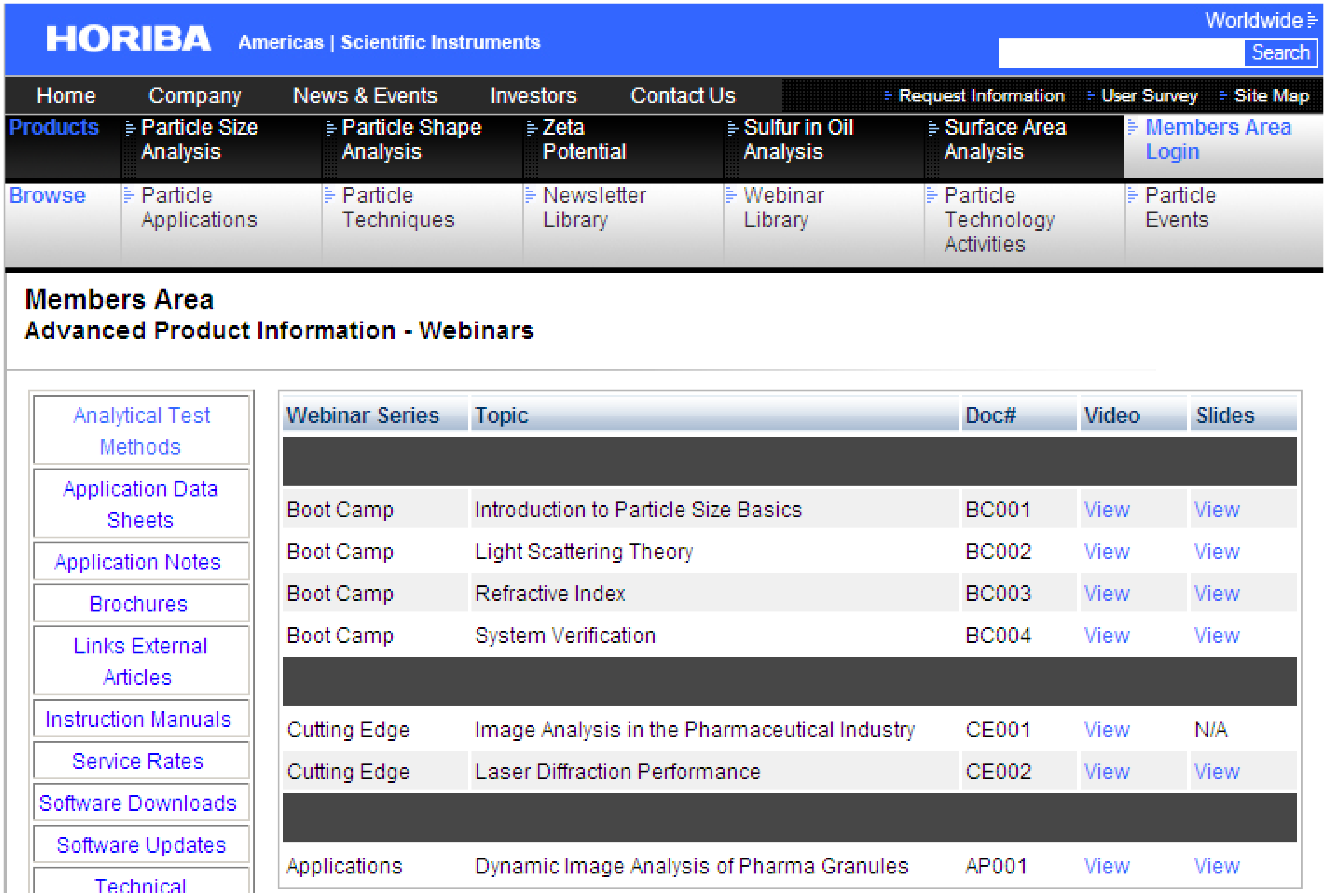

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Boot Camp	System Verification	BC004	View	View
Cutting Edge	Image Analysis in the Pharmaceutical Industry	CE001	View	N/A
Cutting Edge	Laser Diffraction Performance	CE002	View	View
Applications	Dynamic Image Analysis of Pharma Granules	AP001	View	View

Thank-you