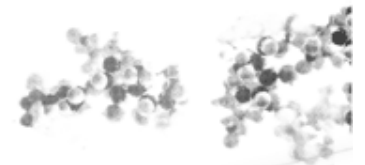
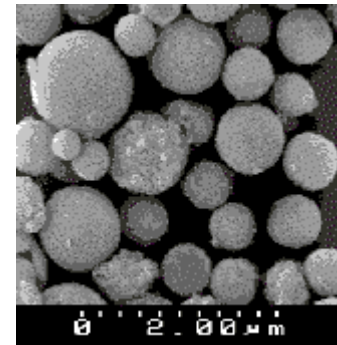
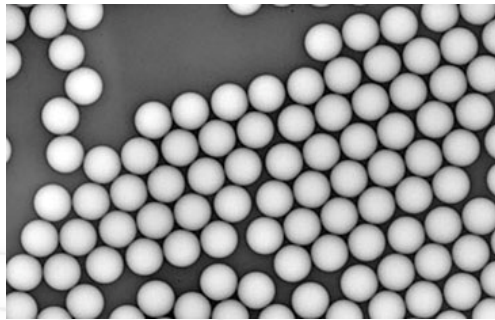




Laser Diffraction System Verification

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Explore the future

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HORIBA

Calibration vs. Verification

- Calibration : enter standard sample(s), adjust instrument response to show expected result
 - Example: particle counters
- Verification: enter standard sample(s), observe if response within accepted range
 - Example: DLS, laser diffraction
- From ISO 13320, 6.5.1 Calibration: “Laser diffraction systems are based on first principles, though with idealized properties of the particles. Thus, calibration in the strict sense is not required. However, it is still necessary and desirable to confirm the correct operation of the instrument by a validation procedure.”

Verification

- From ISO 13320: “Primary validation can be made with any certified or standard reference material, acceptable to the practice of the end-users' industries.”
- “Certified or standard reference materials consisting of a known distribution having a range of spherical particles over one decade of size are preferred.”
- Note:
 1. This implies using a polydisperse standard
 2. Most people still using monodisperse standards
 3. Most polydisperse standards are not over one decade of size

Monodisperse Standards

- Very narrow distribution
- Only tests central point
 - Not d10, d90
- Available in sizes 20 nm – 1000 μm
- Mostly suspensions
- Easy to use
- Relatively inexpensive
- Verifies optics only
- 1 μm particles will stay in suspension even if sampler pump broken



www.thermo.com

1690	Polystyrene Spheres (1 μm)
1691	Polystyrene Spheres (0.3 μm)
1692	Polystyrene Spheres (3 μm)
1961	Polystyrene Spheres (30 μm)
1963a	Polystyrene Spheres (0.1 μm)
1964	Polystyrene Spheres (0.06 μm)
1965	Polystyrene Spheres (10 μm) (on slide)

www.nist.gov



www.polysciences.com

Monodisperse Standards

- No official pass/fail criteria
- So make your own
- HORIBA IQ/OQ:
 - 0.1, 1.0, 12, 100 μm
 - Mean +/- 5% from certified value
- Why measure so many sizes?
 - Two should cover all detectors
 - Larger sizes cost more
- Which sizes?
 - No one says measure near actual sample size

20 nm
30 nm
40 nm
50 nm
60 nm
70 nm
80 nm
90 nm
100 nm
125 nm
150 nm
200 nm
220 nm
240 nm
270 nm
300 nm
350 nm
400 nm
450 nm
500 nm
500 nm
560 nm
600 nm
700 nm
800 nm
900 nm

Sizes available
from Thermo.
Still Duke
Scientific to me.

1.0 μm
1.0 μm
1.1 μm
1.3 μm
1.6 μm
1.8 μm
2.0 μm
2.5 μm
3.0 μm
4.0 μm
5.0 μm
6.0 μm
7.0 μm
8.0 μm
9.0 μm
10 μm
12 μm
15 μm
20 μm
25 μm
30 μm
40 μm
50 μm
60 μm
70 μm
80 μm
100 μm
115 μm
140 μm
160 μm
200 μm
240 μm
280 μm
300 μm
400 μm
500 μm
550 μm
650 μm
750 μm
1000 μm

Polysperse Standards

- Defined (certified) distribution
- Defined procedure and pass/fail criteria (ISO and USP)
- Can buy directly from NIST (or other sources)
- Tests entire instrument

SRM	Description	Particle Diameter Distribution (μm)
1003c	Glass Beads	20 to 45 (635 to 325 mesh)
1004b	Glass Beads	40 to 150 (270 to 120 mesh)
1017b	Glass Beads	100 to 400 (140 to 45 mesh)
1018b	Glass Beads	220 to 750 (60 to 25 mesh)
1019b	Glass Beads	750 to 2450 (20 to 10 mesh)

www.nist.gov

SRM	Description	Particle Diameter, nominal (nm)
8011	Gold Nanoparticles	10 nm
8012	Gold Nanoparticles	30 nm
8013	Gold Nanoparticles	60 nm

Not really polydisperse?

Polysperse Standards

- Now good range of sizes available
- Don't recommend 0.1-1 μm
 - Also testing ability to disperse particles
- Can buy in proper quantities for given samplers
 - No sub-sampling concerns
- Only option for dry powder feeders
- No point in measuring more than one size range

Nominal Size (μm)	Catalogue Number	Nom. Wt. Per Vial (g)	Sold in 10 bottle sets. Price per Set:		
			£	€*	\$*
0.1 - 1 μm	PS180	0.01	206	315	415
	PS181	0.02	240	365	485
1 - 10 μm	PS190	0.025	69	105	140
	PS191	0.05	92	140	185
	PS192	0.10	115	175	235
	PS193	0.25	156	240	315
	PS194	0.50	206	315	415
3 - 30 μm	PS200	0.025	59	90	120
	PS201	0.05	69	105	140
	PS202	0.10	92	140	185
	PS203	0.25	115	175	235
	PS204	0.50	156	240	315
10 - 100 μm	PS205	1.0	206	315	415
	PS211	0.05	59	90	120
	PS212	0.10	80	125	165
	PS213	0.25	102	155	205
	PS214	0.50	146	225	295
	PS215	1.0	194	295	390

www.whitehousescientific.com/



Note: Whitehouse also supplies monodisperse

NIST 1003c



National Institute of Standards & Technology

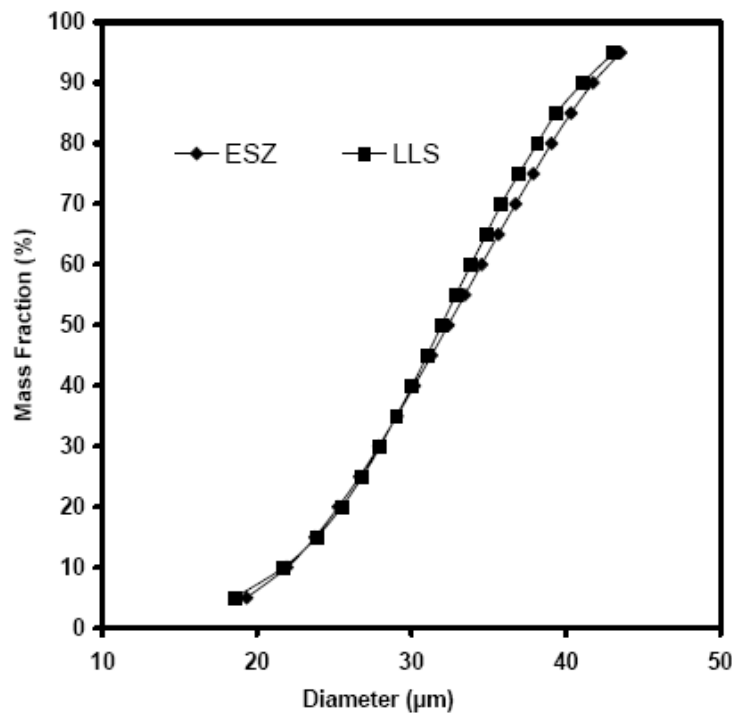
Very technical,
modern look

Certificate of Analysis

Standard Reference Material[®] 1003c

SRM 1003c

Table 1. Certified Diameter Values



Cumulative Mass Fraction Finer* (%)	Diameter (µm)	Standard Uncertainty Homogeneity (µm)	Standard Uncertainty Measurement (µm)	Type B Standard Uncertainty (µm)	Combined Standard Uncertainty (µm)	Expanded** Uncertainty (µm)
5	18.9	0.00	0.43	0.41	0.59	1.2
10	21.8	0.15	0.24	0.41	0.50	1.0
15	23.7	0.14	0.26	0.41	0.50	1.0
20	25.3	0.10	0.30	0.41	0.51	1.0
25	26.7	0.10	0.30	0.41	0.51	1.0
30	27.9	0.09	0.27	0.41	0.50	1.0
35	29.0	0.12	0.25	0.41	0.49	1.0
40	30.1	0.12	0.24	0.41	0.49	1.0
45	31.1	0.09	0.26	0.41	0.49	1.0
50	32.1	0.03	0.29	0.41	0.50	1.0
55	33.1	0.00	0.33	0.41	0.52	1.0
60	34.1	0.00	0.37	0.41	0.55	1.1
65	35.2	0.00	0.41	0.41	0.58	1.2
70	36.2	0.00	0.47	0.41	0.62	1.2
75	37.4	0.00	0.48	0.41	0.63	1.3
80	38.6	0.00	0.46	0.41	0.62	1.2
85	39.8	0.00	0.49	0.41	0.64	1.3
90	41.4	0.00	0.36	0.41	0.54	1.1
95	43.3	0.00	0.25	0.41	0.48	1.0

Note: different techniques always give different results

ISO 13320 : Real World Samples

- Test all samples 3 times for “repeatability”
- I call this “reproducibility”
 - 3 independent measurements
 - Prepare, measure, drain, repeat
- Calculate mean & coefficient of variation (COV) for d₁₀, d₅₀, d₉₀
 - $COV = (st\ dev/mean) * 100$
 - $COV < 3\%$ at median d₅₀
 - $COV < 5\%$ at d₁₀ & d₉₀
 - Double limits below 10 μm

Note: actual text reads

x_{10}, x_{50}, x_{90}

Only Germans use x,
ROW uses d

Guess who supervised
writing ISO 13320...

ISO13320 “Validation”

- “The response of a laser diffraction instrument is considered to meet this standard if the mean value of the x_{50} coming from at least three independent measurements deviates less than 3 % from the certified range of values of the Certified or Standard Reference Material, i.e. the mean value together with its standard deviation; the mean values for the x_{10} and x_{90} should deviate less than 5 % from the certified range of values.”

ISO 13320 “Validation”

- 6.3.2 Precautions e) Validate the instrument operation with respect to both precision and accuracy at regular time intervals by measuring a control sample of known size distribution (see 6.4 and 6.5.2).
- Therefore, two parts to the verification test. Measure standard 3 times. Calculate mean value at d₁₀, d₅₀, d₉₀ for accuracy. Calculate COV for precision.
 - Precision:
 - COV < 3% at median d₅₀
 - COV < 5% at d₁₀ & d₉₀
 - Accuracy:
 - d₅₀ within 3% of “certified range of values”
 - d₁₀ & d₉₀ within 5% of “certified range of values”

Example: NIST 1003

- Only need d10, d50, d90 values
- Note “Expanded Uncertainty”
- D10: $d = 21.8 \mu\text{m}$ w/ 1.0 uncertainty
- Pass/fail:

- $21.8 \cdot .95 = 20.71 \mu\text{m}$
- $21.8 \cdot 1.05 = 22.89 \mu\text{m}$
- Range = $20.71 - 22.89 \mu\text{m}$ or
- $(21.8 - 1) \cdot .95 = 19.76 \mu\text{m}$
- $(21.8 + 1) \cdot 1.05 = 23.94 \mu\text{m}$
- Range = $19.76 - 23.93 \mu\text{m}$

- IMHO include the uncertainty, I doubt you will ever be challenged. If so, point to the paper trail.

Table 1. Certified Diameter Values

Cumulative Mass Fraction Finer* (%)	Diameter (μm)	Standard Uncertainty Homogeneity (μm)	Standard Uncertainty Measurement (μm)	Type B Standard Uncertainty (μm)	Combined Standard Uncertainty (μm)	Expanded** Uncertainty (μm)
5	18.9	0.00	0.43	0.41	0.59	1.2
10	21.8	0.15	0.24	0.41	0.50	1.0
15	23.7	0.14	0.26	0.41	0.50	1.0
20	25.3	0.10	0.30	0.41	0.51	1.0
25	26.7	0.10	0.30	0.41	0.51	1.0
30	27.9	0.09	0.27	0.41	0.50	1.0
35	29.0	0.12	0.25	0.41	0.49	1.0
40	30.1	0.12	0.24	0.41	0.49	1.0
45	31.1	0.09	0.26	0.41	0.49	1.0
50	32.1	0.03	0.29	0.41	0.50	1.0
55	33.1	0.00	0.33	0.41	0.52	1.0
60	34.1	0.00	0.37	0.41	0.55	1.1
65	35.2	0.00	0.41	0.41	0.58	1.2
70	36.2	0.00	0.47	0.41	0.62	1.2
75	37.4	0.00	0.48	0.41	0.63	1.3
80	38.6	0.00	0.46	0.41	0.62	1.2
85	39.8	0.00	0.49	0.41	0.64	1.3
90	41.4	0.00	0.36	0.41	0.54	1.1
95	43.3	0.00	0.25	0.41	0.48	1.0

* The cumulative mass fraction finer is the portion of SRM 1003c smaller than the certified diameter value.

** The uncertainty at each percentile, computed according to the ISO and NIST Guides [4,5], is an expanded uncertainty at the 95% level of confidence.

Example: NIST 1003

■ d50 pass/fail (3%)

- $(32.1 - 1) \cdot .97 = 30.17 \mu\text{m}$

- $(32.1 + 1) \cdot 1.03 = 34.09 \mu\text{m}$

- Range = 30.17 – 34.09 μm

■ d 90 pass/fail (5%)

- $(41.4 - 1) \cdot .95 = 38.38 \mu\text{m}$

- $(41.4+1) \cdot 1.05 = 44.52 \mu\text{m}$

- Range = 38.38 – 44.52 μm

■ Note: d5 – d 95 range is 18.9 – 43.3, hardly “one decade”, being addressed in next version of ISO 13320

Table 1. Certified Diameter Values

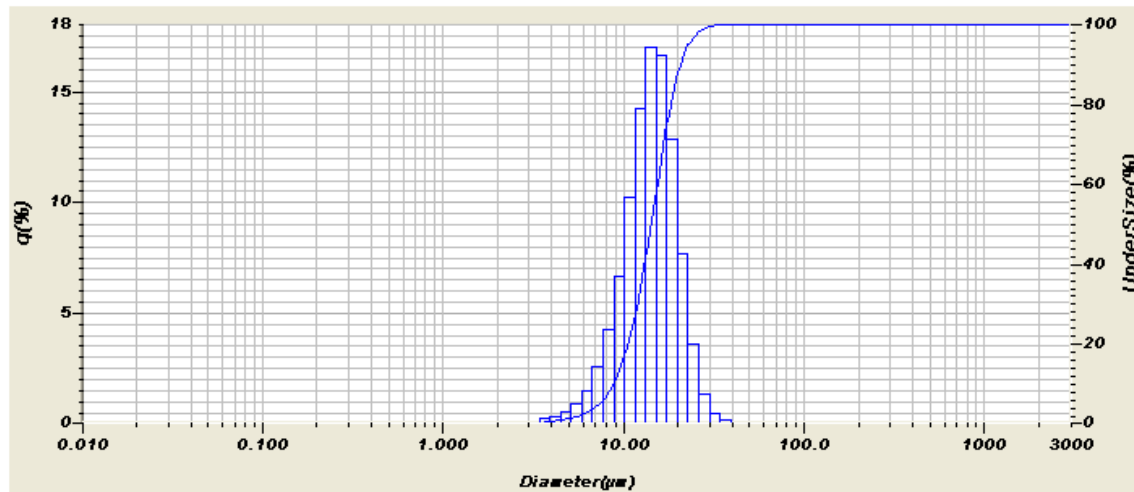
Cumulative Mass Fraction Finer* (%)	Diameter (μm)	Standard Uncertainty Homogeneity (μm)	Standard Uncertainty Measurement (μm)	Type B Standard Uncertainty (μm)	Combined Standard Uncertainty (μm)	Expanded** Uncertainty (μm)
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10	21.8	0.15	0.24	0.41	0.50	1.0
15	23.7	0.14	0.26	0.41	0.50	1.0
20	25.3	0.10	0.30	0.41	0.51	1.0
25	26.7	0.10	0.30	0.41	0.51	1.0
30	27.9	0.09	0.27	0.41	0.50	1.0
35	29.0	0.12	0.25	0.41	0.49	1.0
40	30.1	0.12	0.24	0.41	0.49	1.0
45	31.1	0.09	0.26	0.41	0.49	1.0
50	32.1	0.03	0.29	0.41	0.50	1.0
55	33.1	0.00	0.33	0.41	0.52	1.0
60	34.1	0.00	0.37	0.41	0.55	1.1
65	35.2	0.00	0.41	0.41	0.58	1.2
70	36.2	0.00	0.47	0.41	0.62	1.2
75	37.4	0.00	0.48	0.41	0.63	1.3
80	38.6	0.00	0.46	0.41	0.62	1.2
85	39.8	0.00	0.49	0.41	0.64	1.3
90	41.4	0.00	0.36	0.41	0.54	1.1
95	43.3	0.00	0.25	0.41	0.48	1.0

* The cumulative mass fraction finer is the portion of SRM 1003c smaller than the certified diameter value.

** The uncertainty at each percentile, computed according to the ISO and NIST Guides [4,5], is an expanded uncertainty at the 95% level of confidence.

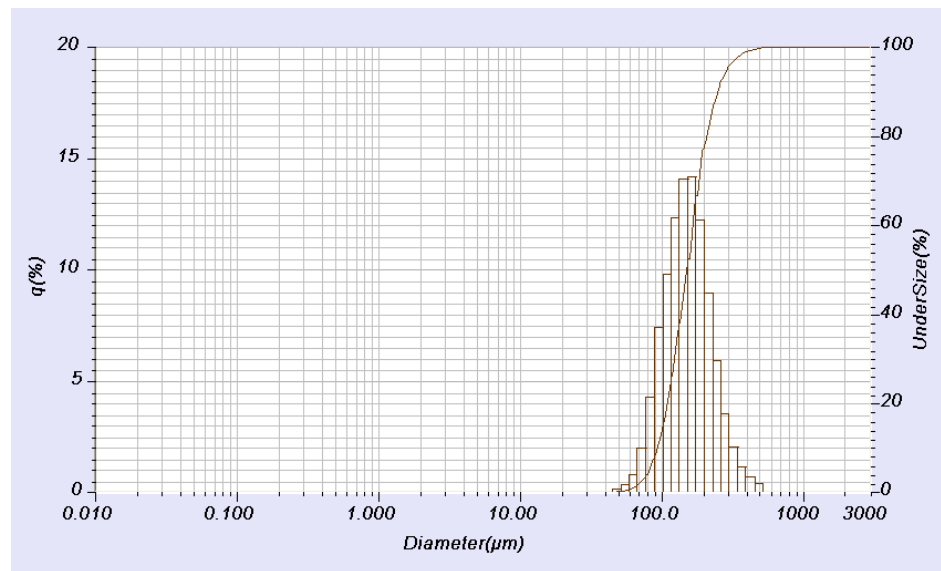
HORIBA LA-950 Data: PS202

PS202 (3-30 μm)	D10	D50	D90
Standard Value (μm)	9.14	13.43	20.34
Uncertainty (μm)	0.86	0.86	1.44
ISO standard error	5%	3%	5%
Lower limit (μm)	7.866	12.193	17.955
Measured Result (μm)	9.721	13.916	18.959
Upper Limit (μm)	10.500	14.719	22.869



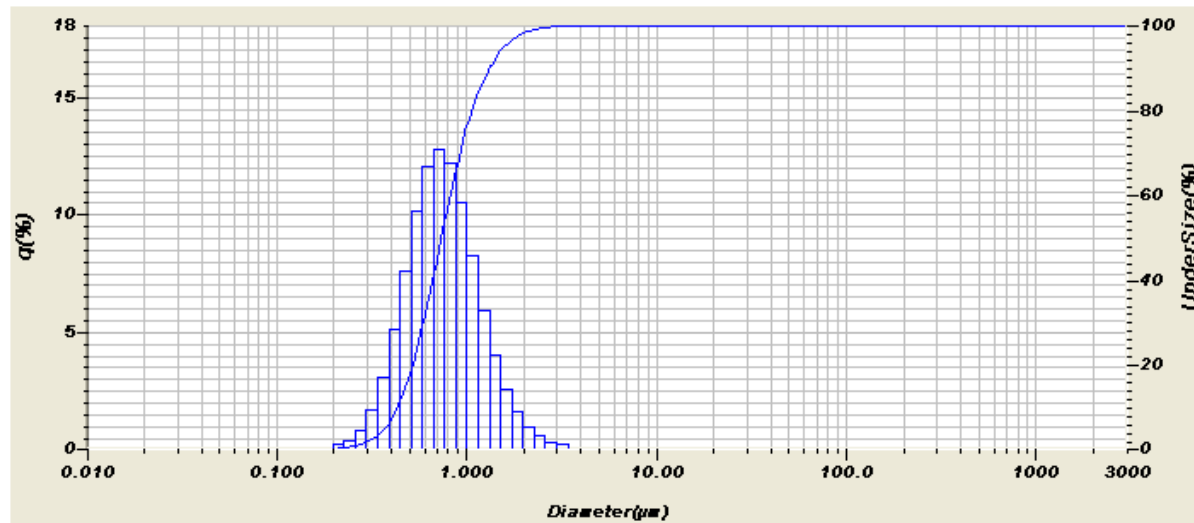
HORIBA LA-950 Data : PS 225

PS225 (50-350 μm)	D10	D50	D90
Standard Value (μm)	93.7	150.5	238.8
Uncertainty (μm)	3.54	2.52	6.02
ISO standard error	5%	3%	5%
Lower limit (μm)	85.652	143.541	221.141
Measured Result (μm)	94.217	153.815	252.542
Upper Limit (μm)	102.102	157.611	257.061



HORIBA LA-950 Data : PS 181

PS181 (0.1-1 μ m)	D10	D50	D90
Standard Value (μ m)	0.36	0.65	1.11
Uncertainty (μ m)	0.06	0.06	0.13
ISO standard error	5%	3%	5%
Lower limit (μ m)	0.285	0.5723	0.931
Measured Result (μ m)	0.434	0.709	1.296
Upper Limit (μ m)	0.441	0.7313	1.302



USP<429>

- Used only in the pharmaceutical industry
- Based on ISO 13320
- Broader limits for reproducibility
- Same limits for verification

LA-950 Calculation Automation

Verification Setting

Parameter: D(v,0.5)

Specification: USP-429

Standard Value: 0.01 μm

Tolerance: \pm 0 μm

Certified range of values:

D(v,0.5) \geq 10 μm \pm 3 %

D(v,0.5) $<$ 10 μm \pm 5 %

Color Selection:

Pass:

Fail:

OK Cancel

Distribution Graph | Data Table | Result Data

Mean Size : 0.18408(μm)

Variance : 1.8988E-3(μm^2)

Median Size : 0.17730(μm)

Mode Size : 0.1649(μm)

Std.Dev. : 0.0436(μm)

Chi Square : 4.162519

R Parameter : 3.7379E-1

Diameter on Cumulative % : (2)10.00 (%) - 0.1345(μm)

 : (9)90.00 (%) - 0.2450(μm)

Cumulative % on Diameter : (1)850.0 (μm) - 100.000(%)

 : (2)600.0 (μm) - 100.000(%)

 : (3)425.0 (μm) - 100.000(%)

 : (4)300.0 (μm) - 100.000(%)

 : (5)212.0 (μm) - 100.000(%)

 : (6)150.0 (μm) - 100.000(%)

 : (7)106.0 (μm) - 100.000(%)

 : (8)75.00 (μm) - 100.000(%)

 : (9)53.00 (μm) - 100.000(%)




 : (10)38.00 (μm) - 100.000(%)

Verification

1.OK 4.3% [D(v,0.5) 0.170 (μm)(\pm 6.000%)]

2.OK 3.5% [D(v,0.1) 0.130 (μm)(\pm 10.00%)]

3.OK 6.5% [D(v,0.9) 0.230 (μm)(\pm 10.00%)]

Data Name	Graph Type	Transmittance(R)	Median Size	R Parameter
andy1'		88.3(%)	0.17730(μm)	0.373795
200801181026014		81.1(%)	9.35329(μm)	0.069234
andy1		88.3(%)	0.17730(μm)	0.373795

Aqueous vs. Solvent

- All results shown were run in H₂O
- What if system is used for solvent?
- Switch over to water – test – back to solvent
- Always form emulsion when switching to H₂O
- Test until system passes???

SAMPLE ID	RUN 1	RUN 2	RUN 3	RUN 4	RUN 5	AVG	Spec ⁺
PS-202 in IPA							
D10	9.31	9.32	9.37	9.37	9.37	9.35	7.87 - 10.50
D50	13.87	13.88	13.95	13.96	13.95	13.92	12.19 - 14.72
D90	19.88	19.89	19.98	20	19.97	19.94	17.96 - 22.87
PS-202 in Hexanes							
D10	10.07	10.13	10.16	10.18	10.24	10.16	7.87 - 10.50
D50	14.96	15.05	15.1	15.12	15.21	15.09	12.19 - 14.72
D90	21.37	21.47	21.51	21.53	21.62	21.50	17.96 - 22.87

← Passes in IPA

← Doesn't in hexane

LA-920 data

Conclusions

- Verify system on a regular basis
 - Current practice: daily to annually
 - Should be risk based decision
 - Run plant on particle size = daily
 - Use for research 3 times/year = annually
- Switch to using polydisperse standards to also test samplers
- Most companies still using monodisperse latex – but be aware of risk and “paper trail” not strong

Thank-you