Setting Attainable and Practical Particle Size Specifications

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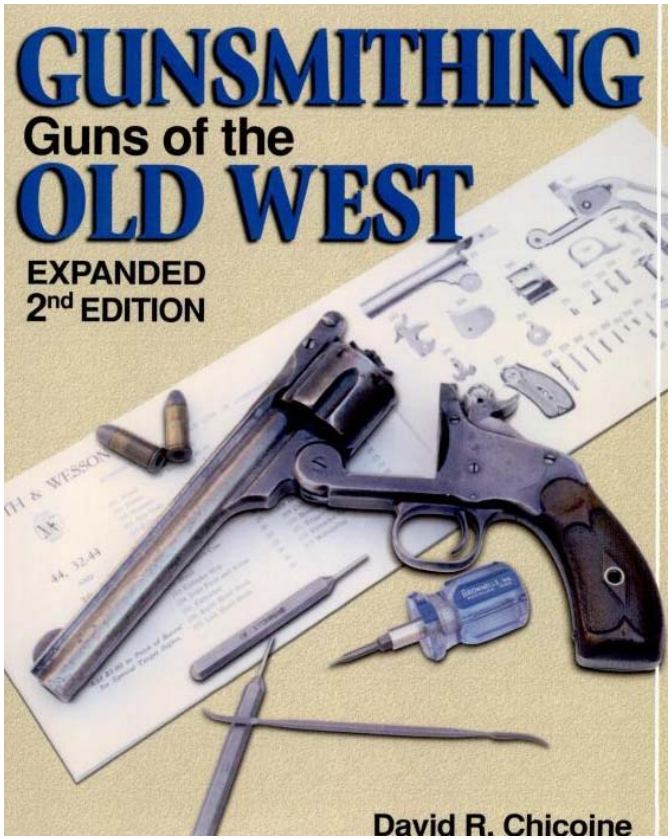
Why Set Specifications?

- Product release (quality)
- Communicate grade to buyers
- Internal requirements
- Required in regulated industries (food & drugs)
- Will focus on drugs, but same concepts applicable to other industries

This is not New!



The grading of blackpowder: Earlier we mentioned the different sizes of gunpowder grains, and about how smaller grains will burn more quickly than the larger ones. The term "grade," when applied to gunpowder refers to the grain size, and *not* to its quality. There are two separate categories of gunpowder grades; "C" and "F" grade. "C" grade is for cannons and large capacity explosive devices. A single "C" being the largest grain size with smaller sizes graded down as, "CC," "CCC," etc. Powder that is meant for small arms purposes uses the letter "F" to denote the grain size with a single "F" (or 1-FG for "1FG" size, "F" grade grain). The more "F's" you see within the powder grade designation, the *smaller* will be the grain size. "FFFG," for example, is very fine, almost a dust and was commonly used as a priming powder for the pans of flintlocks.

Examples (Sieves)

Retained on 8 Mesh	0.5	Maximum
Retained on 16 Mesh	2	Maximum
Through 200 Mesh	30	Maximum

The following convention is used to characterize particle size by mesh designation:
a "+" before the sieve mesh indicates the particles are retained by the sieve;
a "-" before the sieve mesh indicates the particles pass through the sieve;
typically 90% or more of the particles will lie within the indicated range.

-4 +40 mesh, then 90% or more of the material will pass through a 4-mesh sieve **and** be retained by a 40-mesh sieve

-40 mesh, then 90% or more of the material will pass through a 40-mesh

Mesh	Micron
No. 20	841
No. 25	707
No. 30	595
No. 35	500
No. 40	420
No. 45	354
No. 50	297
No. 60	250
No. 70	210
No. 80	177
No. 100	149
No. 120	125
No. 140	105
No. 170	88
No. 200	74
No. 230	63
No. 270	53
No. 325	44
No. 400	37

Example (TiO_2)

Item No.	R-1	RM-1
TiO_2 Content %	98.0	94.0
Whiteness		Better
Brightness	96.5	
pH Value	6.5-8.5	6.5-8.5
Mesh Residue 45 µ m max %	0.05	0.05
Tint-Reducing Power min	1700	95
Oil Absorption g/100g max	21	23
Volatile AT 105°C % max	0.5	0.80
Specific Receptivity Ω cm min	90	80
Water dispersibility, % min		90
Rutile Content min %	97.0	98.0
Application	Paints, Plastics, Rubber, Paper, Grocery	Coating, Plastic, Paper, Rubber, Printing inc.

Does this mean 0.06% fails?? They are the same numbers!

TYPICAL PROPERTIES	
TiO_2 content	94%
Inorganic coating	Alumina
Organic treatment	Present
Crystal size	0.25µm
Specific gravity	4.05 g/cm³
Loss at 105°C (i)	0.6% max
Bulk density (tamped) (ii)	1.3 g/cm³
Oil absorption (iii)	17 cm³/100g pigment
Water demand (iv)	24 cm³/100g pigment
Durability	Durable
ISO 591 classification	R2
ATSM D476 designation	II, III, IV

Easier to understand, but:
How was it measured?
Dispersion?
Ultrasound?

Specification Definition*

- "a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described"

- "chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product"

*ICH HARMONISED TRIPARTITE GUIDELINE, SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES , Q6A, Current *Step 4* version, 6 October 1999

Pharmaceutical: FDA Guidance

ICH HARMONISED TRIPARTITE GUIDELINE

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

Q6A

3. GUIDELINES

3.1 Specifications: Definition and Justification

3.1.1 Definition of Specifications

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use.

FDA Guidance

3.3 Specific Tests / Criteria

3.3.1 New Drug Substances

b) Particle size: For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and / or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided.

Decision tree #3 provides additional guidance on when particle size testing should be considered.

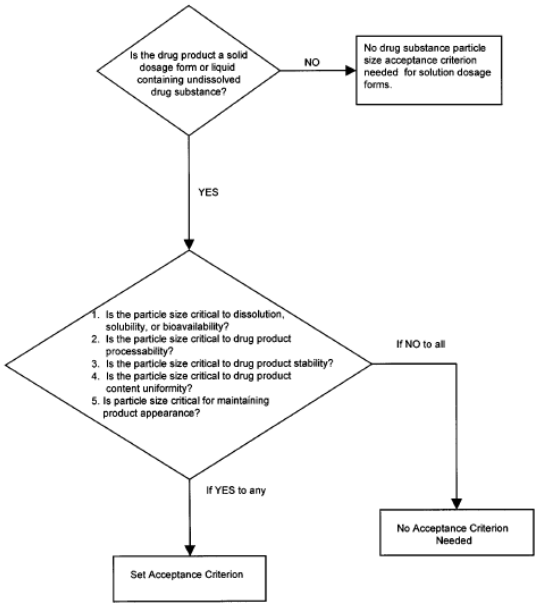
Is the drug a solid oral dosage form or suspension?

↓ **Yes**

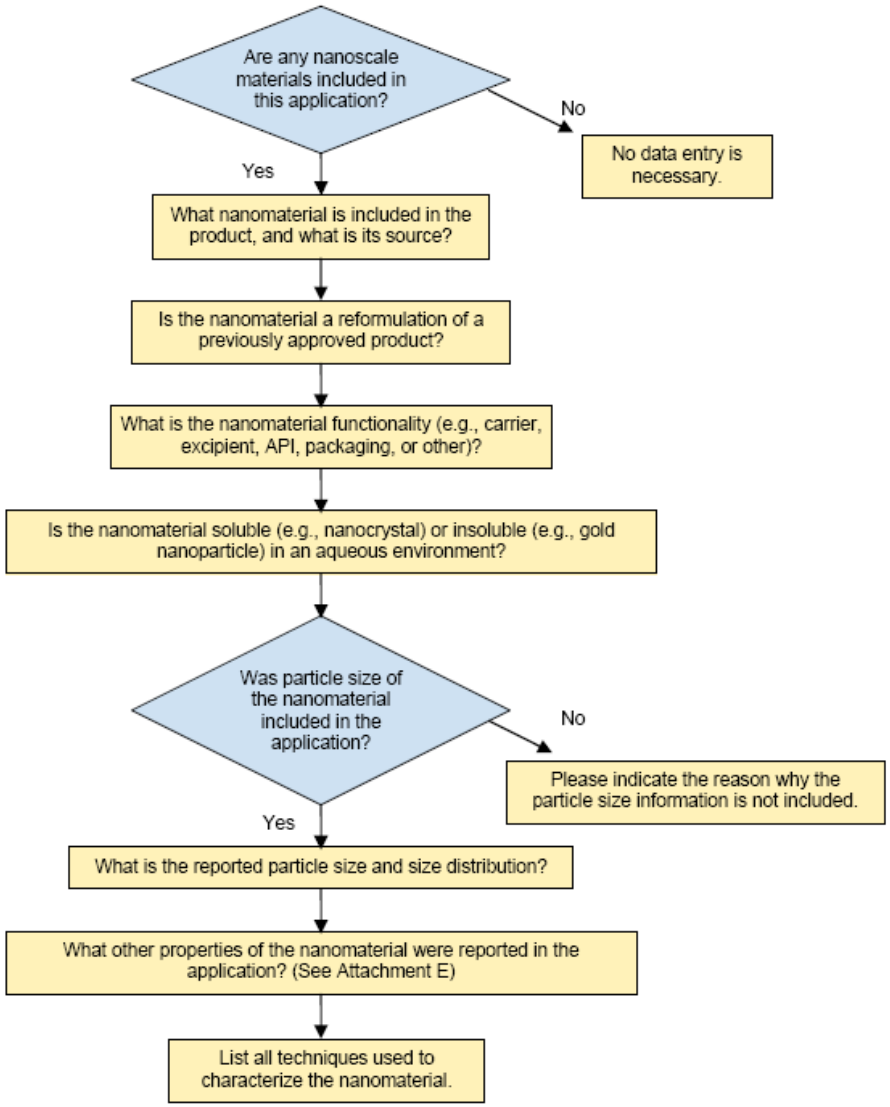
Is particle size critical to:
Dissolution, solubility, bioavailablility?
Processability?
Stability?
Content uniformity?
Maintaining appearance?

↓ **Yes**

Set Acceptance Criterion



FDA: Nanoparticles

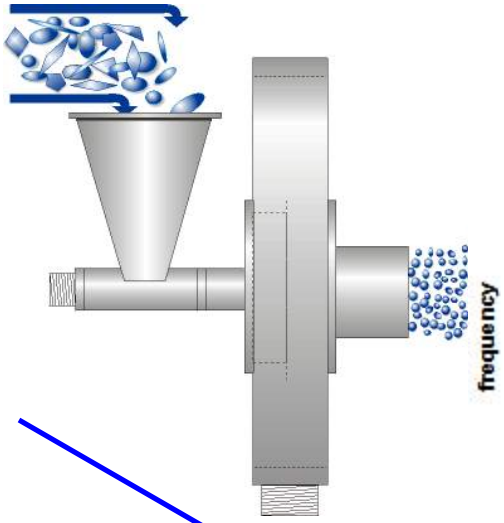


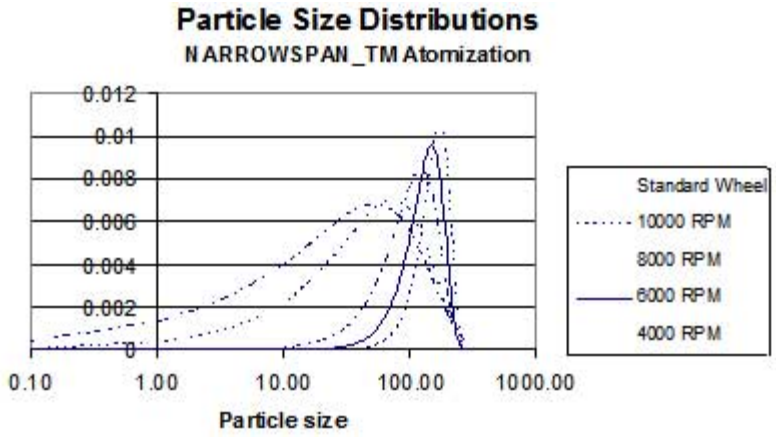
Attachment A: Nanotechnology Product Evaluating Questions

1) This review contains new information added to the table below: _____Yes _____No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No_____; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?_____
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____; API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____ (Complete 8) ; No_____(Go to 9)
8) What is the reported particle size? Mean particle size_____ ; Size distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10) What other properties of the nanomaterial were reported in the application (see Attachment E)? _____
11) List all methods used to characterize the nanomaterial. _____

Particle Size and Processability

- Milling/size reduction
- Mixing/blending
- Separation
- Filtration
- Granulation
- Homogenization
- Crystallization





Narrow particle size distributions minimize segregation problems during mixing – more homogeneous distribution of components in final product

Particle Size and Dissolution

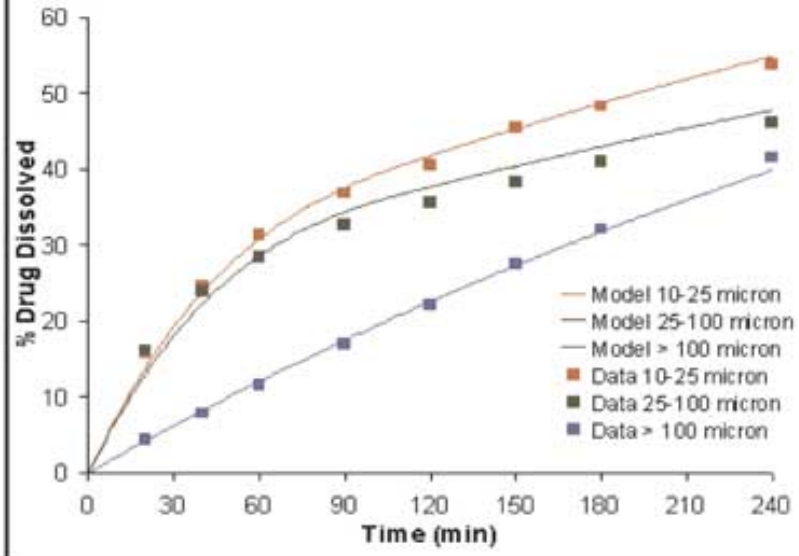
Equation 1.

$$\frac{dX_S}{dt} = -\frac{3DX_0^{1/3}X_S^{2/3}}{\rho h r_0}\left(C_S - \frac{X_d}{V}\right)$$

XS is the mass of solid drug (mg),
t is time (minutes),
D is the drug diffusivity (cm2/min),
X0 is the initial drug mass (mg),
r is the drug density (mg/mL),
h is the diffusion layer thickness (cm),
r_0 is the initial particle radius (cm),
CS is the drug solubility (mg/mL),
Xd is the mass of dissolved drug (mg),
V is the volume of dissolution media (mL).

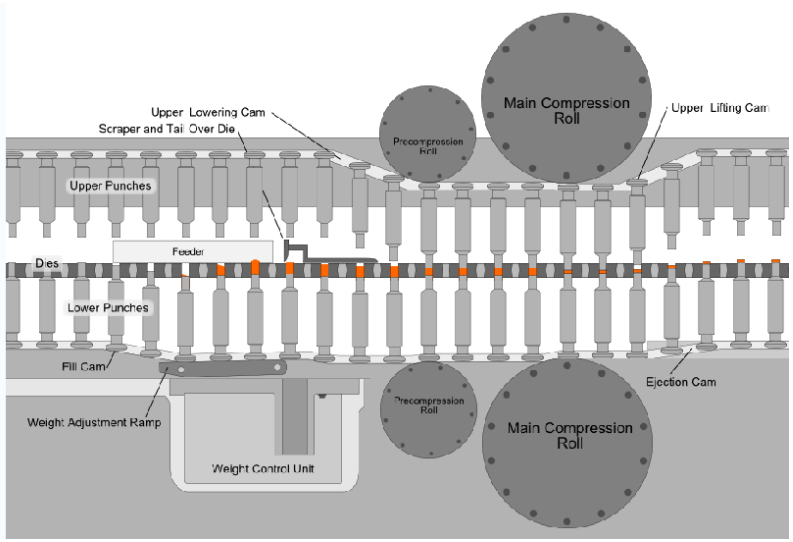
FIGURE 4

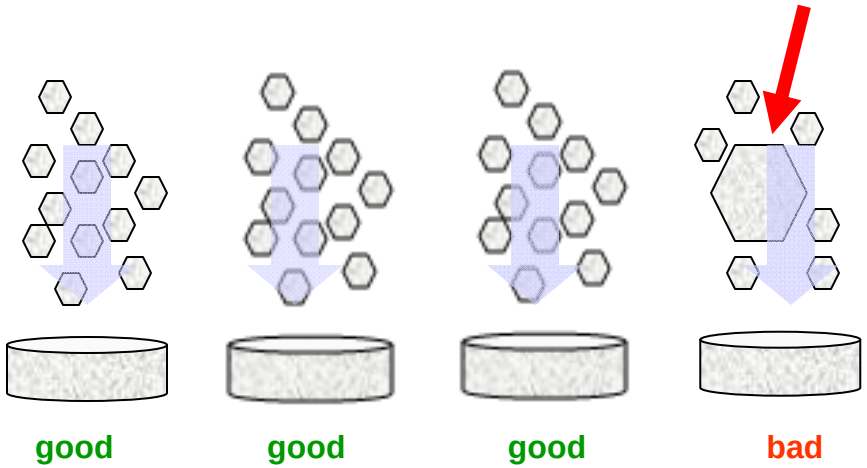
Ondansetron Dissolution as a Function of Particle Size Fractions at pH 6.8. Data are From Model Predictions (Solid Lines) and Data Collected in Dissolution Experiments (Data Points).



David R. Friend, PhD; Gregory E. Parry, PhD; T. Francis, PhD; Gary Kupperblatt, PhD; Suggy S. Chrai, PhD; and Gerald Slack,
Mathematical Modeling of a Novel Controlled-Release Dosage Form
Drug Delivery Technology,

Content Uniformity





Idealized concept:

- Powder particles compacted into tablet
- All particles are active ingredients
- Small particles = specified dose
- Large particle = over dose

Content Uniformity*

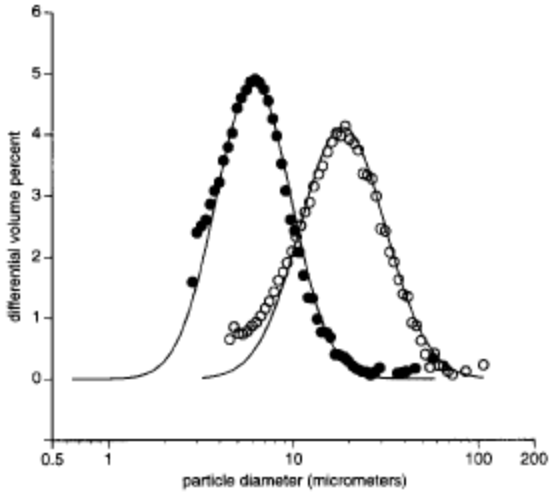


Fig. 1. Particle size distributions of Bantam-milled drug (○) and Jet-milled drug (●). Simulated lines were drawn using geometric mean particle sizes of 18.5 and 6.1 μm and geometric standard deviation of 1.7 and 1.6 for the Bantam and Jet-milled drug, respectively.

$$\text{mass}_{ni} = \frac{\text{mass}_i}{\sum_{i=1}^{100} \text{mass}_i} \times \text{dose}$$

The volume v_i and mass m_i of a single particle of radius was calculated as follows:

$$v_i = \frac{4}{3}\pi r_i^3 \quad (7)$$

$$m_i = v_i \rho \quad (8)$$

where ρ is the drug density.

Percent of intent	Number of unit doses within the given percent of intent range			
	Experimental		Simulated	
	Bantam	Jet	Bantam	Jet
70–74				
74–78				
78–82				
82–86				
86–90	1			
90–94	5			
94–98	13	5	483 249	
98–102	20	59	313 436	1000 000
102–106	16		145 337	
106–110	7		45 537	
110–114	1		9744	
114–118			2191	
118–122	1		447	
122–126			58	
126–130	1		1	

*Zhang, Y, Johnson, K, Effect of drug particle size on content uniformity of low-dose solid dosage forms, International Journal of Pharmaceutics 154 (1997) 179-183

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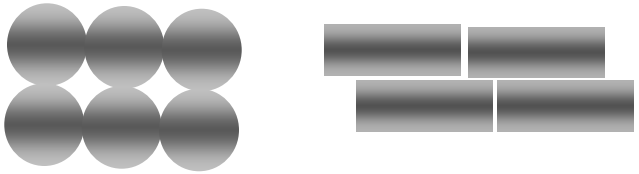
Tablets

- Size of active ingredient effects content uniformity
- Size influences tablet hardness
- Size and shape effects packing
- Size and shape effect powder flow



Suspensions

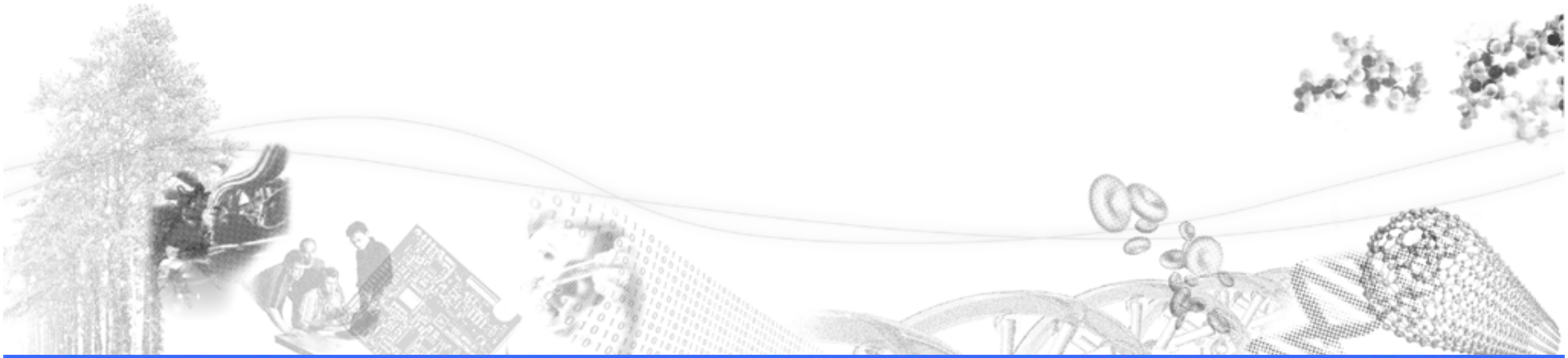
- Dissolution and absorption
- Content uniformity
- Ability to stay in suspension
- Feel in mouth

Only API's? No, Also Excipients

- Particle size and physical characteristics critical in selection and performance

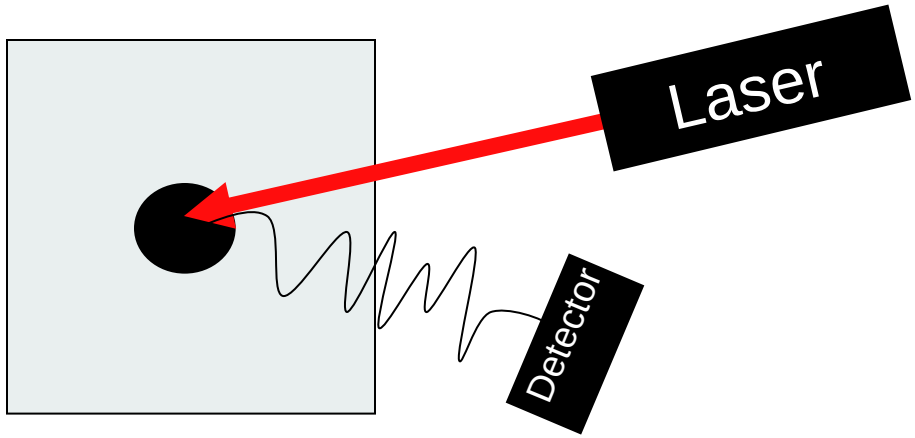
HPC Grade			SSL	SL	L
Material	Lactose (g)		700	700	700
	Corn starch (g)		300	300	300
	8% HPC aqueous solution (g)		375	375	375
Property of granule	Particle size distribution (%)	1400μ on	0.2	0.2	-
		500μ	0.2	0.2	0.4
		355μ	0.4	0.6	1.7
		250μ	1.3	2.1	8.4
		180μ	4.0	6.0	14.4
		150μ	8.0	9.6	15.6
		106μ	22.1	22.1	24.7
		75μ	30.3	26.9	19.6
		75μ under	33.6	32.3	15.0
	Bulky density (kg/cm3)	Loose	90	95	130
		packed	0.5	0.47	0.46
Property of tablet	Hardness (kg)		14	14	12
	Friction loss (%)		0.2	0.2	0.2
	Disintegration time (min)		6	8	9

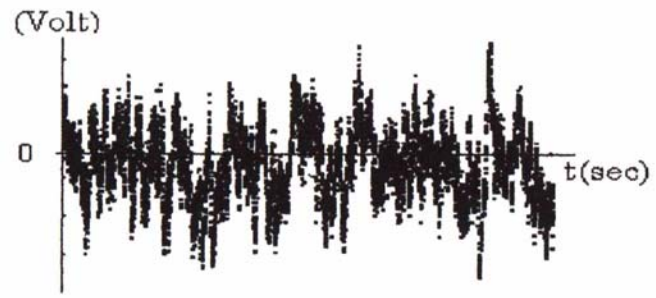
Techniques and Specifications



DLS: Brownian Motion

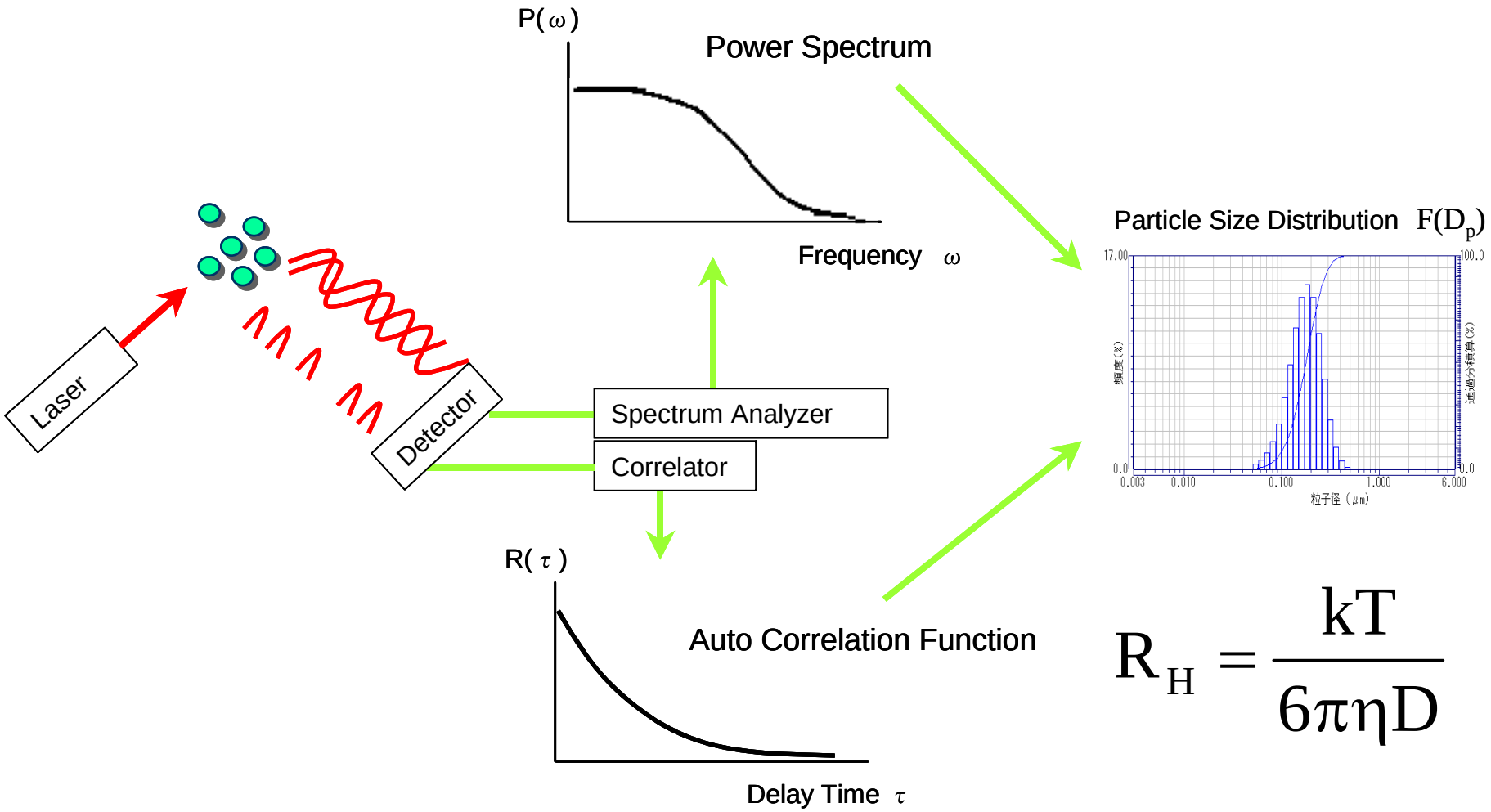
- Particle is randomly diffusing from Brownian motion
  - Larger particles will diffuse more slowly
  - Smaller particles will diffuse more quickly
- Scatter light off this diffusing particle
- Measure the frequency shift of the signal





Frequency Shifted Signal

Two Approaches: Correlator or Power Spectrum



$$R_H = \frac{kT}{6\pi\eta D}$$

ISO 22412: PSA by DLS

- Correlation method or frequency analysis
- Measure at least 3 times
- Record average particle size $\overline{X}_{DLS}$ & PI
- Repeatability better than 5%
- Check for sedimentation
- Dilution study, use most dilute if changes
- Verification: within 2% of 100nm standard, repeatability < 2%, PI< 0.2
  - –All specs too tight for reality
  - –Within 5% OK

DLS Specifications

- Only z average & PI defined in ISO
- Can convert intensity to volume distribution
  - Requires RI of sample
- Can dramatically alter reported values
- Typically used for industrial products where D10, D50 & D90 familiar

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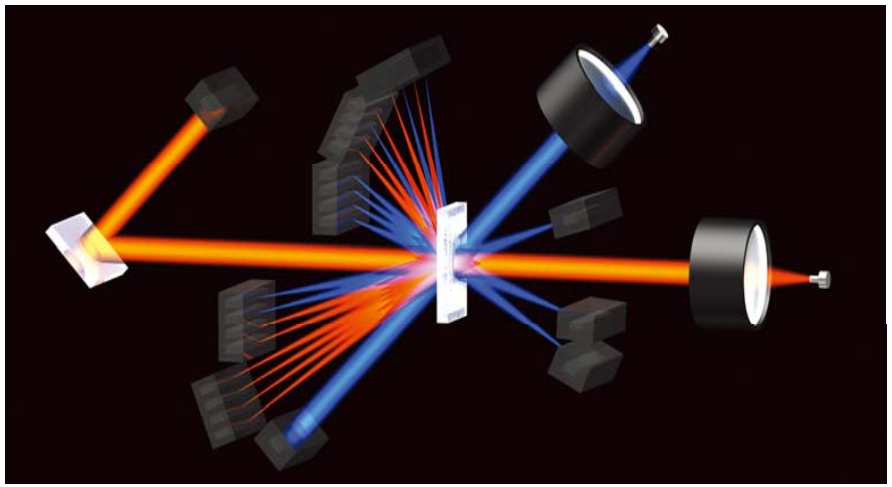
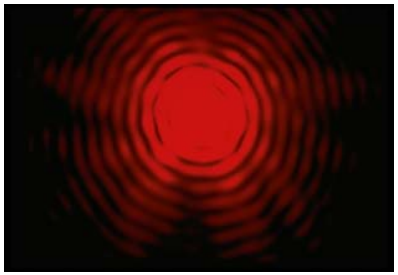
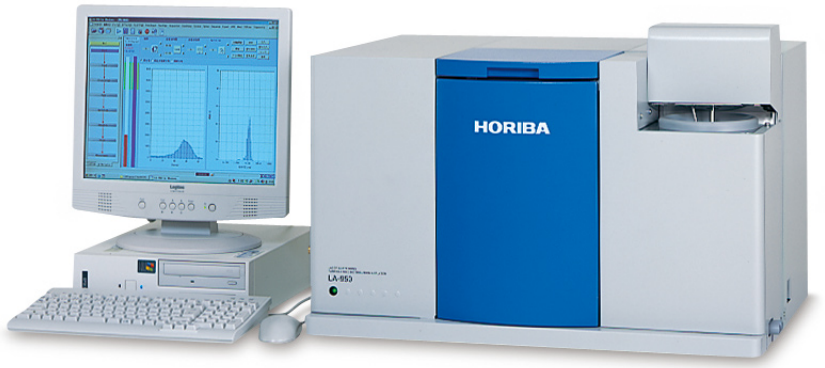
Laser Diffraction

Particle size 0.01 – 3000 µm







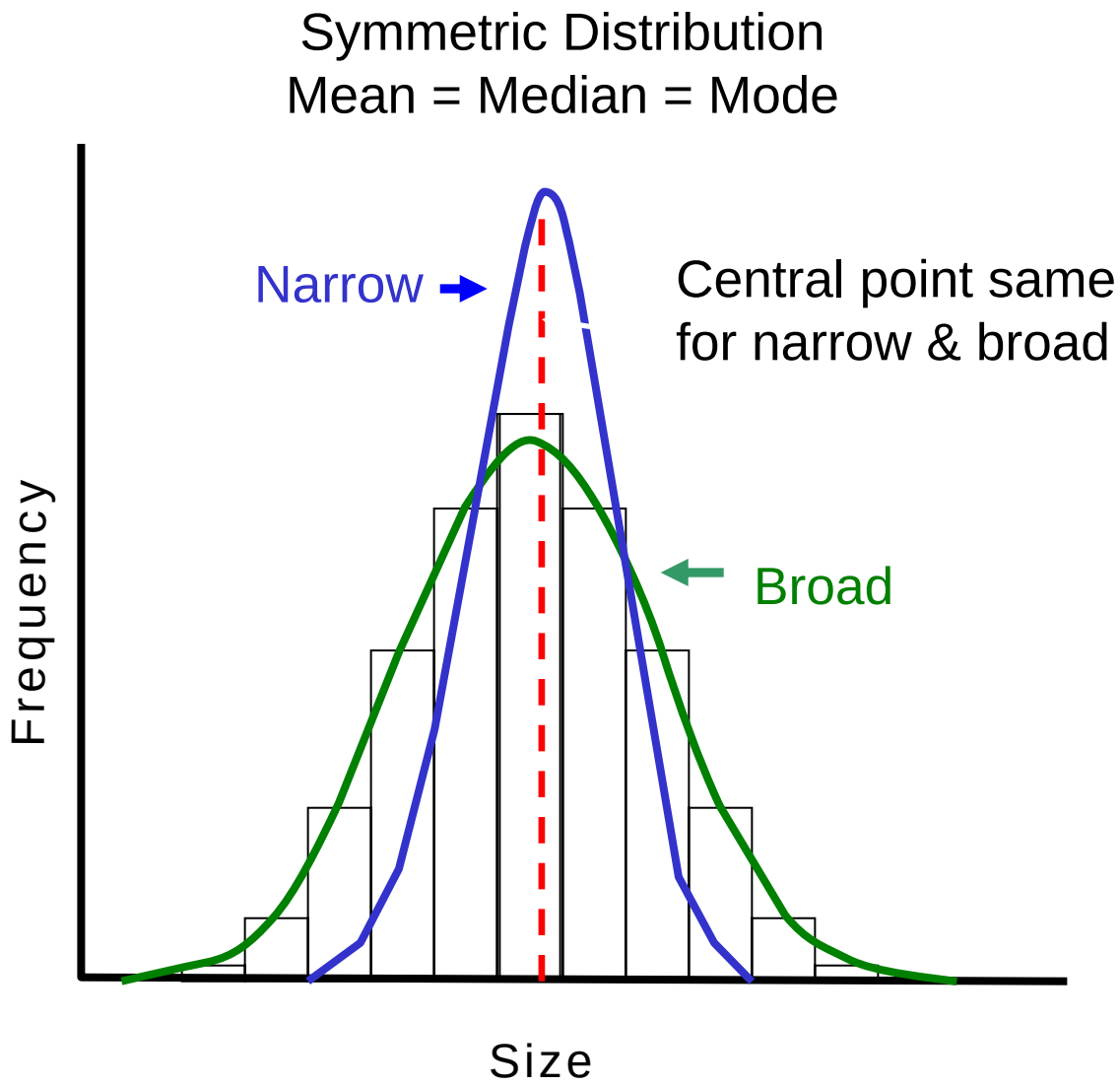
- Converts scattered light to particle size distribution
- Quick, repeatable
- Most common technique

Distribution Parameters

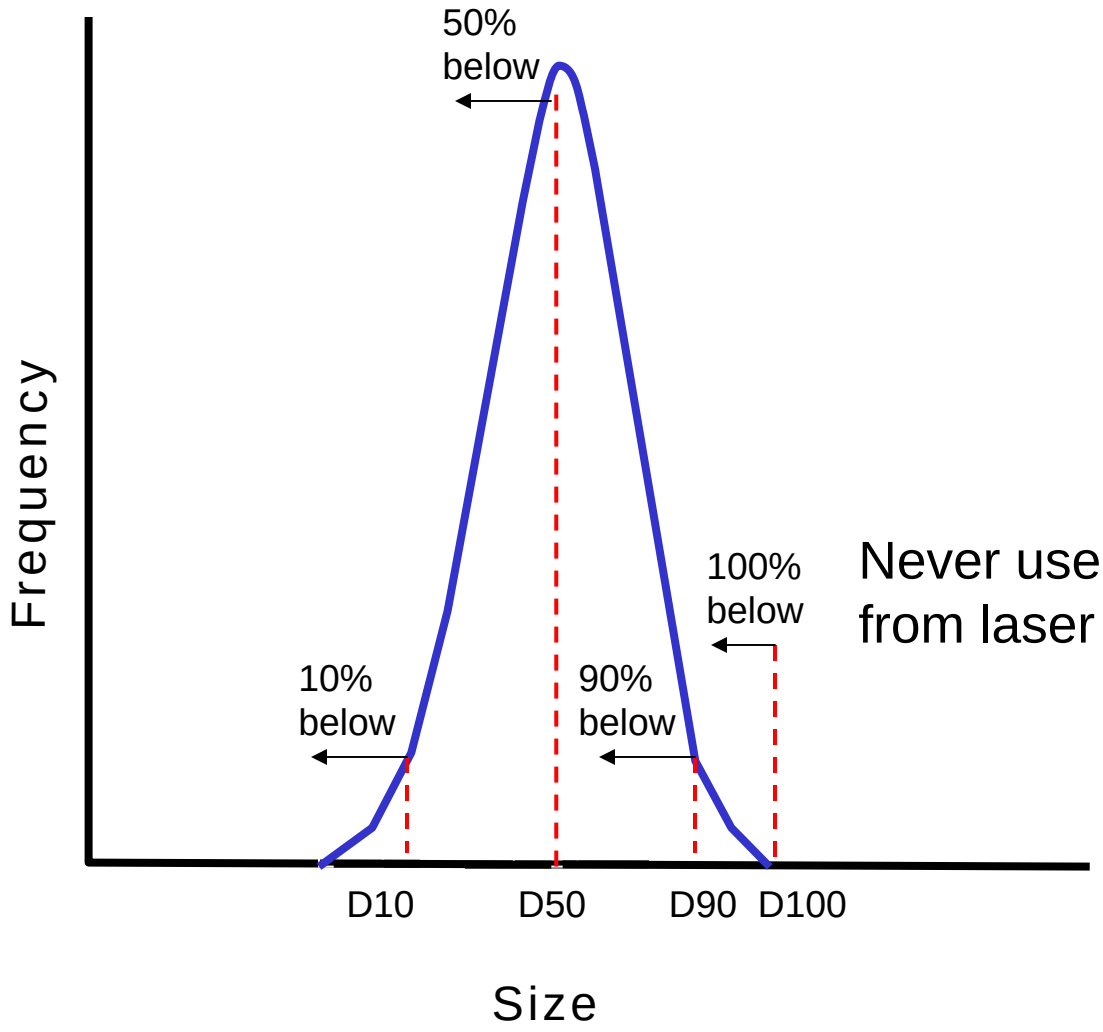
Mode - Peak of the distribution

Median - 50% Point (50% above - 50% below)

Mean – Weighted Average - Center of Gravity of Distribution

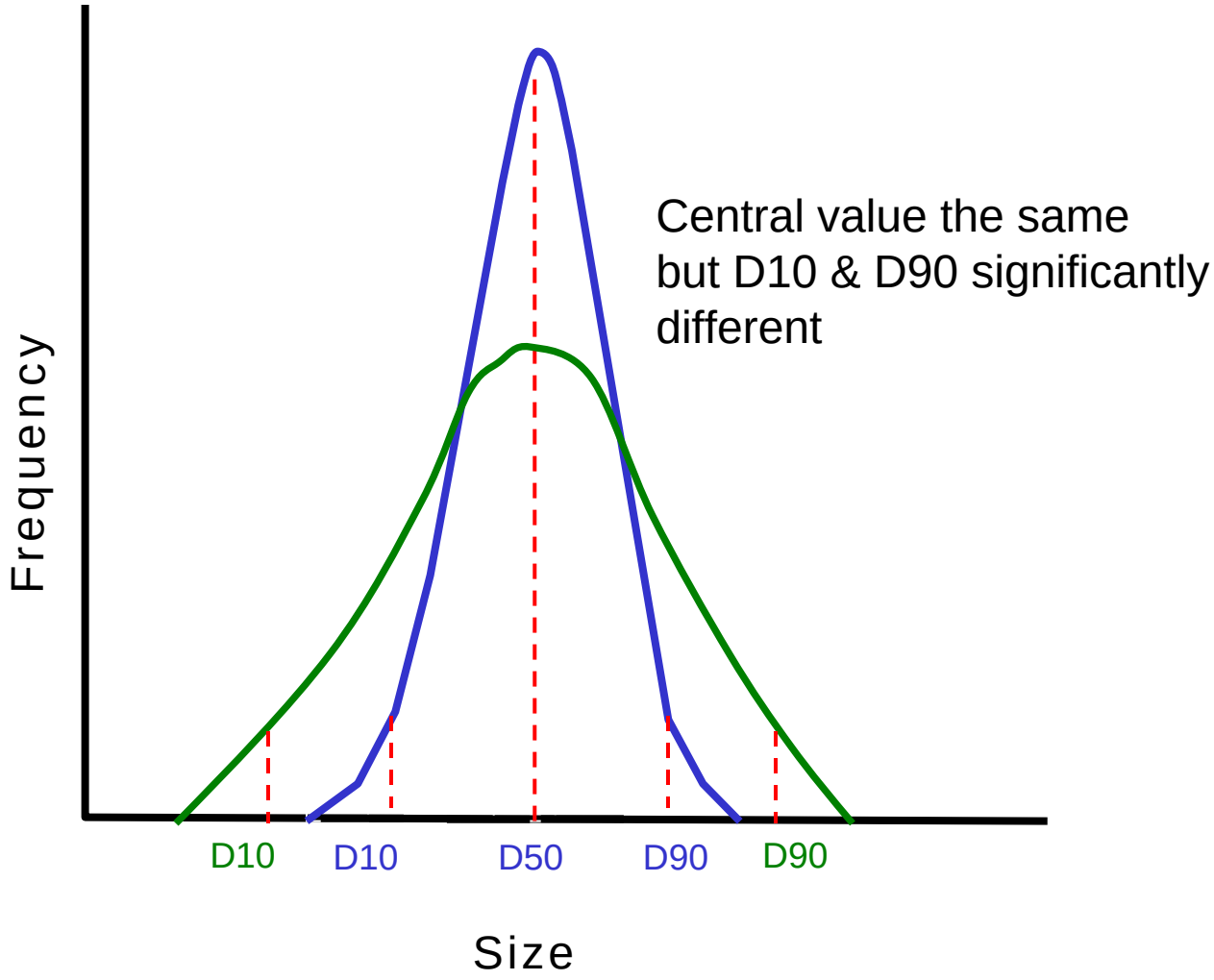


Other Data Points: D10, D50, D90

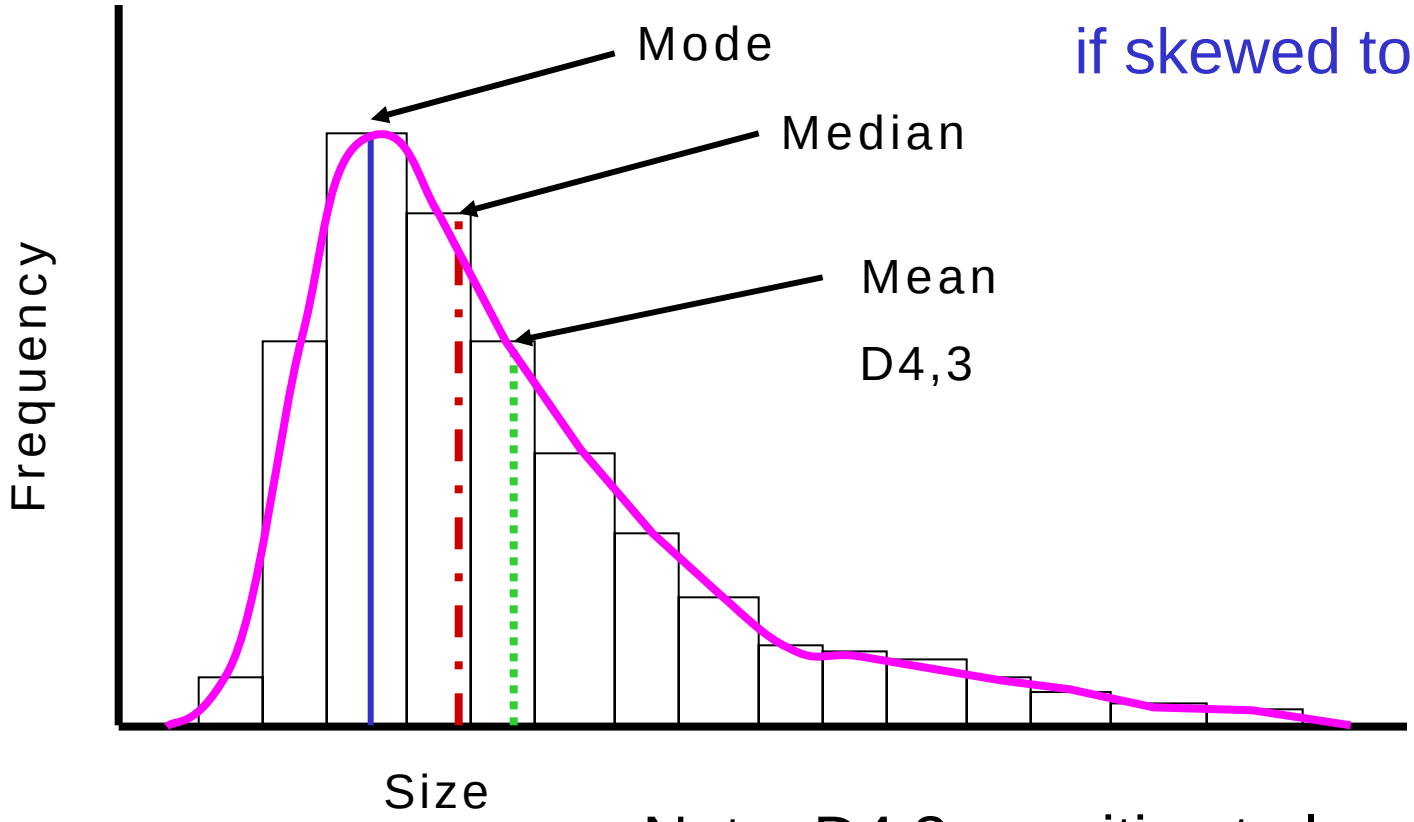


Never use D100
from laser diffraction

Other Data Points: D10, D50, D90



Distribution Parameters



Mode<Median<Mean
if skewed to larger sizes

Note: D4,3 sensitive to large particles

Volume Mean Diameter

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

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

Setting a D [4,3] specification will emphasize the presence of large particles

Mean Size

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

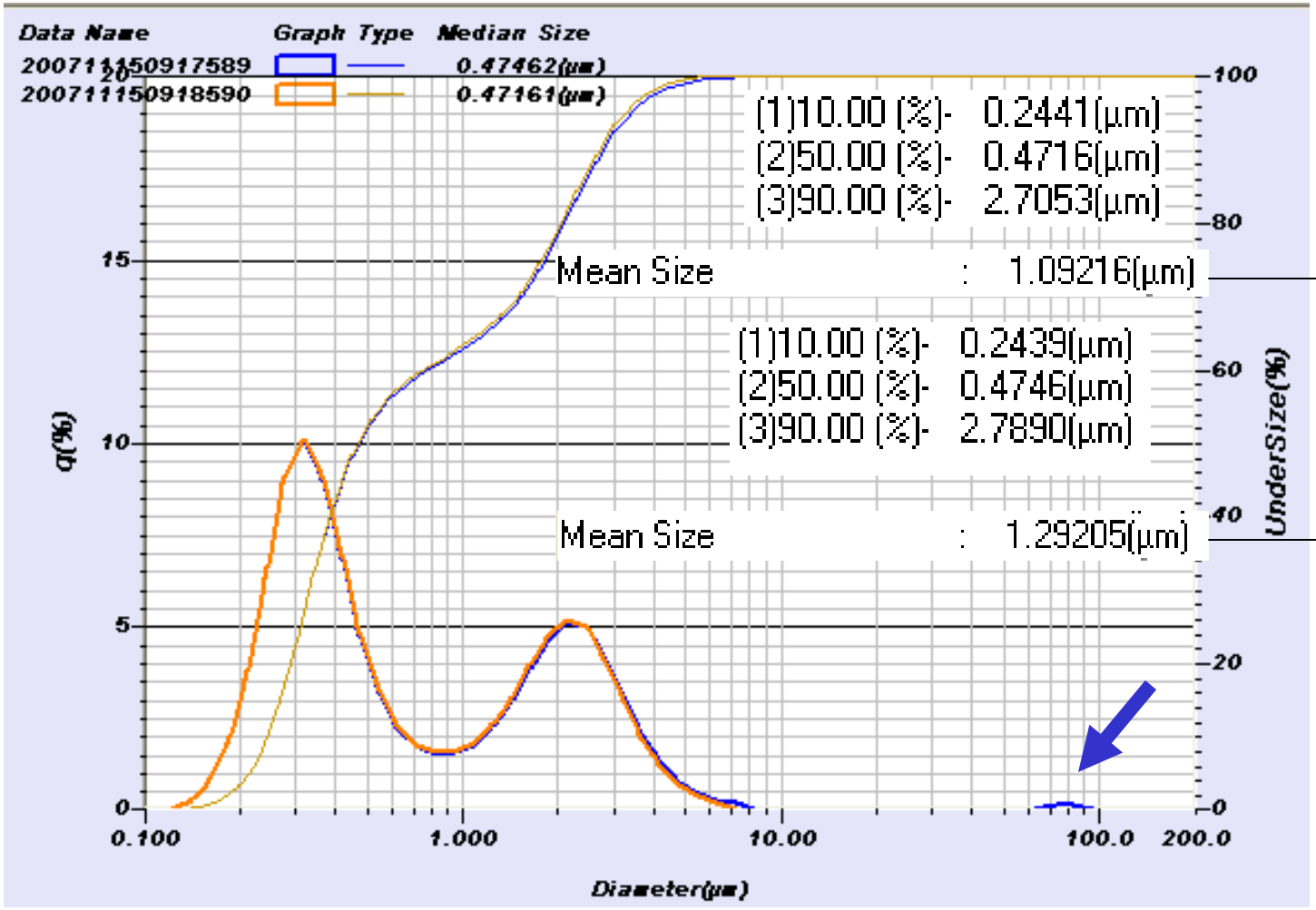
Mean Diameter = $\Sigma\{q(J) \times X(J)\} / \Sigma\{q(J)\}$

J : Particle Diameter Division Number

q(J) : Frequency Distribution Value (%)

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

D 4,3 Volume Mean

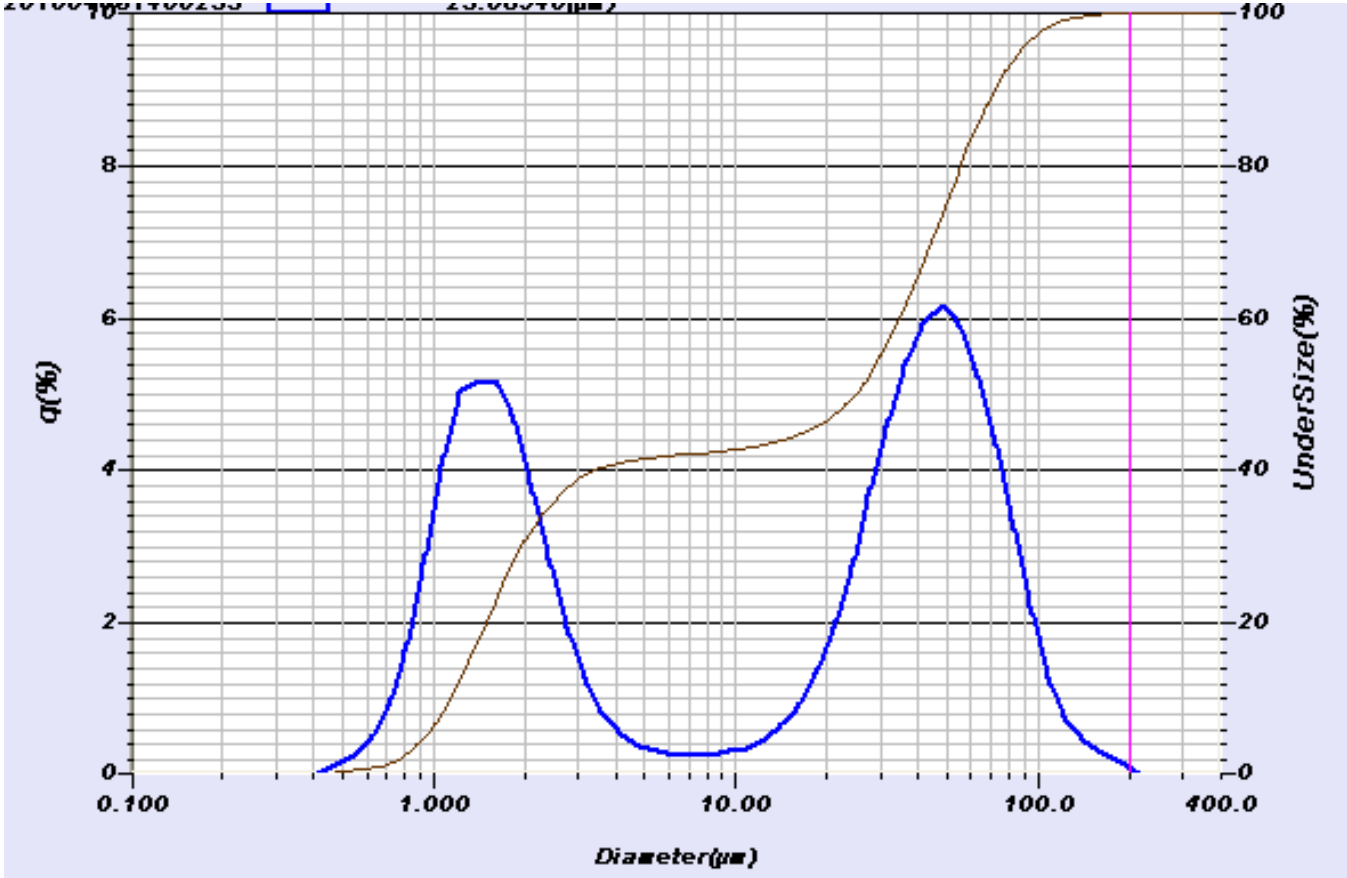


15% difference

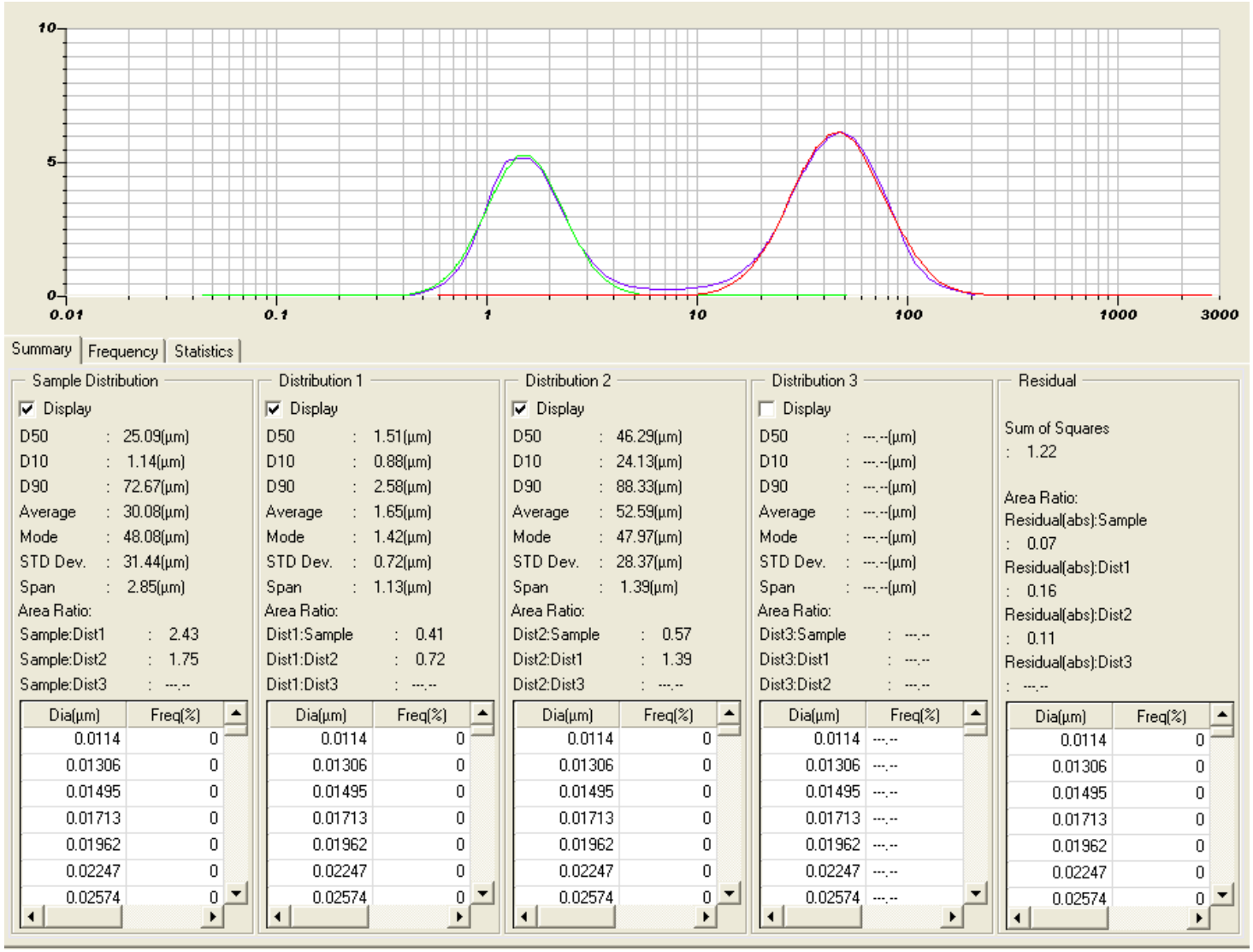
Classic example: CMP slurries

Bimodal Distribution

Which numbers to use for specifications?
D50 still an option, but some prefer finer details



Bimodal Distribution Result Details



Laser Diffraction Standards

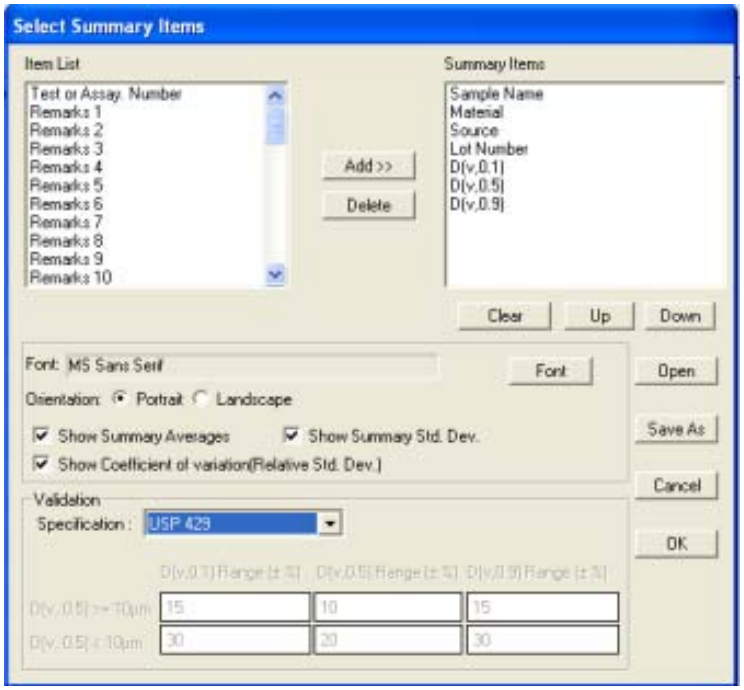
- Standards good source for guidance to methods & specifications
  - ISO13320
  - Pharmaceutical: EP 2.9.31 & USP<429>
- All based on ISO standard
- Test Reproducibility
  - Don’t believe anything unless it’s reproducible
- Verify your system
  - On a regular basis using polydisperse standards

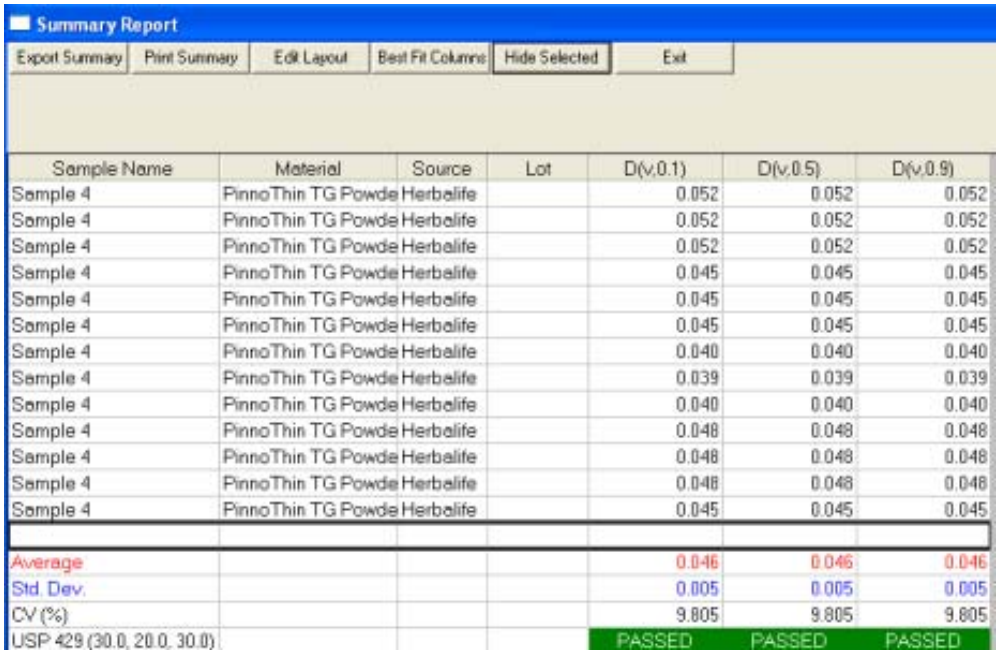
Reproducibility

- Prepare & measure sample 3 times
- Record D10, D50, D90
- Calculate average D10, D50, D90 and COV
  - ISO: COV < 3% at median x_{50}
    COV < 5% at x_{10} & x_{90}
  - EP/USP: COV < 10% at median x_{50}
    COV < 15% at x_{10} & x_{90}
  - Can double COV values when D50 <10 µm
- Part of specification? Perhaps internal

Calculation Automation

From LA-950 Software





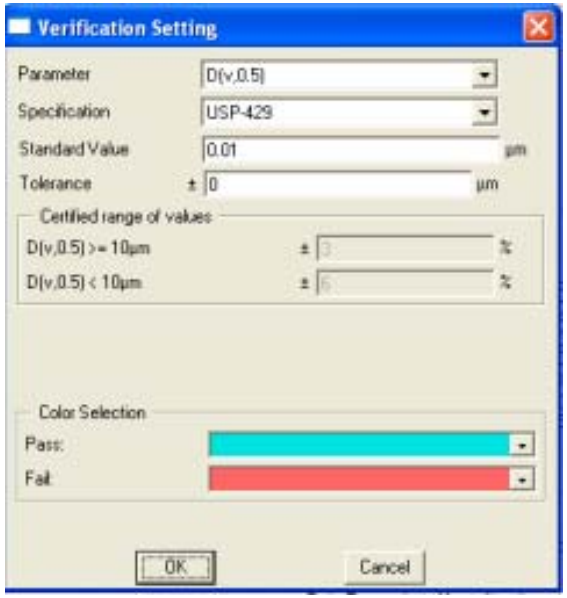
Sample Name	Material	Source	Lot	D(v,0.1)	D(v,0.5)	D(v,0.9)
Sample 4	PinnoThin TG Powde	Herbalife		0.052	0.052	0.052
Sample 4	PinnoThin TG Powde	Herbalife		0.052	0.052	0.052
Sample 4	PinnoThin TG Powde	Herbalife		0.052	0.052	0.052
Sample 4	PinnoThin TG Powde	Herbalife		0.045	0.045	0.045
Sample 4	PinnoThin 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

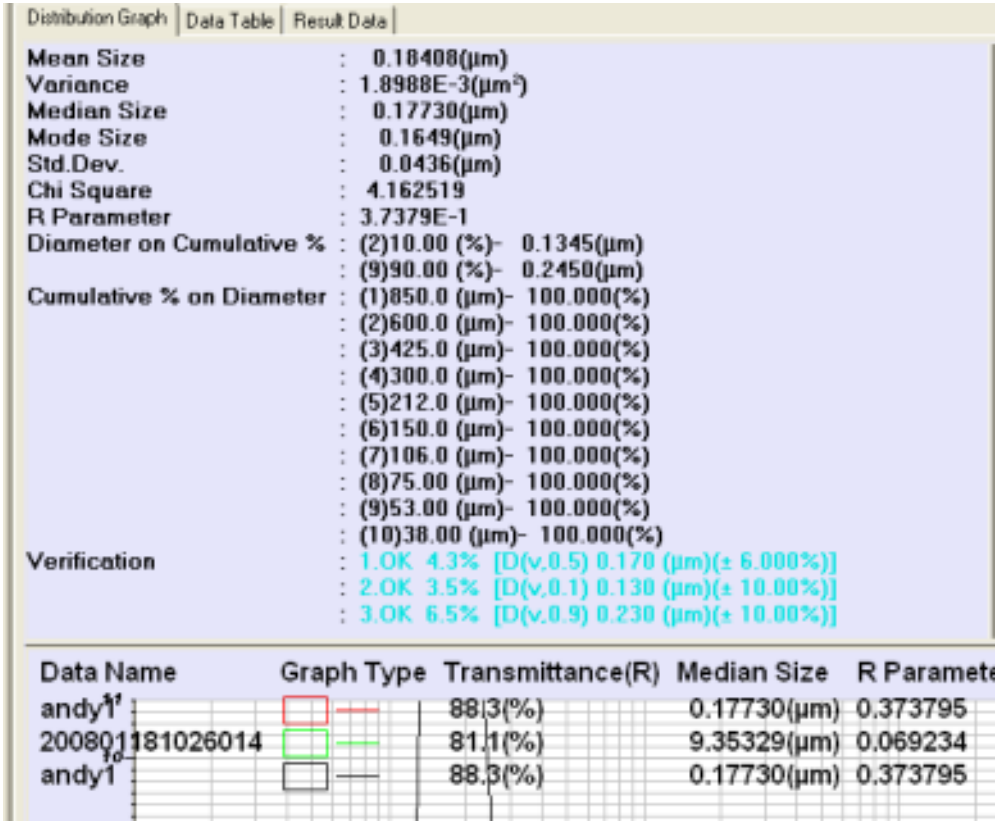
System Verification

- Use polydisperse standard
  - Whitehouse, NIST
- 3 independent measurements, calculate mean
- Accuracy:
  - X50 <3% certified range of values
  - X10 & X90 < 5% certified range of values
- Repeatability
  - COV X50 < 3%
  - COV X10 & X90 < 5%

Calculation Automation

From LA-950 Software





Pharmaceutical Specifications

- What Information Should be Included?

Analytical procedures (sampling, dispersion, system suitability, etc.)

- Method Validation (precision, ruggedness, dispersion stability, robustness, etc.)
- Acceptance Criteria (upper and lower limits)
- Representative plots of particle size distribution measurements should be included well as the method validation report.

HORIBA

Justification

- Justification should be presented for each procedure and each acceptance criterion included
- Should refer to relevant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate.
- Additionally, a reasonable range of expected analytical and manufacturing variability should be considered.

Example Specifications

- Dv50 = 25 µm ± 15%
  - 21.2 to 28.8 µm
- Dv10 = 8 µm ± 25%
  - 6 to 10 µm
- Dv90 = 75 µm ± 25%
  - 56.2 to 93.7 µm
- Maybe D[4,3]

Dv50 NMT 25 µm

Dv10 NMT 8 µm

Dv90 NMT 75 µm

Looks busy

Looks cleaner
Sufficient?

Both better than: Average = 25

Example Specification from FDA Website

Tests	Acceptance criteria	Analytical procedure	Test results for Lot#15531
Appearance	A white, crystalline powder.	Visual	Complies
Identification A: IR B: UV	A. IR: Corresponds to RS B. UV: Absorptivities at xxx nm, do not differ by more than 3.0% from the reference standard.	USP<197M> USP<197U>	Complies Complies
Heavy metals	NMT 20 ppm	USP<231>	LT 20 pm
Assay	98.0-102.0%	USP method	99.5%
Residual solvents	Methanol: NMT 3000 ppm Methylene Chloride: NMT 600 ppm Toluene NMT 890 ppm	USP <467>	 300 ppm 150 ppm 80 ppm
Related Substances	Specified Impurities* RC 1: NMT 0.15% RC 2: NMT 0.25% RC 3: NMT 0.25 % Any unspecified impurity: NMT 0.10% (each) Total impurities: NMT 0.75%	method #41	 LT 0.05% LT 0.05% 0.10% LT 0.05% 0.30 %
Polymorphic Form (XRD)	Ratio of peak at 2θ= xx to peak at 2θ=yy: LT 5%	method #47	LT 1%
Particle size (Laser Diffraction)	D90: NMT 30 µm D50: NMT 15 µm D10: NMT 5 µm	method #48	20 µm 10 µm 2.5 µm

*RC 1: [impurity identity]

Pharmaceutical Reference*

*John, E, How to Set Specifications for the Particle Size Distribution of a Drug Substance?, American Pharmaceutical Review, April 2009, 72-77

	x10	x50	x90
mean, n = 6	0.8µm	1.8µm	3.9µm
STDrel, n = 6	13%	9%	13%
min	0.7µm	1.7µm	3.5µm
max	0.9µm	1.9µm	4.8µm
DEVrel (min, max)	29%	12%	37%

Table 1. Characteristic values of the particle size distributions (PSD) of six batches of Drug Substance A in terms of mean values, relative standard deviations, min. max. values and relative deviations between them.

Includes manufacturing and analytical variability over 3 years

FDA Reference*

Regulatory Issues on Particle Size Specifications

Zhigang Sun, Ph.D.

Office of Generic Drugs

Center for Drug Evaluation and Research

Food and Drug Administration

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Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA

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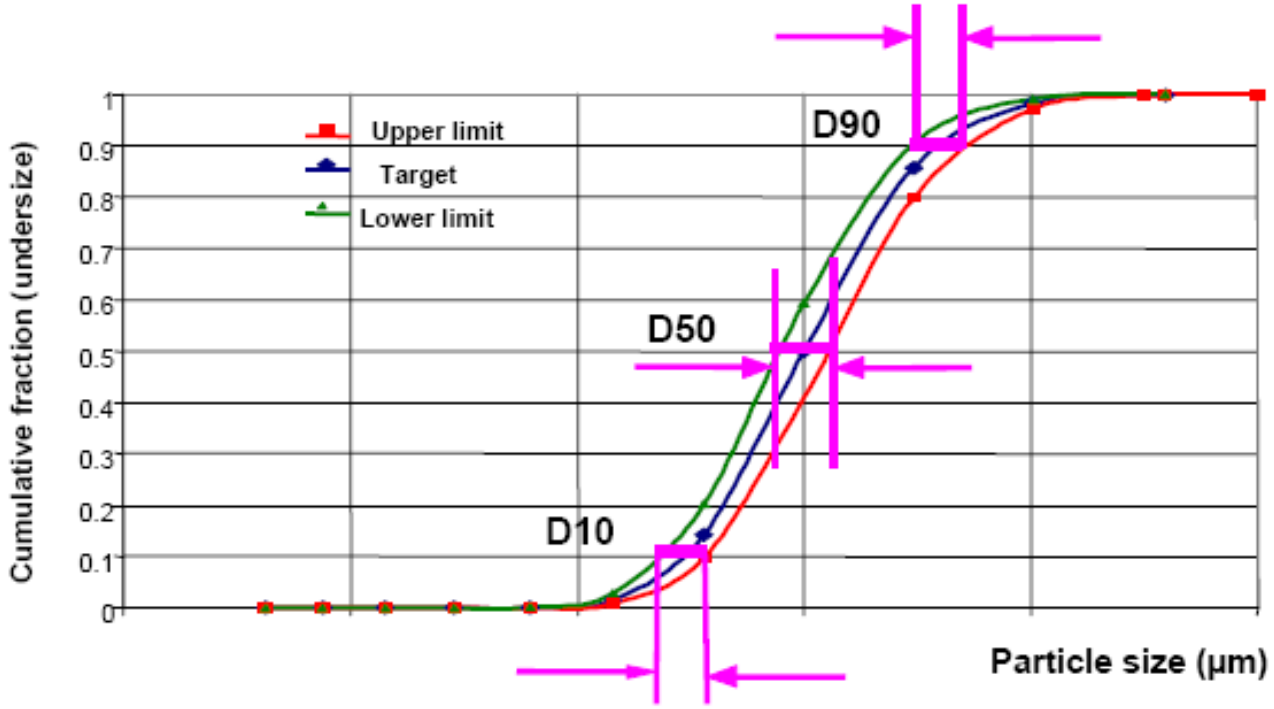
*http://www.aapspharmaceutica.com/meetings/workshops/Arden/presentations/Regulatory_Issues_on_Particle_Size-_Sun.pdf

FDA Reference*

Acceptance Criteria for Laser Diffraction



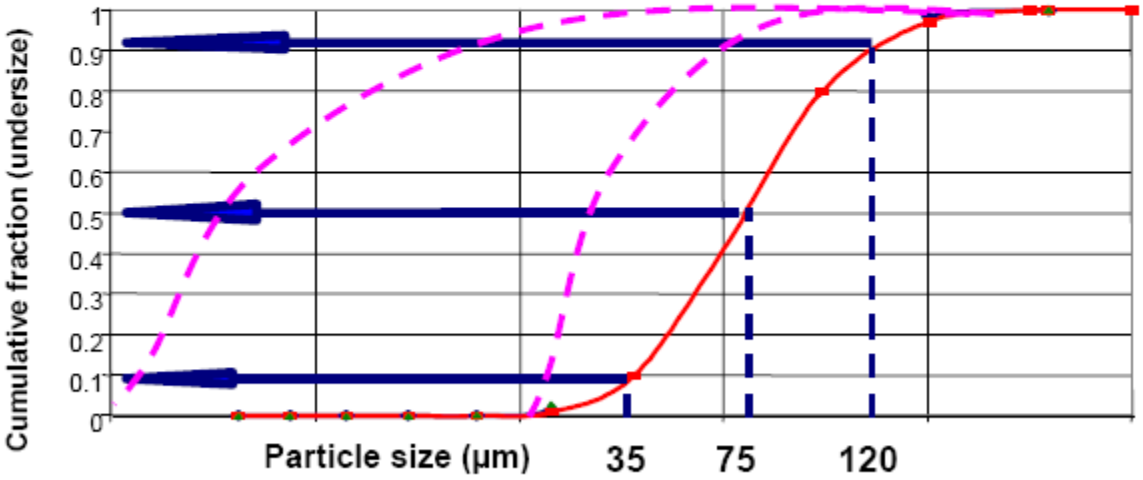
Upper and lower limits of D10, D50, and D90 are established based upon prior knowledge or design of experiment (DOE) studies.

Inadequate LD Criteria

Spec. (Laser Diffraction)
D10: NMT 35 µm
D50: NMT 75 µm
D90: NMT 120 µm

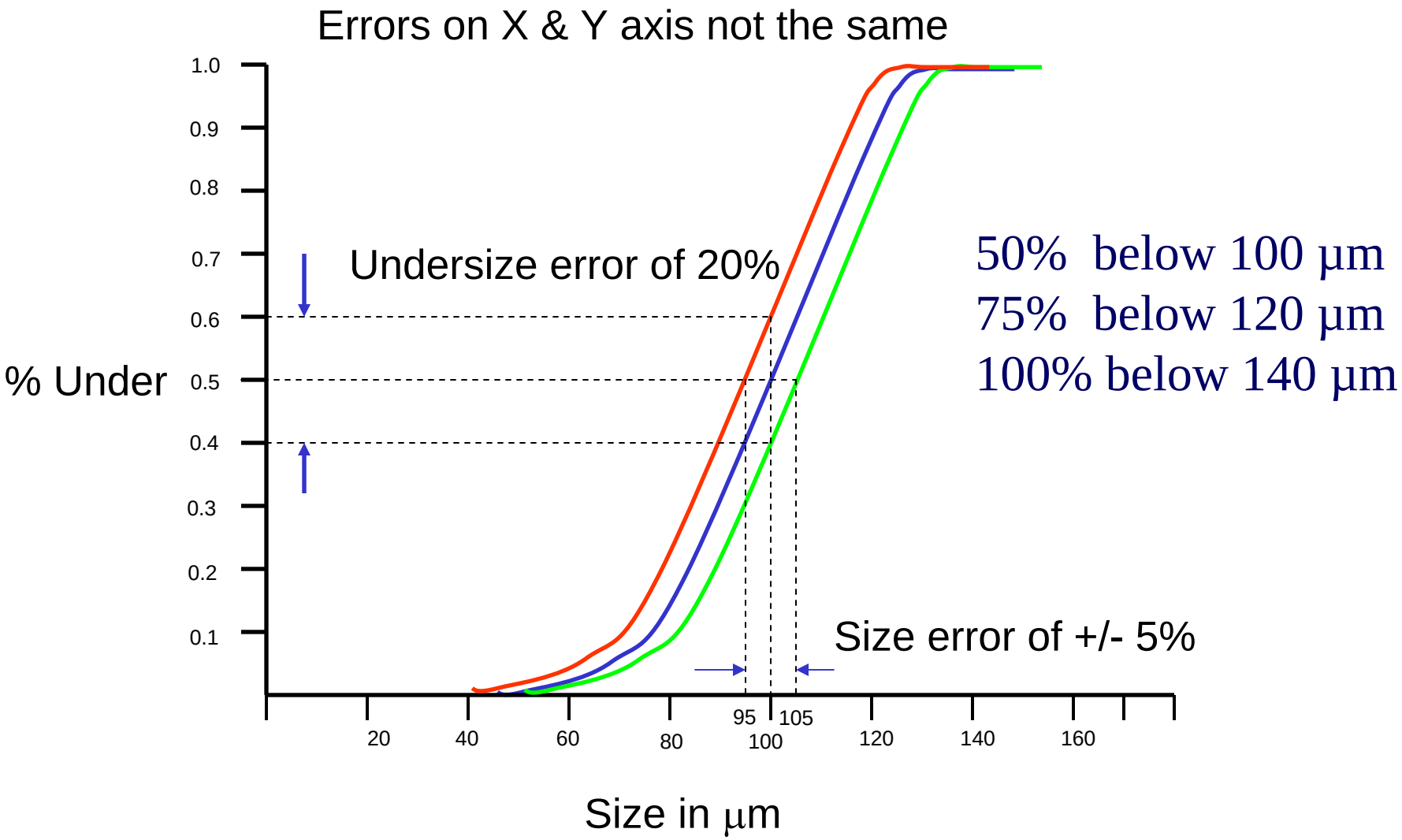
Spec. (Laser Diffraction)
90% particles: NMT 100 µm

Testing results
D90: 3.7 – 6.2 µm



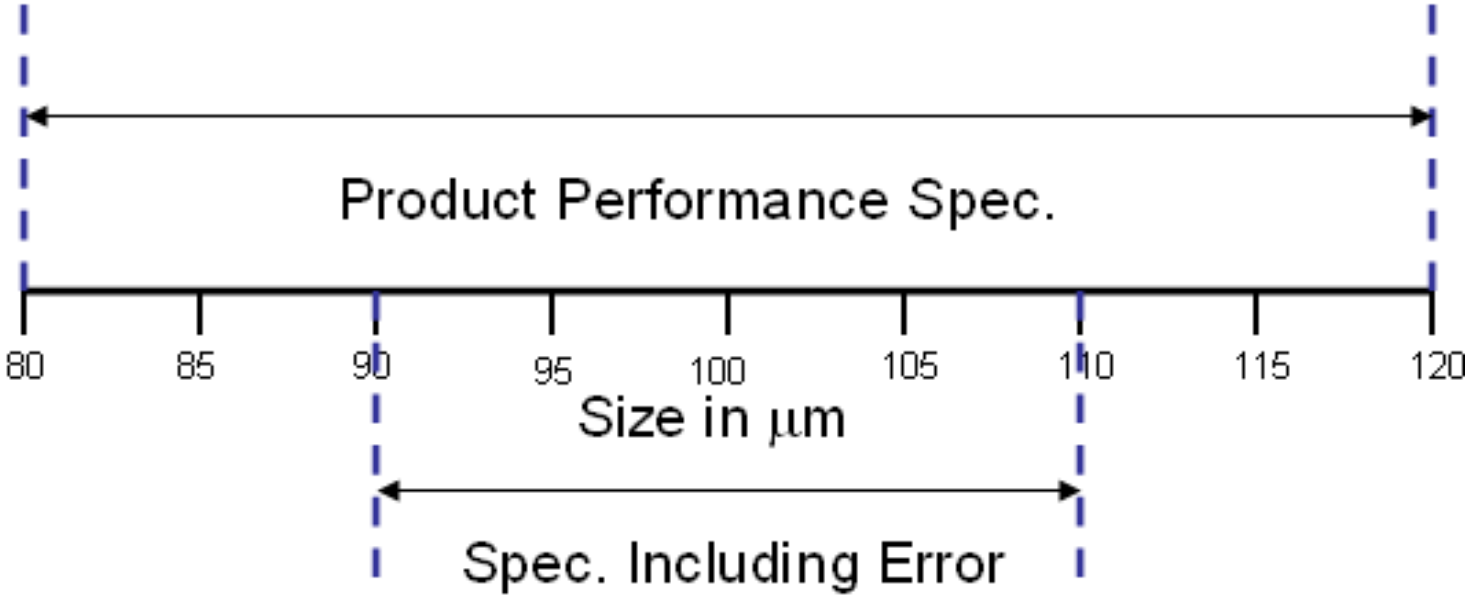
One-sided limit is not adequate without scientific justification.

Specification on X or Y Axis



Specification with Error

Must tighten internal spec by lab error %
Then product always within performance specification



http://www.spcpress.com/pdf/Manufacturing_Specification.pdf, By David Wheeler

Specification with Error

- Must tighten internal spec by lab error
- Therefore minimize lab error makes life easier
- How to minimize error?
  - Get sampling right
  - Structured method development
  - Eye on the goal: reproducibility

Conclusions

- Specifications based on product performance
- Tighten internal specification to include measurement error
- Report results in format created by instrument
  - Zave & PI intensity from DLS
  - Volume results from laser diffraction
- Standards provide help to set specifications
- Avoid Dv100 with laser diffraction
- Use D 4,3 if performance sensitive to small amount of large particles

http://www.horiba.com/scientific/products/particle-characterization/

To Learn More

http://www.horiba.com/scientific/products/particle-characterization/