Assessing Particle Counting Techniques to Improve the Regulatory Review of Complex Colloidal Drug Products

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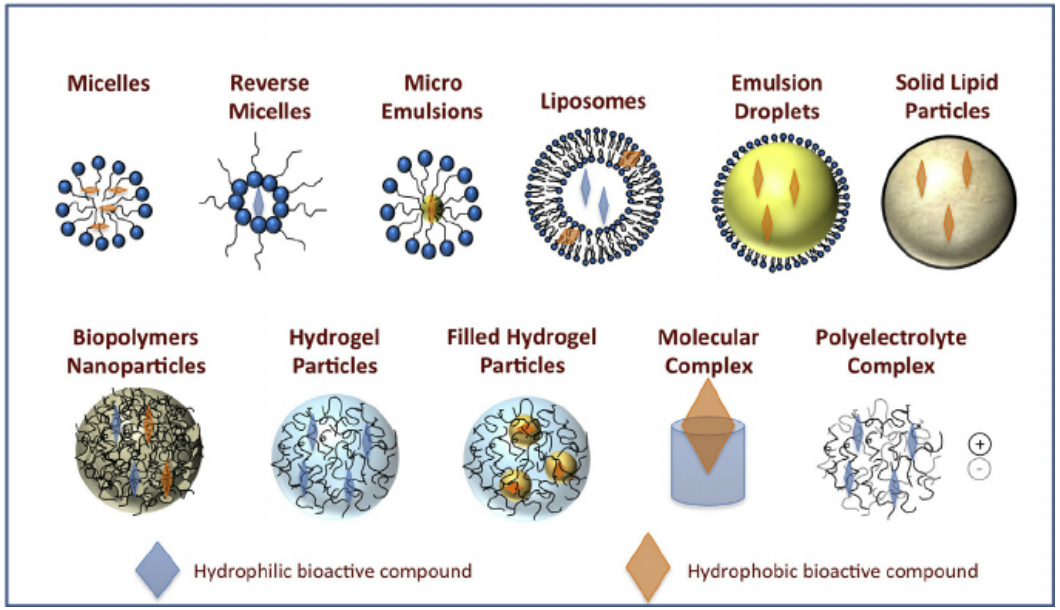
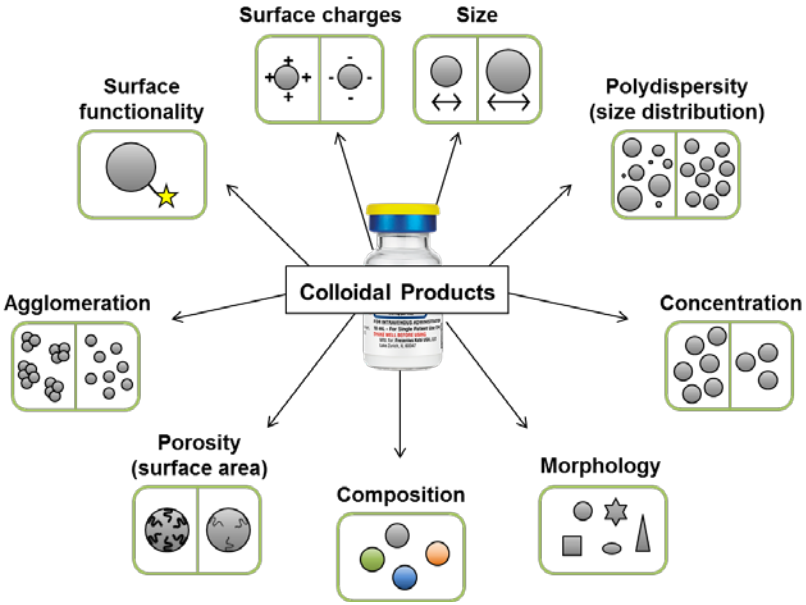
Outline

- Colloidal Drug Delivery System: Injectable emulsion
  - Physiochemical properties: Globule size distribution, particle concentration, morphological characteristics and stability.
- Validation of high resolution single particle counting techniques
  - Nanoparticle Tracking Analysis (NTA).
  - Tunable Resistive Pulse Sensing (TRPS).
  - Reference: Dynamic Light Scattering (DLS)
- Particle size and concentration analysis for 1% Propofol Injection Emulsion
  - Batch-to-Batch sameness assessment.
  - Reference-to-Generic sameness assessment.

Colloids in Drug Delivery System





Ref. J.J. Iris, *et. al., Trends Food Sci Tech*. 2015.

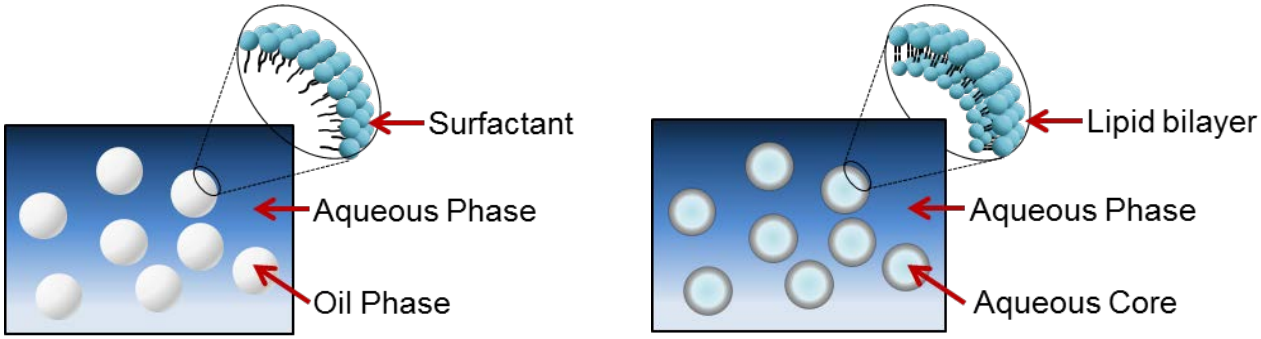
- Broad size range: nanometer – micrometer
- Complex shapes and structure
- In vitro physicochemical properties
  - Viscosity profile as a function of applied shear
  - pH, Osmolality, free acid concentration
  - Zeta potential of the formulation
- Particle diameter represents a specific property of the particle

Colloids in Drug Delivery System: O/W Emulsion and Liposomal Products

Purpose:
To increase bioavailability (oral absorption or drug solubility)
To reduce toxicity of active pharmaceutical ingredients

Based on application:
Oral , Topical (skin, nasal, ocular, rectal, and vaginal), and Parenteral application (intravenous injection).

Products:
- Cyclosporine **emulsion**, Difluprednate emulsion,
- Doxorubicin HCl **liposome** injection, Amphotericin B liposome injection,
- Iron sucrose injection, Iron dextran injection, Sodium ferric gluconate injection, Ferumoxytol injection, and etc.



In vitro Physicochemical Properties of Injectable Emulsion

Draft Guidance on Propofol

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Propofol

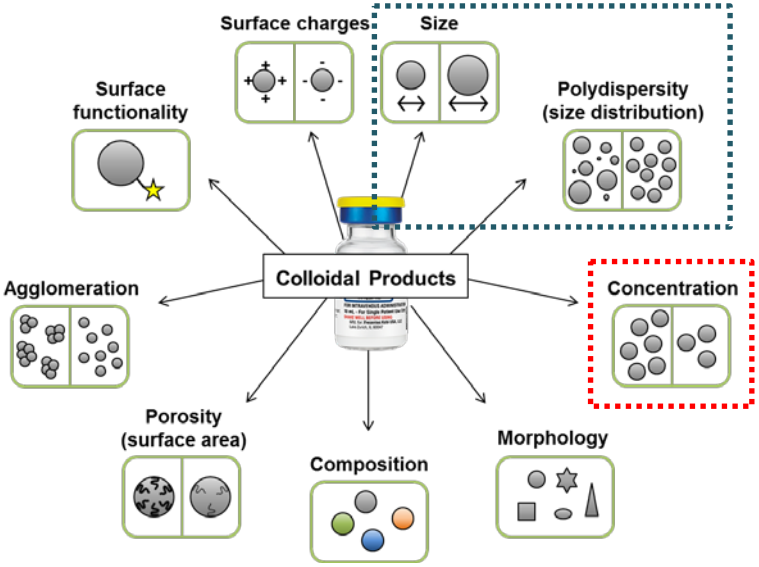
Dosage Form; Route: Injectable; injection

Strength: 10 mg/ mL

Recommended Study: Two options: In vitro or In vivo studies

I. In vitro option:

To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all the following criteria should be met:



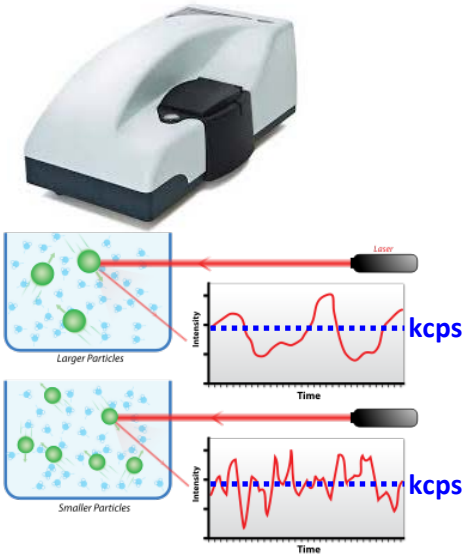
- **Product Specific Guidance (PSG)**
  - *In vitro testing for BE*
    - Component (Q1)/ Composition (Q2) in the formulation
    - Physicochemical equivalence
      - **Globule size distribution (GSD)**

- **Purposes**
  - *Batch-to-Batch Sameness*
    - To ensure **product quality** and consistency
    - To assess physiochemical properties (e.g. stability, agglomeration, delivered dose amount, and drug release rate)
  - *Brand-to-Generic Sameness*
    - To ensure structural sameness of generic products (**bioequivalence** assessment)
    - To ensure therapeutic equivalence

Could the particle concentration be one of critical attributes?

Evaluating Current Particle Analyzers

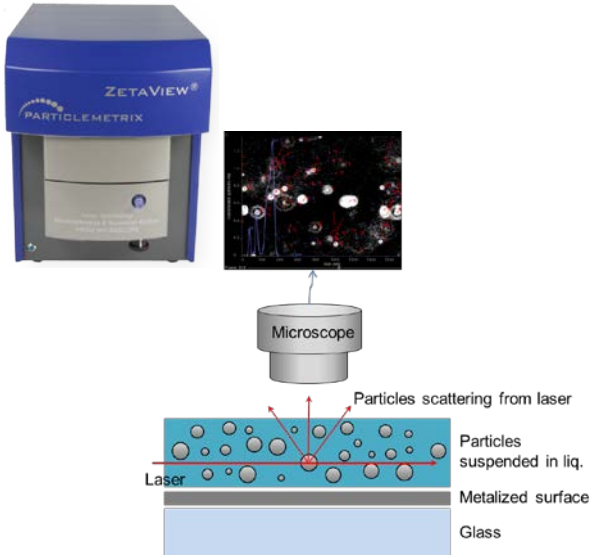
Dynamic Light Scattering (DLS)



Commonly employed instrument
ISO 22412:2008
Ensemble Size: $D_t = \frac{2k_B T}{3r_h \pi \eta}$

Concentration C_2
$\propto$ Mean count rate (kcps)

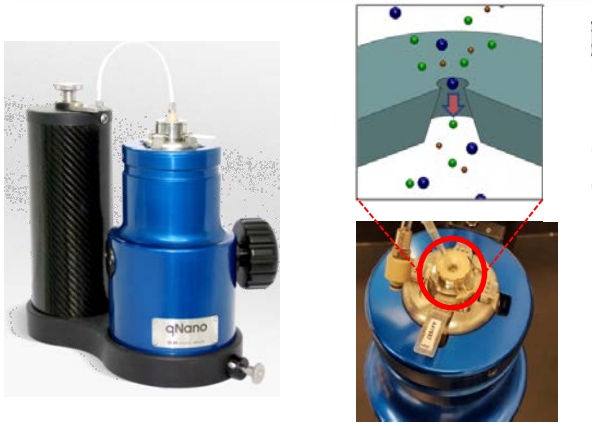
Nanoparticle Tracking Analysis (NTA)



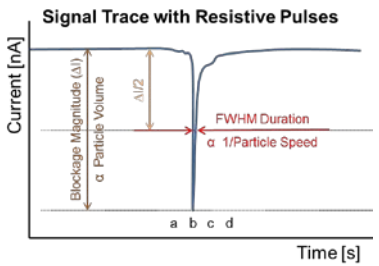
Newer instrument
ISO 19430:2016
Single particle: $D_t = \frac{2k_B T}{3r_h \pi \eta}$

Concentration C_2
$= \frac{\text{Number of tracked nanoparticles}}{\text{Analytical Volume}}$

Tunable Resistive Pulse Sensing (TRPS)



The Newest instrument
Single particle:



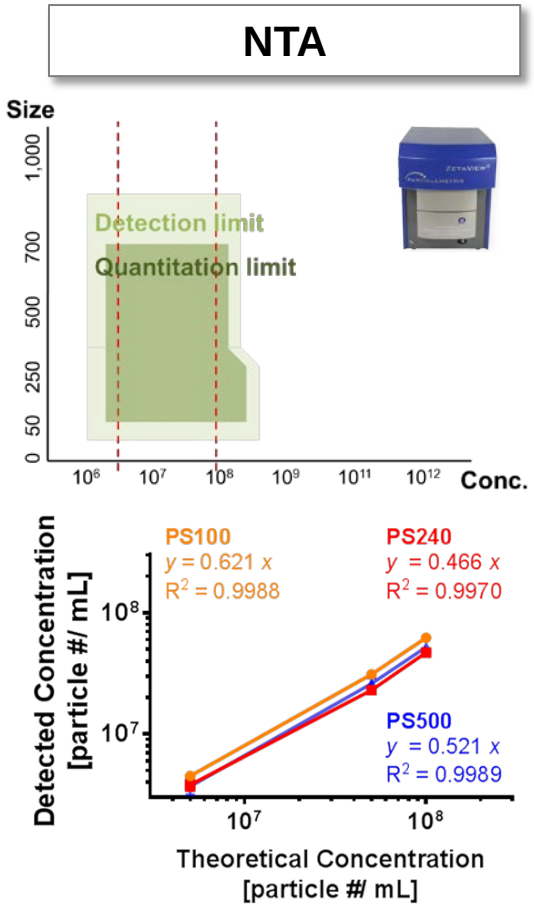
Concentration C_2
$= C_1 \times \left(\frac{\text{Sample Freq of resistive pulses}}{\text{Stand Freq of resistive pulses}}\right)$

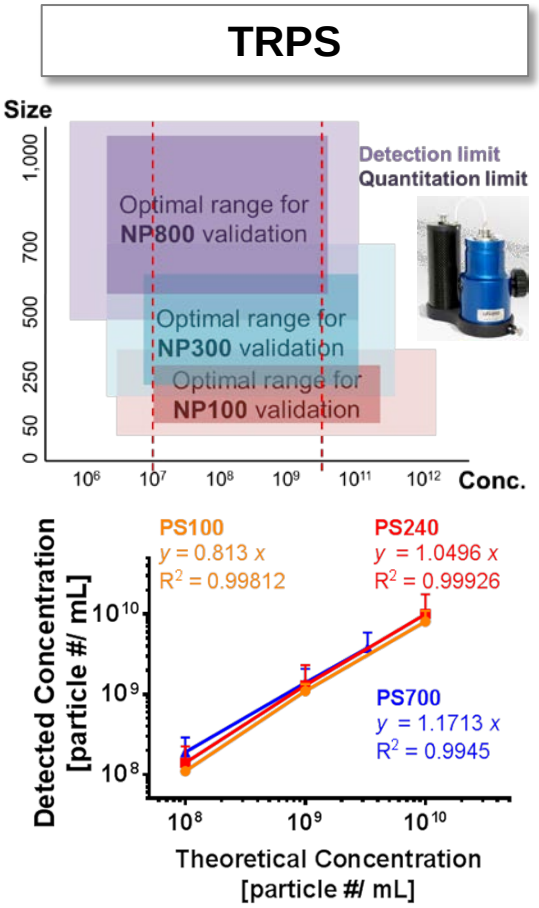
Can New Single Particle Counting Methods Accurately Measure the Concentration?

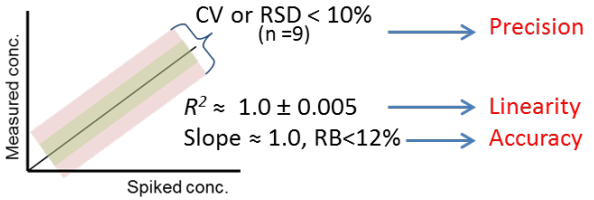
Evaluating Analytical Capabilities: Concentration Measurement Detection and Quantification Limits

Validation for single particle analyzers (linearity, accuracy, and precision)

: An accurate and precise measurement over a wide analytical range is important for product development and regulatory use.







	NTA	TRPS
Intra-day variation	4.3% - 8.3%	47.9% - 101.2%
Inter-day variation	3.9%	14.3%
Precision (total)	7.0%	61.7%

Polystyrene nanosphere standards 240 nm, 1E8/mL

	NTA	TRPS
Linearity	High	
Accuracy	Intermediate	High
Precision	High	Low

Evaluating Measurement Robustness: Impact of Polydispersed Samples

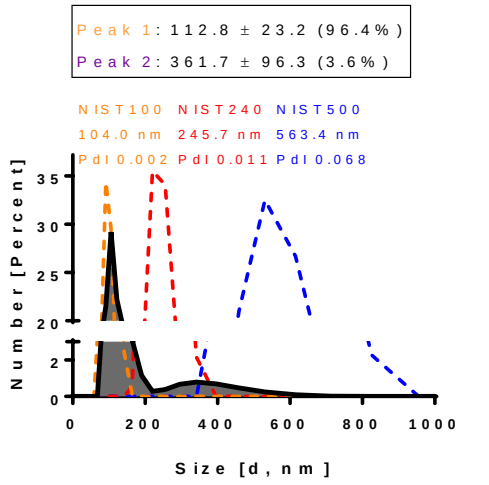
Validation for single particle analyzers (robustness)

: It is important that techniques are sensitive and accurate to measure polydispersed dispersions that can arise from manufacture and/or storage.

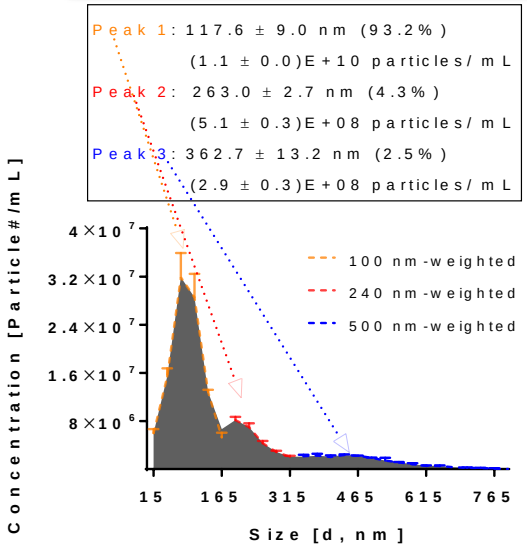
Mixture of equal masses of polystyrene nanospheres

: 100 nm (6.0E+10/mL, 94%), 240 nm (3.3E+09/mL, 5%), and 500 nm (5.0E+08/mL, 1%).

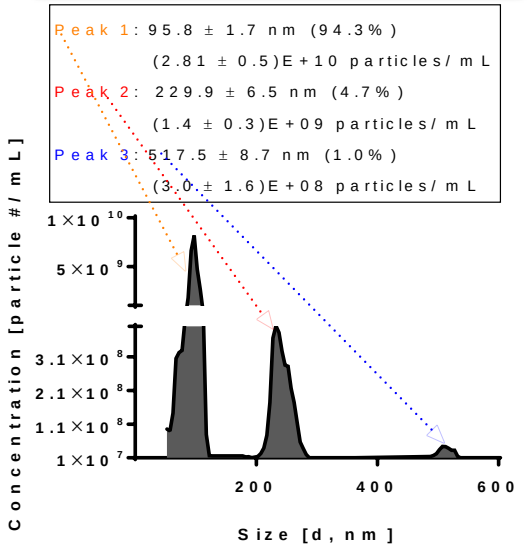
DLS



NTA



TRPS



	DLS	NTA	TRPS
Size	Lowest resolution	Intermediate resolution	Highest resolution
Concentration ratio%	intermediate	Close to the actual	Closest to the actual

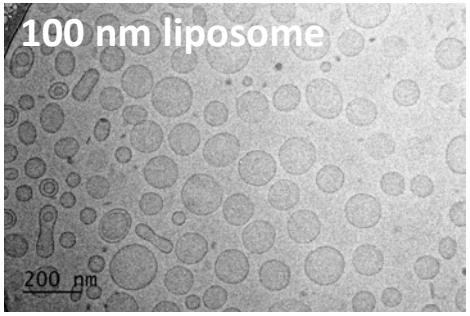
Liposomal Components do not Affect Particle Analysis

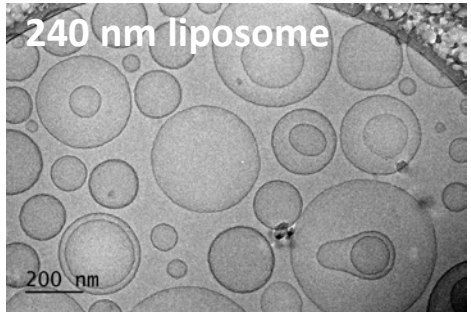
Validation for single particle analyzers (liposomes)

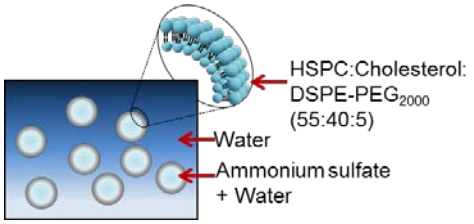
: Instrument accuracy should not be affected by particle material properties.

: A large majority of complex drug products are formulated as liposomes.

Material	RI
Water	1.33
PS	1.57
Phospholipid	1.44
Soybean oil	1.47







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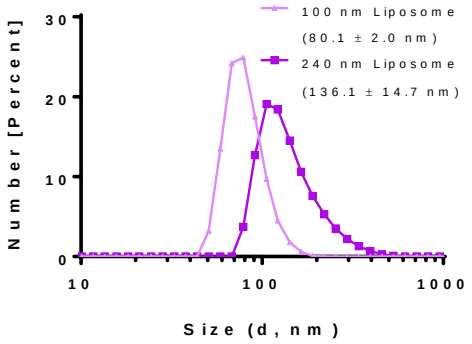
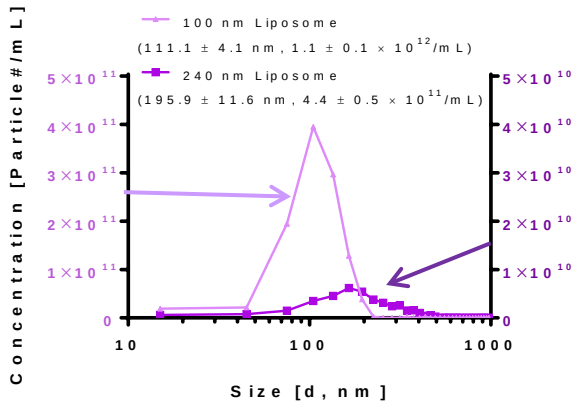
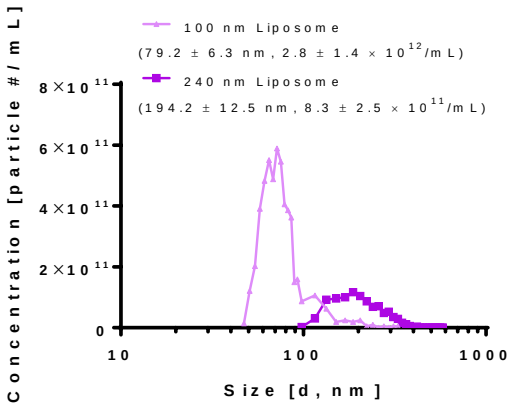


NTA



TRPS



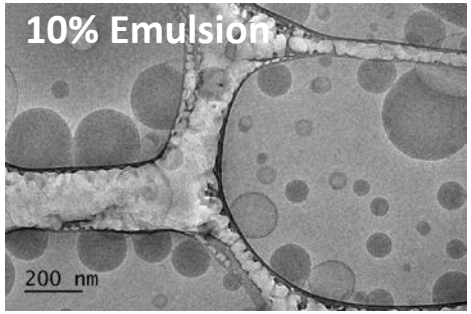
The size and concentration measurements are sensitive measure of product difference. i.e., as the size increased, the concentration decreased at equal mass (Q1/Q2 sameness).

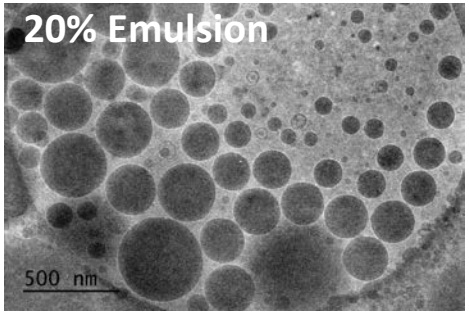
Emulsion Components do not Affect Particle Analysis

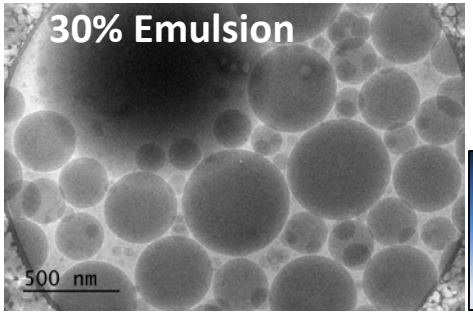
Validation for single particle analyzers (emulsion)

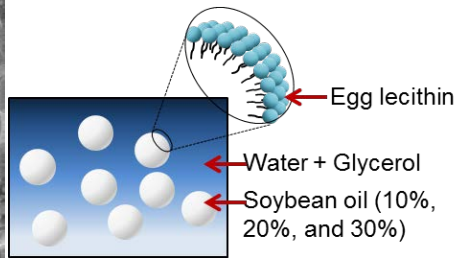
: Instrument accuracy should not be effected by particle material properties.

: A large majority of complex drug products are formulated as oil-in-water emulsions.

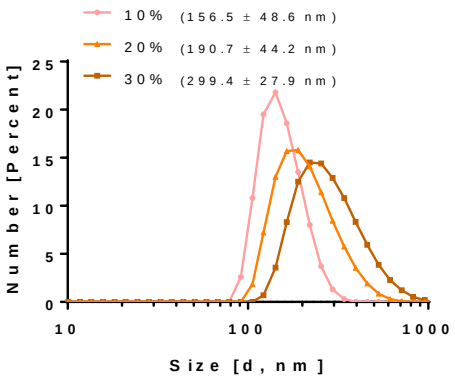




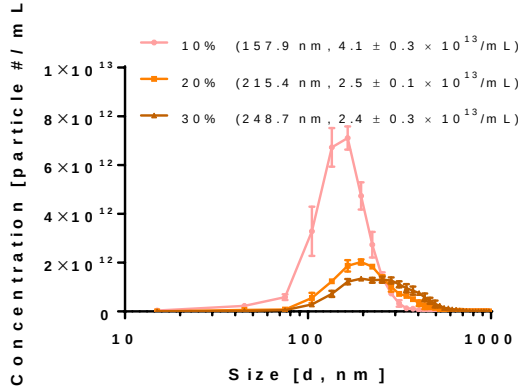




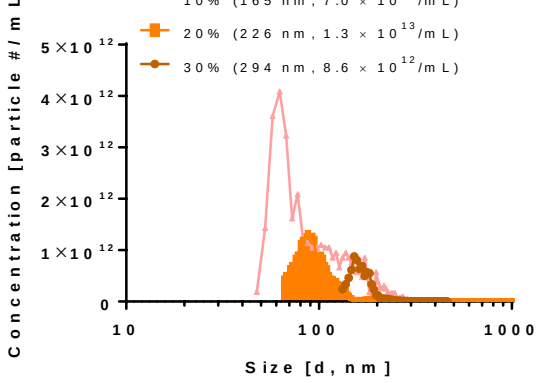
DLS



NTA

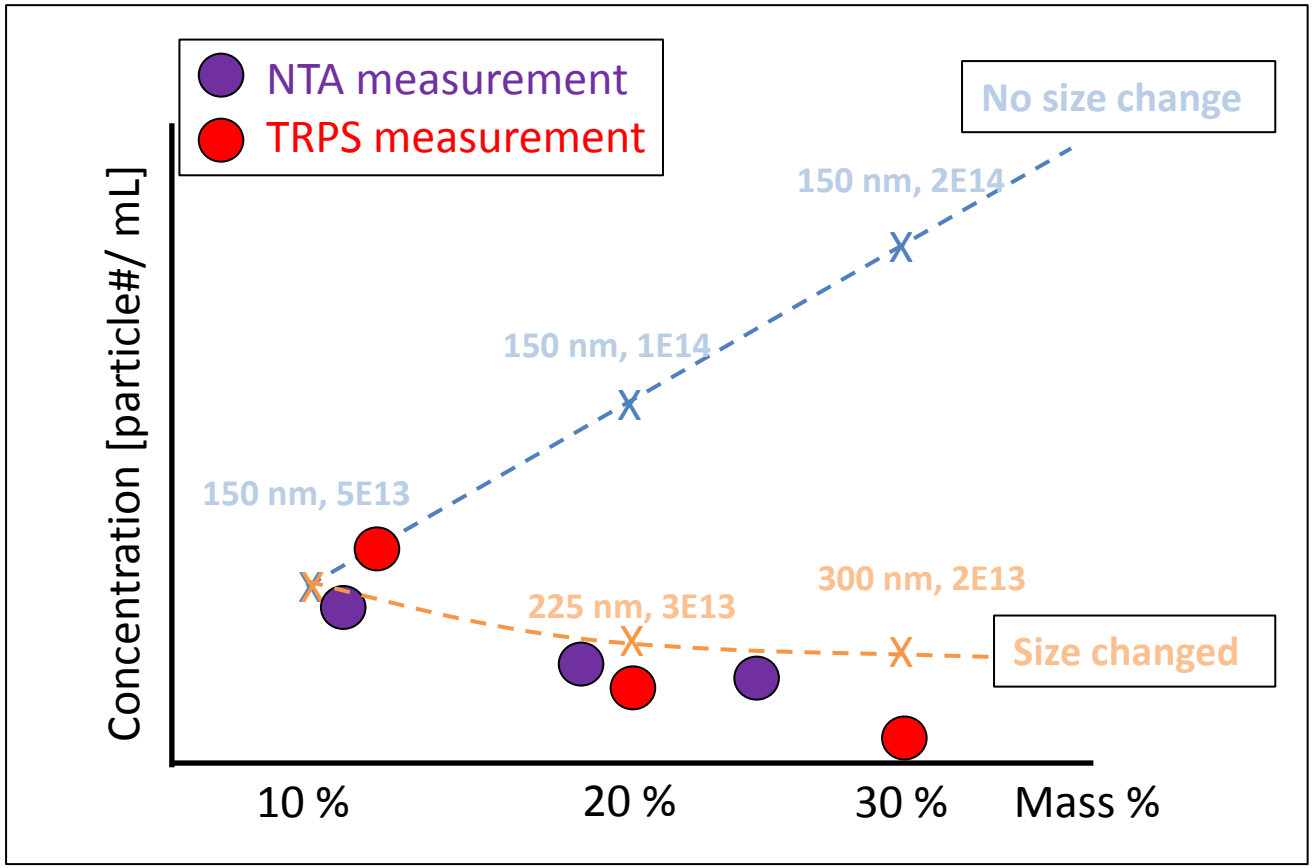


TRPS



As the portion of oil mass increases (Q1 sameness and Q2 difference), both particle size and concentration are changed.

Particle Size is still More Sensitive to Measure the Product Differences



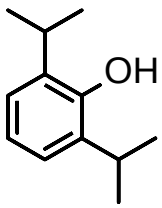
$$\text{Concentration} \propto \frac{\text{Mass}}{(\text{Particle diameter})^3}$$

The size is still more sensitive measure of product difference, but the concentration measurement supports that. i.e., the size increased rather than the concentration as expected.

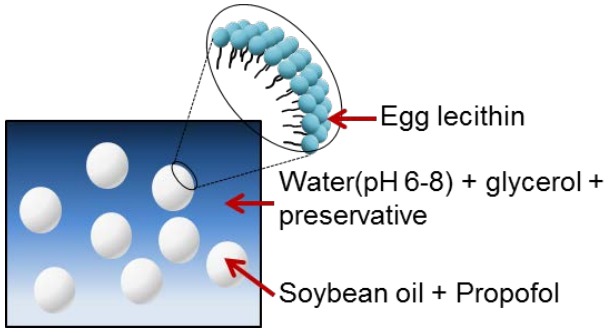
Assessing Product Quality of Approved Injectable Emulsion

Propofol 1% Oil-in-Water Injectable Emulsion

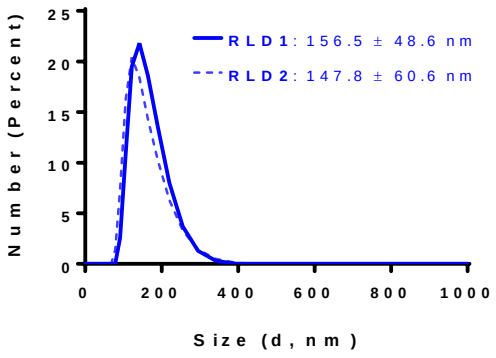
: Products need to meet physicochemical specifications to ensure batch-to-batch product quality .



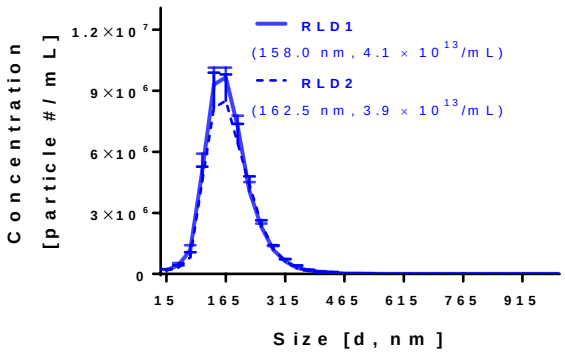
$C_{12}H_{18}O$
Mw. 178.28
Solubility: 124 mg/L
pKa: 11.1
Log P: 3.8



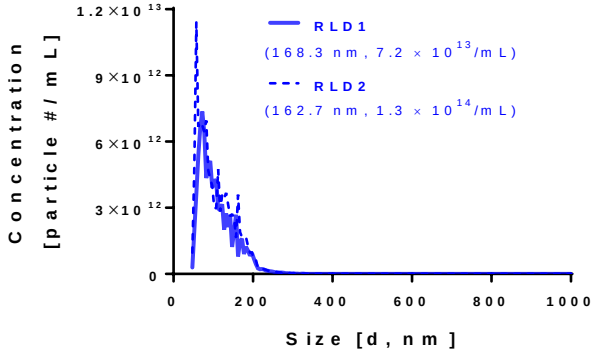
DLS



NTA



TRPS



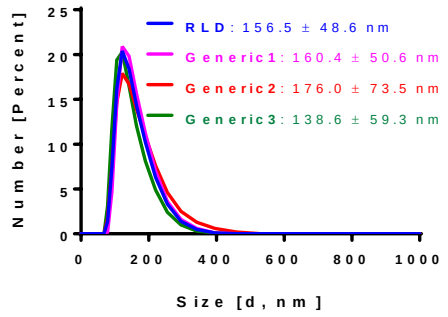
All techniques detect no significant differences in particle size and concentration distribution between batches of reference-listed drug (RLD, brand name drug).

Assessing Reference-to-Generic Sameness of Injectable Emulsion Products

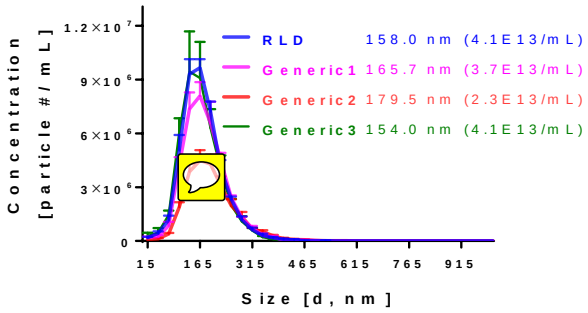
1 Reference-listed drug (RLD) and 3 Generics with qualitatively (Q1) and quantitatively (Q2) same formulations

: Ensuring a generic product has comparable physicochemical properties to the innovator product is key to supporting determination of product equivalence.

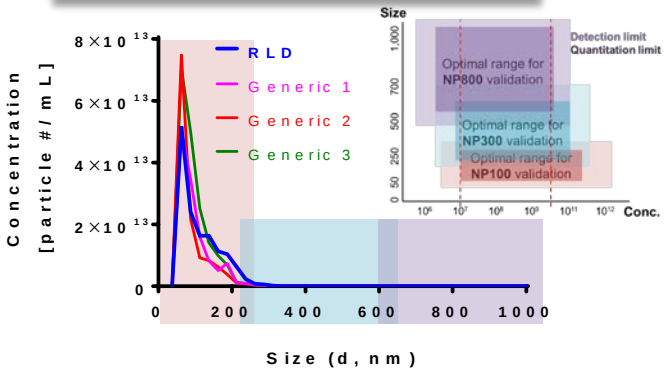
DLS

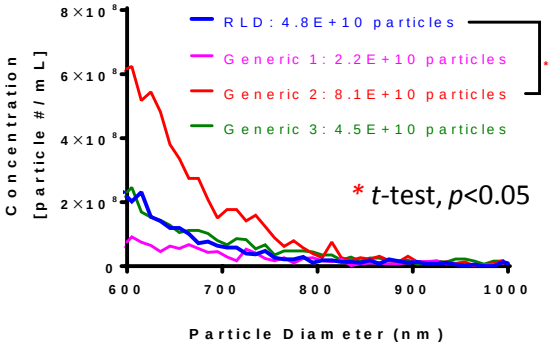


NTA



TRPS





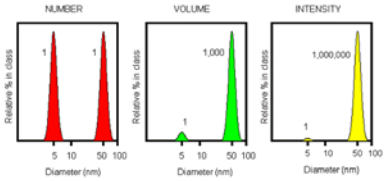
- Acceptance criteria: Population Bioequivalence(D_{50}-SPAN, 95% CI).
- Size distribution: All products pass PBE criteria.
- Particle concentration distribution could be used to support the PSD-based assessment.

Conclusions

- The assessment of *in vitro* physicochemical properties of colloidal products is important to ensure their pharmaceutical quality and bioequivalence. For this regulation purpose, the validation of analytical techniques is essential prior to analyze the difference between the complex products.

- Propofol IV injection is a monodispersed oil-in-water emulsion product.
  - Minimal batch-to-batch variance
  - Reference-to-generic variance in acceptance criteria for particle size specification range
  - Population bioequivalence using particle size distribution and particle concentration

- Each technique has different detection mechanisms, advantages and limits.
- *DLS*:
  - Well-established



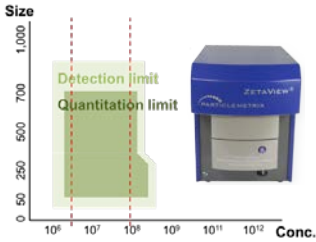
Ref. www.malvern.de.

$I \propto r^6$

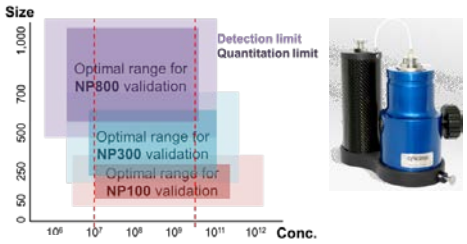
  - The lowest resolution: not suitable for heterogeneous products with a broad distribution due to its higher sensitive to large particles

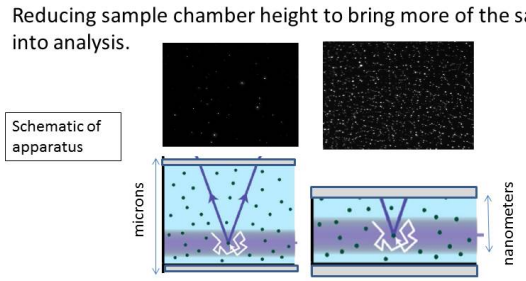
Conclusions (Continuous)

- *NTA*:
  - High repeatability/reproducibility/precision
  - Intermediate robustness/accuracy
  - Semi-automatic system
  - High camera setting-dependency/ Uncertainty from arbitral analytical volume



- *TRPS*:
  - High accuracy/size-based fraction
  - Low repeatability/reproducibility/precision
  - High calibration-dependency/ Least automatized



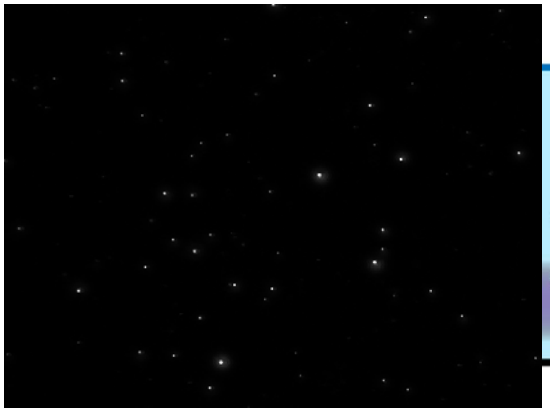


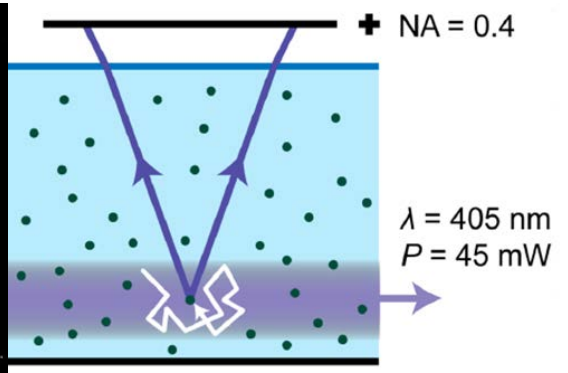
Ongoing Project with NIST to Develop a Simple and Practical NTA with Better Accuracy

FDA

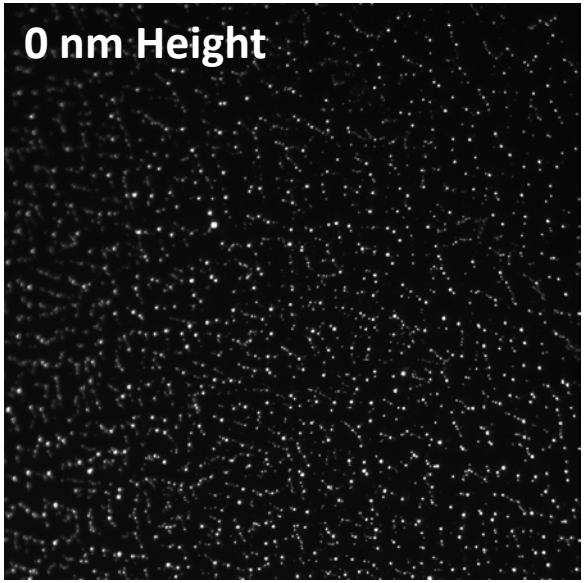
NIST National Institute of Standards and Technology U.S. Department of Commerce

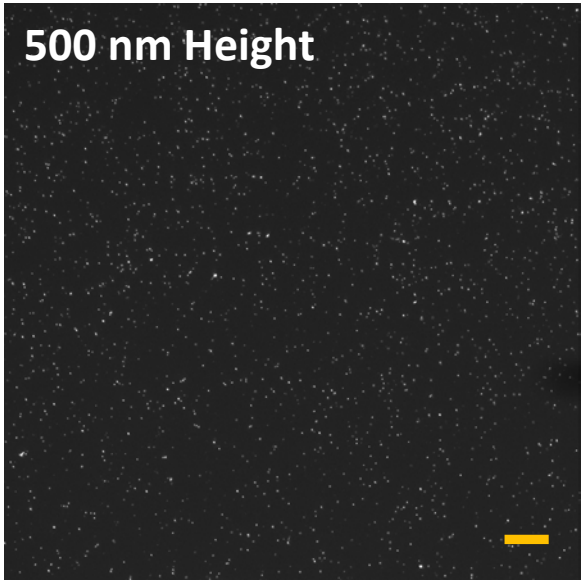
- NTA is close to USP acceptance criteria for analytical method validation.
  - Significant sample dilution required
  - Analytical volume
  - Multiple focal planes

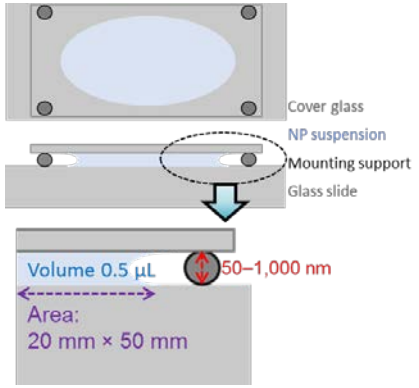




Ref. Edwin van der Pol, et. al., *Nano Lett.* 2014.







1,000x diluted Propofol emulsion
Dispersed in DDI water
20x (NA0.8); LED (460 nm); Ex100 ms
5x faster; scale: 100 µm

Acknowledgements

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