Characterization of Nanomaterials

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Outline

- Overview of regulatory consideration about nanomaterials
- Characterization of nanomaterials
- Consideration for generic nano product development and characterization
- Regulatory research in nano drug product characterization

Nanomaterials (US FDA)

- Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1–100 nm), and
- Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer

Considering whether an FDA regulated product involves the application of nanotechnology
http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

Nanomaterials

Health Canada

Any manufactured substance or product and any component material, ingredient, device, or structure to be nanomaterial if:

• It is at or within the nanoscale in at least one external dimension, or has internal or surface structure at the nanoscale, or;

• It is smaller or larger than the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena.

For the purposes of this definition:
• "nanoscale" means 1 to 100 nanometres, inclusive;
• "nanoscale properties/phenomena" means properties which are attributable to size and their effects; these properties are distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material; and
• "manufactured" includes engineering processes and the control of matter.

Policy Statement on Health Canada's Working Definition for Nanomaterial, Oct 6, 2011

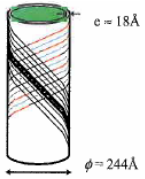
EMA

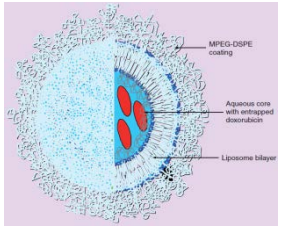
- Nanomedicine is defined as the application of nanotechnology in view of making a medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometre scale

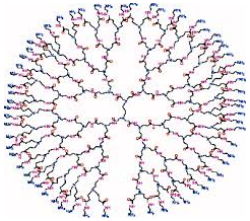
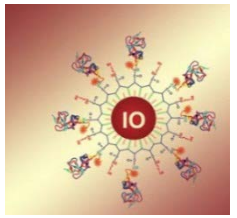
- Nanotechnology is defined as the production and application of structures, devices and systems by controlling the shape and size of materials at nanometre scale. The nanometre scale ranges from the atomic level at around 0.2 nm (2Å) up to around 100 nm.

FDA's Position on Nanomaterials

"The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit examination. However, FDA does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful."



Regulatory Consensus on Nanomaterials

1st International Workshop on Nanomedicines (2010)

" - The current regulatory framework based on benefit/risk approach and including risk management plan and environmental risk assessment is adequate for development and evaluation of current applications in pharmaceuticals.

.....

- Current regulatory experience allows the assessment of many aspects of nanomedicines, but there is a scientific gap between the current knowledge and the more advanced and emerging nanomedicines. Scientific research to fill the gap"

Regulatory Pathways for FDA-regulated Drug Products Containing Nanomaterials

- 505(b)(1), 505(b)(2), and 505(j) apply to drug products containing nanomaterials

- All current CDER guidance documents, recommendations, and requirements for the evaluation and maintenance of quality, safety, and efficacy of products apply to drug products containing nanomaterials

Regulatory Pathways

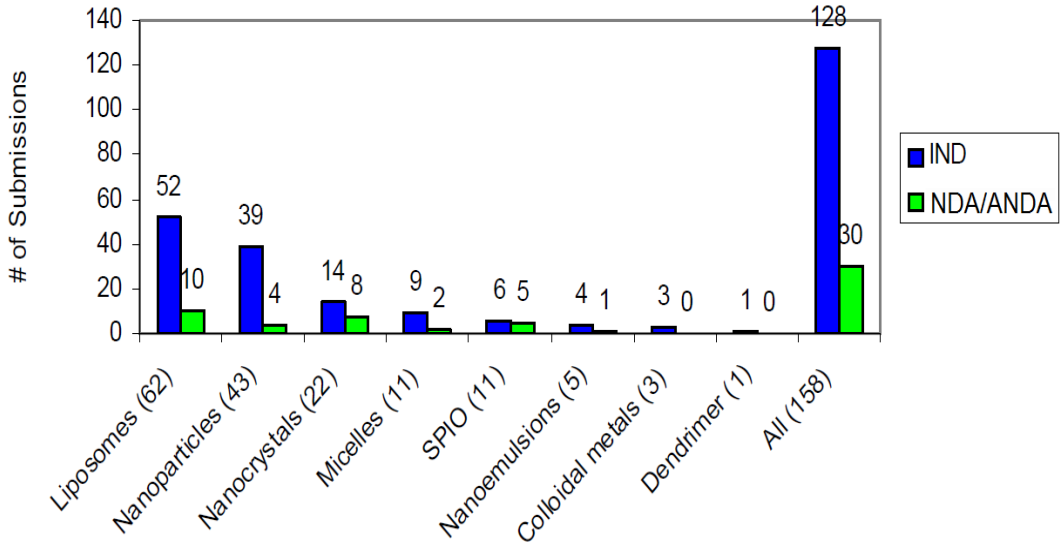
505(b)1	505(b)2	505(j)
• contains full reports of investigations of safety and effectiveness • Data either owned by the applicant or for which the applicant has obtained a right of reference	• contains full reports of investigations of safety and effectiveness • where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use	contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and intended use, among other things to a previously approved application (the reference listed drug (RLD).
Requires extensive data to establish saftey and effectiveness, adequate production methos, appropriate labeling	Provide information to establish	No requests of clinical safety/efficacy studies but are required to establish bioequivalence to the RLD.
Doxorubicin HCl injection Pharmacia and Upjohn, 1974	Doxorubicin HCl liposome injection (Doxil) Janssen, 1995	Generic doxorubicin HCl liposome injection Sun Pharm, 2013

FDA Guidance on Nanotechnology to Industry

- Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology
- Safety of Nanomaterials in Cosmetic Products
- Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives
- Draft Guidance for Industry – Use of Nanomaterials in Food for Animals
- Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues
- Draft Guidance for Industry and FDA Staff - 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device

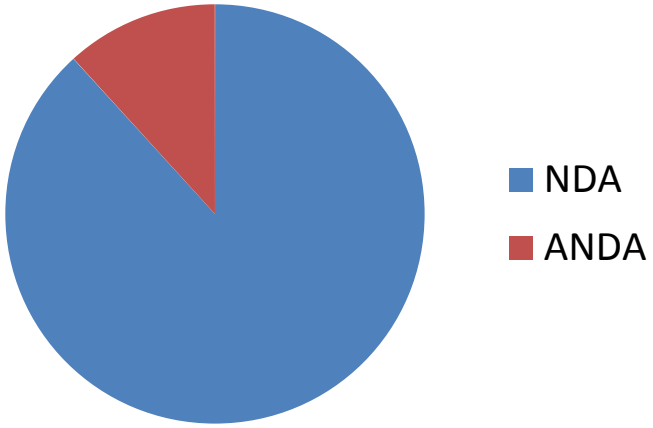
http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301114.htm#guidance

Nano Drug Submissions and Approvals (US FDA)



IND/NDA/ANDA submissions containing nanomaterials (by 2012)

Approved NDA/ANDA products containing nanomaterials (by 2015)



Total > 50

Sadrieh, N. 2012 Overview of CDER Experience with Nanotechnology-related Drugs. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315773.pdf

Types of Approved Nanomaterials

Platform	Example		
	Name	NDA Approval	Indication
Liposome	DOXIL® (Doxorubicin)	1995[1]	Cancer
Inorganic nanoparticle	FERRLECIT® (Sodium ferric gluconate complex)	1999[2]	Anemia
Protein nanoparticle	ABRAXANE® (Paclitaxel)	2005	Cancer
Polymer nanoparticle	MACUGEN® (Pegaptanib sodium)	2004	Macular degeneration.
Emulsion	RESTASIS® (Cyclosporine)	2002	To increase tear production
Lipid complex	AMPHOTEC® (Amphotericin B)	1996	Invasive aspergillosis
Nanotube	SOMATULINE DEPOT® (Lanreotide acetate)	2007	Acromegaly
Nanocrystal	TRICOR® (Fenofibrate)	2004[3]	Hypercholesterolemia
Micelle	TAXOTERE®(Docetaxel)	1996	Cancer

[1] First ANDA approval in 2013
[2] First ANDA approval in 2011
[3] First ANDA approval in 2011

Characterization of Nanomaterials

21 CFR 314.50(d) requires:

- Full description of physical and chemical characteristics and stability for the drug substance
  - Particle size, crystalline form, surface area/volume/coatings, etc…
- Identity
- Strength
- Quality
- Purity
- Potency
- Bioavailability
- Manufacturing Process and Controls
- Analytical procedures

Including alternative procedures

Physico-chemcial characterizations

- Nanomaterial components
  - Lipids/carbohydrates
  - Free drug vs nanomaterial-associated drug
  - ….
- Nanomaterial higher order structure
  - Size, size distribution
  - Morphology
  - Surface properties
  -……
- Nanomaterial performance
  - In vitro release
  -…..

Instrumentation

- **Spectroscopy**
  - Mass Spectroscopy
  - Nuclear Magnetic Resonance
  - UV-Vis
  - Infrared
  - Raman
  - Fluorescence
  - Refractive Index
  - XPS
- **Chromatography/Separations**
  - HPLC
  - GC
  - FPLC
  - Size Exclusion
  - Asymmetric Field-flow Fractionation
  - Centrifugal FFF
  - Disc Centrifuge
  - Analytical Ultracentrifugation
  - Capillary Electrophoresis
  - Gel Electrophoresis
- **Microscopy**
  - Transmission Electron Microscopy
  - Scanning Electron Microscopy
  - Atomic Force Microscopy
- **Scattering/Diffraction**
  - Dynamic Light Scattering/ZP
  - Static Light Scattering
  - Electron Diffraction
  - X-ray Diffraction
  - Neutron Diffraction
- **Other**
  - Surface Plasmon Resonance
  - Polarimetry
  - Laser Diffraction
  - Microchannel Resonator
  - Nanoparticle Tracking (Nanosight)
  - Coulter Counter (qNano)
  - Liquid Surface Area (Acorn; NMR)
  - Gas Adsorption System (BET)
  - Charge Titration (ZP)
  - TGA/DSC

Particle Size Analysis Method

Technology	Advantages	Limitations	Notes
Dynamic light scattering (DLS)	- Ease of use and fast analysis - Broad dynamic range, ~ 1 to 1,000 nm - High sensitivity and reproducibility for monodisperse,homogenous samples	- Low resolution for polydisperse, heterogeneous samples - Requires transformative calculations with assumptions that must be considered when interpreting data – particularly with polydisperse samples - Assumes spherical shaped particles	Coupling to a separation technique (e.g., SEC or FFF)
Electron microscopy (SEM, TEM, Cryo-TEM)	- Visual size measurement and morphology properties - Good for electron dense particles	- Labor intensive and time consuming - Sample prep and staining may affect particle character and produce artifacts - Limited representation	Cryo-TEM for “soft” particle

Atomic force microscopy, Nanoparticle tracking analysis…..

Adapted from 2015 Nano Alliances Report

Dynamic Light Scattering Particle Size Reporting

Nanoemulsion
Stock diluted 1000-fold in water
25° C, RI = 1.332, η = 0.890 cP
Low volume quartz cuvette, b = 10 mm
633 nm laser λ, 173° scattering angle

Polydispersed multimodal peaks observed in intensity- and volume-weighted distribution.

Single peak observed in number-weighted distribution.

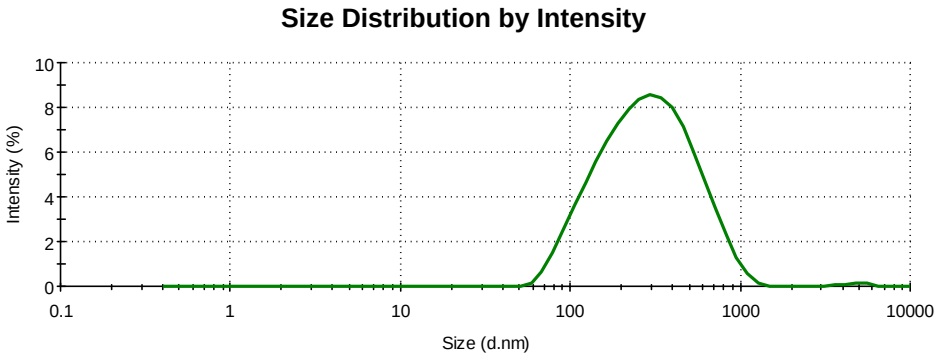
Intensity-weighted distribution used for reporting size.

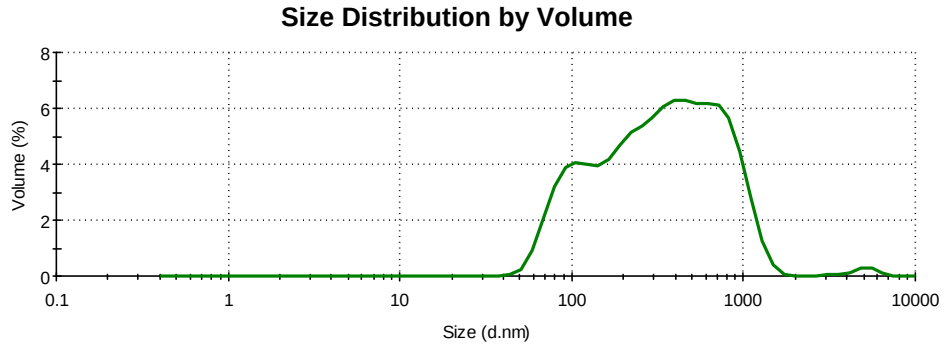
Volume-weighted distribution used for relative amounts.

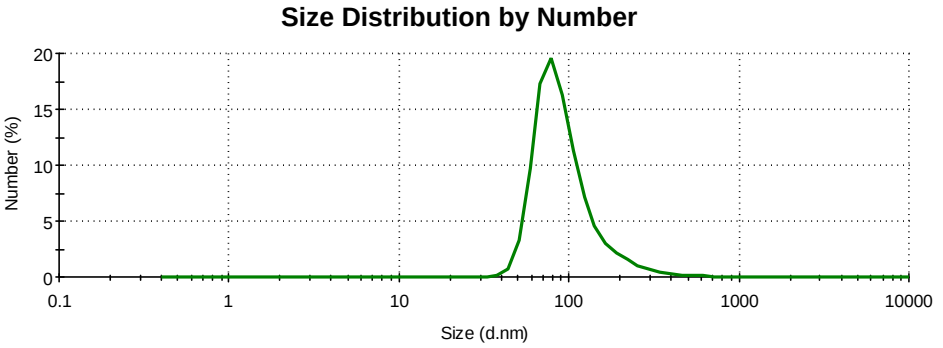
Number-weighted distribution should be avoided because several assumptions are involved in the transformation.

http://www.malvern.com/en/support/resource-center/technical-notes/TN101104IntensityVolumeNumber.aspx

Courtesy of Anil Patri







Results are an average of at least 10 measurements

Dynamic Light Scattering
Sample Preparation - Filtration

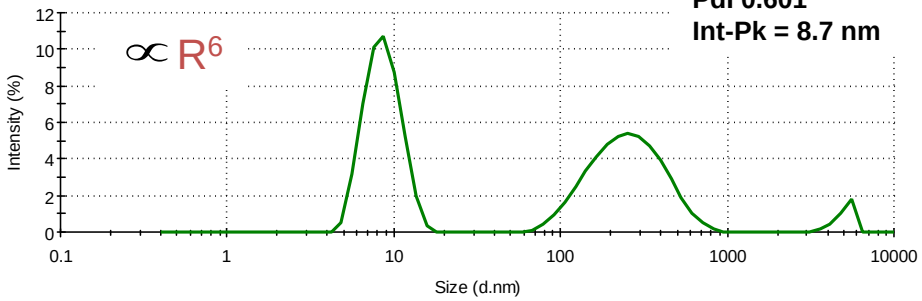
G6-NH_2 dendrimer in PBS
2 mg/mL,
25° C, RI = 1.334, η = 0.911 cP
Low volume quartz cuvette, b = 10 mm
633 nm laser λ, 173° scattering angle

- **Note the Z-Average and PdI for unfiltered sample**
- **Importance of filtering samples**

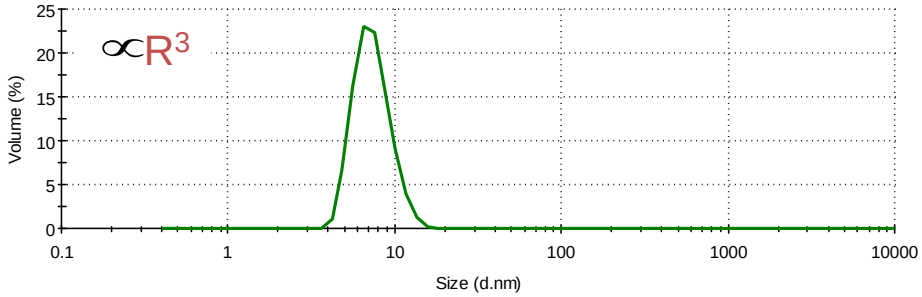
Sample not filtered

Size Distribution by Intensity

Z-Average 43.5 nm
PdI 0.601
Int-Pk = 8.7 nm



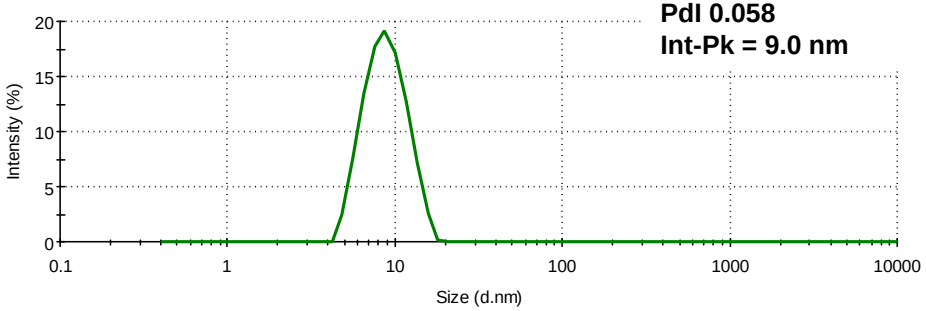
Size Distribution by Volume



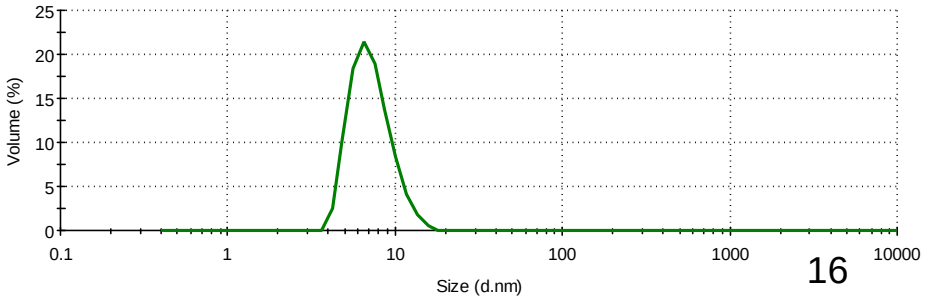
Sample 0.02 µm filtered

Size Distribution by Intensity

Z-Average 8.4 nm
PdI 0.058
Int-Pk = 9.0 nm



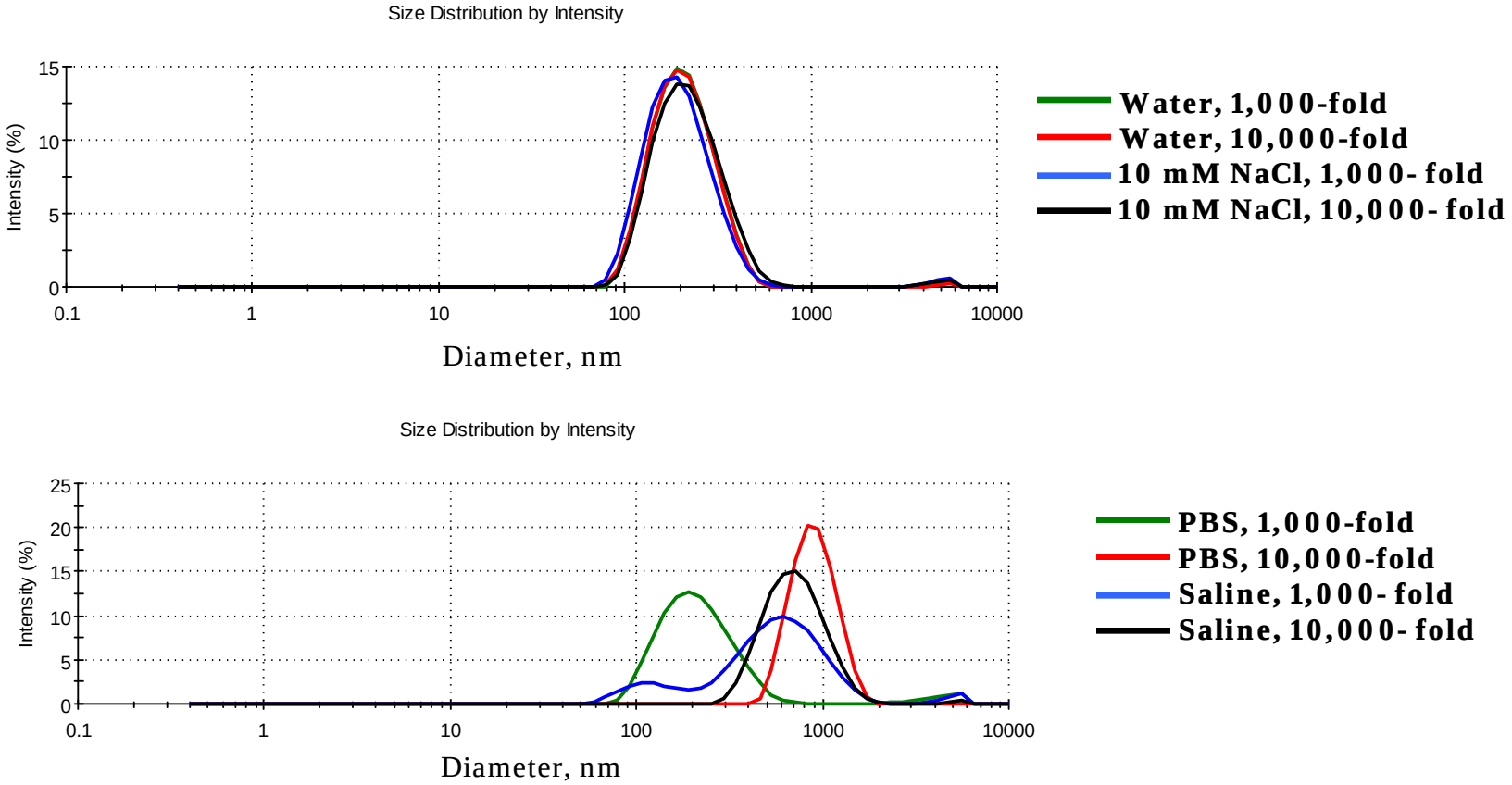
Size Distribution by Volume



Results are an average of at least 10 measurements

Courtesy of Anil Patri

Dynamic Light Scattering Sample Preparation - Dilution

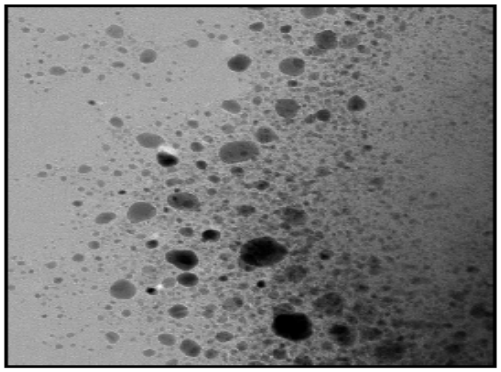


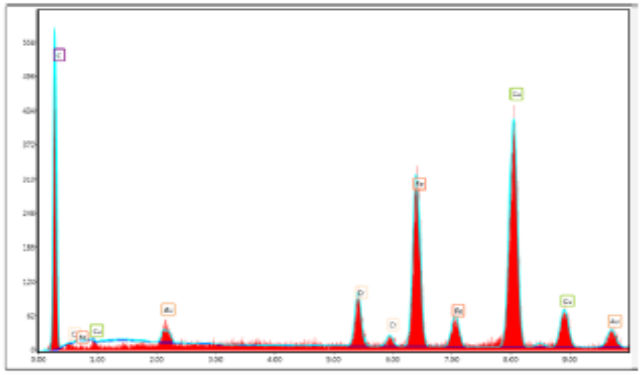
Size may be environment dependent; may depend on the solvent and concentration.

Courtesy of Anil Patri

Temperature Effect on Particle Size Distribution by TEM

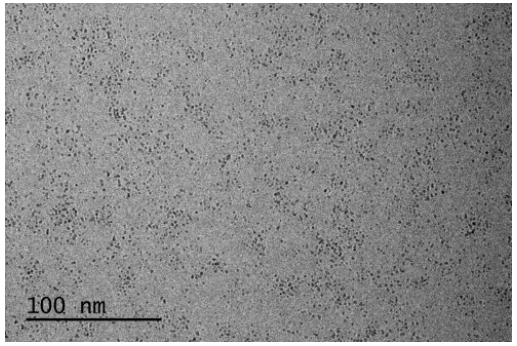
Room Temperature TEM

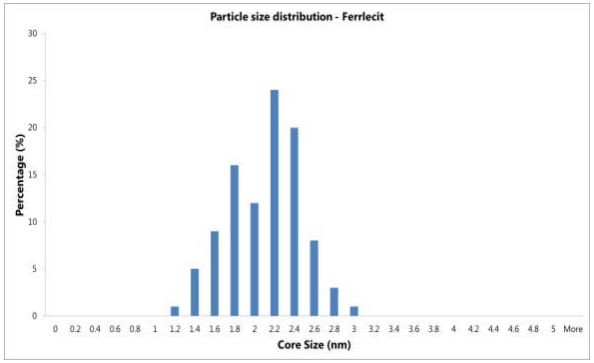




Size range (nm): 1.8-27.0

Cryo-TEM





Core size (nm): 2.0 ± 0.4

Wu, Y., Petrochenko, P., Chen, L., Wong, S.Y., Absar, M., Choi, S., Zheng, J., 2016. Core size determination and structural characterization of intravenous iron complexes by cryogenic transmission electron microscopy. Int J Pharm 505, 167-174.

Generic Drugs

- Generic drugs are copies of reference listed drug (RLD)
- Same in active ingredient, dosage form, safety, strength, routes of administration….

http://www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf

New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)

FDA

NDA

1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspection
6. Animal Studies
7. Clinical Studies
8. Bioavailability

ANDA

1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspection
6. Bioequivalence

FDA Scientific Considerations on Generic Products Referencing Nanomaterials

- **Oral products containing nanomaterials**

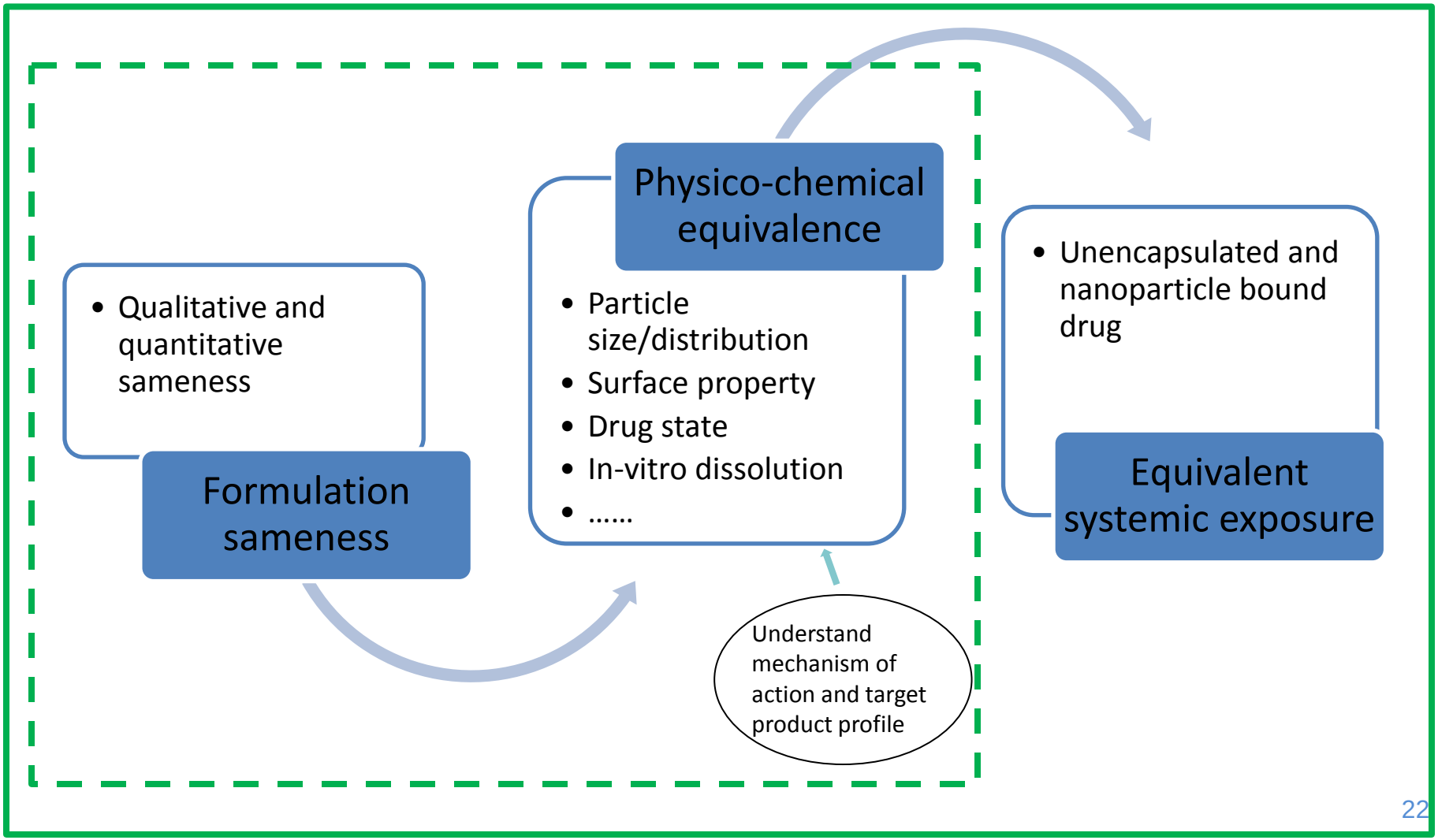
  - Can opt not to use nanotechnologies but other approaches to improve bioavailability

  - If different nanotechnology platforms used, e.g., solid lipid nanoparticles instead of nanocrystals, evaluate any potential for specific uptake.

- **Parenteral or topical products containing nanomaterial**

  - Test and reference products have equivalent particle size distribution and other attributes unless there is scientific evidence that these attributes are not critical to safety or efficacy for the product in question

Paradigm for Equivalence Recommendation of Parenteral Nanomaterials



US Generic Nano Drug Landscape

- Generic nano drug product approved
  - sodium ferric gluconate injection (2011)
  - doxorubincin HCl liposome injection (2013)
  - Oral products containing nanocrystals

- FDA product-specific equivalence guidance developed
  - doxorubicin HCl liposome injection (2010)
  - verteporfin liposome injection
  - amphotericin B liposome injection
  - daunorubicin liposome injection
  - sodium ferric gluconate injection
  - ferumoxytol injection
  - iron sucrose injection
  - cyclosporine emulsion
  - lanreotide acetate injection
  - paclitaxel albumin-bound particles for injectable suspension

Draft Guidance on Doxorubicin Hydrochloride

Contains Nonbinding Recommendations

Draft Guidance on Doxorubicin Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Doxorubicin hydrochloride

Dosage Form; Route: Liposome injection; intravenous

Recommended Studies: Two studies

When the test and reference pegylated liposome products

- have the same drug product composition and
- are manufactured by an active liposome loading process with an ammonium sulfate gradient and
- have equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates.

The following clinical and in vitro studies are recommended to demonstrate bioequivalence:

In Vivo Bioequivalence Study:

1. Type of study: Fasting*
   Design: Single-dose, two-way crossover in vivo
   Strength: 50 mg/vial or 20 mg/vial
   Dose: 50 mg/m^2
   Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug (RLD) or the reference standard product.

Analytes to measure (in appropriate biological fluid): Free doxorubicin and liposome encapsulated doxorubicin.

Bioequivalence based on (90% CI): AUC and Cmax for free doxorubicin and liposome encapsulated doxorubicin.

Note: the pivotal bioequivalence study should be conducted using test product produced by the proposed commercial scale manufacturing process.

In Vitro Study:

2. Type of study: Liposome Size Distribution
   Design: in vitro bioequivalence study on at least three lots of both test and reference products

   Parameters to measure: D10, D50, D90

   Bioequivalence based on (95% upper confidence bound): D50 and SPAN [(i.e. D90-D10)/D50] or polydispersity index using the population bioequivalence approach.

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http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm

Doxil® Shortage

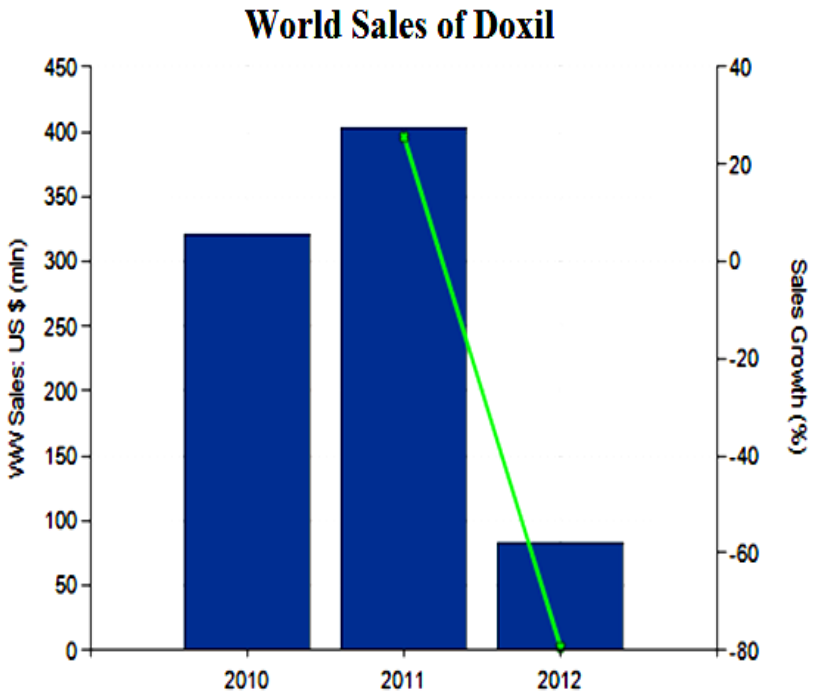
Hospitals

- Switch to more expensive substitutes
- Time/money for training staff
- Risks of medical error

Patients

"It's like you're out in the ocean and the guy on the lifeboat says, 'Sorry, they ran out of life rings.' "

The New York Times

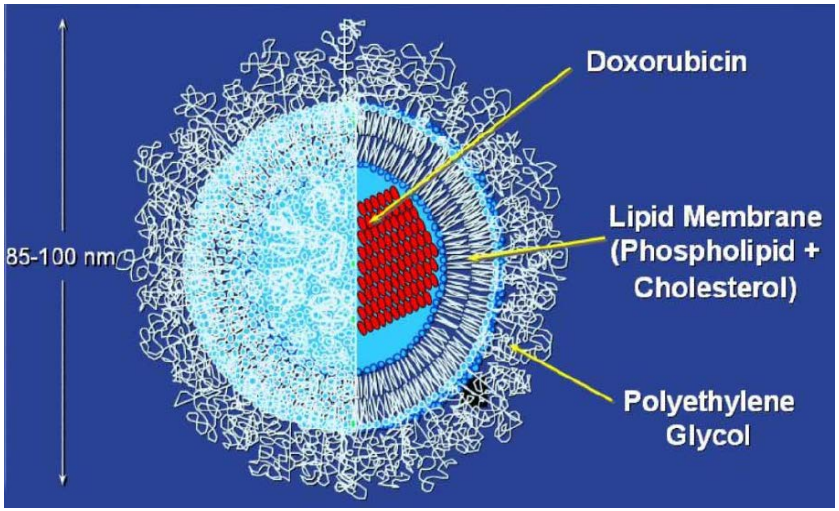


www.evaluatepharma.com

2013 Generic Approval Alleviated the Doxil Shortage

Liposomes

Proprietary Name: Doxil®
Generic Name:
Doxorubicin HCl liposome injection
Indication and regimen:
Aids-related Kaposi's Sarcoma
Ovarian cancer
Multiple myeloma with bortezomib



Mechanism of Action

- Passively targets tumor sites due to its small size and persistence in the circulation (EPR effect)
- Free doxorubicin HCl becomes available at the tumor cell. The exact mechanism of release is not understood.
- Doxorubicin HCl binds DNA and inhibits nucleic acid synthesis.

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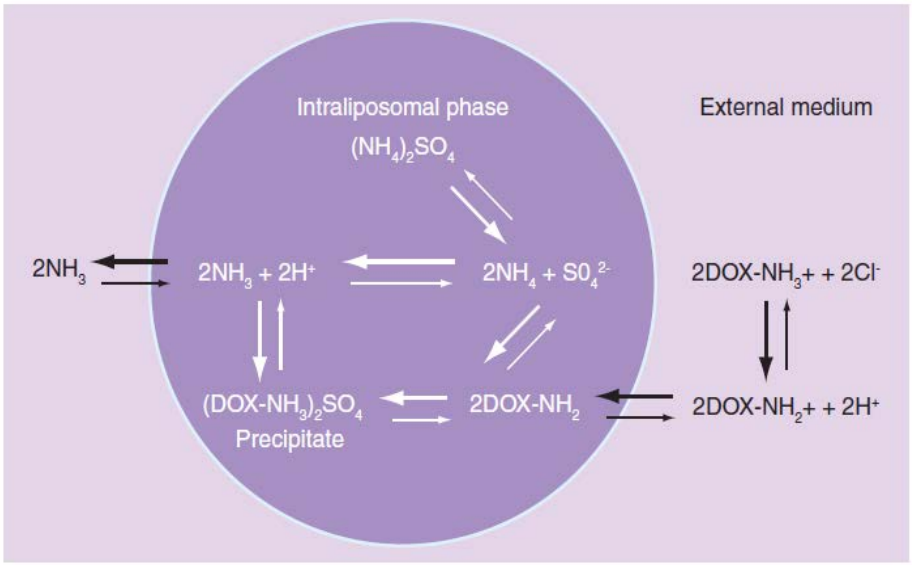
Doxorubicin HCl liposome Preparation

Drug loading mechansim



Active loading of doxorubicin into the intraliposome aqueous phase by ammonium sulfate gradient

Manufacturing steps

- Liposome formation
- Extrusion
- Dilfiltration
- Incubation with drug solution
- Dilution, sterile filtration, aseptic filling and packaging

Generic Doxorubicin HCl Liposome Development

- Same drug product composition

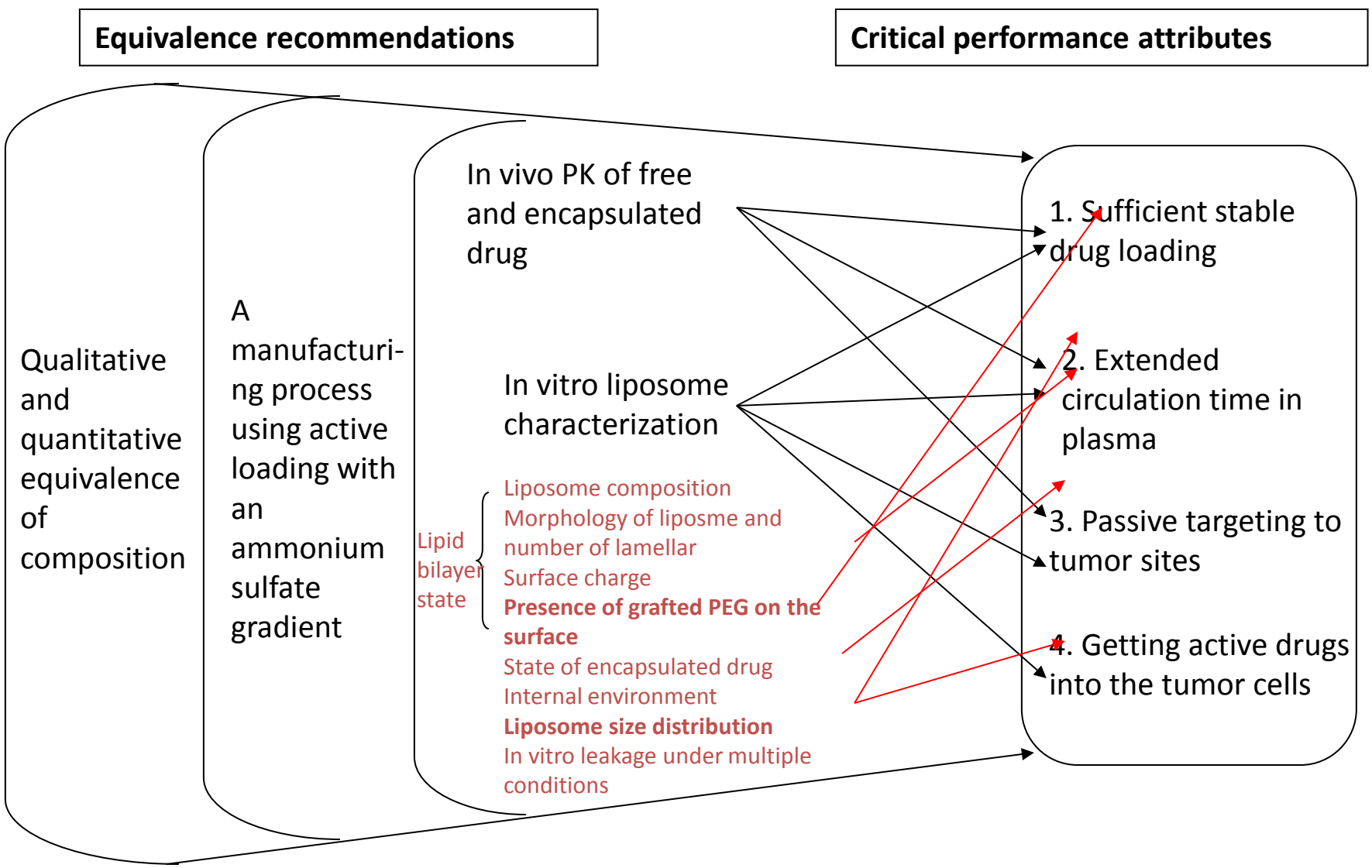
- Same manufacturing process with the same loading mechanism

- Equivalent in vitro liposome characteristics

Liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage

- Equivalent in vivo plasma pharmacokinetics of free and liposome encapsulated drug

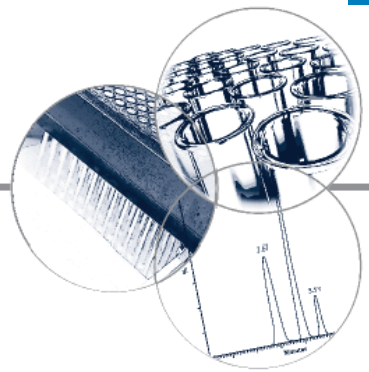
Characterization with a Purpose



In Vitro Liposome Characterization and Techniques

Characteristics	Analytical methods
Lipid composition (e.g., lipid quantities, free and encapsulated drug, internal and total sulfate conc., histidine and sucrose conc., drug to lipid ratio)	HPLC
State of encapsulated drug	Cryo TEM, XRD
Internal environment (e.g., pH, volume)	NMR, ESR, and others
Liposome morphology & number of lamella	TEM, Cryo-TEM, AFM
Lipid bilayer phase transition	DSC
Liposome size distribution	DLS, EM
Grafted PEG at the liposome surface	NMR
Surface charge	Zeta potential measurement
In vitro drug leakage	Multiple release conditions

REVIEW



In vitro and *in vivo* characterizations of PEGylated liposomal doxorubicin

One challenge in developing a nanoparticle drug-delivery system is understanding the critical physicochemical properties that may impact its *in vivo* performance and establishing analytical techniques that can adequately characterize *in vitro* and *in vivo* properties. Doxil®/Caelyx®, a PEGylated liposomal doxorubicin (PLD), is one of the leading approved nanoparticle product used in cancer therapy. In this review, we use PLD as an example to illustrate identification of key *in vitro* and *in vivo* characteristics. The following characteristics, including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, lamellarity, grafted polyethylene glycol at the liposome surface, electrical surface potential or charge, and *in vitro* leakage, are considered

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E-mail: robert.lionberger@fda.hhs.gov

• The opinions expressed in this review by the authors do not necessarily reflect the views or policies of the US FDA.

FUTURE SCIENCE part of fsg

Bioanalysis (2011) 3(3), 333–344

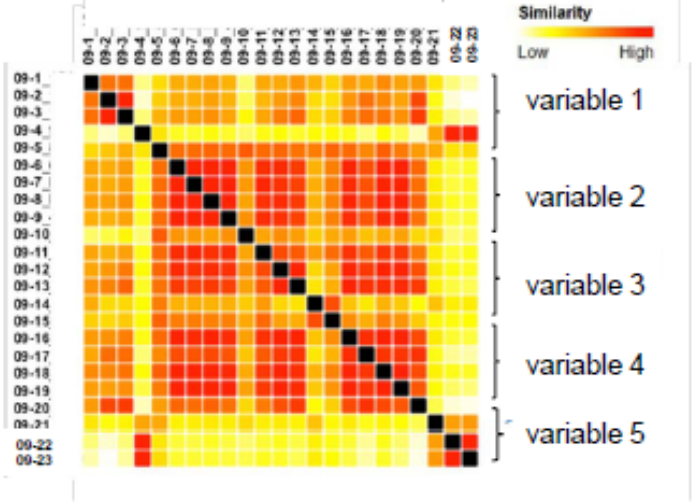
Physico-chemical Characterization

Formulation and manufacturing variables

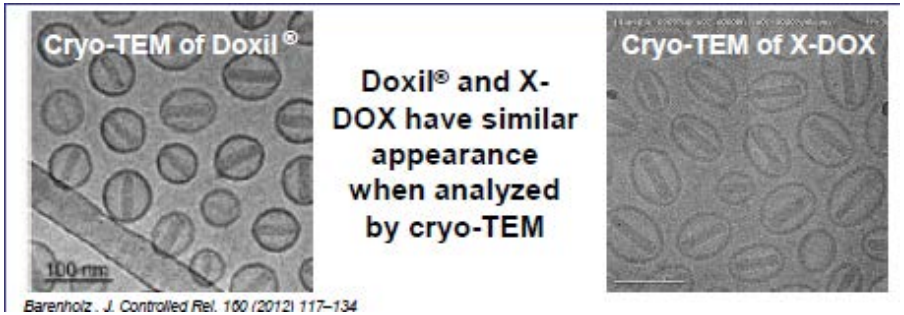
Variable	Variance
Diameter	154.3 nm
Diameter	114.1 nm
Diameter	126.4 nm
Diameter	94.5 nm
Diameter	83.1 nm
Cooling rate	60 °C to room temp
Cooling rate	In room temp air
Cooling rate	In room temp water
Cooling rate	In 4 °C air
Cooling rate	In ice water bath
Am.SO4 conc.	200 mM
Am.SO4 conc.	225 mM
Am.SO4 conc.	250 mM
Am.SO4 conc.	275 mM
Am.SO4 conc.	300 mM
Drug/lipid	0.108 wt/wt (129.6 g/mol)
Drug/lipid	0.106 wt/wt (127.2 g/mol)
Drug/lipid	0.126 wt/wt (151.2 g/mol)
Drug/lipid	0.159 wt/wt (190.8 g/mol)
Drug/lipid	0.175 wt/wt (210.0 g/mol)
	(HSPC/Chol/PEG-DSPE)
Lipid source	Lipoid/Avanti/Lipoid
Lipid source	Lipoid /Spectrum/Lipoid
Lipid source	Avanti /Avanti /Lipoid
Lipid source	Avanti/Spectrum /Lipoid
POPC L-DOX	Lipoid /Avanti /Lipoid

1U01FD004893-01

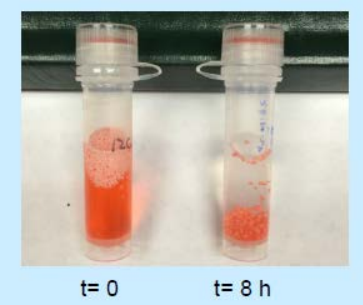
Small Angle X-Ray Scattering (SAXS) Analysis of different liposomal doxorubicin formulations



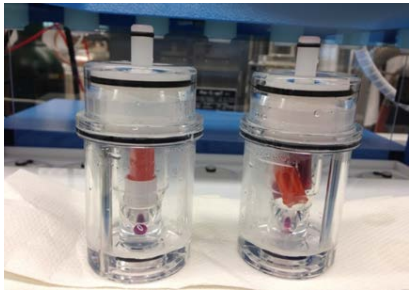
- Some patterns of similarity are observed for groups of formulations



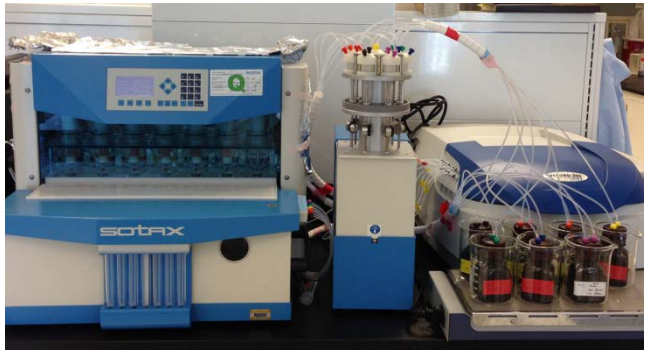
In-vitro Dissolution of Liposomal Products

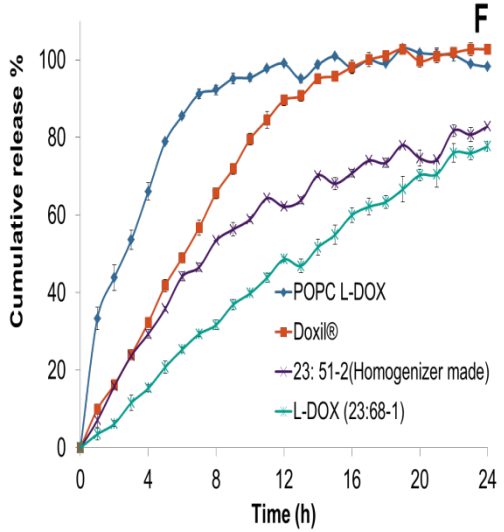


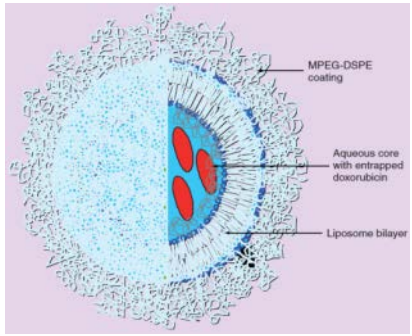
Single vial in vitro dissolution

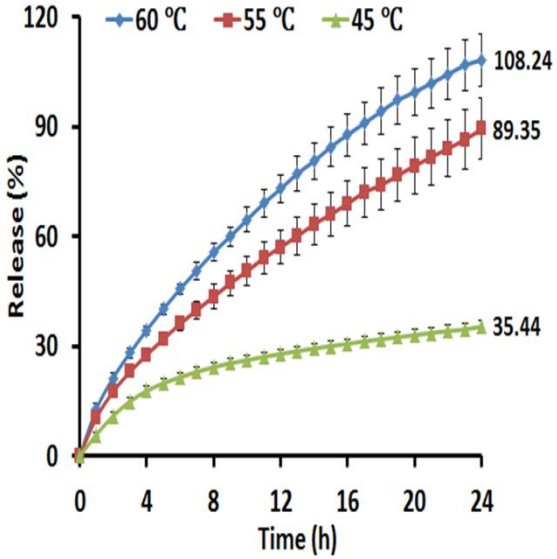


USP dissolution apparatus 4









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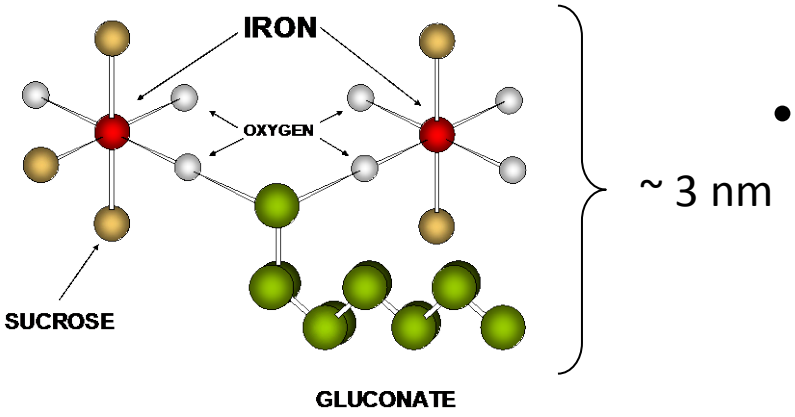
Iron Complex

Proprietary Name Ferrlecit®

Generic Name Sodium ferric gluconate in sucrose

Indication

Treatment of iron deficiency anemia in adult patients with chronic kidney disease



Mechanism of Action

- Iron particles undergo phagocytosis.
- The particles are dismantled in the lysosome of macrophages.
- Iron ions then become part of the intracellular labile iron pool.
- Transferrin will bind and deliver iron where needed.
- Excess iron is stored in the form of ferritin or hemosiderin.

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Generic Iron Complex Development

- ANDA applicants must use the same chemistry
  - Iron colloid products are synthesized by using well-documented chemistry

    $Fe^{3+} + OH^-/H_2O \rightarrow Fe(OH)^{2+}$

    $Fe(OH)^{2+} \rightarrow [Fe(OH)n] \rightarrow \beta\text{-}[FeO(OH)]n$

    $\beta\text{-}[FeO(OH)]n + \text{gluconate} + \text{sucrose} \rightarrow \beta\text{-}[FeO(OH)]n(\text{gluconate})p(\text{sucrose})m$

- Physico-chemical equivalence

- Equivalent pharmacokinetics

Physico-chemical Characterization and Techniques of Iron Complex Product

Analytical Method	Characterization
Size exclusion chromatography (SEC)	Molecular weight determination
Analytical ultracentrifugation (AUC)	Molecular weight average and range
Dynamic light scattering (DLS)	Particle size, distribution, and uniformity
Elemental analysis	Ratio of elemental iron to elemental carbon
Electron spin resonance (ESR)	Spectroscopic characterization of the iron electronic state
Polarography (voltammetry)	Reduction potential
X-ray diffraction (XRD)	Determine iron core crystalline order
Mossbauer spectroscopy	Confirm the nature of the iron environment in the particle core
UV/Vis	Confirm the nature of the iron environment in the particle core

Overall

Iron core

Shell

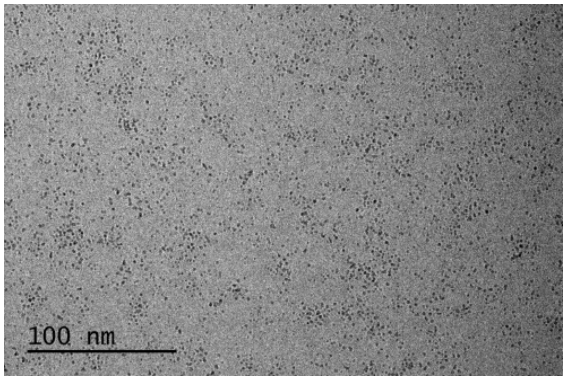
Particle Size Distribution by Dynamic Light Scattering (DLS)

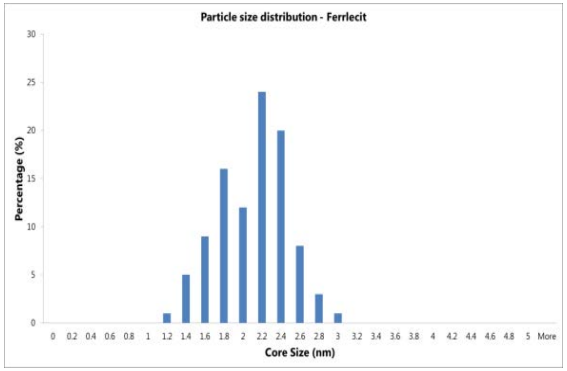
Drug product (Lot #)	Diluent	Z-average diameter (nm)	Intensity-weighted diameter (nm)	Volume-weighted diameter (nm)	PDI Value
Ferrlecit® (D2C283A)	18 MΩ H_2O	12.7	15.8 (98.5%)	8.4 (86.4%)	0.208
Ferrlecit® (D2C593A)	18 MΩ H_2O	12.8	15.7 (100%)	9.5 (100%)	0.177
Generic SFG (132296.1)	18 MΩ H_2O	11.3	13.3 (99.3%)	8.2 (100%)	0.173
Ferrlecit® (D2C283A)	10 nM NaCl	11.9	14.1 (100%)	8.7 (100%)	0.148
Ferrlecit® (D2C593A)	10 nM NaCl	12.5	14.1 (99.6%)	9.2 (100%)	0.156
Generic SFG (132296.1)	10 nM NaCl	11.0	12.8 (100%)	8.4 (100%)	0.138
Ferrlecit® (D2C283A)	Saline	11.5	13.9 (100%)	9.0 (100%)	0.163
Ferrlecit® (D2C593A)	Saline	12.1	14.5 (100%)	8.8 (100%)	0.158
Generic SFG (132296.1)	Saline	10.5	12.1 (100%)	8.1 (100%)	0.123

- The sample was diluted 100 times with filtered 18 MΩ water, 10 nM NaCl, and saline solution.
- The results are based on size distributions which represent an average of ≥ 30 measurements.
- DLS laser wavelength 633 nm, the detector is 173º backscattered detector.

Particle Size Distribution of the Iron Core by Cryo-TEM

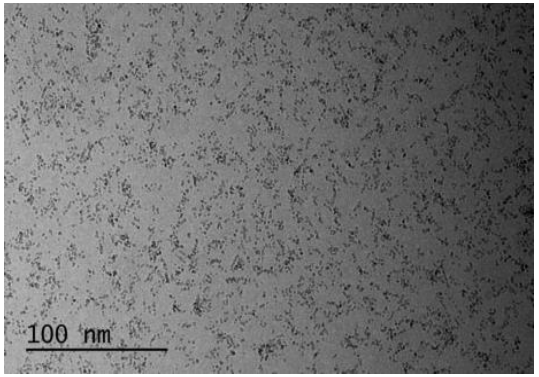
Ferrlecit®

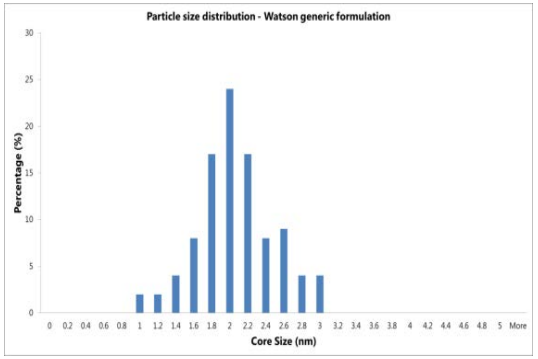




Core size (nm): 2.0 ± 0.4

Generic





Core size range (nm): 2.0± 0.4

Wu, Y., Petrochenko, P., Chen, L., Wong, S.Y., Absar, M., Choi, S., Zheng, J., 2016. Core size determination and structural characterization of intravenous iron complexes by cryogenic transmission electron microscopy. Int J Pharm 505, 167-174.

Zeta Potential and Viscosity

Drug product (Lot #)	Viscosity	Zeta potential	
	Viscosity (cps) with 60 RPM at 23°C	Zeta potential (mV)	pH
Ferrlecit® (D2C283A)	0.88 ± 0.01	-7.95	7.23
Ferrlecit® (D2C593A)	0.87 ± 0.01	-6.77	7.25
Generic SFG (132296.1)	0.88 ± 0.01	-7.89	7.25

Regulatory Research on Characterization of Nanomaterials

Excipients are critical to maintain nanomaterial higher order structure

Excipients can be from different origins and contain concomitant (production related) components or processing aids

Lack of compendial standards for nanomaterial excipients

Characterization and standards development of excipients used in nanomaterials

Regulatory Research on Characterization of Nanomaterials

Separation of free and nanomaterials associated drug may induce drug leakage

Separation process is lengthy

Simultaneous separation and quantification of free drug and nanomaterial associated drugs

Regulatory Research on Characterization of Nanomaterials

In vitro and in vivo release of drug from nanomaterials not correlated

Lack of standard method to characterize drug release

Bio-relevant in vitro dissolution method development

Summary

- Current regulatory framework is sufficient to support nanomaterial development and approval
- Nanomaterial development requires solid understanding of critical attributes and corresponding characterization techniques
- Product-specific characterization of generic and reference nanomaterials to ensure equivalent physico-chemical properties are essential for generic nano products
- Further regulatory research in characterization of nano drug are encouraged

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FDA U.S. FOOD & DRUG ADMINISTRATION

Thank You

Any question?

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