Regulatory Research in Nanomedicine

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AAPS Annual Guidance Forum, Silver Spring, MD
September 11, 2018

Outline

- Current US landscape of nanotechnology drug products and FDA guidance
- FDA nanotechnology regulatory research program
- CDER nanotechnology regulatory research focus
- Conclusions

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

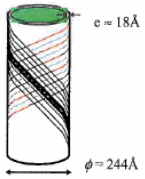
Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

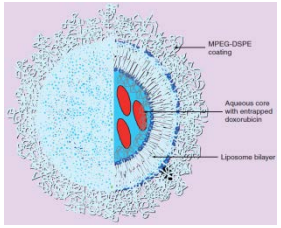
http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

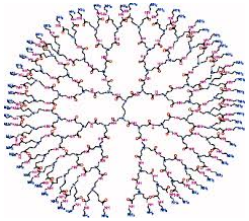
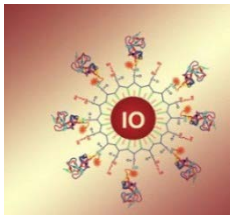
FDA's Position on Nanomaterials

"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."

FDA's Approach to Regulation of Nanotechnology Products
https://www.fda.gov/scienceresearch/specialtopics/nanotechnology/ucm301114.htm



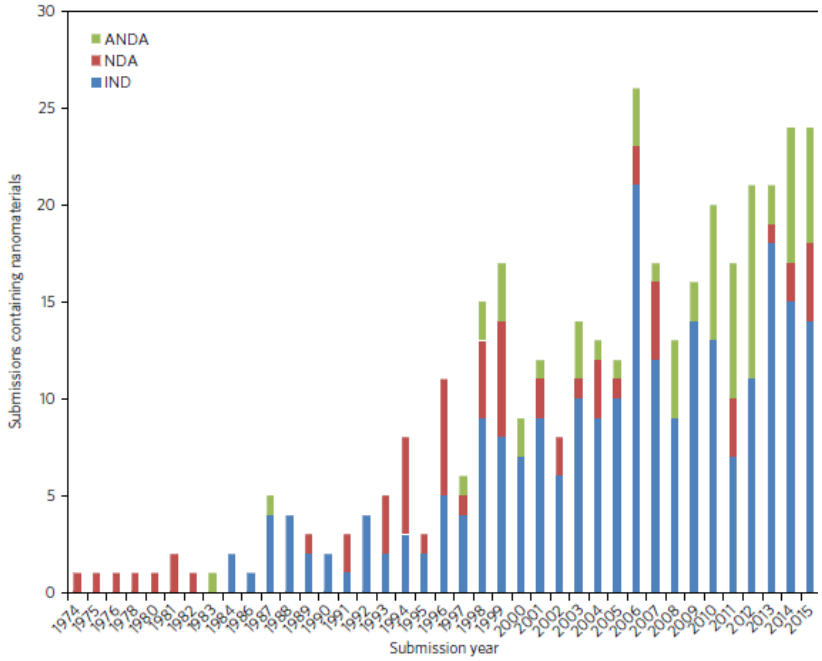
nature nanotechnology

ANALYSIS

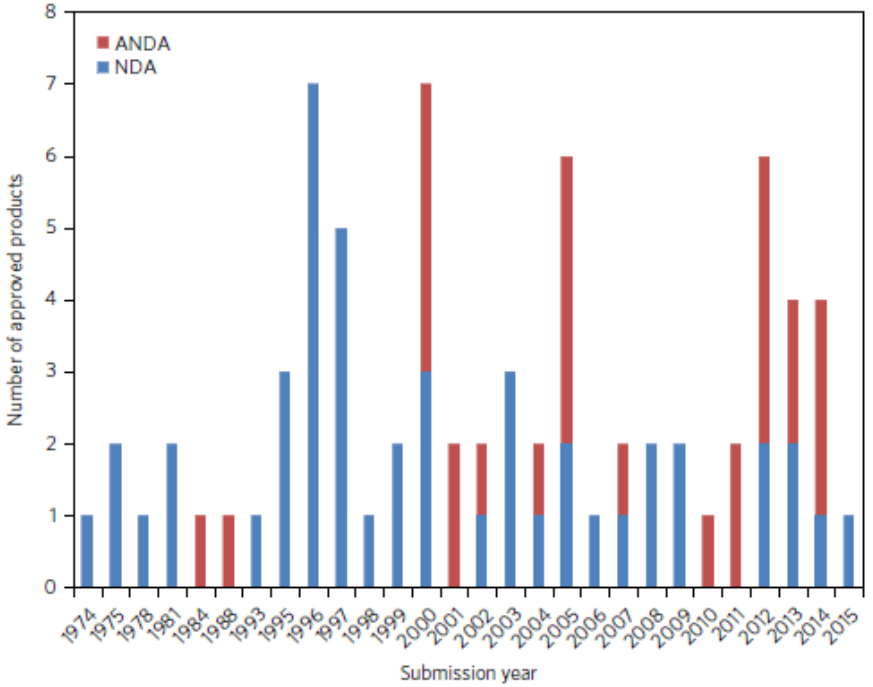
PUBLISHED ONLINE: 24 APRIL 2017 | DOI: 10.1038/NNANO.2017.67

The evolving landscape of drug products containing nanomaterials in the United States

Sheetal R. D'Mello, Celia N. Cruz, Mei-Ling Chen, Mamta Kapoor, Sau L. Lee and Katherine M. Tyner*

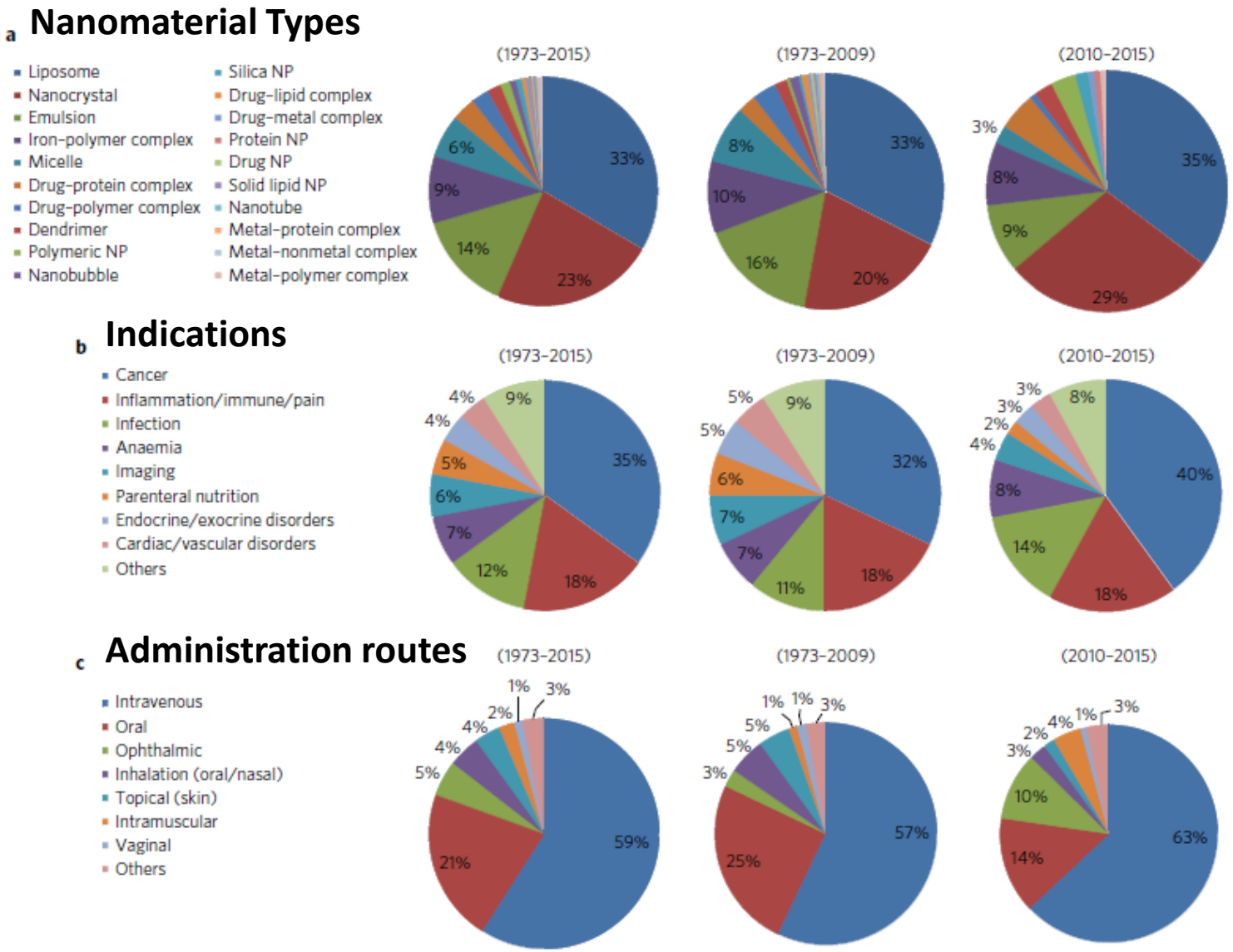


No. of nanomaterial product applications submitted to CDER



CDER approved drug products containing nanomaterials

Distribution of Nanomaterial Use in Drug Submissions



D' Mello et al. The evolving landscape of drug products containing nanomaterials in the United States. Nature Nanotechnology, published online. Apr 24, 2017

Guidance Related to Nanotechnology Drug Products

Final Guidance

- Final Guidance for Industry - Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology
- Final Guidance for Industry - Safety of Nanomaterials in Cosmetic Products
- Final Guidance for Industry - 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
- Final Guidance for Industry - Use of Nanomaterials in Food for Animals

Draft Guidance

- Draft Guidance for Industry - Drug Products, Including Biological Products, that Contain Nanomaterials

Class Specific Guidance

- Final Guidance for Industry - Liposome Drug Products. Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation

Product-Specific Guidance

- https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm

FDA Nanotechnology Regulatory Science Research Program

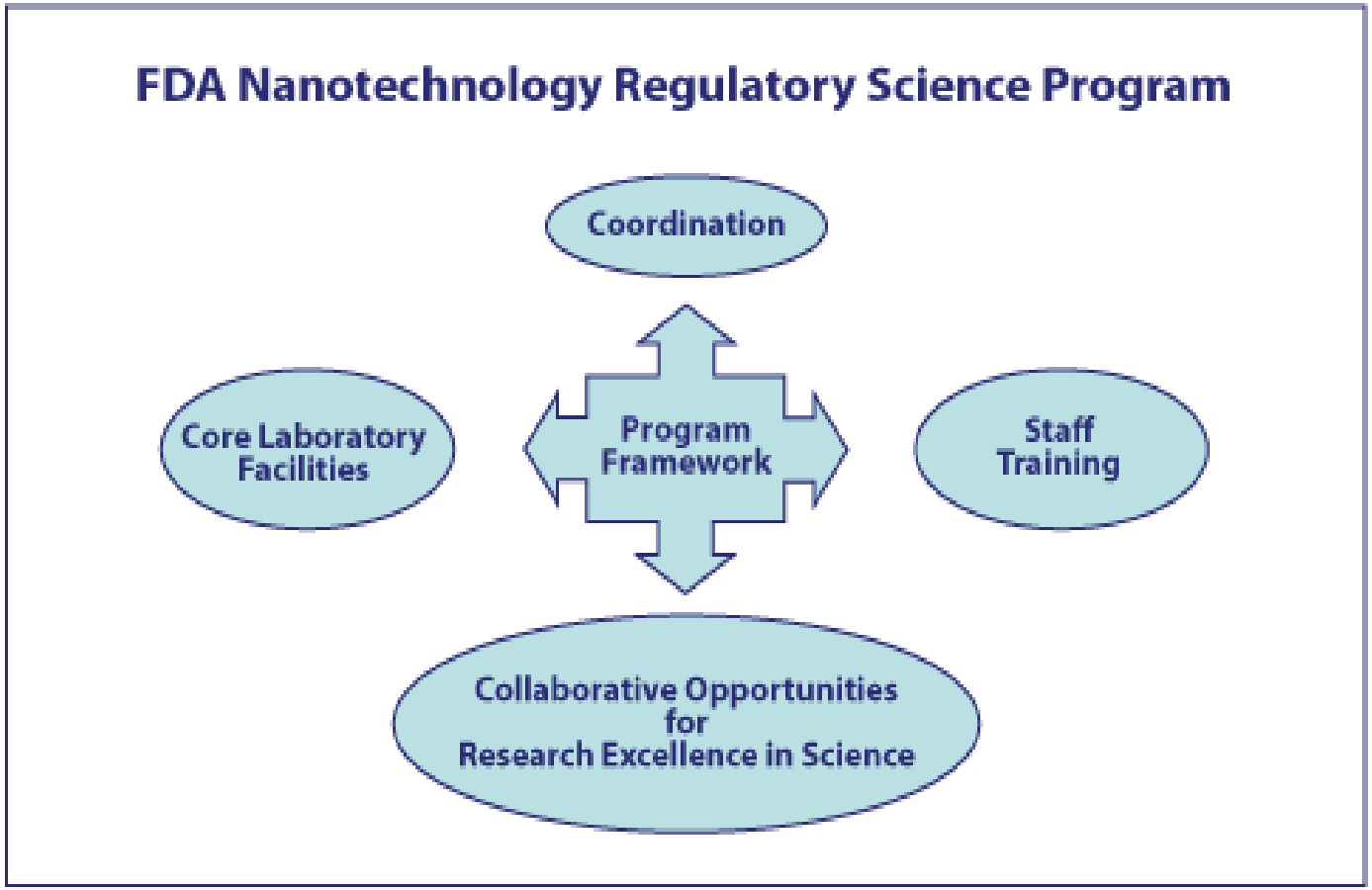
Goal

- Foster the development of FDA-regulated products that may contain nanomaterials or otherwise involve the application of nanotechnology.

- Establish the tools, methods, and data to assist in regulatory decision-making, while also providing in-house scientific expertise and capacity that is responsive to nanotechnology-related FDA-regulated products.

2013 Nanotechnology Regulatory Science Research Plan
https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm273325.htm#outcomes

FDA Nanotechnology Regulatory Science Research Program



2013 Nanotechnology Regulatory Science Research Plan
https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm273325.htm#outcomes

FDA Nanotechnology Partnership

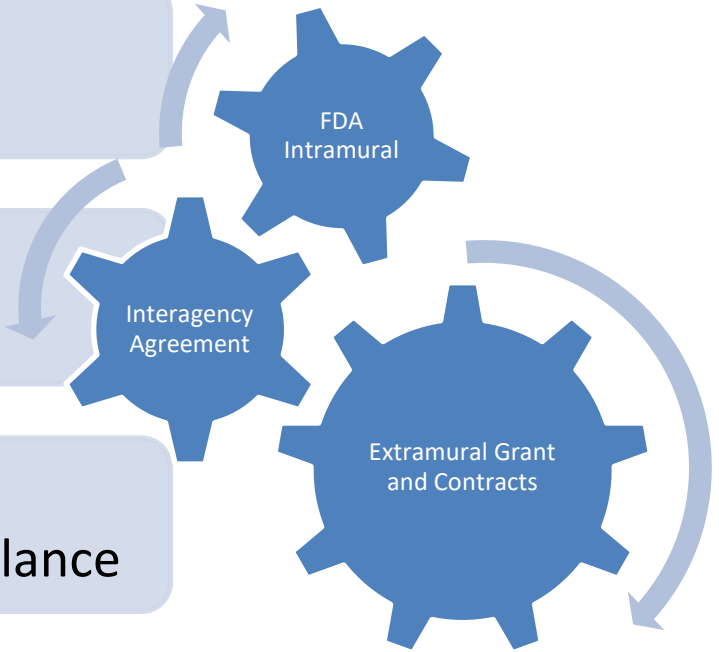
- **FDA-NCI-NIST**
- **FDA-Johns Hopkins University**
- **FDA-ANH NanoTechnology Initiative (FANTI)**

NCI: National Cancer Institute; NIST: National Institute of Standards and Technology
ANH: Alliance for NanoHealth

https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm208110.htm

CDER Nanotechnology Research Focus

Quality	• Characterization • Manufacturing
Safety	• Drug exposure • Toxicity
Equivalence	• In vitro characterization • In vivo pharmacokinetics
Post-market surveillance	• Lab investigation • Passive and active surveillance



FDA U.S. FOOD & DRUG ADMINISTRATION

Nanotechnology Quality Research

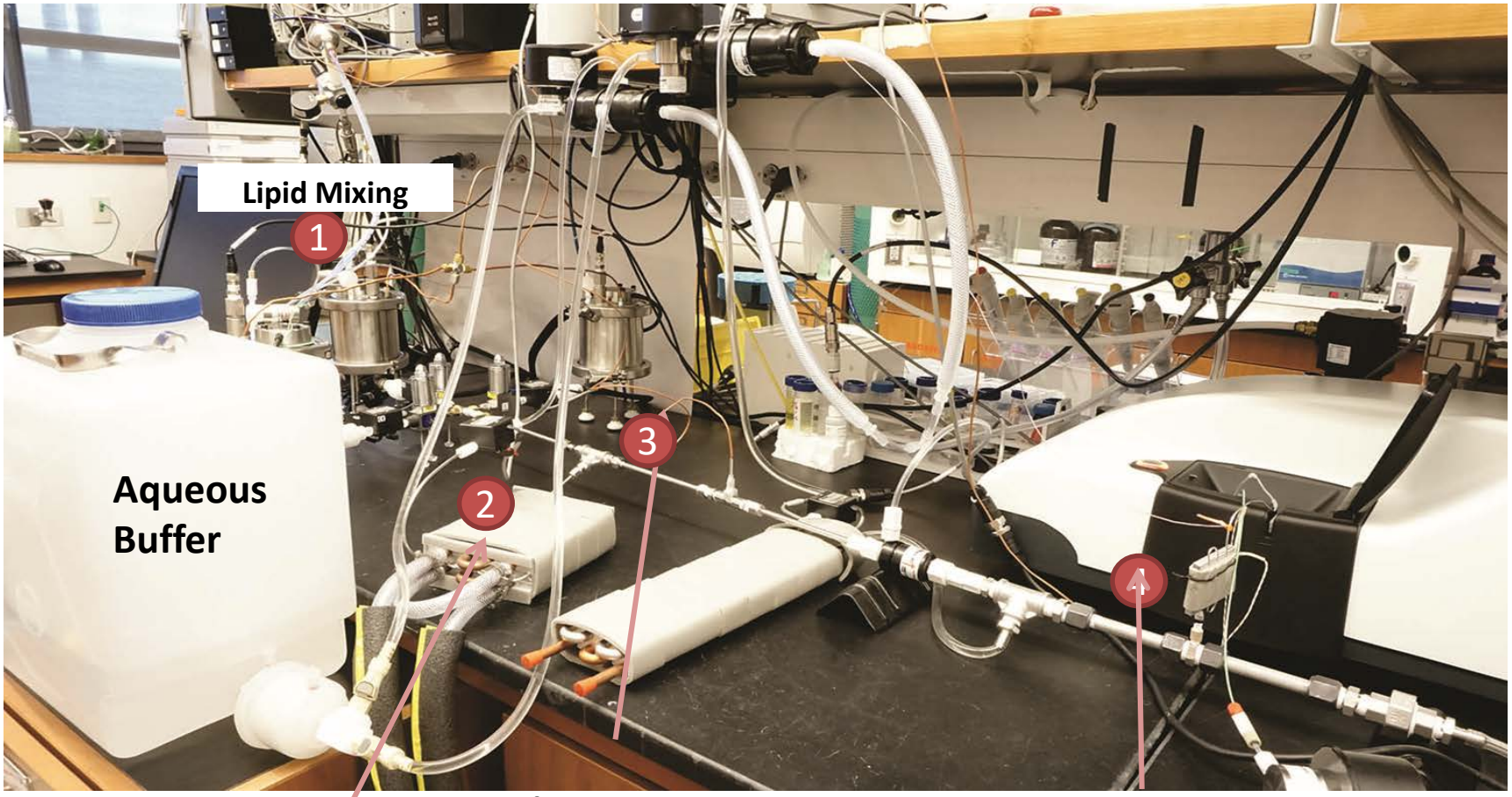
Nanotechnology Quality Research Focus

- Develop a platform for continuous manufacturing of nanomaterials to afford better control over the manufacturing and quality control process

- Conduct quality analytics of nanomaterials

- Promote Quality by Design (QbD) to improve product quality for nanomaterials (e.g., excipient, process)

Liposome Continuous Manufacturing



Picture courtesy of Drs. Dianne Burgess from University of Connecticut and Xiaoming Xu from the FDA

Regulatory Impact: Promote continuous manufacturing for nanomaterials and better process control

Product Quality Analytics

The AAPS Journal, Vol. 19, No. 3, May 2017 (© 2017)
DOI: 10.1208/s12248-017-0049-9

Review Article

Theme: Nanotechnology in Complex Drug Products: Learning from the Past, Preparing for the Future
Guest Editors: Katherine Tyner, Sau (Larry) Lee, and Marc Wolfgang

Liposomal Drug Product Development and Quality: Current US Experience and Perspective

Mamta Kapoor,[1] Sau L. Lee,[1] and Katherine M. Tyner[1,2]

Received 12 November 2016; accepted 25 January 2017; published online 3 February 2017

ABSTRACT. Research in the area of liposomes has grown substantially in the past few decades. Liposomes are lipid bilayer structures that can incorporate drug substances to modify the drug's pharmacokinetic profile thereby improving drug delivery. The agency has received over 400 liposomal drug product submissions (excluding combination therapies), and there are currently eight approved liposomal drug products on the US market. In order to identify the pain points in development and manufacturing of liposomal drug products, a retrospective analysis was performed from a quality perspective on submissions for new and generic liposomal drug products. General analysis on liposomal drug product submissions was also performed. Results indicated that 96% of the submissions were Investigational New Drug (IND) applications, 3% were New Drug Applications (NDAs), and the remaining 1% was Abbreviated New Drug Applications (ANDAs). Doxorubicin hydrochloride was the most commonly used drug substance incorporated into the liposomes (31%). The majority of the liposomal products were administered via intravenous route (84%) with cancer (various types) being the most common indication (63%). From a quality perspective, major challenges during the development of liposomal drug products included identification and (appropriate) characterization of critical quality attributes of liposomal drug products and suitable control strategies during product development. By focusing on these areas, a faster and more efficient development of liposomal drug products may be achieved. Additionally, in this way, the drug review process for such products can be streamlined.

KEY WORDS: control strategy; critical quality attributes; doxil; in-process controls; lipid excipient; liposomal drug product; liposome submission.

The AAPS Journal, Vol. 19, No. 5, September 2017 (© 2017)
DOI: 10.1208/s12248-017-0126-0

Review Article

Theme: Nanotechnology in Complex Drug Products: Learning from the Past, Preparing for the Future
Guest Editors: Katherine Tyner, Sau (Larry) Lee, and Marc Wolfgang

Physicochemical Characterization of Iron Carbohydrate Colloid Drug Products

Peng Zou,[1,2] Katherine Tyner,[1] Andre Raw,[1] and Sau Lee[1]

Received 7 April 2017; accepted 13 July 2017; published online 31 July 2017

Abstract. Iron carbohydrate colloid drug products are intravenously administered to patients with chronic kidney disease for the treatment of iron deficiency anemia. Physicochemical characterization of iron colloids is critical to establish pharmaceutical equivalence between an innovator iron colloid product and generic version. The purpose of this review is to summarize literature-reported techniques for physicochemical characterization of iron carbohydrate colloid drug products. The mechanisms, reported testing results, and common technical pitfalls for individual characterization test are discussed. A better understanding of the physicochemical characterization techniques will facilitate generic iron carbohydrate colloid product development, accelerate products to market, and ensure iron carbohydrate colloid product quality.

KEY WORDS: ferumoxytol; iron colloid; iron dextran; iron sucrose; sodium ferric gluconate.

- Identified major quality issues in liposome product applications
- Reviewed mechanisms, reported testing results, and common technical pitfalls for physico-chemical characterization tests of iron complex.

Regulatory Impact: Facilitate efficient development of nanomaterial drug products and streamline the review process of these products

U.S. FOOD & DRUG ADMINISTRATION

Nanotechnology Safety Research

Nano Size TiO_2 Safety in Sunscreen

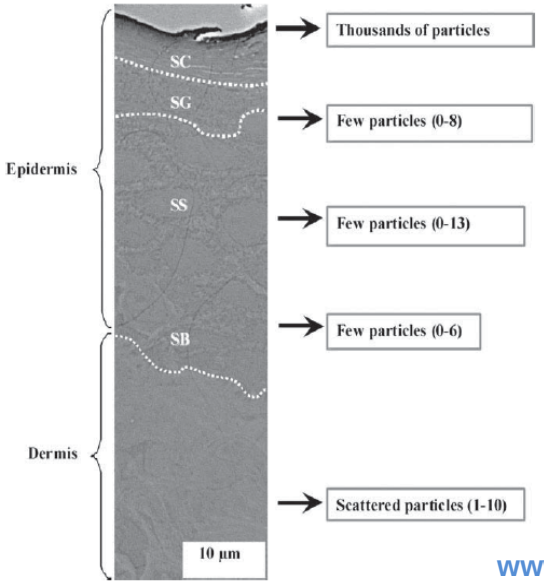
TOXICOLOGICAL SCIENCES **115(1)**, 156–166 (2010)
doi:10.1093/toxsci/kfq041
Advance Access publication February 15, 2010

Lack of Significant Dermal Penetration of Titanium Dioxide from Sunscreen Formulations Containing Nano- and Submicron-Size TiO_2 Particles

Nakissa Sadrieh,*,[1] Anna M. Wokovich,† Neera V. Gopee,‡ Jiwen Zheng,§ Diana Haines,§,¶ David Parmiter,§ Paul H. Siitonen,‡ Christy R. Cozart,‡ Anil K. Patri,§ Scott E. McNeil,§ Paul C. Howard,‡ William H. Doub,† and Lucinda F. Buhse†

Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland 20993; †Division of Pharmaceutical Analysis, Office of Testing and Research, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, St Louis, MO 63101; ‡Division of Biochemical Toxicology, National Center for Toxicological Research (NCTR), FDA, Jefferson, Arkansas 72079; §Nanotechnology Characterization Laboratory, Science Applications International Corporation-Frederick, Inc., National Cancer Institute at Frederick, Frederick, Maryland 21702; and ¶Pathology Histotechnology Laboratory, Science Applications International Corporation-Frederick, Inc., National Cancer Institute at Frederick, Frederick, Maryland 21702

Representation of TiO2 particle distribution in different layers of minipig abdominal skin (longitudinal slice of skin) exposed to submicron TiO2 showing the results from the cross section analysis of each skin layer. Numbers in parentheses are estimates of the numbers of TiO2 particles observed in each layer. Abbreviations are: SC, stratum corneum; SS, stratum spinosum; SG, stratum granulosum; and SB, stratum basale.



Regulatory impact: Inclusion of nano-sized TiO2 does not pose a significant health threat

Biodistribution and Toxicity Upon Repeated Dosing of Durable Nanoparticles

Weaver *et al. Particle and Fibre Toxicology* (2017) 14:25
DOI 10.1186/s12989-017-0206-4

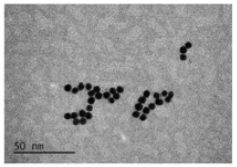
Particle and Fibre Toxicology

RESEARCH Open Access

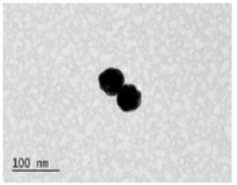
Evaluating the potential of gold, silver, and silica nanoparticles to saturate mononuclear phagocytic system tissues under repeat dosing conditions

James L. Weaver[1], Grainne A. Tobin[1], Taylor Ingle[2], Simona Bancos[1], David Stevens[1], Rodney Rouse[1], Kristina E. Howard[1], David Goodwin[1], Alan Knapton[1], Xiaohong Li[1], Katherine Shea[1], Sharron Stewart[1], Lin Xu[1], Peter L. Goering[3], Qin Zhang[3], Paul C. Howard[2], Jessie Collins[2], Saeed Khan[2], Kidon Sung[2] and Katherine M. Tyner[1*]

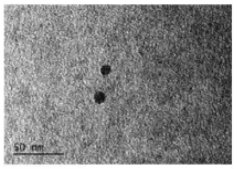
Gold: 10 nm



Silver: 50 nm



Silica: 10 nm



Repeated dosing with gold, silver, and silica nanoparticles did not saturate bioaccumulation in liver or spleen macrophages.

While no toxicity was observed with gold and silver nanoparticles throughout the 8 week experiment, some effects including histopathological and serum chemistry changes were observed with silica nanoparticles starting at week 3.

No major changes in the splenocyte population were observed during the study for any of the nanoparticles tested.

U.S. FOOD & DRUG ADMINISTRATION

Nanotechnology Equivalence Research

Regulatory Impact: Support product-specific guidance development to guide generic nanotechnology drug product development and facilitate ANDA review and approval of these products

Is ANDA Pathway Suitable for Nanomaterials?

The AAPS Journal (2018) 20:92
DOI: 10.1208/s12248-018-0255-0

Commentary

Reflections on FDA Draft Guidance for Products Containing Nanomaterials: Is the Abbreviated New Drug Application (ANDA) a Suitable Pathway for Nanomedicines?

Marden Emily,[1] Ntai Ioanna,[2] Bass Scott,[3] and Flühmann Beat[2,4]

Received 1 June 2018; accepted 12 August 2018

Abstract. The US Food and Drug Administration (FDA) recently released a draft guidance for industry titled "Drug Products, Including Biological Products, that Contain Nanomaterials." The FDA's attention to the unique safety and efficacy aspects of drugs containing nanomaterials is commendable. This Draft Guidance succeeds in acknowledging the complexity of these products, as well as the challenges associated with approving safe and therapeutically equivalent complex generic versions. However, the challenge posed by the manufacturing process for drugs containing nanomaterials is insufficiently addressed. The critical quality attributes of such products cannot be properly defined, and therefore it is not possible to design informative comparative physicochemical assessments for equivalence. As a consequence, the 505(j) Abbreviated New Drug Application (ANDA) pathway, currently advised as the standard from the FDA, is not suitable for the approval of complex generic products. Drawing from the successful story of biologics, we propose instead a stepwise totality-of-evidence approach, demonstrating similarity and including clinical studies when deemed necessary, as an appropriate alternative to the 505(j) ANDA pathway.

KEY WORDS: complex generic; FDA; nanomedicines; nanosimilar; non-biological complex drugs (NBCDs).

FDA Answer: YES

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

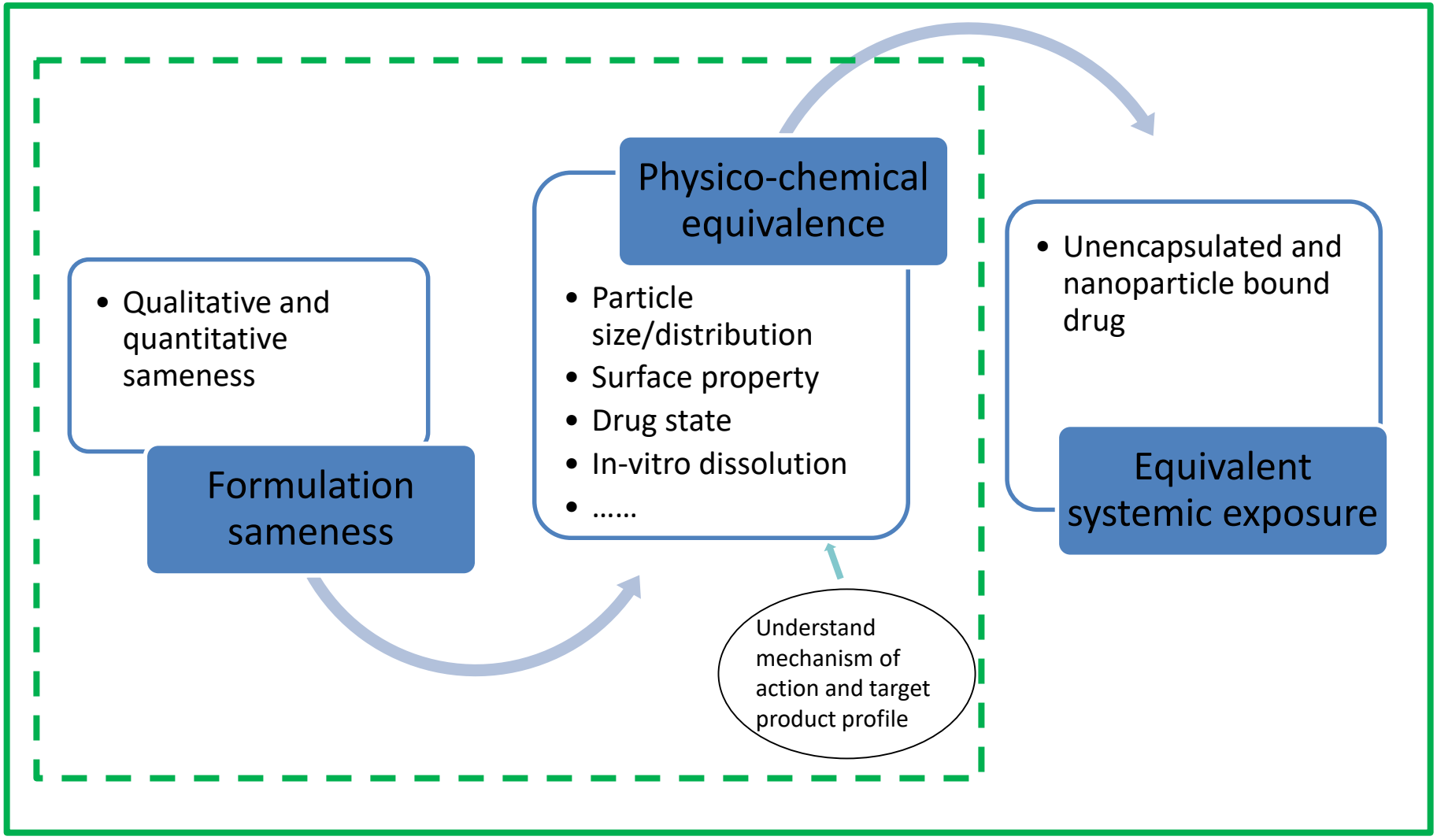
NDA

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

US FDA Paradigm for Equivalence Recommendation of Parenteral Nanomaterials



Zheng N, Zou P, Sun D, Jiang W. Scientific and regulatory considerations for generic complex drug products containing nanomaterials. AAPS J. 2017, 19(3):619-631.

Current EMA Bioequivalence Approach for Doxorubicin HCl liposomes

2013 EMA Reflection Paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposome product

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500140351.pdf

2018 EMA Doxorubicin HCl liposomes Product Specific Guideline

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/06/WC500251058.pdf

Requirements for bioequivalence demonstration (PKWP)*

Bioequivalence study design	**Single dose study:** Any dose (but no dose adjustments for toxicities during the study) in e.g. stable ovarian/breast cancer patients. **Background:** Dose proportional pharmacokinetics.
	Cross-over
	Other critical aspects: The single dose study may need to be conducted with standardized light meals rather than in the fasting state due to patient's needs.
Analyte	☐ **total drug** ☒ **encapsulated drug** ☒ **unencapsulated drug** ☐ **doxorubicinol (metabolite)** **Other critical aspects:** Unencapsulated drug concentrations must be achieved by means of appropriate bioanalytical methods rather than by subtracting encapsulated from total drug.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, partial AUCs (e.g. AUC_{0-48h} and $AUC_{48-tlast}$) **Background/justification:** Partial AUCs should ensure profile comparability for the encapsulated compound.
	90% confidence interval acceptance limits: 80.00 – 125.00%
Additional information can be added if considered necessary	**To be noted**: Proving equivalent efficacy and safety of a liposomal formulation developed to be similar to an innovator product is considered a step-wise approach which in addition to the pharmacokinetic study also takes account of quality and non-clinical comparison, where appropriate.

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}, C_T, ss and partial AUC. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.

Nanotechnology Equivalence Research Focus

- Help accurate determination of formulation composition
- Optimize analytical methods to characterize formulation components, particle size, and other properties
- Develop in vitro dissolution methods
- Develop bioanalytical methods for quantification of un-encapsulated and encapsulated drug in plasma

DOXIL Formulation Composition

OGD - Office of Testing and Research (OTR) Collaboration

Current DOXIL Labeling

- The STEALTH liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphati-dylcholine (HSPC), 9.58 mg/mL; and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 0.6 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH liposomes.

Previous labeling states ammoinium sulfate approximately 2 mg/ml

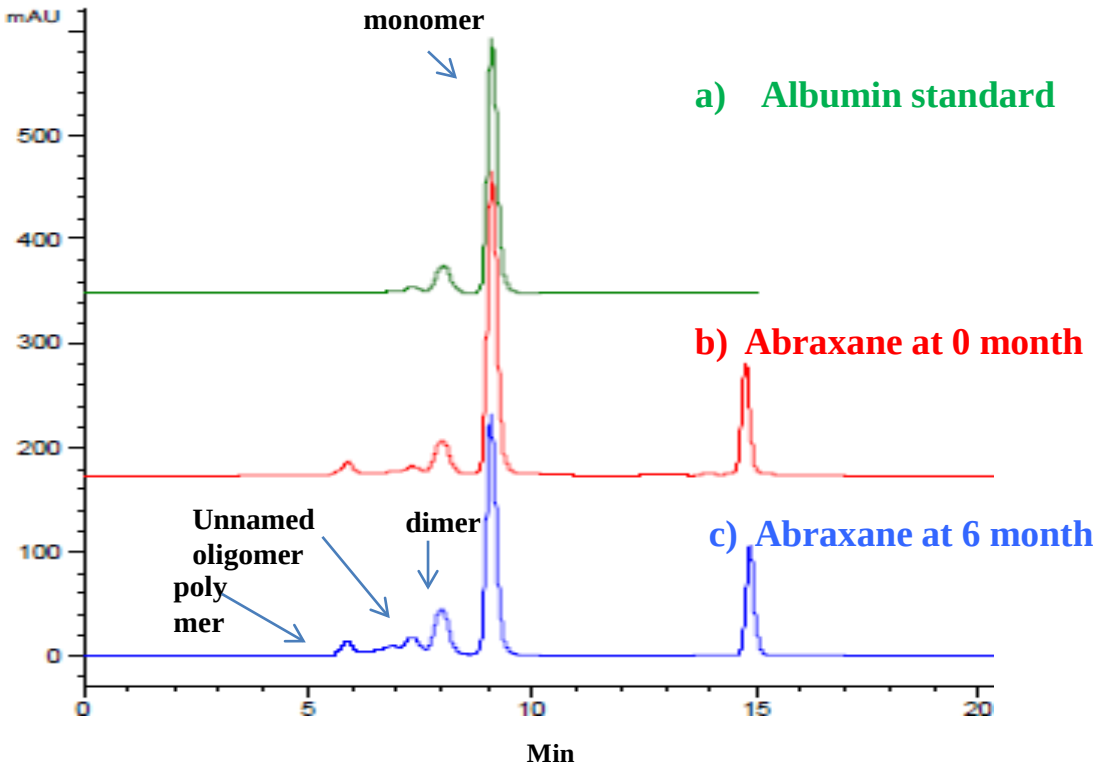
Inaccurate

DOXIL labeling was updated to reflect the accurate formulation composition.

FDA developed analytical methods to measure ammonium sulfate, histidine, and sucrose content to support determination of Q1/Q2 sameness of generic drug products.

Excipient Characterization in ABRAXANE

OGD - Office of Testing and Research (OTR) Collaboration



Paclitaxel suspension product specific guidance https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320015.pdf

Additional in vitro characterization are recommended to demonstrate the sameness between the test and reference products in terms of particle morphology, particle size, surface potential, paclitaxel crystallinity, fraction of free and bound paclitaxel or albumin in reconstituted suspension, nature of bond between paclitaxel and albumin, and in vitro release kinetics. In addition, albumin, the only excipient in the final product, is critical to the formulation. The characterization of the oligomeric status of albumin in both the albumin excipient and the final drug product is also recommended. The in vitro characterization tests are recommended to be conducted on three batches of the ANDA and RLD products (at least one ANDA batch should be produced by the commercial scale process).

Characterization of oligomeric status of albumin in ABRAXANE to support product equivalence recommendation for generic drug applications

Hongping Ye and Wenlei Jiang. Characterization of Paclitaxel and Albumin Oligomeric Status in ABRXAME during Storage. 2016 NYAS Conference: Equivalence of Complex Drug Products: Scientific and Regulatory Challenges, New York, NY

Direct Quantification of Unencapsulated Doxorubicin (Dox) Using Capillary Electrophoresis

OGD- Office of Regulatory Affairs (ORA) Collaboration

Separation of unencapsulated and nanomaterials associated drug may induce drug leakage

Separation process is lengthy

Simultaneous separation and quantification of unencapsulated and liposome encapsulated drugs

International Journal of Pharmaceutics 549 (2018) 109–114

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Direct quantification of unencapsulated doxorubicin in liposomal doxorubicin formulations using capillary electrophoresis

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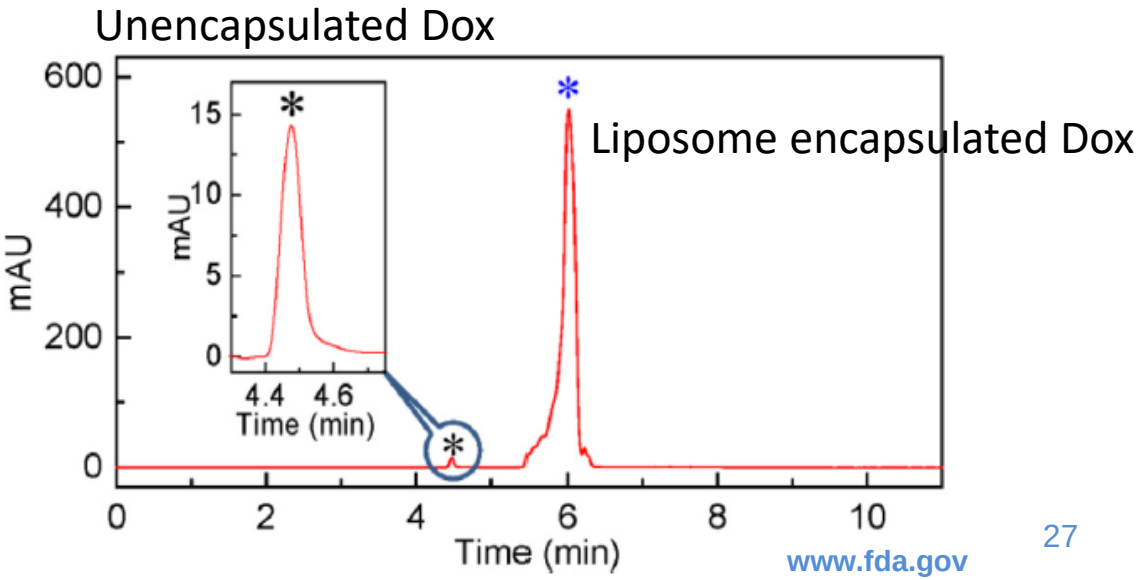
[b] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, United States



Morphological Characterization of Iron Complex by Cryo-TEM

OGD-Center for Device and Radiological Health (CDRH) Collaboration

International Journal of Pharmaceutics 505 (2016) 167–174

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

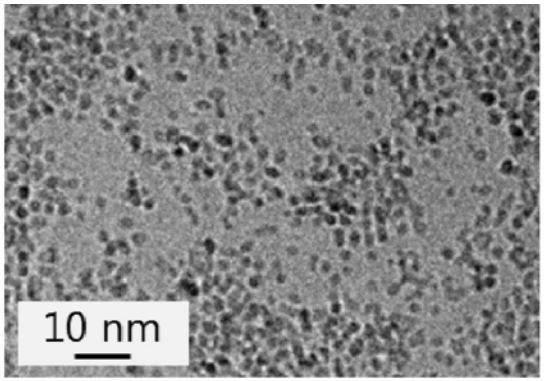
journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

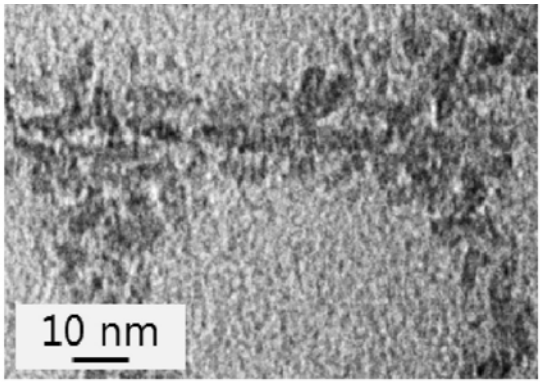
Core size determination and structural characterization of intravenous iron complexes by cryogenic transmission electron microscopy

Yong Wu[a], Peter Petrochenko[b], Lynn Chen[a], Sook Yee Wong[b], Mohammad Absar[b], Stephanie Choi[b,*], Jiwen Zheng[a,*]

[a] Division of Biology, Chemistry and Materials Science, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD 20993, United States
[b] Division of Therapeutic Performance, Office of Research Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, United States



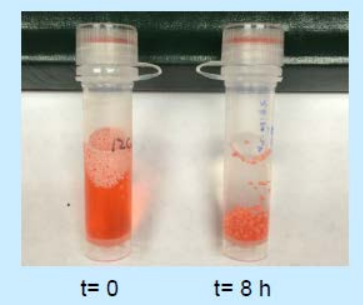
Cryo-TEM disperses IV iron particles in a frozen-hydrate state.



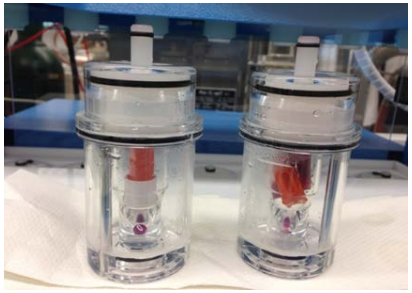
Room temperature sample preparation causes IV iron particles to aggregate during drying.

In-vitro Dissolution of Liposomal Products

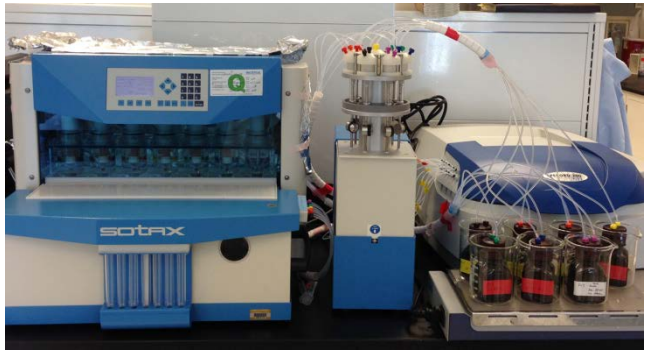
OGD-Zoneone Pharma-University of Michigan Collaboration

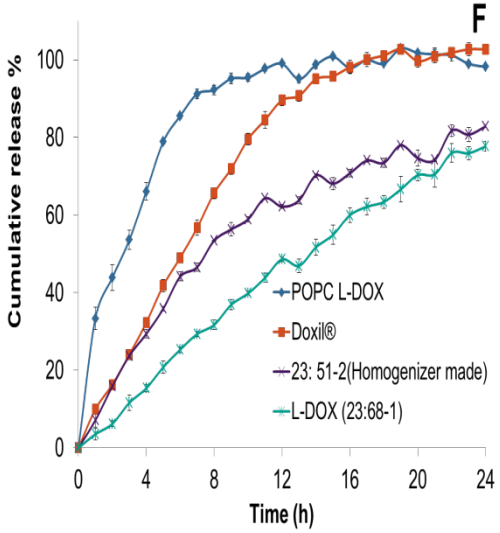


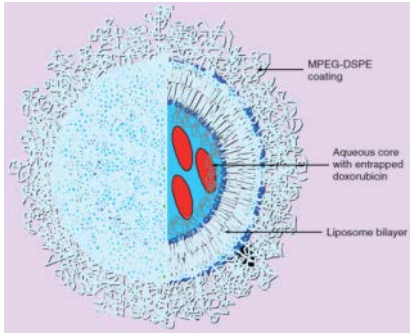
Single vial in vitro dissolution

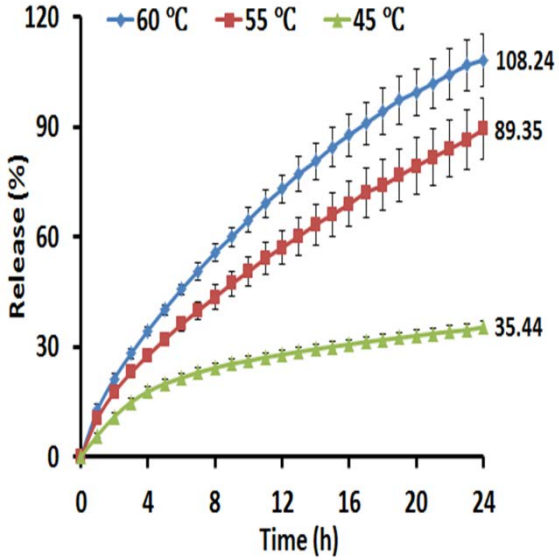


USP dissolution apparatus 4









Yuan W, Kuai R, Dai Z, Yuan Y, Zheng N, Jiang W, Noble C, Hayes M, Szoka FC, Schwendeman A. Development of a Flow-Through USP-4 Apparatus Drug Release Assay to Evaluate Doxorubicin Liposomes. AAPS J. 2017, 19 (1): 151-160

Determination of Labile Iron in Iron Complex

OGD- Albany College of Pharmacy Collaboration

Table 1 Summary of labile iron assays evaluated *in vitro*

Labile iron assay	Assay method	Approximate LOD[a]	Practical limitations	*In vitro* limitations
Rhodamine fluorescence Conversion	Redox active iron	30 μM Fe	Reaction product is very sensitive in ambient conditions and degrades rapidly.	Abolished signal in the presence of agent complex.
Bleomycin detectable iron (BDI)	Redox active iron	10 μM Fe	Multiple reagents and pipetting steps required may reduce accuracy. Narrow assay dynamic range (10-100μM).	Strong interference in the presence of agent complex.
Directly chelatable iron (DCI): FL-DFO	Chelatable iron	2 μM Fe	Narrow assay dynamic range (~2-~60μM).	Abolished fluorescence in the presence of agent complex.
HPLC-DFO	Chelatable iron	50 μM Fe[b]	Duration to complete analysis.	Apparent kinetic increase of labile iron upon incubation with DFO when agents are present (correctable using kinetic analysis to back-calculate labile iron at t = 0).

[a]The assay limit of detection (LOD) as employed was estimated in y as the intercept plus 3 times the standard error of the fit.
[b]Routinely achievable, sufficient for scope of work.

A. Barton Pai, D. E. Meyer, B. Bales, V. Cotero, M.P. Pai, N. Zheng, W. Jiang, Performance of redox active and chelatable iron assays to determine labile iron release from intravenous iron formulations. Clin Transl Sci. 2017 May;10(3):194-200.

Table 1
Summary of *in vitro* rate of release constant (iKr) and the maximum labile iron concentration (iCmax) by formulation (estimate [95% confidence interval]).

Formulation	iKr (h^{-1})	iCmax (μM)
Venofer	0.0369 [0.0326, 0.0411]	138 [115, 161]
Ferrlecit	0.0318 [0.0256, 0.0381]	595 [572, 618]
SFG complex	0.0282 [0.0237, 0.0327]	411 [392, 430]
INFeD	0.0277 [0.0231, 0.0323]	155 [144, 166]
Feraheme	0.0263 [0.0229, 0.0296]	278 [254, 302]
GEH121333	0.0442 [0.0362, 0.0521]	174 [166, 182]

Table 2
Summary of the mean (% coefficient of variation) *in vivo* labile iron concentration-time parameters by formulation (n = 10 animals).

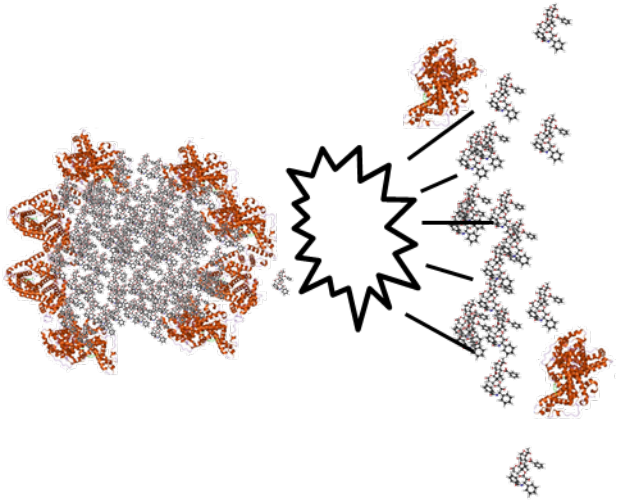
Formulation	Cmax (μM)	$AUC_{0\text{-}4h}$ (μM•h)	Half-life (h)
Venofer	206 (18.8)	403 (20.1)	2.15 (37.5)
Ferrlecit	216 (38.0)	432 (31.2)	2.72 (50.6)
SFGC	227 (21.8)	438 (15.5)	3.20 (72.7)
InFeD	156 (35.0)	495 (29.3)	6.00 (50.1)
Feraheme	102 (38.3)	338 (35.1)	9.41 (48.6)
GEH121333	413 (21.6)	1311 (20.6)	10.4 (33.3)

Cmax, maximum concentration, $AUC_{0\text{-}4h}$, area under the curve from time 0–4 h.

A. B. Pai, M. P. Pai, D. E. Meyer, B. Bales, V. Cotero, N. Zheng, W. Jiang, In vitro and in vivo DFO-chelatable labile iron release f release profiles among commercially available intravenous iron nanoparticle formulations. Regulatory Toxicology and Pharmacology. 2018, 97:17-23.

ABRAXANE Behavior Upon Dilution

OGD – OTR -CDRH Collaboration



Paclitaxel protein-bound suspensions undergo a burst release below a critical concentration. Particles rapidly dissolve releasing drug into solution.

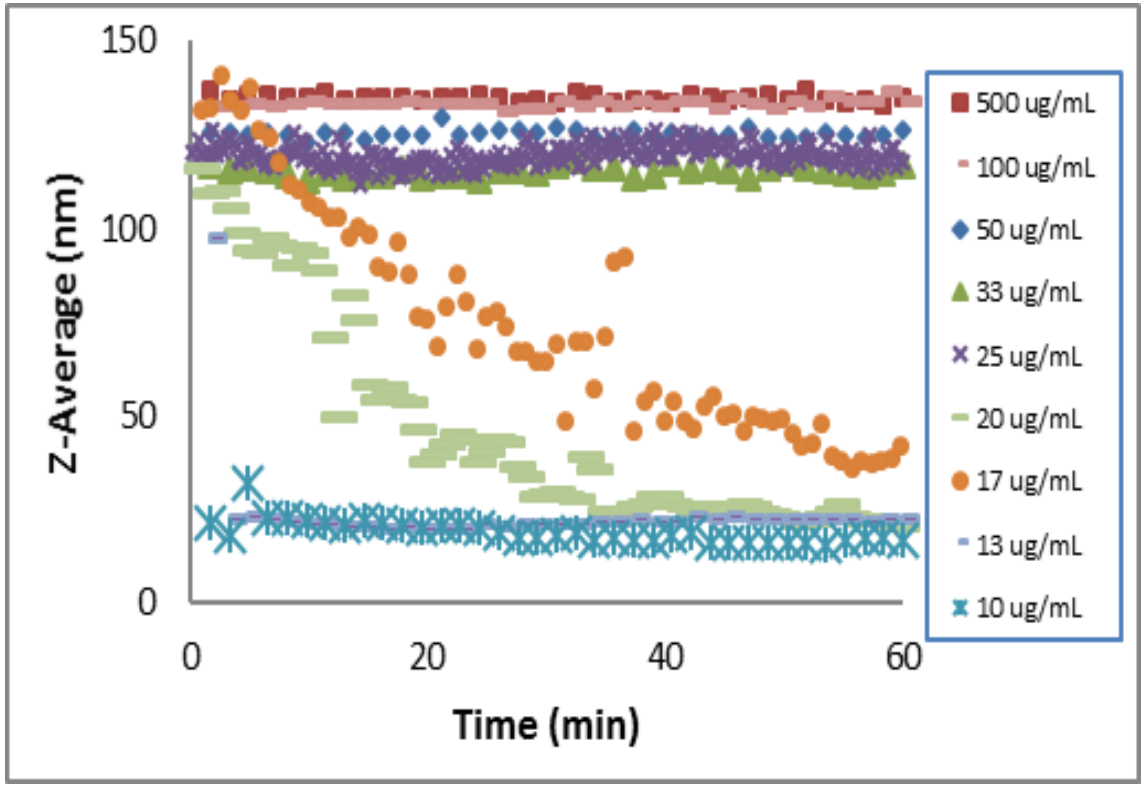


Image courtesy of Peter Petrochenko

Continuous Monitoring of Albumin-Bound Paclitaxel Dissolution Profiles Using Dynamic Light Scattering and In Situ UV/Vis Fiber-Optic Probes. Peter Petrochenko, Sook Wong, Yong Wu, Jiwen Zheng, Xiaoming Xu, Stephanie Choi, Darby Kozak. AAPS Denver, CO (Nov 13–17, 2016)

U.S. FOOD & DRUG ADMINISTRATION

Nanotechnology Post-market Research

Regulatory Impact: Assure the safety and efficacy of approved nanotechnology drug products

Nanotechnology Post-market Research Focus

- Develop versatile surveillance methods to monitor safety and efficacy of approved nanotechnology drug products

- Conduct proactive and reactive lab investigation on nanotechnology drug products

Post-market Surveillance of Iron Complex Drug Products

Original Investigation JAMA. 2015;314(19):2062-2068. doi:10.1001/jama.2015.15572

Comparative Risk of Anaphylactic Reactions Associated With Intravenous Iron Products

Cunlin Wang, MD, PhD; David J. Graham, MD, MPH; Robert C. Kane, MD; Diqiong Xie, PhD; Michael Wernecke, BA; Mark Levenson, PhD; Thomas E. MaCurdy, PhD; Monica Houstoun, PharmD; Qin Ryan, MD, PhD; Sarah Wong, MPH; Katrina Mott, MPH; Ting-Chang Sheu, MPH; Susan Limb, MD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MSc; Marsha E. Reichman, PhD

Figure 1. Trend of First-Time Use by IV Iron Product

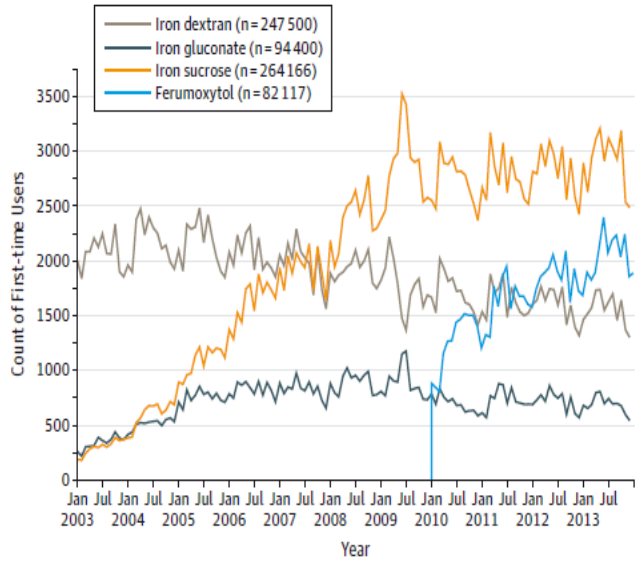
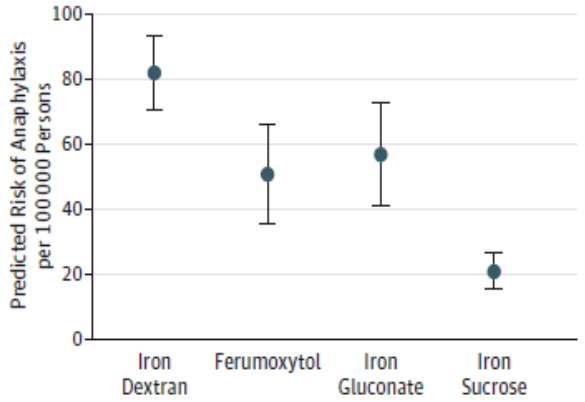


Figure 3. Adjusted Predicted Risk of Anaphylaxis at Cumulative Dose of 1000 mg

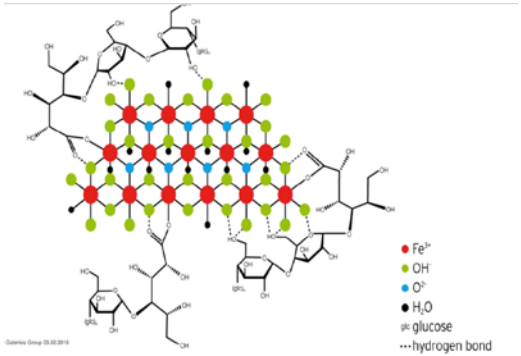


Adjusted for age, coronary heart disease, and hypertension. Error bars indicate 95% CIs.

Among patients in the US Medicare nondialysis population with first exposure to IV iron, the risk of anaphylaxis was highest for iron dextran and lowest for iron sucrose.

FDA Proactive Lab Investigation on Marketed Brand and Generic Iron Products

OGD-OTS/DARS-OTR-CDRH-NCTR Collaboration



IV iron: iron (III)-oxyhydroxide form stabilized by a carbohydrate complex which leads to nano-sized colloidal structures.

"Issue"

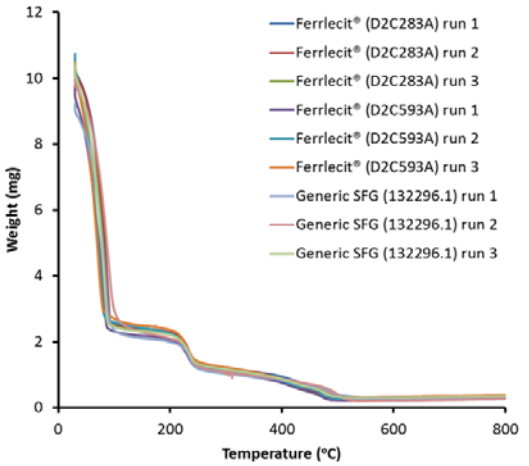
- EMA and FDA have different recommendation about equivalence demonstration

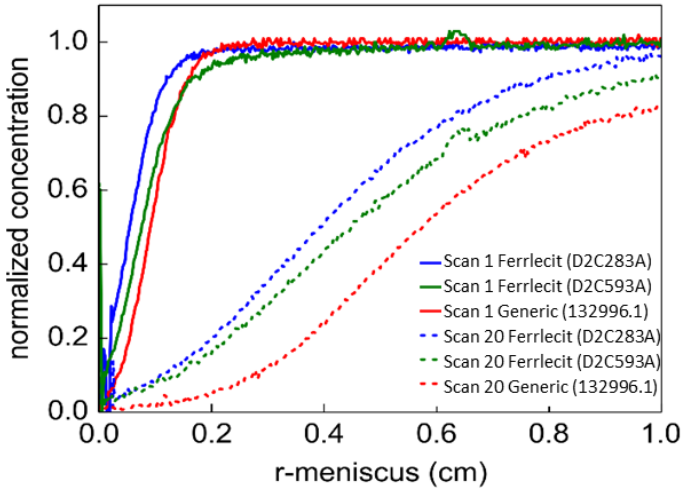
- "Iron sucrose similar" products marketed outside the US were approved under much less rigorous standards. Some had safety/efficacy concerns.

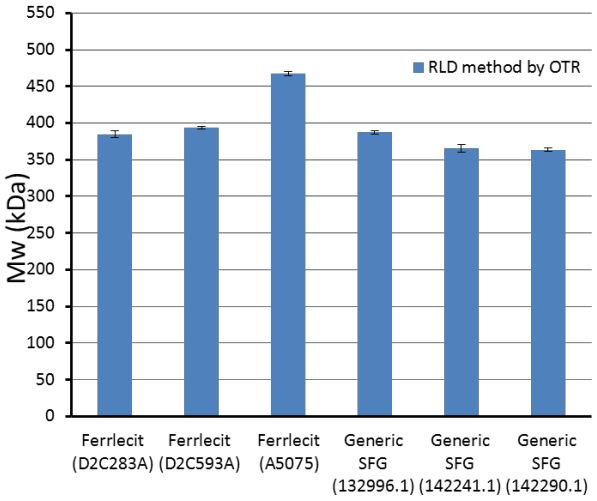
Physico-chemical Characterization

Drug product (Lot #)	Particle Size Distribution by Dynamic light scattering (DLS)			Iron core size by atomic force microscopy (nm)	Elemental Fe conc. in formulations (mg/mL)
	Diluent	Z-average diameter (nm)	PDI Value		
Ferrlecit® (D2C283A)	10 nM NaCl	11.9	0.148	2.2 ± 0.4	12.1
Ferrlecit® (D2C593A)	10 nM NaCl	12.5	0.156	2.6 ± 0.4	12.2
Generic SFG (132296.1)	10 nM NaCl	11.0	0.138	2.6 ± 0.3	12.6

Thermal Stability





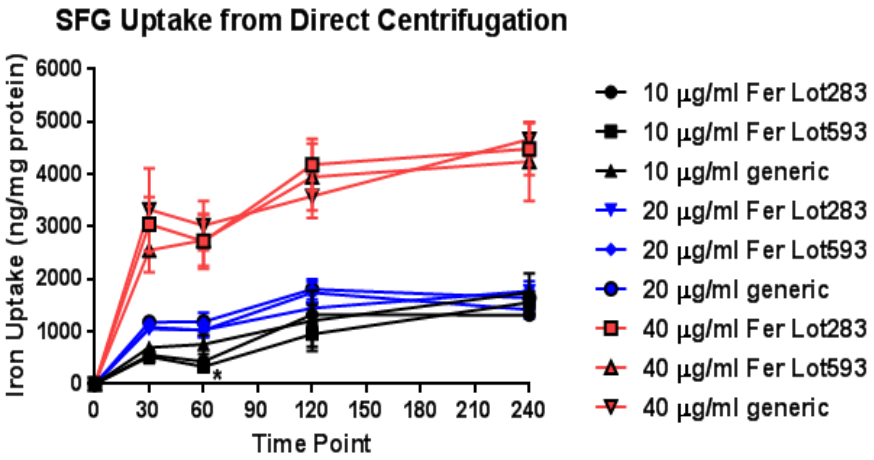


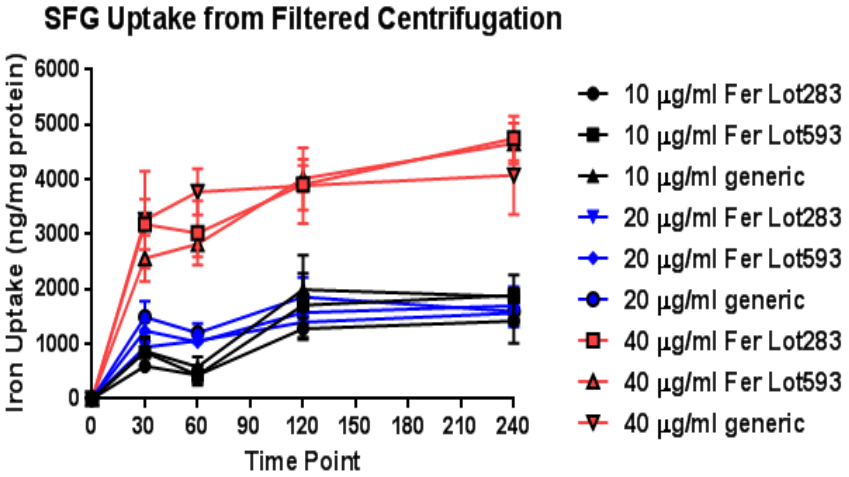
www.fda.gov

Sun D, Rouse R, Patel V, Wu Y, Zheng J, Karmakar A, Patri AK, Chitranshi P, Keire D, Ma J, Jiang W. Comparative Evaluation of US Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: Physicochemical Characterization. Nanomaterials. 2018 Jan 5;8(1).

Cellular Uptake

Comparison of iron uptake in HL-60 cells

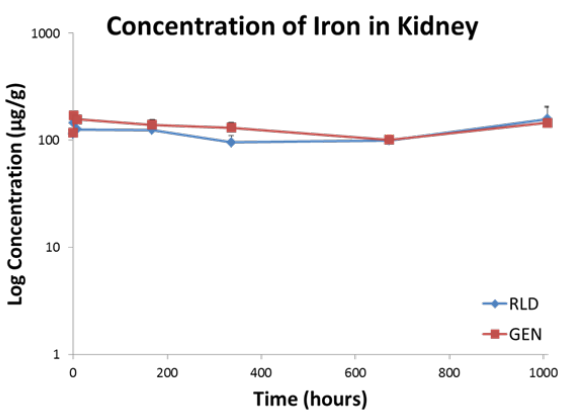


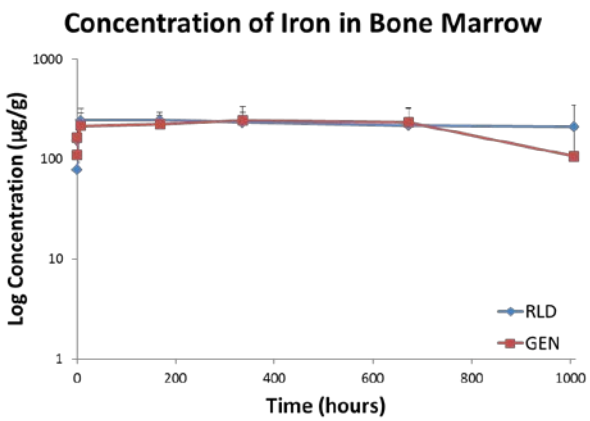


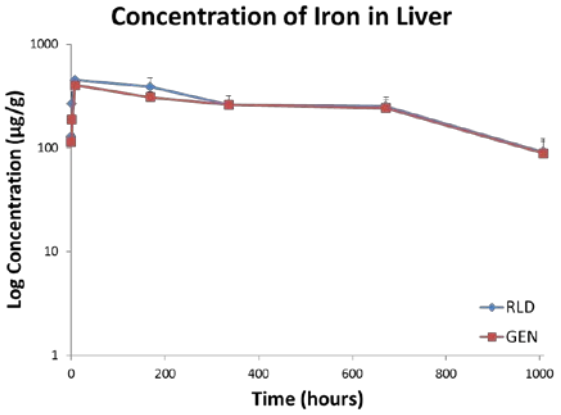
- Three macrophage derived cell lines (U937, HL-60, THP-1) were selected to conduct the cellular uptake.
- The overall trends of cellular iron uptake very similar between the generic drug and its reference listed drug (Ferrlecit®) in three human macrophage cell lines.

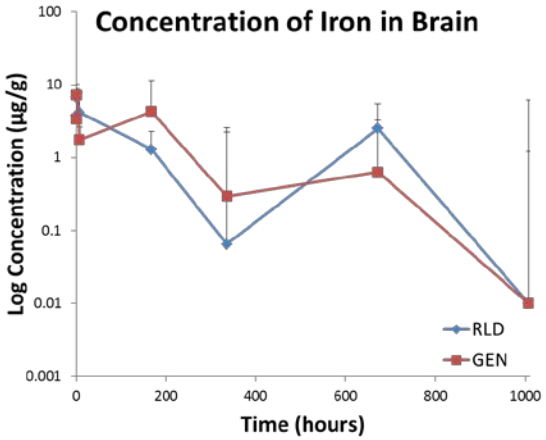
Wu M, Sun D, Tyner K, Jiang W, Rouse R. Comparative Evaluation of US Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: In Vitro Cellular Uptake. Nanomaterials. 2017 Dec 15;7(12).

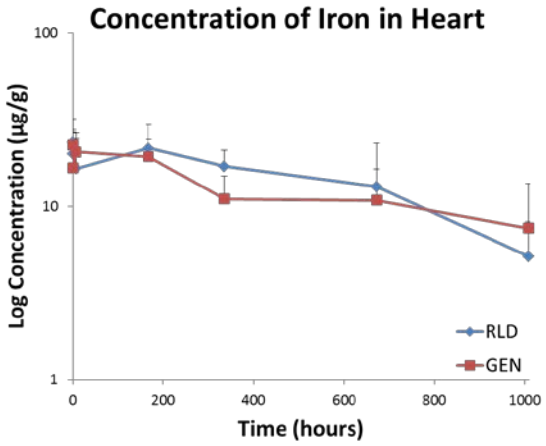
Bio-distribution of Colloidal Iron in Rats

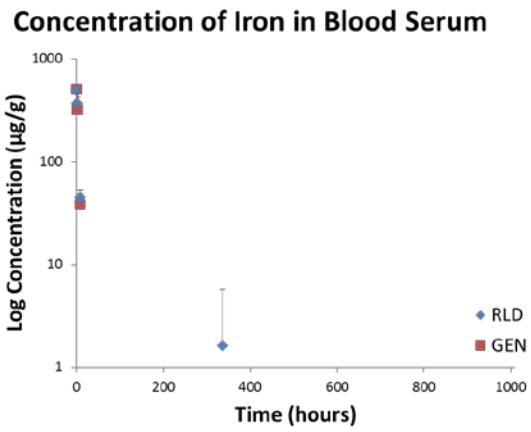












No significant difference in overall bio-distribution

Beekman CR, Matta M, Thomas CD, Mohammad A, Stewart S, Xu L, Chockalingam A, Shea K, Sun D, Jiang W, Patel V, Rouse R. Comparative Evaluation of US Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: Biodistribution after Intravenous Dosing in Rats. Nanomaterials. 2017 Dec 28;8(1).

GDUFA Funded Research Projects on Nanotechnology Products

Extramural Projects

- Evaluation of Dissolution Methods for Complex Parenteral Liposomal Formulations
  - Site PI: Bradley Anderson (University of Kentucky)
  - Grant #: 1 U01 FD004892-01
- Development of a Liposome Doxorubicin Product Drug Release Assay
  - Site PI: Peter Working (ZoneOne Pharma, Inc.)
  - Grant #: 1 U01 FD004893-01
- An in vitro-in vivo correlation model to predict serum non-transferrin bound iron
  - Site PI: Amy Barton Pai (Albany College of Pharmacy and Health Sciences)
  - Grant #: 1 U01 FD004889-01
- Evaluation of In Vitro Release Methods for Liposomal Amphotericin B
  - Site PI: Peter Working (ZoneOne Pharma, Inc.)
  - Grant #: 1 U01 FD005249-01
- Evaluation of Iron Species in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate
  - Site PI: Sarah Michel (University of Maryland)
  - Grant #: 1 U01 FD005266-01
- Novel Method to Evaluate Bioequivalence of Nanomedicines
  - Site PI: Stephan Stern, National Characterization Laboratory
  - Contract #: IAA-224-16-3001S
- Critical process parameters for the preparation of Amphotericin B liposomes
  - Site PI: Alex Nivorozhkin, Neo-Advent Technologies LLC
  - Contract #: HHSF223201610093C
- Physiologically based pharmacokinetic model for drugs encapsulated into liposomes
  - Site PI: Yanguang Cao (University of North Carolina)
  - Grant #: 1U01FD005206

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

GDUFA Funded Research Projects on Nanotechnology Products

Ongoing Intramural Projects

- Application of cryo-electron microscopy (cryo-EM) for morphological characterization of complex nano-drug products to improve the review of in vitro bioequivalence studies
  - FDA Collaborator: Jiwen Zheng, Yong Wu
  - FDA Center/Office/Division: CDRH/OSEL/DBCMS
- Nanoparticle Tracking in Nanofluidic Slits: A Powerful and Practical Method to Measure Liposomal Drug Products
  - FDA Collaborator: Jiwen Zheng
  - FDA Center/Office/Division: CDRH/OSEL/DBCMS
  - External Collaborator: Samuel Stavis
  - National Institute for Standards and Technology (NIST)
- Investigation into reported differences in Doxil® and generic liposomal doxorubicin formulations: Physicochemical Characterization, in vitro biocompatibility & in vivo efficacy and biodistribution evaluation
  - FDA Collaborator: Anil Patri
  - FDA Center/Office/Division: NCTR
- Physical and Chemical Characterizations of Lipid Based Complex Pharmaceutical Formulations
  - FDA Collaborator: Thilak Mudalige
  - FDA Center/Office/Division: ORA

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

CDER Nanotechnology Research Resources

- **CDER Nanotechnology Program**

https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm309677.htm

- **GDUFA Regulatory Science Report: Nanotechnology: Physiochemical Characterization of Nano-Sized Drug Products**

https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549163.htm

- **GDUFA Regulatory Science Report: Nano Drug Products: Clinical Pharmacology and In Vivo Correlation**

https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549183.htm

Summary

- FDA recognizes the complexity on nanotechnology drug products and encourages regulatory research
- CDER regulatory research on nanotechnology products focuses on quality, safety, equivalence, and post-market surveillance of these products
- Collaborative regulatory research in nanotechnology drug products
  - Facilitate efficient drug product development
  - Ensure approved drug safety and efficacy
  - Support guidance development
  - Streamline review process
  - Promote international harmonization

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Siyam Ansar

Zone One Pharma
Frank Szoka
Charles Noble
Mark Hayes

University of Michigan
Anna Schwendman
Amy Barton Pai (previously at Albany College of Pharmacy)

Nanocore Facility/CDRH/FDA
Jiwen Zheng
Yong Wu

NCTR/FDA
Anil Patri

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank You

Any question?

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