Regulating Generic Nanotechnology Drug Products: Guidance and Standards

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Stresa, Italy

September 26, 2019

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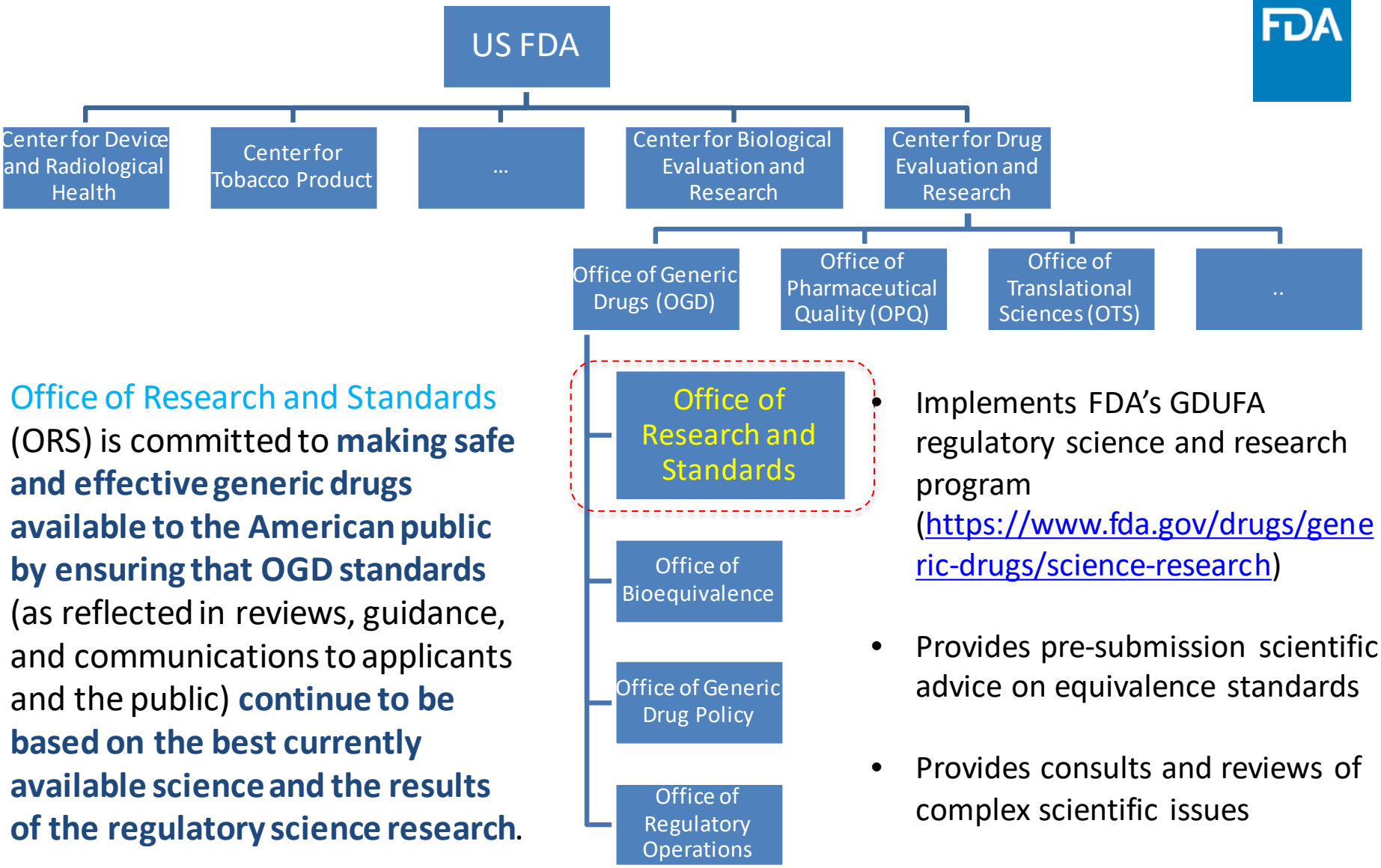
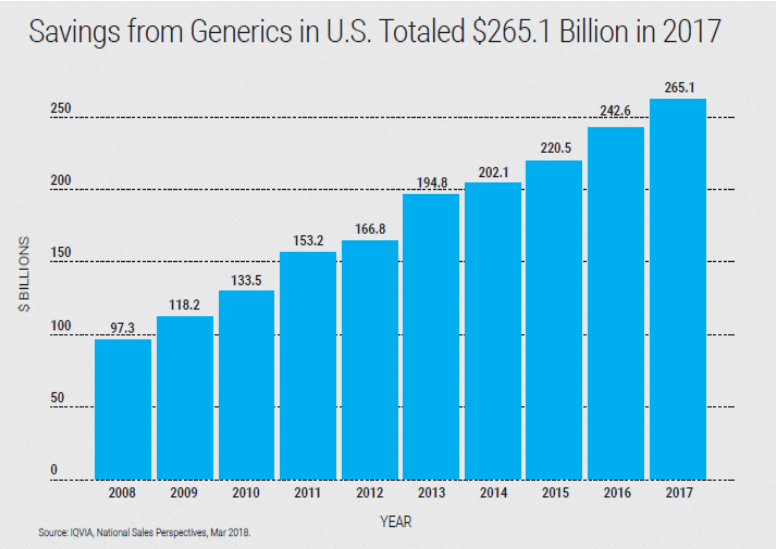


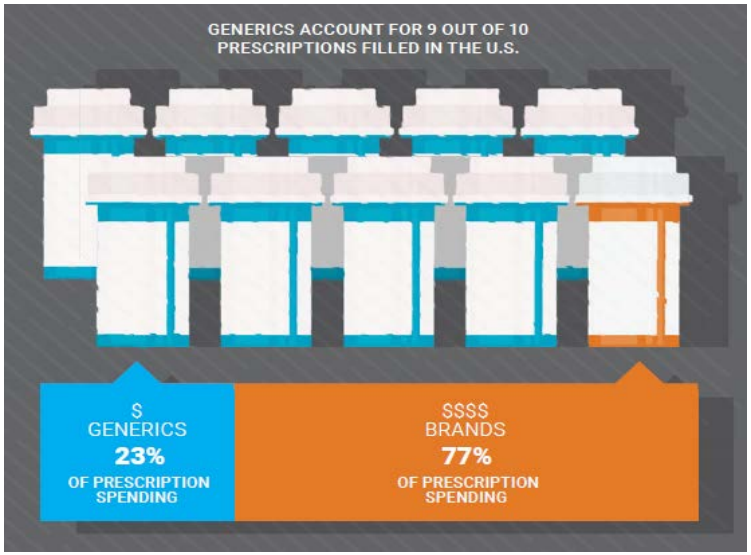
Office of Research and Standards (ORS) is committed to **making safe and effective generic drugs available to the American public by ensuring that OGD standards** (as reflected in reviews, guidance, and communications to applicants and the public) **continue to be based on the best currently available science and the results of the regulatory science research**.

- Implements FDA's GDUFA regulatory science and research program (https://www.fda.gov/drugs/generic-drugs/science-research)
- Provides pre-submission scientific advice on equivalence standards
- Provides consults and reviews of complex scientific issues
- Ensures therapeutic equivalence of approved generic drugs

Generic Drugs

- Generic drugs are “copies” of their respective reference listed drugs (RLDs)
- Generally, this means the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling and is bioequivalent





https://accessiblemeds.org/sites/default/files/2018_aam_generic_drug_access_and_savings_report.pdf

nature nanotechnology

ANALYSIS

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

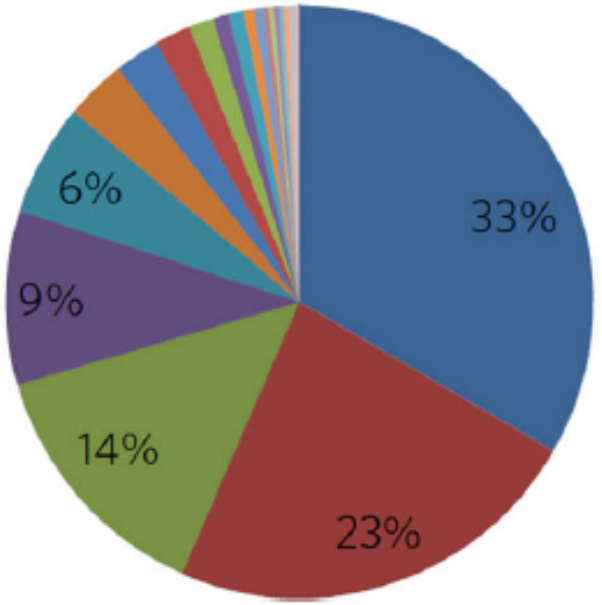
FDA

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*

(1973-2015)

- Liposome
- Nanocrystal
- Emulsion
- Iron-polymer complex
- Micelle
- Drug-protein complex
- Drug-polymer complex
- Dendrimer
- Polymeric NP
- Nanobubble
- Silica NP
- Drug-lipid complex
- Drug-metal complex
- Protein NP
- Drug NP
- Solid lipid NP
- Nanotube
- Metal-protein complex
- Metal-nonmetal complex
- Metal-polymer complex



www.fda.gov

FDA Approved Nanotechnology Products

Platform	Examples			
	Name	New Drug Application (NDA) Approval	Indication	1st Abbreviated New Drug Application (ANDA) Approval
Liposome	DOXIL® (Doxorubicin)	1995	Cancer	2013
Inorganic nanoparticle	FERRLECIT® (Sodium ferric gluconate complex)	1999	Anemia	2011
Protein nanoparticle	ABRAXANE® (Paclitaxel)	2005	Cancer	None
Polymer nanoparticle	MACUGEN® (Pegaptanib sodium)	2004	Macular degeneration	None
Emulsion	RESTASIS® (Cyclosporine)	2002	To increase tear production	None
Lipid complex	AMPHOTEC® (Amphotericin B)	1996	Invasive aspergillosis	None
Nanotube	SOMATULINE DEPOT® (Lanreotide acetate)	2007	Acromegaly	None
Nanocrystal	TRICOR® (Fenofibrate)	2004	Hypercholesterolemia	2011
Micelle	TAXOTERE®(Docetaxel)	1996	Cancer	None

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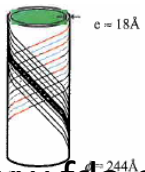
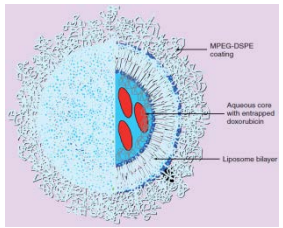
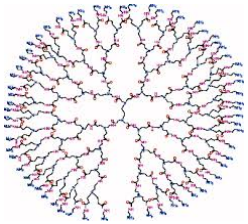
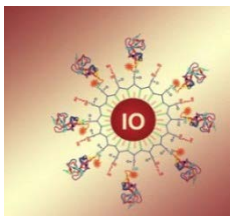
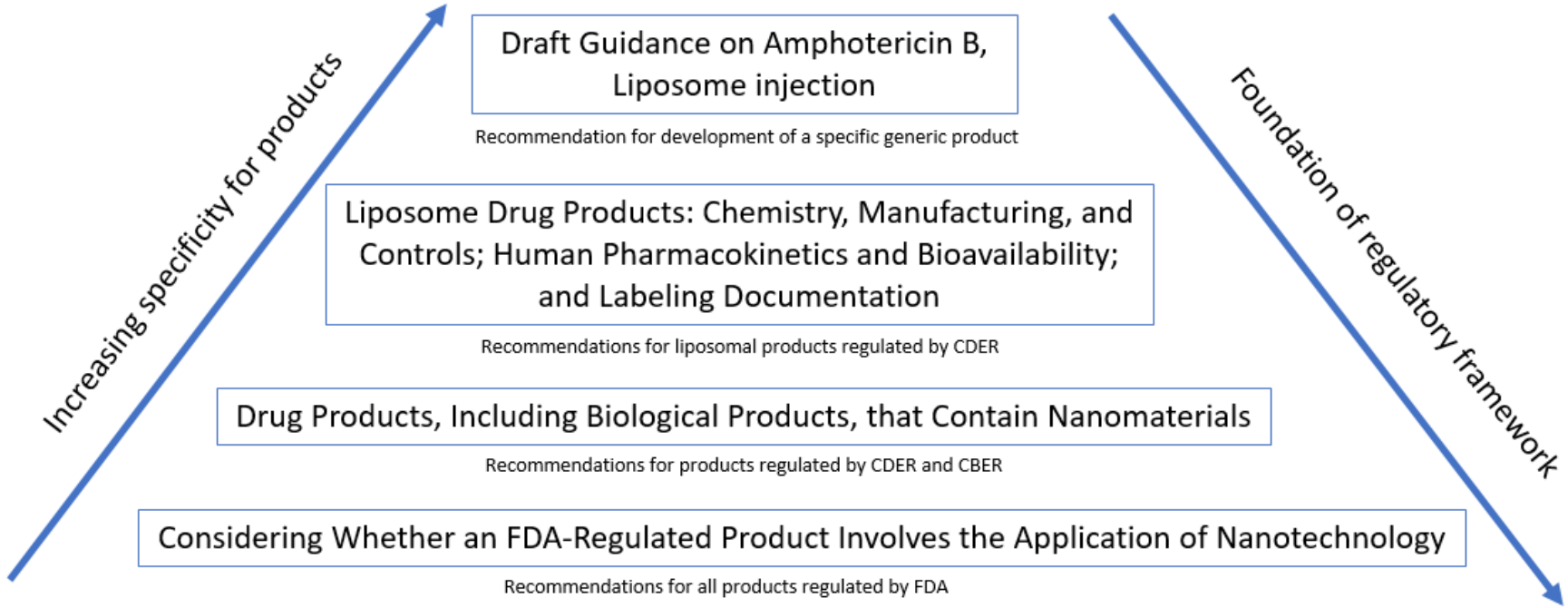


www.fda.gov

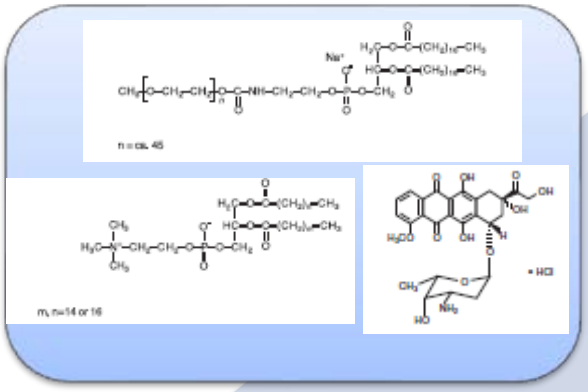
U.S. FDA Guidance Related to Nanotechnology Products

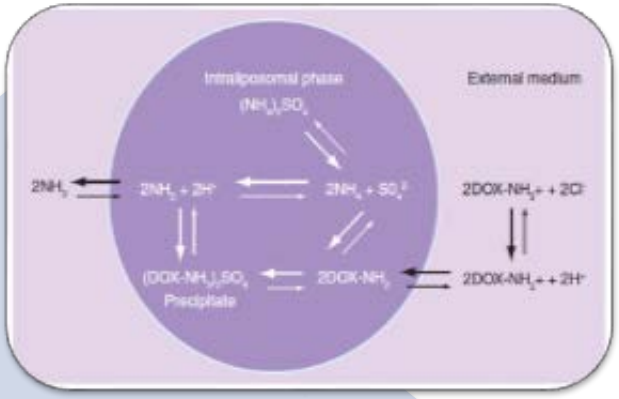


Vlieger, J, et al. Report of the AAPS Guidance Forum on the FDA Draft Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials. The AAPS Journal (2019) 21: 56

U.S. FDA Product-Specific Guidance for Doxorubincin HCl Liposomes

Qualitative (Q1) and Quantitative (Q2) sameness

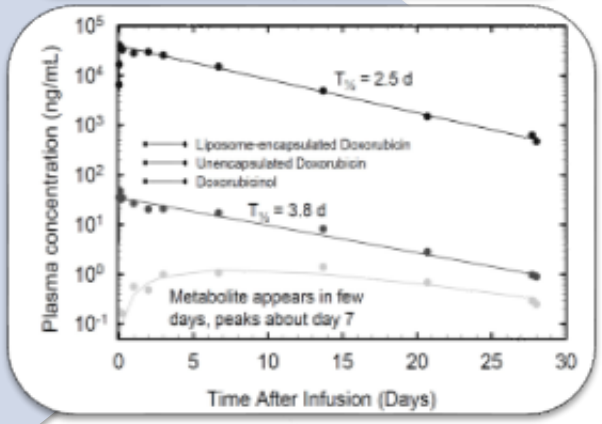




Same remote loading manufacturing process

No details about he methods

aracteristics	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



Equivalent physico-chemical characteristics

Equivalent free and liposome associated drug exposure

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Jiang W, Lionberger R, Yu L, In vitro and in vivo characterizations of PEGlyated liposome doxorubicin. Bioanalysis. 2011 Feb;3(3):333-44
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf

Standards

- Measurement standards
  - International systems of units

- Reference standards*

  - Materials that are certified by a national standards laboratory to verify a quantitative measurement.

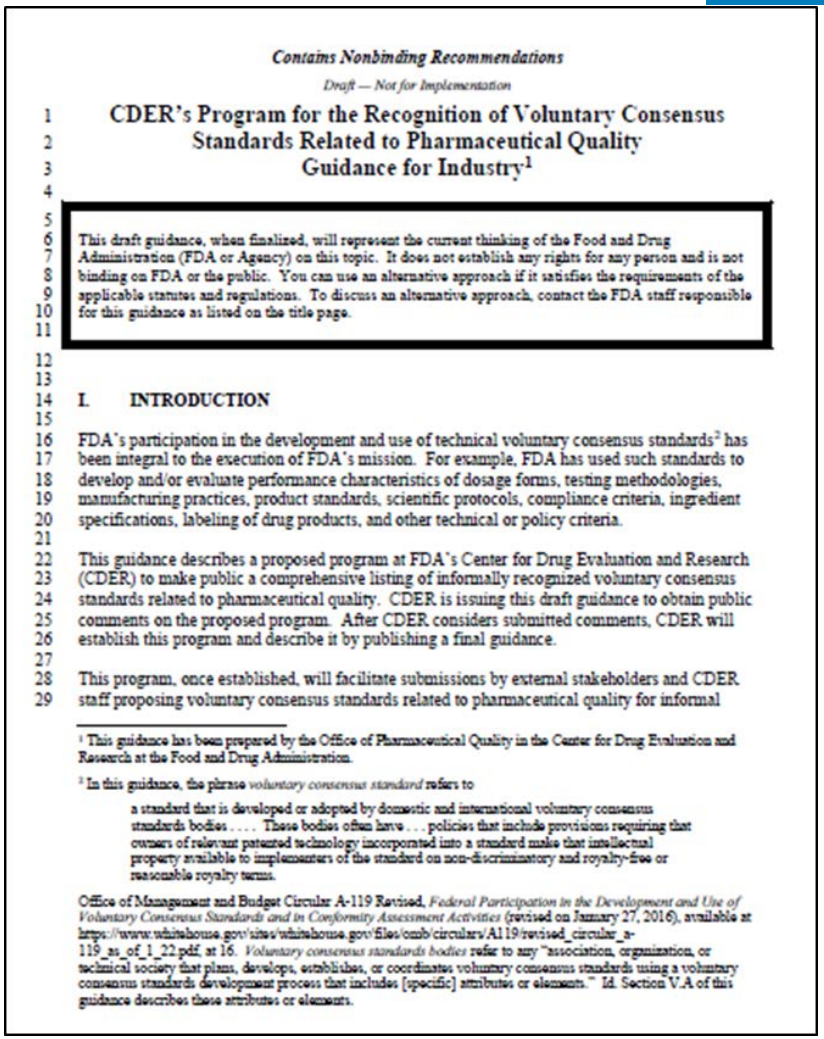
- Documentary standards

  - agreed-upon terminology or standard language; means for conducting measurements; performance characteristics of instruments or commercial products

* The term reference standard here is different from the reference standard used in Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.

www.fda.gov

https://www.nano.gov/you/standards



Contains Nonbinding Recommendations

Draft — Not for Implementation

CDER's Program for the Recognition of Voluntary Consensus Standards Related to Pharmaceutical Quality Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or 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 FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA's participation in the development and use of technical voluntary consensus standards[2] has been integral to the execution of FDA's mission. For example, FDA has used such standards to develop and/or evaluate performance characteristics of dosage forms, testing methodologies, manufacturing practices, product standards, scientific protocols, compliance criteria, ingredient specifications, labeling of drug products, and other technical or policy criteria.

This guidance describes a proposed program at FDA's Center for Drug Evaluation and Research (CDER) to make public a comprehensive listing of informally recognized voluntary consensus standards related to pharmaceutical quality. CDER is issuing this draft guidance to obtain public comments on the proposed program. After CDER considers submitted comments, CDER will establish this program and describe it by publishing a final guidance.

This program, once established, will facilitate submissions by external stakeholders and CDER staff proposing voluntary consensus standards related to pharmaceutical quality for informal

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

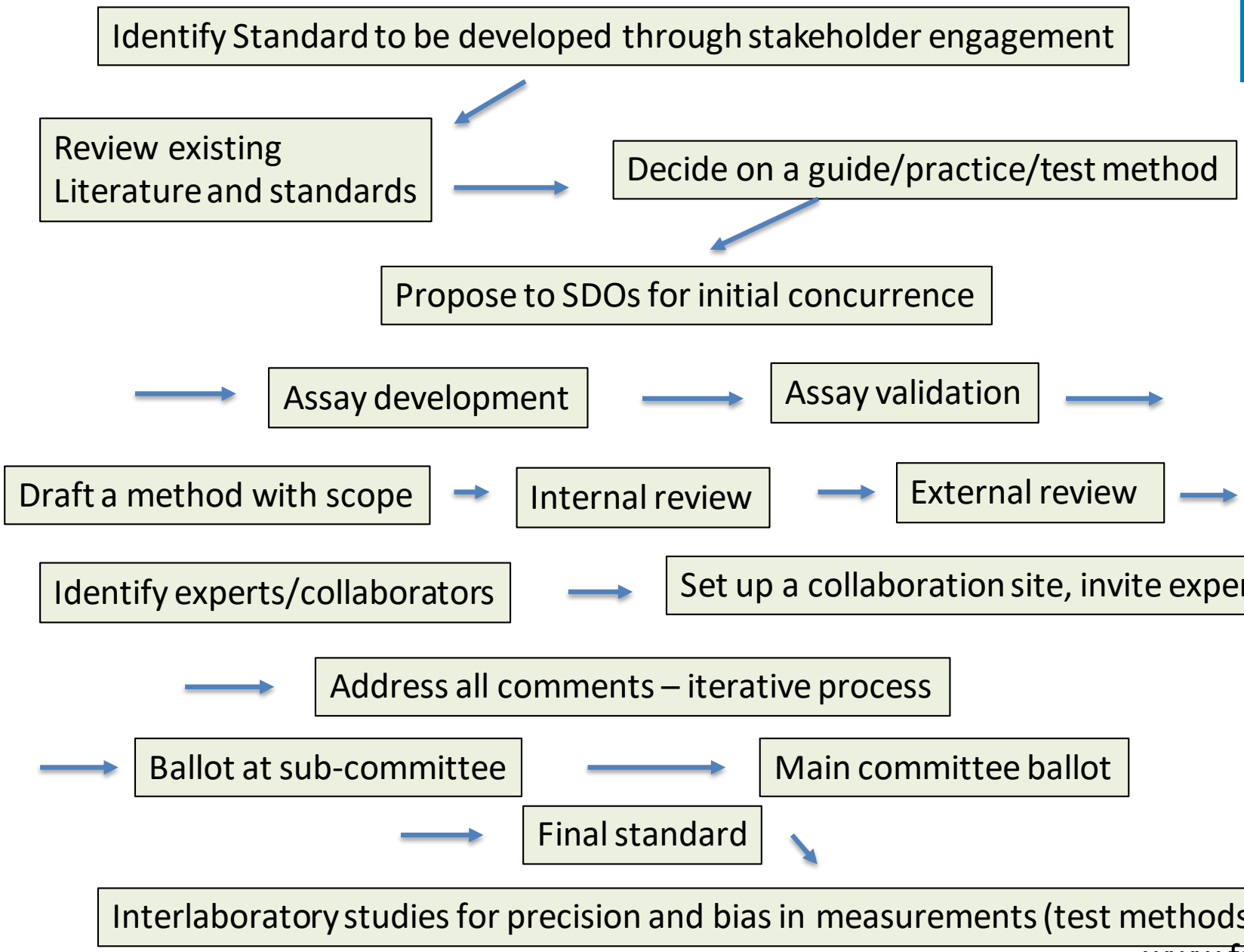
[2] In this guidance, the phrase *voluntary consensus standard* refers to

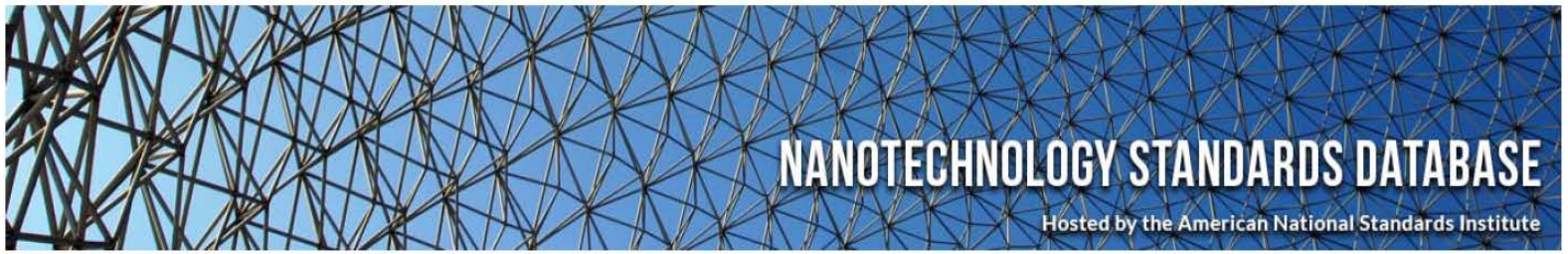
> a standard that is developed or adopted by domestic and international voluntary consensus standards bodies . . . . These bodies often have . . . policies that include provisions requiring that owners of relevant patented technology incorporated into a standard make that intellectual property available to implementers of the standard on non-discriminatory and royalty-free or reasonable royalty terms.

Office of Management and Budget Circular A-119 Revised, *Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities* (revised on January 27, 2016), available at https://www.whitehouse.gov/sites/whitehouse.gov/files/omb/circulars/A119/revised_circular_a-119_as_of_1_22.pdf, at 16. *Voluntary consensus standards bodies* refer to any "association, organization, or technical society that plans, develops, establishes, or coordinates voluntary consensus standards using a voluntary consensus standards development process that includes [specific] attributes or elements." Id. Section V.A of this guidance describes these attributes or elements.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cders-program-recognition-voluntary-consensus-standards-related-pharmaceutical-quality

Documentary consensus standards development





Log in

Links to Relevant Activities

ANSI-NSP

ASTM E56 Committee

BAM NanoScale Reference Materials Database

IEC TC 113 Nanotechnology standardization for electrical and electronic products and systems

ISO TC 229 Nanotechnologies

TAPPI Nanotechnology

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Clicking the designated number listed under the *"Record #"* category displays the full contents of a particular entry.

Filters

Items found: **154**

Record #	Source (e.g. developer/organization)	Acronym (e.g. ISO, IEC)	Identifier (e.g. document designation number)	Title of document	Scope/description	Keywords	Type of Docun
137	International Organization for Standardization	ISO	TR 19733	Nanotechnologies - Matrix Of Properties And Measurement Techniques For Graphene And Related Two-Dimensional (2D) Materials	This document provides a matrix which links key properties of graphene and related...	Graphene, 2-d materials, measurement methods, structural properties	a. Star

www.fda.gov

http://nanostandards.ansi.org/tiki-index.php?page=DataEntryOutputPub

Received: 7 March 2018 | Revised: 26 April 2018 | Accepted: 9 May 2018

DOI: 10.1002/wnan.1531

WILEY WIREs NANOMEDICINE AND NANOBIOTECHNOLOGY

ADVANCED REVIEW

Mapping of the available standards against the regulatory needs for nanomedicines

Blanka Halamoda-Kenzaoui[1] | Uwe Holzwarth[1] | Gert Roebben[2] | Alessia Bogni[1] | Susanne Bremer-Hoffmann[1]

BOX 1

MAJOR GAPS IN STANDARDS FOR NANOMEDICINES

1. Methods for:
   - Drug loading and drug release from nanocarriers
   - Evaluation of the interaction with the immune system, in particular immunogenicity
   - Investigation of the protein corona
   - Detection of nanomaterial in biological tissues
2. Guidance for assessment of the comparability of methods
3. Reference materials relevant for nanomedicine
4. Evaluation of the suitability and recognition of standards developed in other sectors

Liposome Standard Needs Top Priorities

- Terminology-liposome specific
- Asymmetric flow field flow fractionation (AF4)
- Lipid excipient stability/degradation/component analysis
- Determination of liposomal encapsulated and free drug/separation of encapsulated and free drug
- Stability of liposome (including in-use stability)
- In vitro drug release testing procedures

International Organization for Standardazation (ISO) Liposome Study Group Discussion Points

Continued Development of Product-Specific Guidances

FDA published product-specific equivalence guidance for nanotechnology drug products

doxorubicin HCl liposome injection
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

….

(Not a complete list)

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Continued Efforts to Promote Harmonization on Evaluation Criteria

U.S. FDA Doxorubicin HCl liposomes Product-Specific Guidance (Recommended 2010, most recent revision 2018)

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

European Medicines Agency (EMA) Doxorubicin HCl liposomes Product-Specific Guideline (Recommended 2018)

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

International Pharmaceutical Regulators Programme (IPRP) Nanomedicine Working Group

ICH Reflection Paper

Further Opportunities for Harmonization of Standards for Generic Drugs[1]

Executive Summary

This reflection paper outlines a strategic approach for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs. As part of this approach, this paper outlines recommendations to develop a series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for (1) non-complex dosage forms and (2) more complex dosage forms and products. To accomplish this work, it is proposed to establish a generic drug discussion group to assist in assessing the feasibility of harmonization of standards for generic drugs and to prioritize work areas.

https://www.ich.org/products/reflection-papers.html

Continued Development of Drug Product Characterization Methods

Physico-chemical characterization

- Particle size/distribution
- Surface property
- Drug state
- In-vitro dissolution

Biological performance test via in vitro test methods

- Production of nitric oxide (NO) by macrophages *in vitro*.
- Internalization by phagocytic cells *in vitro*
- ….

Liposome Physico-chemical Characterization

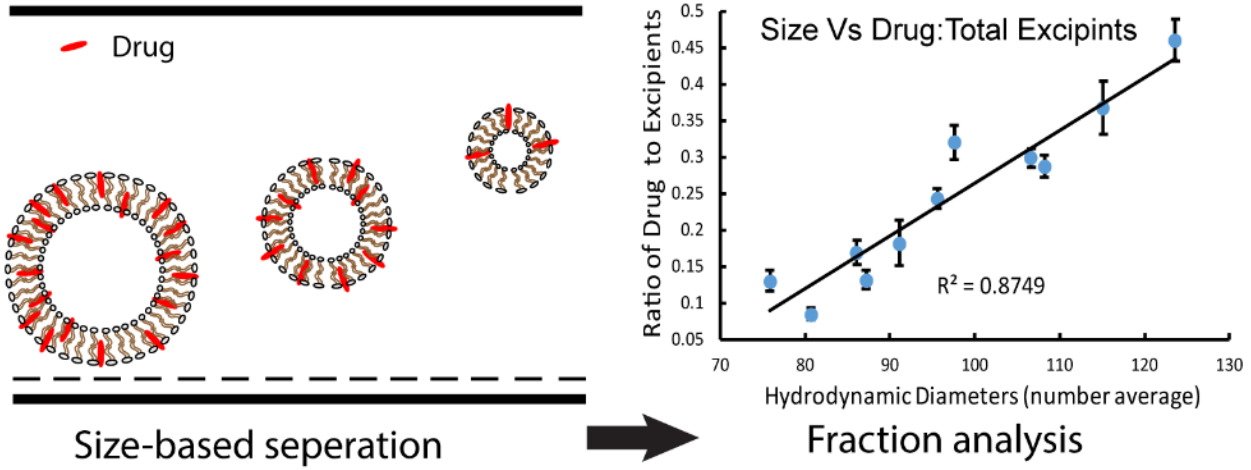
Liposome components
- Lipids
- Unencapsulated drug vs liposome associated drug

…

Liposome higher order structure
- Particle size
- Morphology
- Lamellarity
- Surface characteristics of the liposomes
- Liposome phase transition temperature

Liposome performance
- In vitro release

Quantification of Lipid Excipients and Active Pharmaceutical Ingredients (APIs) in Liposomes



International Journal of Pharmaceutics 569 (2019) 118603

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

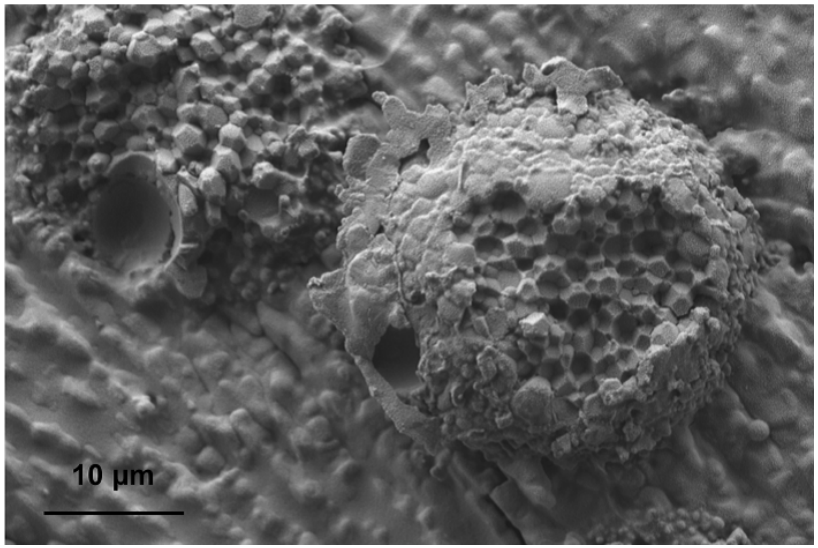
journal homepage: www.elsevier.com/locate/ijpharm

Evaluation of size-based distribution of drug and excipient in amphotericin B liposomal formulation

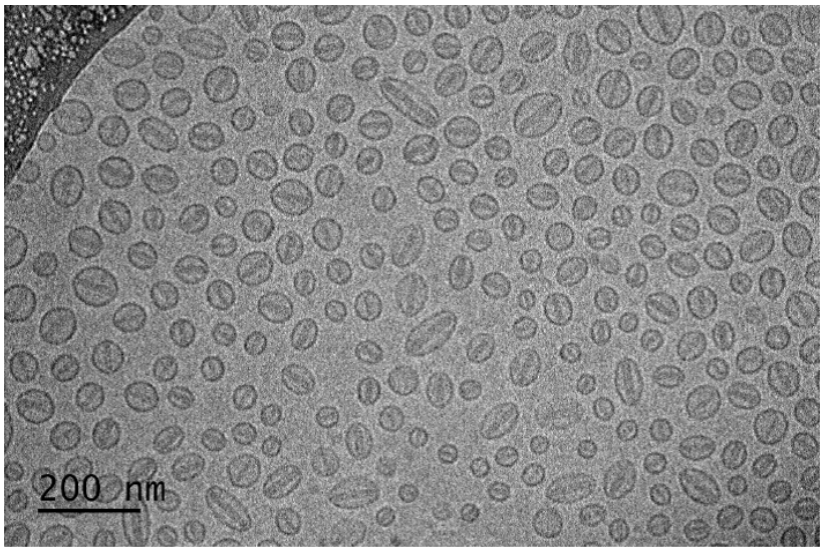
Desiree Van Haute[a], Wenlei Jiang[b,*], Thilak Mudalige[a,*]

[a] Arkansas Laboratory, Office of Regulatory Science, Office of Regulatory Affairs, US Food and Drug Administration, Jefferson, AR 72079, United States
[b] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, United States

Morphological Characterization of Liposome Products by Cryo-Transmission Electron Microscopy (TEM)



Bupivacaine Liposomes



Doxorubicin HCl Liposomes

Image Courtesy of Yong Wu and Jiwen Zheng

Optimize Cryo-TEM experimental conditions and standardize analytical procedures

Determination of Labile Iron in Iron Complex

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.

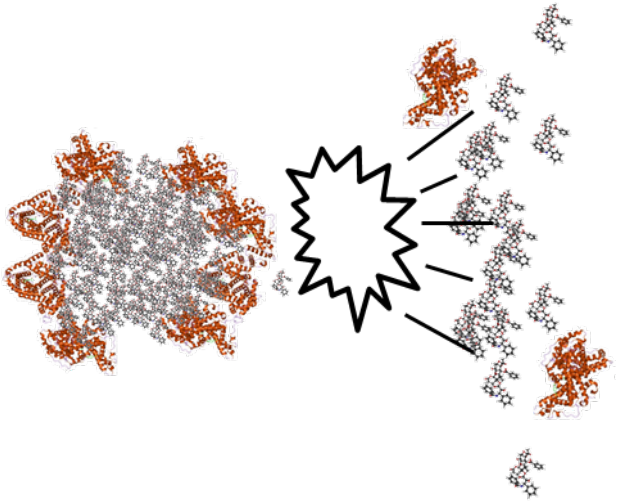
A. Barton Pai, D. E. Meyer, B. Bales, V. Cotero, M.P. Pai, N. Zheng, W. Jiang, Performance of redox active and chelatable iron assays to determine labile iron release from intravenous iron formulations. Clin Transl Sci. 2017 May;10(3):194-200.

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]

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



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

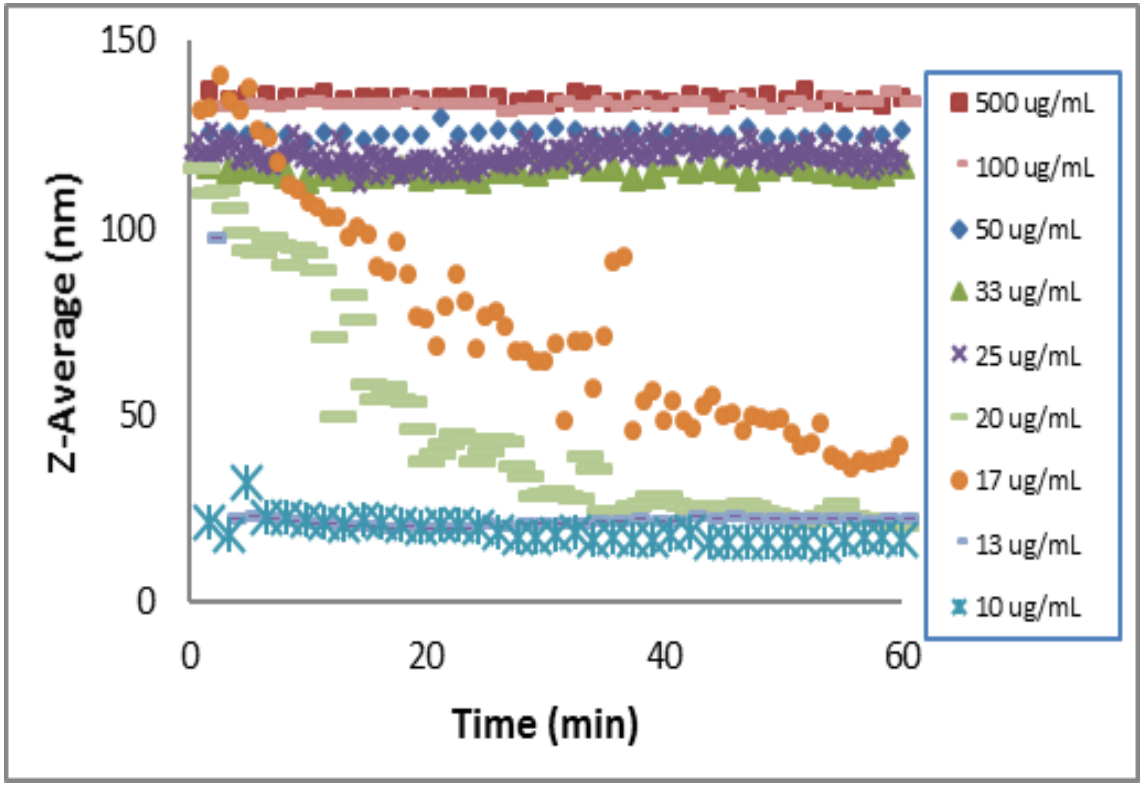


Image courtesy of Peter Petrochenko

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)

Considerations on Characterization Methods to Standards Development

- Most methods highly product-specific
- Multiple methods developed by different labs
- Advanced analytical methods vs readily available methods
- Biorelevant dissolution vs standard dissolution methods
- Interlaboratory selection
- Standards development timeline
- Protocol vs standard

Current status of the proposed work items

Work item	category	Assay	Assay development	Assay validation	Work item draft	Initial review	Collaboration area /draft comments	Review	Subcommittee Ballot	Main committee	Final Standard
	Standard Practice	Cryo-TEM of Liposomes	✓	✓	✓	✓	✓	✓	✓	✓	**E3143-18b**
WK60373	Test method	Chemotaxis	✓	✓	✓	✓	✓	✓	✓		
WK60554	Test method	Nitric oxide	✓	✓	✓	✓	✓	✓			
WK60553	Guide	Phagocytosis	✓	✓	✓	✓	✓				
WK67980	Test method	PEG coating quantitation HPLC-ELSD	✓	✓	✓						
WK67984	Test method	Lipid quantitation UPLC-MS	✓	✓	✓						
WK67983	Test method	Lipid quantitation HPLC-ELSD	✓	✓	✓						
WK67982	Test method	Lipid quantitation HPLC-CAD	✓	✓	✓						
WK63310	Guide	Hyperspectral imaging	✓								

Summary

- Documentary standards are complementary to product-specific guidance for generic nanotechnology drug product development

- To support generic nanotechnology drug product development and review
  - Continue developing product-specific guidance
  - Promote harmonization of assessment criteria
  - Support characterization method development into standards

Acknowledgements

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OPQ/CDER/FDA

Kathryn Tyner

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank You

Any question?

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