

FDA NanoDay Symposium

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Standards Development at FDA

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Disclaimer: The views expressed are of the presenters and should not be considered as the official position or policy of U.S. FDA

Outline

- Importance of Standards
 - Global Summits to identify standards needs
 - Standards development at FDA
 - Future needs
-
- Draft Standards Review at FDA
 - Consensus Standards Recognition



Importance of Standards

- Standards facilitate evaluation of products
- Increase predictability, streamline premarket review
- Industry can utilize consensus standards recognized by regulatory agencies¹
- Harmonization
- Use of standards is voluntary

- Requires maturity of science, expertise & consensus
- Readily available equipment and methods for wider use

1. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>

Standards Development in Nanotechnology



Reference Material Standards



- National Institute of Standards and Technology (NIST)
- Joint Research Center (JRC/EC)
- National Measurement Institute (NMI, Australia)
- National Research Council Canada (NRC)

Consensus Standards



- ASTM International E56
- International Organization for Standardization (ISO) TC 229
- Organisation for Economic Co-operation and Development (OECD) Working Party on Manufactured Nanomaterial (WPMN)
- United States Pharmacopeia (USP)
- European Pharmacopoeia (Ph.Eur)

Industry engagement is needed for Nanotechnology standards development

A list of Standards Needs

Conclusions from GSRS15, October 2015, Parma

Participants: FDA, NIST, EMA, EFSA, ECHA, OECD, NMI, EC, NanoReg, JRC

- **Pristine Nanomaterials**
 - **Reference Materials**
 - Liposomes
 - Quantitative surface coatings (species, coverage)
 - Number concentration in aqueous solution
 - Multi-modal by size (same nanomaterial)
 - Shape (needs to be specified)
 - **Documentary Standards**
 - DLS standard test method with specifications for regulatory use
 - Surface coating: composition and stability measurement method
 - Surface coating: zeta potential measurement method
 - Guidance document for tiered approach for methods to measure size and size distribution
 - Asymmetric Flow/Sedimentation Field Flow Fractionation (ISO/PWI, Japan)
 - Electron microscopy technical specification: SEM (ISO/PWI 19749 USA); TEM (ISO/PWI USA/Japan); cryogenic TEM; and low-voltage TEM
 - **Other needs**
 - Updated public database of reference materials: *hosted by BAM or NIST?*
- **NMs in Complex Matrices**
 - **Reference Materials**
 - Simulated body fluids (no nanomaterials)
 - (Specific) nanomaterial in (specific) media
 - Controlled agglomeration nanomaterial
 - **Documentary Standards**
 - Drug substance release rate from a liposome
 - Quantitation of nanomaterials in blood
 - Quantitation of NMs in tissue
 - Guide for sample preparation for variety of methods, *e.g.*, SEM, TEM, ICP-MS (will be material-dependent)
 - Speciation: relative and total concentrations (*e.g.*, ions, complex NMs)
 - Migration of nanomaterials in food packaging materials
 - Guideline for harmonization performance criteria

Prioritized List of Standards Needs



Nanotechnology Standards and Applications



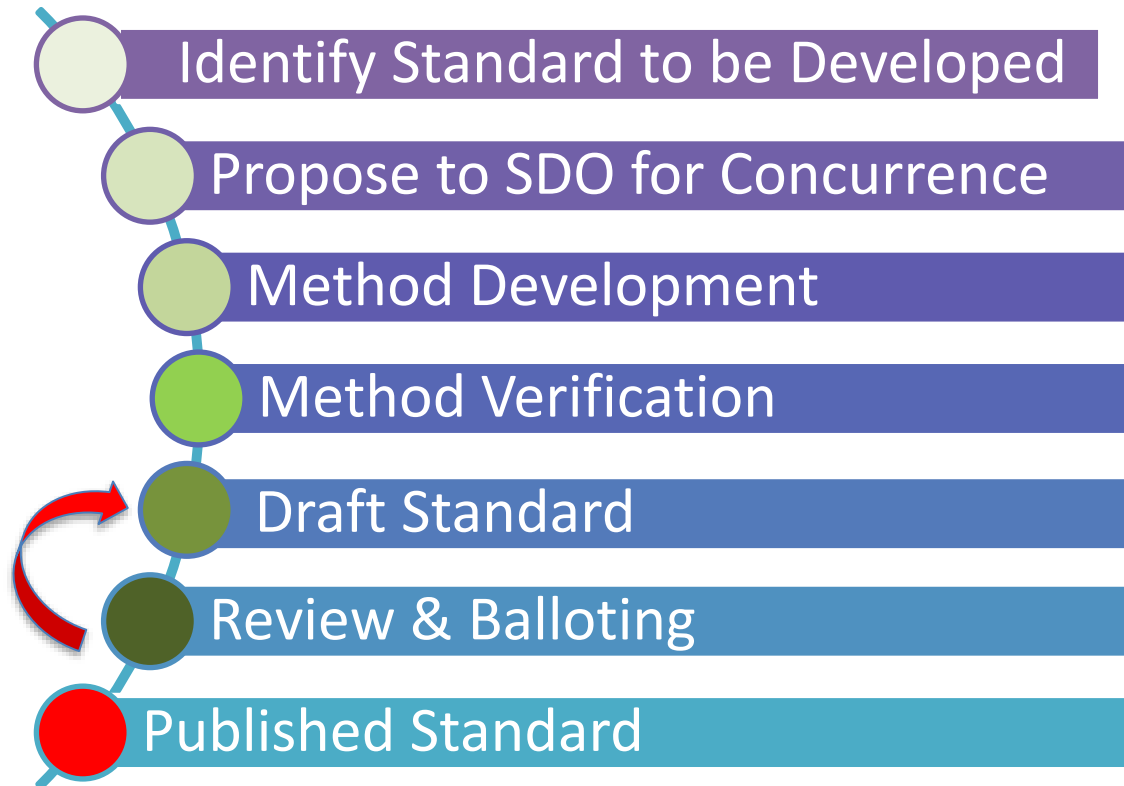
A collaborative effort by global regulatory, standards, and research agencies and organizations and stakeholders from academia and industry to identify standards needs

- Nanotechnology-derived Drug Products
- Nanotechnology-derived Medical Devices
- Liposomal drug products
- Nanomaterials in Food and Food Contact Materials
- Targeted Nanomaterials for Biomedical Applications
- Nanomaterials in Personal Care Products

Prioritized list of standards needs:
Analytical, In vitro,
Reference Material

<https://www.fda.gov/media/161634/download>

Consensus Standards Development Process



Industry Stakeholder Participation is Important

Liposomal Lipid Quantitation

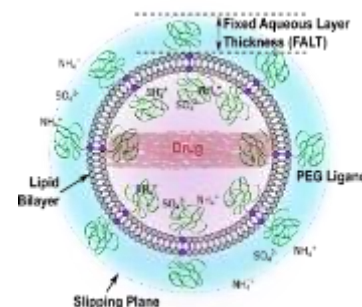
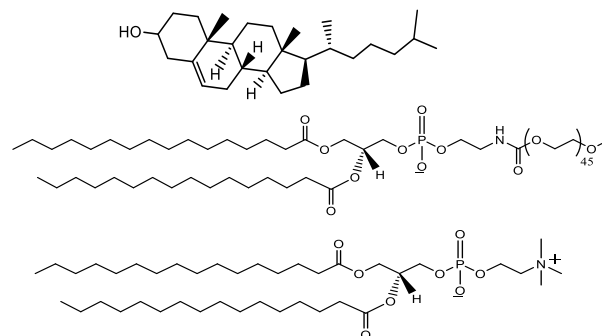


Lipid composition and concentration are key attributes in determining the quality and efficacy of a liposomal drug product, as they influence the stability of liposomes, drug incorporation, release, and pharmacokinetic properties.

Cholesterol

DSPE-PEG2000

1,2-distearoyl-sn-glycero-3-phosphoethanolamine
-N-[amino(polyethylene glycol)-2000]



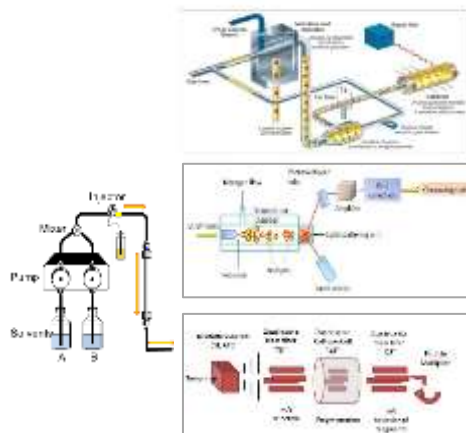
HPLC-CAD

Universal detectors
Easily Available
Affordable
Low maintenance
Less experienced user

HPLC-ELSD

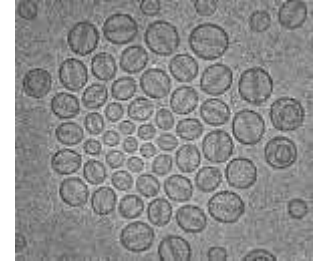
Higher sensitivity
Higher resolution
Expensive
High maintenance
More experienced user

UHPLC-TQMS



Standards Developed by the Nanocore

- ASTM E3143-18b, Standard Practice for Performing Cryo Transmission Electron Microscopy of Liposomes
- ASTM E3297-21 Standard Test Method for Lipid Quantitation in Liposomal Formulations Using High Performance Liquid Chromatography (HPLC) with a Charged Aerosol Detector (CAD)
- ASTM E3323-21 Standard Test Method for Lipid Quantitation in Liposomal Formulations Using High Performance Liquid Chromatography (HPLC) with an Evaporative Light-Scattering Detector (ELSD)
- ASTM E3324-22 Standard Test Method for Lipid Quantitation in Liposomal Formulations Using Ultra-High-Performance Liquid Chromatography (UHPLC) with Triple Quadrupole Mass Spectrometry (TQMS)
- ASTM E3238-20, Standard Test Method for Quantitative Measurement of the Chemoattractant Capacity of a Nanoparticulate Material in vitro
- ASTM E3351-22 Standard Test Method for Detection of Nitric Oxide Production In Vitro



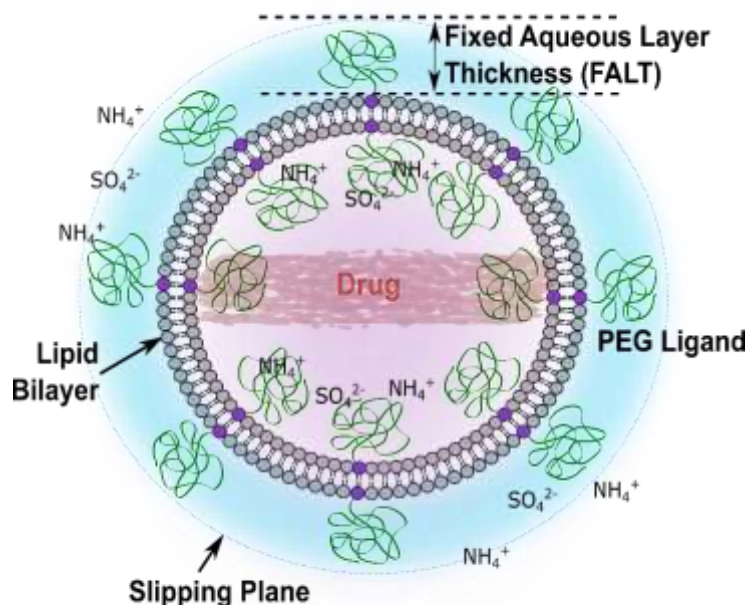
Collaboration with other stakeholders

- ASTM E3247-20, Standard Test Method for Measuring the Size of Nanoparticles in Aqueous Media Using Dynamic Light Scattering
- ASTM E3275-21, Standard Guide for Visualization and Identification of Nanomaterials in Biological and Nonbiological Matrices Using Darkfield Microscopy/Hyperspectral Imaging (DFM/HSI) Analysis

Volunteers needed to participate in the interlaboratory studies for these the test methods

Future Standards

- Priority based on critical quality attributes important for product quality
- Drug component
- Ionic components
- Impurities/degradants
- Surface attributes



Future Standards needs in Nanotechnology



- Survey on Best Practices and Standards in Nanotechnology
 - Update the current and upcoming standards needs
 - Physicochemical characterization, quality and equivalence assessment
 - Drug delivery, gene delivery and combination products
- University of Maryland: Center for Research on Complex Generics (CRCG)

https://umaryland.az1.qualtrics.com/jfe/form/SV_6orpUOEFegdsbBA



We need your input

Acknowledgments



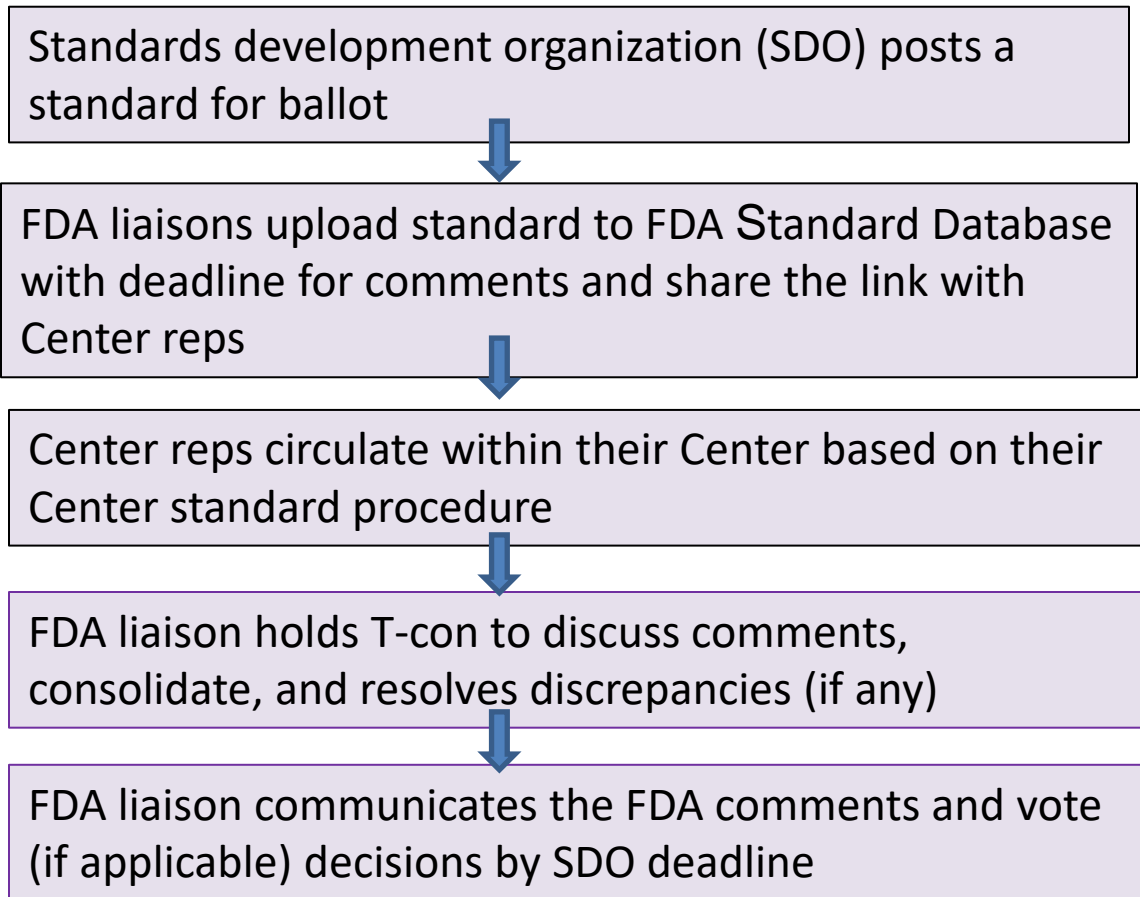
- National Toxicology Program/NIEHS
- National Institute of Standards and Technology
- Nanocore team members
- Nanotechnology Task Force
- Standards sub-committee members
- Nanotechnology Reviewer Network at FDA
- Global coalition (GCRSR) Nano WG members
- International Pharmaceuticals Regulators Program Nano WG members
- ASTM International E56 Subcommittee, ISO TC229, OECD WPMN
- Metrology Institutes (NIST, NMI, NRC, JRC)
- U.S Pharmacopeia
- ICCVAM NanoWG
- Industry stakeholders
- US-EU Communities of Research

FDA NTF Standard Sub-Committee



- Consolidate FDA comments for nanotechnology standards up for review.
- Prioritize nanotechnology standards based on FDA's needs
- Assist in the development of nano standards

Standard Subcommittee Standard Review Process



Center for Devices and Radiological Health (CDRH) Standards Recognition Program



- FDA Modernization Act of 1997
 - Revised 514 (c) (1) (A)
 - Added ability to **formally recognize standard**, “all or in part”
 - Added ability to accept a formal **Declaration of Conformity**
- 21st Century Cure Act of 2016
 - Added to 514 (c)
 - Transparency of regulatory decisions on use of standards
- Publication of Recognized Standards in Federal Register (FR) recognizing all or part of appropriate standards
 - Currently 1200 recognized standards (**20 standards for nano**)

CDRH Standards Recognition



- Recognition of a standard **does not** supersede other aspects of the FD&C Act and its implementing regulations for marketing or investigating medical devices in the U.S.
- The use of consensus standards generally **satisfies only one part** of a premarket submission
- It **may not**, on its own, provide sufficient basis for a regulatory decision

CDRH Standards Recognition



- CDRH Specialty Task Group (STG)
 - Identifies existing and needed standards
 - Coordinates assessment of standard's use to meet regulatory requirement
 - Recommends recognition of standards
- Stakeholder can request recognition of specific standard
 - Electronically through CDRHStandardsStaff@fda.hhs.gov
 - Title of the standard
 - Reference number and date
 - Name of the SDO
 - A proposed list of devices or device types
 - A brief discussion of the testing or performance or other characteristics that would be addressed by the standard

STG Decisions on Standards Recognition



- Recognition
 - complete/entire standard
- Recognition in part
 - excluding certain clauses or sections
- Non-Recognition

CDRH Recognized Standards Database



<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>

Recognized Consensus Standards

[FDA Home](#) [Medical Devices](#) [Databases](#)

This database provides the most up-to-date list of voluntary consensus standards to which FDA will accept a Declaration of Conformity. After FDA has decided to recognize a standard, we will update our online database to reflect the decision even before formal recognition of the standard occurs by publication in the Federal Register. Publications in the Federal Register to the lists of recognized consensus standards can be accessed at <https://www.fda.gov/medical-devices/standards-and-conformity-assessment-program/federal-register-documents>.

[Learn More](#)

Search Database



Standards Organization	All Standards Organizations		
Standard Designation Number <small>Note: numbers only, e.g., 14871, 60601-1</small>		Recognition Number	
Standards Title or Keywords <small>Note: do not include standard designation number</small>	<input type="checkbox"/> Included in ASCA pilot?		
Specialty Task Group Area	Nanotechnology		
Product Code		Regulation Number (e.g., 888.1111)	
Date of Entry		to	
		Sort	Date of Entry (9-0)
		Clear Form	Search

Nanotechnology Standards Recognized by FDA



Date of Entry	Specialty Task Group Area	Recognition Number	Standards Developing Organization	Standard Designation Number and Date	Title of Standard
12/20/2021	Nanotechnology	16-15	ISO	19749 First edition 2021-07	Nanotechnologies - Measurements of particle size and shape distribution by scanning electron microscopy
12/20/2021	Nanotechnology	16-20	ASTM	E3275-21	Standard Guide for Visualization and Identification of Nanomaterials in Electron and Neutron Scattering Images Using Unified Microscopy/Chemical Analysis (UP-MCA) Analysis
12/21/2020	Nanotechnology	16-17	ISO	21363 First edition 2020-06	Nanotechnologies - Measurements of particle size and shape distribution by transmission electron microscopy
12/21/2020	Nanotechnology	16-18	ASTM	E3247-20	Standard Test Method for Measuring the Size of Nanoparticles in Aqueous Media Using Dynamic Light Scattering
07/06/2020	Nanotechnology	16-15	ASTM	E3025-16	Standard Guide for Tensile Research for Polymer and Characterization of Some Nanomaterials in Textiles
07/06/2020	Nanotechnology	16-16	ISO	ITS 21362 First edition 2016-06	Nanotechnologies - Analysis of nano-objects using an analytical flow and centrifugal field flow fractionation
07/15/2019	Nanotechnology	16-13	ISO	ITS 16527 First edition 2017-06	Nanotechnologies - Electron spin resonance (ESR) as a method for measuring reaction rates or species in ESR-generated by metal oxide nanomaterials
07/15/2019	Nanotechnology	16-14	ISO	TR 11360 First edition 2010-07-15	Nanotechnologies - Methodology for the classification and categorization of nanomaterials
01/14/2019	Nanotechnology	16-2	ASTM	E2535-07 (Reapproved 2018)	Standard Guide for Handling Unlabeled Engineered Nanoscale Particles in Conventional Settings
01/14/2019	Nanotechnology	16-5	ASTM	E2899-11 (Reapproved 2017)	Standard Guide for Size Measurement of Nanoparticles Using Atomic Force Microscopy
01/14/2019	Nanotechnology	16-6	ASTM	E2663-12 (Reapproved 2018)	Standard Guide for Measurement of Electrochemical Mobility and Zeta Potential of Nanosized Colloidal Materials
01/14/2019	Nanotechnology	16-7	ASTM	E2634-12 (Reapproved 2018)	Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by Nanoscale Tracking Analysis (NTA)
01/14/2019	Nanotechnology	16-8	ASTM	E2678-07 (Reapproved 2018)	Standard Practice for Estimation of Mean Nano-Parameters and Standard Deviations of Particle Size Distributions
01/14/2019	Nanotechnology	16-11	ISO	ITS 13121 First edition 2011-05-15	Nanotechnologies - Nanomaterial risk evaluation
01/14/2019	Nanotechnology	16-12	ISO	ITS 17200 First edition 2013-06-01	Nanotechnologies - Nanoparticles in powder form - Characterization and measurement(s)
06/07/2018	Nanotechnology	16-9	ISO	ITS 13016 First edition 2012-05-15	Nanotechnologies - Guidance on physico-chemical characterization of engineered nanomaterials for toxicological assessment (includes ISO TR 24504 and ISO TR 24524)
06/07/2018	Nanotechnology	16-10	ISO	29761 First edition 2016-09-15	Nanotechnologies - Endpoints test on nanomaterial samples for in vitro systems - Limited attention to acute (LTA) test
04/04/2016	Nanotechnology	16-1	ASTM	E2490-09 (Reapproved 2015)	Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by Photon Correlation Spectroscopy (PCS)
06/14/2015	Nanotechnology	16-4	ISO	TS 60004-6 First edition 2013-11-01	Nanotechnologies - Vocabulary - Part 6: Nano object characterization
01/27/2015	Nanotechnology	16-3	ISO	TS 14101 First edition 2012-11-01	Surface characterization of solid nanoparticles for nanomaterial specific toxicity screening: P-31B method

Acknowledgments



- FDA NTF Standard Sub-Committee Members
- CDRH Standard Management Staffs
- FDA OCS Standard Staffs

