FDA NanoDay Symposium

11 October 2022

Standards Development at FDA

Anil K. Patri, Ph.D.

National Center for Toxicological Research

Jiwen Zheng, Ph.D.

Center for Devices and Radiological Health

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 agencies[1]
- 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

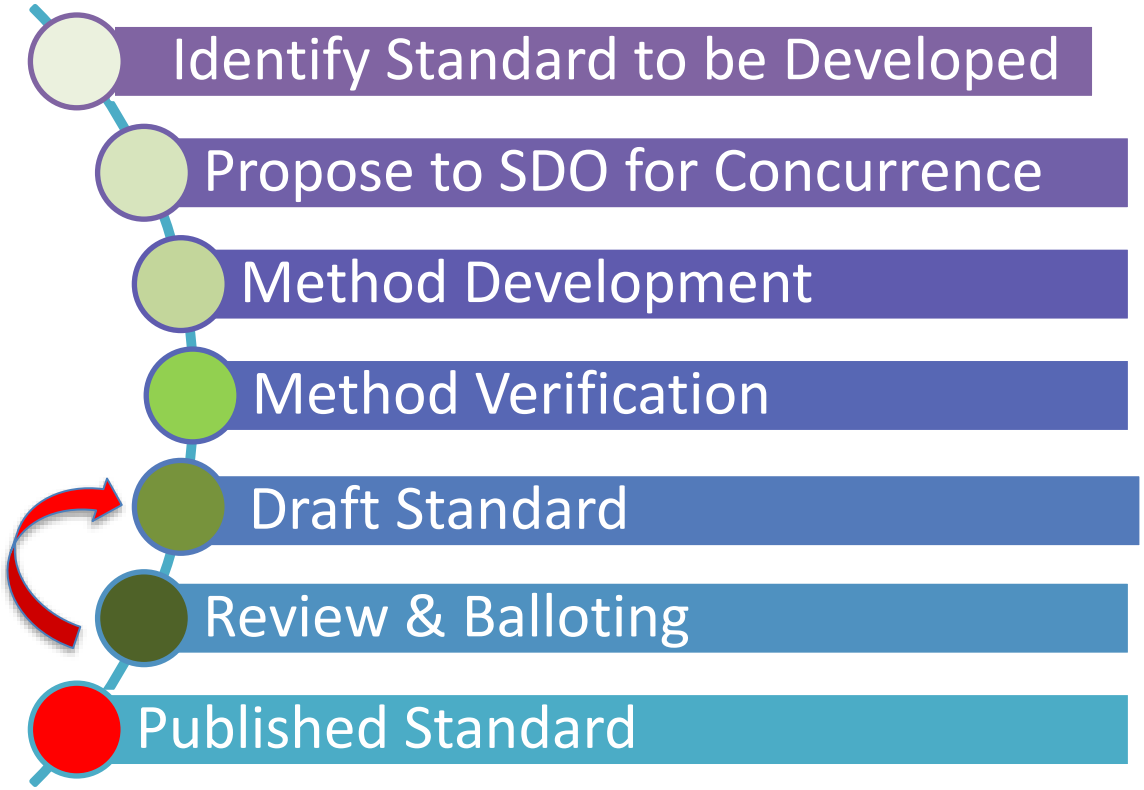
A collaborative effort by global regulatory, standards, and research agencies and organizations and stakeholders from academia and industry to identify standards needs

- 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

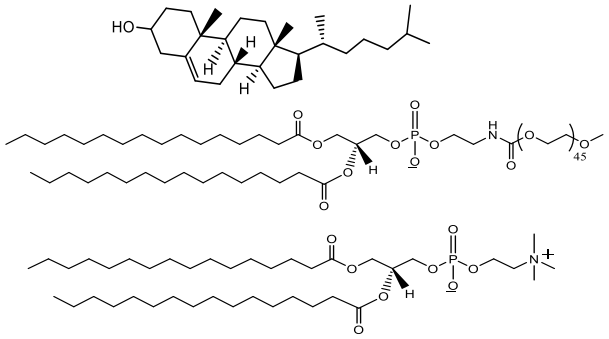
Liposomal Lipid Quantitation

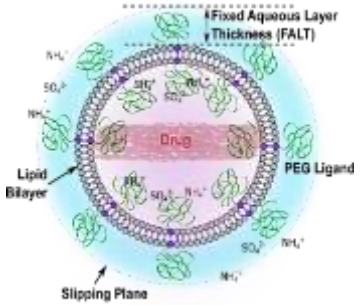
Lipid composition and concentration are key attributes in determining the quality and efficacy of a liposomal drug product, as they influence the stability of liposomes, drug incorporation, release, and pharmacokinetic properties.

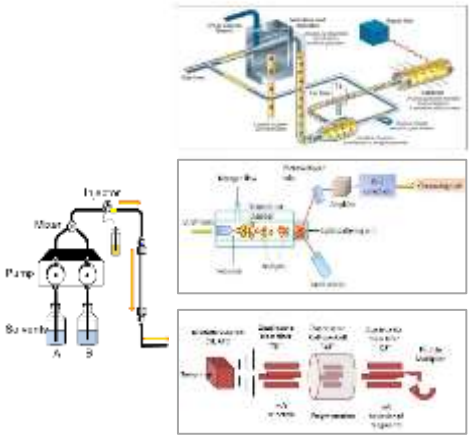
Cholesterol

DSPE-PEG2000
1,2-distearoyl-sn-glycero-3-phosphoethanolamine
-N-[amino(polyethylene glycol)-2000]

HSPC
Hydrogenated (soy) L-α-phosphatidylcholine







HPLC-CAD

HPLC-ELSD

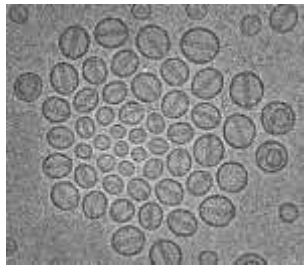
- Universal detectors
- Easily Available
- Affordable
- Low maintenance
- Less experienced user

UHPLC-TQMS

- Higher sensitivity
- Higher resolution
- Expensive
- High maintenance
- More experienced user

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



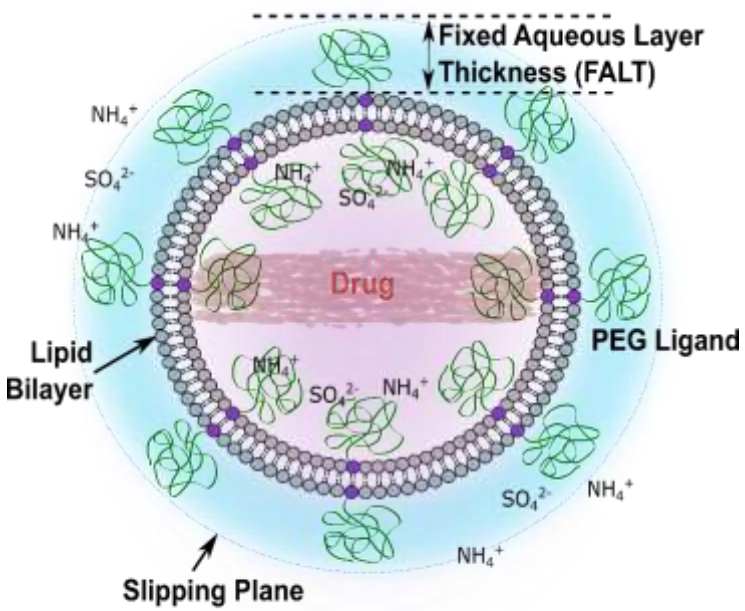
Collaboration with other stakeholders

- 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

https://www.astm.org/get-involved/technical-committees/committee-e56/subcommittee-e56/jurisdiction-e5608

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

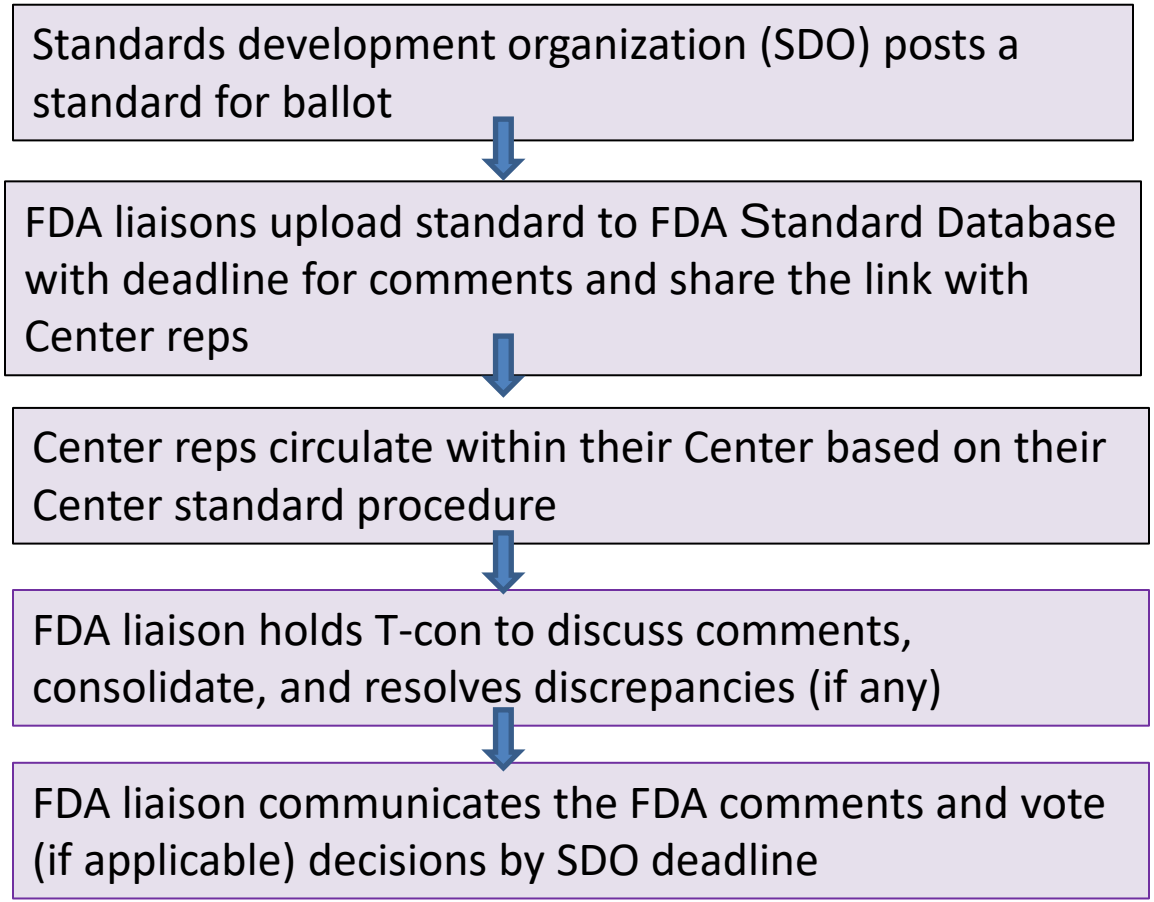
Acknowledgments

- 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

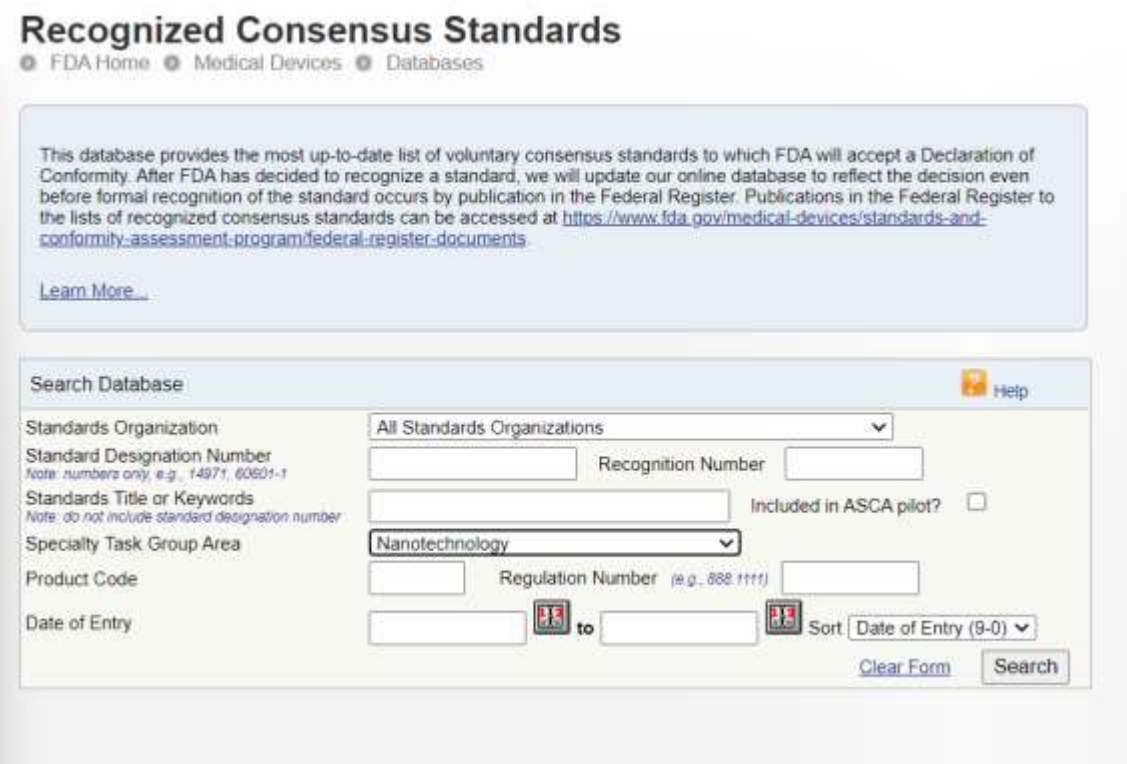
- Stakeholder can request recognition of specific standard
  - Electronically through CDRHStandardsStaff@fda.hhs.gov
  - Title of the standard
  - Reference number and date
  - Name of the SDO
  - A proposed list of devices or device types
  - A brief discussion of the testing or performance or other 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



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	18-19	ISO	19749 First edition 2021-07	Nanotechnologies - Measurements of particle size and shape distributions by scanning electron microscopy
12/20/2021	Nanotechnology	18-20	ASTM	E3275-21	Standard Guide for Visualization and Identification of Nanomaterials in Biological and Nonbiological Matrices Using Darkfield Microscopy/Hyperspectral Imaging (DF/HSI) Analysis
12/21/2020	Nanotechnology	18-17	ISO	21363 First edition 2020-06	Nanotechnologies - Measurements of particle size and shape distributions by transmission electron microscopy
12/21/2020	Nanotechnology	18-18	ASTM	E3247-20	Standard Test Method for Measuring the Size of Nanoparticles in Aqueous Media Using Dynamic Light Scattering
07/06/2020	Nanotechnology	18-15	ASTM	E3025-16	Standard Guide for Tiered Approach to Detection and Characterization of Silver Nanomaterials in Textiles
07/06/2020	Nanotechnology	18-16	ISO	/TS 21362 First edition 2018-06	Nanotechnologies - Analysis of nano-objects using asymmetrical flow and centrifugal field-flow fractionation
07/15/2019	Nanotechnology	18-13	ISO	/TS 18827 First edition 2017-06	Nanotechnologies - Electron spin resonance (ESR) as a method for measuring reactive oxygen species (ROS)-generated by metal oxide nanomaterials
07/15/2019	Nanotechnology	18-14	ISO	/TR 11360 First edition 2010-07-15	Nanotechnologies - Methodology for the classification and categorization of nanomaterials
01/14/2019	Nanotechnology	18-2	ASTM	E2535-07 (Reapproved 2018)	Standard Guide for Handling Unbound Engineered Nanoscale Particles in Occupational Settings
01/14/2019	Nanotechnology	18-5	ASTM	E2859-11 (Reapproved 2017)	Standard Guide for Size Measurement of Nanoparticles Using Atomic Force Microscopy
01/14/2019	Nanotechnology	18-6	ASTM	E2865-12 (Reapproved 2018)	Standard Guide for Measurement of Electrophoretic Mobility and Zeta Potential of Nanosized Biological Materials
01/14/2019	Nanotechnology	18-7	ASTM	E2834-12 (Reapproved 2018)	Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by Nanoparticle Tracking Analysis (NTA)
01/14/2019	Nanotechnology	18-8	ASTM	E2578-07 (Reapproved 2018)	Standard Practice for Calculation of Mean Size/Diameters and Standard Deviations of Particle Size Distributions
01/14/2019	Nanotechnology	18-11	ISO	/TR 13121 First edition 2011-05-15	Nanotechnologies - Nanomaterial risk evaluation
01/14/2019	Nanotechnology	18-12	ISO	/TS 17200 First edition 2013-06-01	Nanotechnology - Nanoparticles in powder form - Characteristics and measurements
06/07/2018	Nanotechnology	18-9	ISO	/TR 13014 First edition 2012-05-15	Nanotechnologies - Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment (Including CORRIGENDUM 1:2014)
06/07/2018	Nanotechnology	18-10	ISO	29701 First edition 2010-09-15	Nanotechnologies - Endotoxin test on nanomaterial samples for in vitro systems - Limulus amebocyte lysate (LAL) test
04/04/2016	Nanotechnology	18-1	ASTM	E2490-09 (Reapproved 2015)	Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by Photon Correlation Spectroscopy (PCS)
08/14/2015	Nanotechnology	18-4	ISO	TS 80004-6 First edition 2013-11-01	Nanotechnologies - Vocabulary - Part 6: Nano-object characterization
01/27/2015	Nanotechnology	18-3	ISO	TS 14101 First edition 2012-11-01	Surface characterization of gold nanoparticles for nanoparticle specific toxicity screening: FT-IR method

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm

Acknowledgments

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION