



U.S. Food and Drug Administration
Protecting and Promoting Public Health

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CDRH Review of Medical Devices Containing Nanoscale Materials

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Disclaimer

CDRH currently has no published policy concerning nanotechnology.

All opinions expressed are entirely my own and do not reflect official Agency policy.



Agenda

- *General Review of Medical Devices (with a focus on diagnostics)*
- *How risk may be mitigated through characterization?*
- *How nanotechnology may influence review of Medical Devices?*



Legal Basis of Regulation

- Authority to regulate medical devices
 - Public Health Service Act
 - Federal Food Drug and Cosmetic Act (FDCA) of 1938
 - Medical Device Amendments 1976
- Other legislation
 - FDA Modernization acts of 1997, 2002 and 2007
 - FDA Science and Innovation Act of 2012 (FDASIA)



What is a Device?

Medical Device: “an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent or similar related article. . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals” (FFDCA 201(h))

-1976 Medical Device Amendments



Definition of IVDs

- *In Vitro* Diagnostic Devices (IVDs) are a subset of medical devices which are “**reagents, instruments, and systems** intended for use in the **diagnosis of disease or other conditions**, including a determination of the state of health, in order to cure, **mitigate, treat, or prevent disease or its sequelae**” (21 CFR 809.3)



Risk-Based Classification of IVDs: Intended Use

- The classification of an IVD is risk-based, and determined based upon the intended use of the device
- Intended Use:
 - General description of the disease or condition that the device will diagnose, treat, prevent cure or mitigate
 - Defines the patient population
 - Defines specific type of specimen
- A single IVD can have multiple intended uses



Intended Use

- A diagnostic device must be safe and effective for its Intended Use.
- For diagnostic devices Intended Use includes:
 - whether data is qualitative (+/-), quantitative (67.65 U/ml) or ordinal (Semi-quantitative)
 - The intended use population, e.g. post-menopausal women
 - The disease state that is being diagnosed, e.g. with stage III or stage IV Breast cancer.
 - The matrix being examined (blood, plasma, tissue, urine)
 - How the test is to be used (as an aid in diagnosis, risk assessment, prognosis, screening, determination of therapy, monitoring).



Intended Use Statement (2)

- Example: Pregnancy Test

“The X urine test is an immunoassay designed for the qualitative determination of human chorionic gonadotropin (hCG) in urine for the early detection of pregnancy. It is intended for professional use.”



Risk-Based Classification of Medical Devices

- The risk of a diagnostic device (IVD) is based on the consequences of a false result.
- **3 Classification levels**
 - **Class I: common, low risk devices**
 - **Class II: more complex, moderate risk**
 - **Class III: most complex, high risk and novel intended uses**



Class I Devices

- Represent common, low-risk devices
- Examples:
- lactic acid (Chemistry)
 - erythrocyte sedimentation rate test (Hematology)
 - differential culture media (Microbiology)
 - Non-Specific Pathology Stains (Pathology)
 - Toothbrush (Dental)
- Most exempt from premarket submission
 - General Controls are required



General Controls

- Applicable to medical devices, regardless of class
- Registration and listing
 - Manufacturers must register their manufacturing facilities, and list the devices they manufacture
- Good Manufacturing Practices (GMP)
 - Devices must be manufactured in a controlled manner as per 21 CFR Part 820 (Quality System Regulation)
- Reporting of Adverse Events and Recalls
- Device Labeling Provisions
 - Prohibition against misbranding, adulteration, false or misleading claims, sales of banned devices
- Maintenance of Records and Provision of reports to FDA



Class II Devices

- Moderate risk devices, tend to be more complex
- Examples:
 - factor deficiency test (hematology)
 - antimicrobial susceptibility test systems (microbiology)
 - thyroid stimulating hormone test system (chemistry)
 - allergen tests (immunology)
 - tracheal tube (anesthesia)
- Premarket Notification [510(k)]
- Special Controls
- General Controls



Premarket Notification: 510(k)

- Submissions may require clinical data
- Summary of FDA's review and basis for decision is posted on the FDA website



Special Controls

- What they are:
 - Special requirements for devices when the general controls alone are insufficient
 - May include:
 - special labeling requirements
 - mandatory performance standards
 - post-market surveillance
- Special controls are described in the regulations and through guidelines which can be found on FDA's website



Class III Devices (PMA)

- Represent highest risk, most complex devices, novel intended uses

Examples:

- Hepatitis B and C, HPV tests
 - Total PSA for prostate cancer screening
 - Continuous Glucose Monitoring Devices
 - Pacemaker
- Submissions often include clinical data-
OIR may allow samples from tissue banks



De novo

- Used for devices:
 - that do not have a legally marketed predicate
 - are not high risk
 - the risks that do exist can be mitigated through Special Controls
- Reviewed for safety and effectiveness
- Used as a mechanism for down classification of devices
 - Special controls implemented
 - Classification published (Class I or Class II)
 - De novo device becomes predicate for future devices of same type with same intended use
- Has been an important tool for novel IVDs
- Direct de Novo petition established for all devices with FDASIA (2012)



Investigational Device Exemptions (IDEs)

- For approval of an IDE application all devices must have a reasonable assurance of SAFETY.
- Investigation establishes EFFECTIVENESS.
- Most IVD investigations are exempt from submitting an IDE (but NOT IRBs) **IF:**
 - test does not introduce energy into a subject
 - test results not returned to patient/physician
 - no invasive measures needed to get sample or samples has been obtained from another procedure



Software/Instruments

- FDA regulates all software/instrumentation used in diagnostic test systems
- Total system validation
- Database integrity
- Cyber-security
- FDA has guidance on how to validate, present data for software:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm>



What is nanotechnology? FDA considerations

- Whether an engineered material or end product has at least one dimension in the nanoscale range ***(approximately 1 nm to 100 nm)***;
- Whether an engineered material or end product exhibits 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.***

- June 2014 FDA Guidance



How to Protect AND Promote the Public Health?

Insure that Medical Products are Safe and Effective for their Intended Use

Insure that Best and Most Innovative Medical Products are Available to the Public

Does the presence of nanotechnology make the medical product better?



Premarket Review

All IVDs (devices) must establish adequate:

Analytical Validity

- How accurately does the measure the analyte? (Or the pacemaker deliver current)
- How reliably?

Clinical performance

- How reliably does the test result reflect the clinical condition? (Or the pacemaker keep the heart beating)

Labeling (21 § CFR 809.10)

- Adequate instructions for use
- Intended use, directions for use, warnings, limitations, interpretation of results, performance summary



Analytical Performance

- OIR recommends many CLSI protocols to evaluate device performance. Other review divisions may recognize consensus standards (e.g. ASTM, ISO)

*Each criterion may be affected by the **characteristics** of the material used in the test.*

- Assess:
 - Repeatability/Reproducibility/**Precision**
 - Accuracy
 - “Truth” – may be a reference method, clinical endpoint, predicate device, etc...
 - Limit of Detection/Limit of Quantitation
 - Linearity
 - **Potential Interferences**/ Cross-Reactivity
 - Cross-contamination / Carry-over
 - **Matrix effects (e.g. Whole blood, serum, plasma)**
 - etc...



Clinical Performance

- If a new clinical study is needed. . .
 - Study should clearly define samples/populations
 - Should represent Intended Use population
 - Prospectively collected (ideal)
 - Clearly defined inclusion/ exclusion criteria
 - Sample size/trial design statistically appropriate
 - Review of new clinical studies
 - Team of experts included in review e.g. statisticians, physicians
 - Use clinical practice and society guidelines in decision-making process
 - Often include input from outside experts, advisory panels as needed



Specific Concerns with Nanotechnology

- wide range of materials (many are new)
 - organic (polymeric, dendrimers, lipid, carbon, biological, etc.)
 - inorganic (metallic, semiconductor, magnetic, clays, etc.)
 - variety of material-dependent unique physical or chemical properties that lend themselves to many potential biomedical applications.

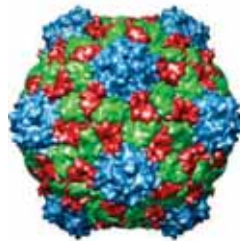
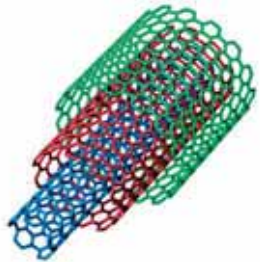


Diversity of “Engineered” Nanomaterials¹

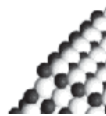
Organic “Soft”

Inorganic “Hard”

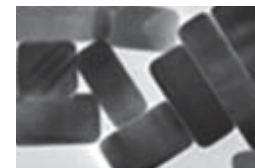
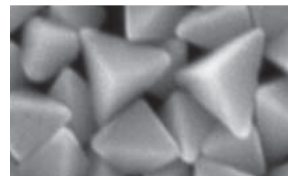
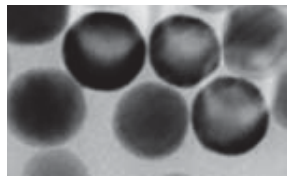
Carbon Polymer Biopolymer Lipid Viral Metallic Silicon Semiconductors Metal oxides



Cd
101/103



Shapes

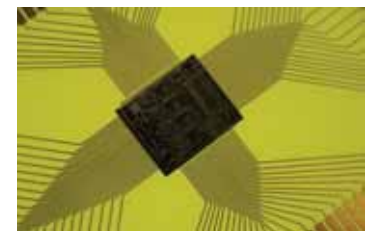


AgNPs

Structures



Textures
(deposition or etching)²



¹ Modified from Cobley et al., Plasmonics 2009, 4, 171; <http://eosl.gtri.gatech.edu/Default.aspx?alias=eosl.gtri.gatech.edu/newnano>; <http://lo.epfl.ch/plasmonicSHRIMP>
² Wikipedia



Nanotechnology in Class II Devices

- In General, the presence of a material that has **never** been used in a medical product is likely to raise questions **UNLESS** the material has been well characterized physically and physiologically.



De novo Classification

- Used for devices:
 - that do not have a legally marketed predicate
 - are not high risk (Class I or Class II)
 - where the **risks that do exist** can be mitigated through Special Controls
- Reviewed for safety and effectiveness
- Used as a mechanism for down classification of devices
 - *Special controls* implemented
 - Classification published
 - *De novo* device becomes predicate for future devices of same type with same intended use



Examples of Guidance Documents

In Vitro Diagnostic Device (IVD) Studies – Frequently Asked Questions

Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"-*DRAFT GUIDANCE*

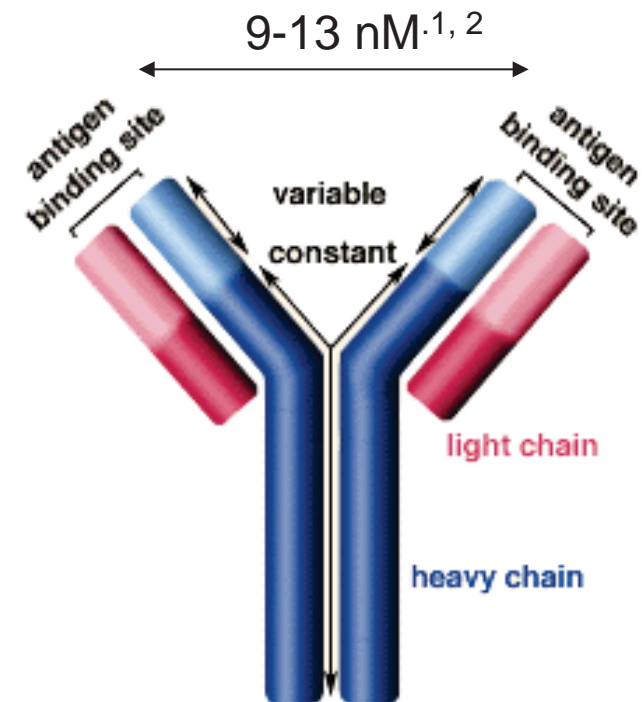
Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests

Guidance Document on the Performance Standard for Electrode Lead Wires and Patient Cables

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology, Guidance for Industry-*DRAFT GUIDANCE*

Antibody Characterization

- Immunoassay Applications (CLSI Guideline)
 - Production (Polyclonal, monoclonal)
 - Purification and processing
 - Characterization
 - Titer
 - Ig Class
 - Cross-reactivity
 - Interference
 - Specificity
 - Affinity
 - Antigens must be characterized.



1. *R.M. Murphy et al. Biophys J.* 1988 July; 54(1): 45–56. 9-13 nm

2. <http://www.biology.arizona.edu/immunology/tutorials/antibody/structure.html>



Nanotechnology characterization

- Necessary to establish understanding and control of nanoparticle synthesis and applications.
- Common techniques:
 - [electron microscopy](#) (TEM, SEM),
 - [atomic force microscopy](#) (AFM),
 - [dynamic light scattering](#) (DLS),
 - [x-ray photoelectron spectroscopy](#) (XPS),
 - [powder X-ray diffraction](#) (XRD),
 - [Fourier transform infrared spectroscopy](#) (FTIR),
 - [matrix-assisted laser desorption/ionization time-of-flight mass spectrometry](#) (MALDI-TOF),
 - [ultraviolet-visible spectroscopy](#), [dual polarization interferometry](#)
 - [nuclear magnetic resonance](#) (NMR).



- Unlike *In Vivo* devices, for *In Vitro* diagnostics the presence of nanotechnology will rarely represent a biocompatibility risk to the **patient** beyond a similar device that does not contain nanotechnology.
- However, manufacturing processes for nanotechnology may effect **workers**, the **environment**, or **device performance**

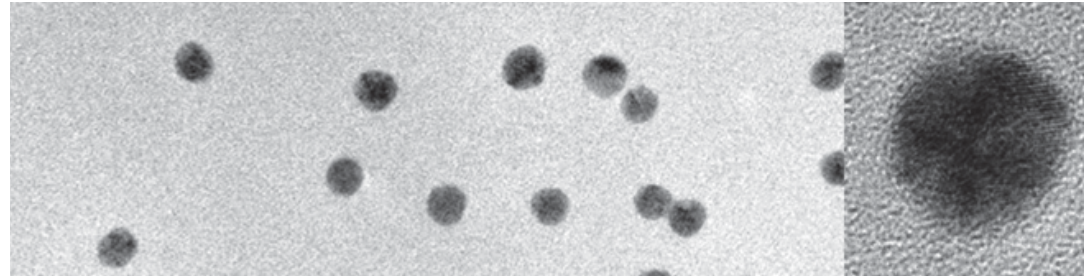


NIST 10 nM Gold Standard-COA



NIST RM 8011

10 nm Gold
Nanoparticle



TEM Analysis

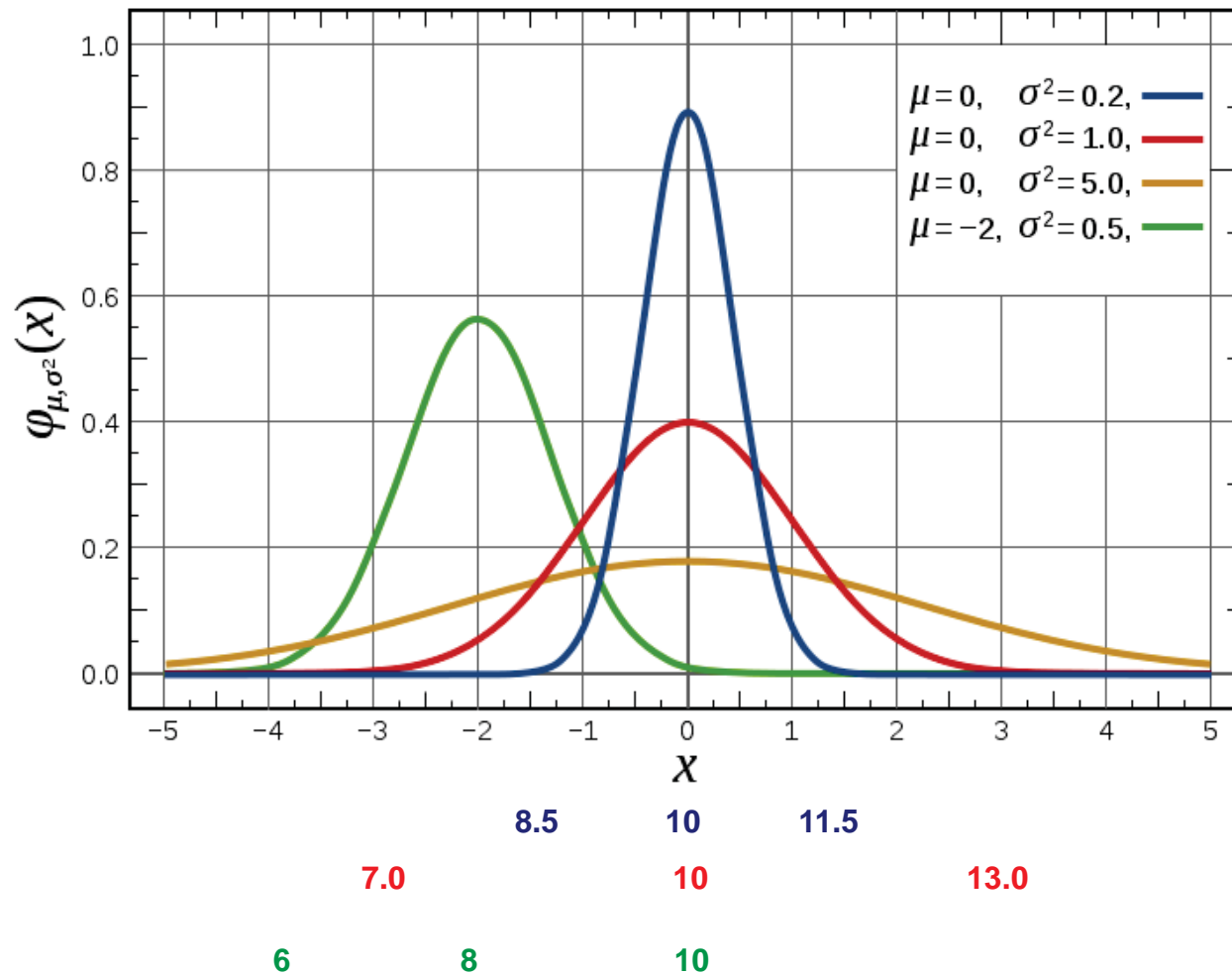
<https://www-s.nist.gov/srmors/certificates/8011.pdf>

Technique	Analyte Form	Particle Size (nm)	% CV
Atomic Force Microscopy (AFM)	Dry, deposited on substrate	8.5 ± 0.3	3.5
Scanning Electron Microscopy (SEM)	Dry, deposited on substrate	9.9 ± 0.1	1.0
Transmission Electron Microscopy (TEM)	Dry, deposited on substrate	8.9 ± 0.1	1.1
Differential Mobility Analysis (DMA)	Dry, aerosol	11.3 ± 0.1	0.9
Dynamic Light Scattering (DLS)	Liquid suspension	13.5 ± 0.1	0.7
Small-Angle X-ray Scattering (SAXS)	Liquid suspension	9.1 ± 1.8	19.8

- *The precision of all of these measurements, except X-ray would be accepted without further question. However, all measure the same property-diameter.*
- *The variability in measurements is 8.5-13.5 nm for a nominal 10 nM particle. So **based on technique**, the variability of size is **15-35%**.*
- *The characterization technique should match the Intended Use.*

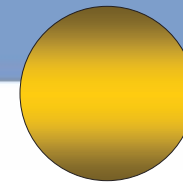


Tolerance:





30 nM



60 nM

NIST 10 nM Gold Standard-COA



10 nM



8.5 nM

V:SA=1:9,770,000 (62%)

15% size underestimate



10 nM

V:SA=1:6,000,000

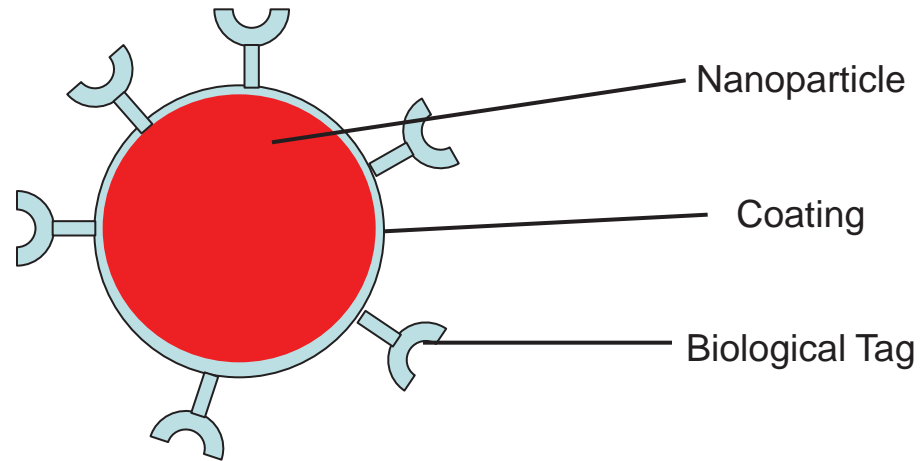


13.5 nM

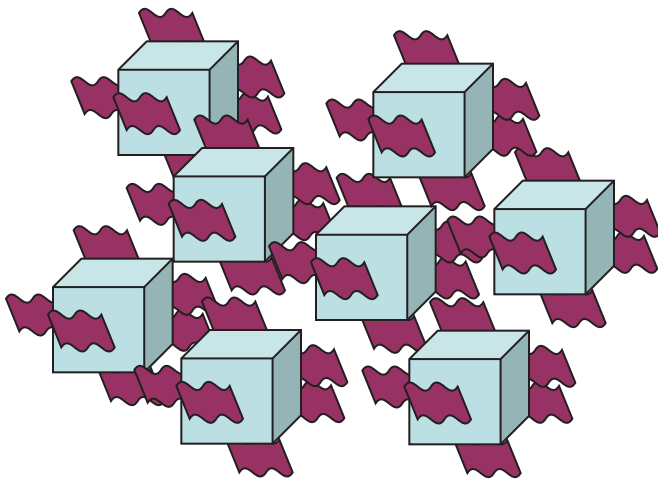
V:SA=1:2,439,000 (59%)

35% size overestimate

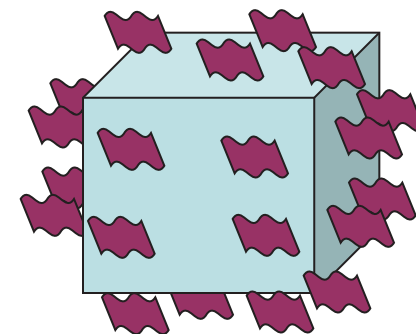
Derivatization



10-20 nM



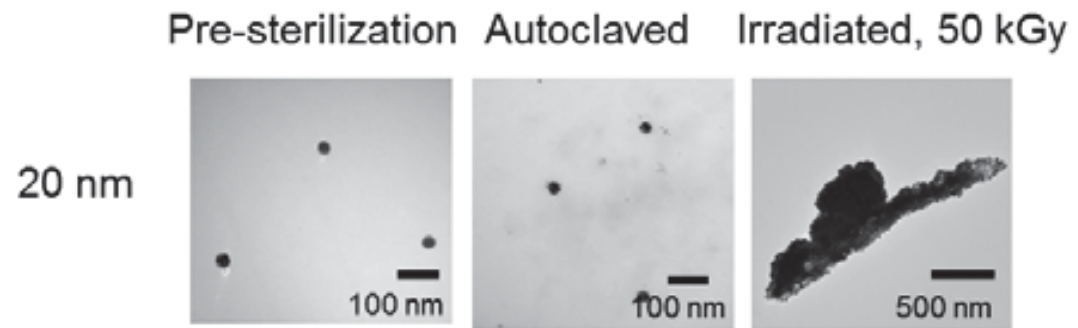
10 nm=48 functional groups/ unit weight



20 nm=24 functional groups/ unit weight

Sterilization

- Filter Sterilization
- UV radiation
- Ethylene Oxide
- Gamma Radiation
- Heat/Pressure



Zheng et al. J Nanomedic Nanotechnol 2011, S:5

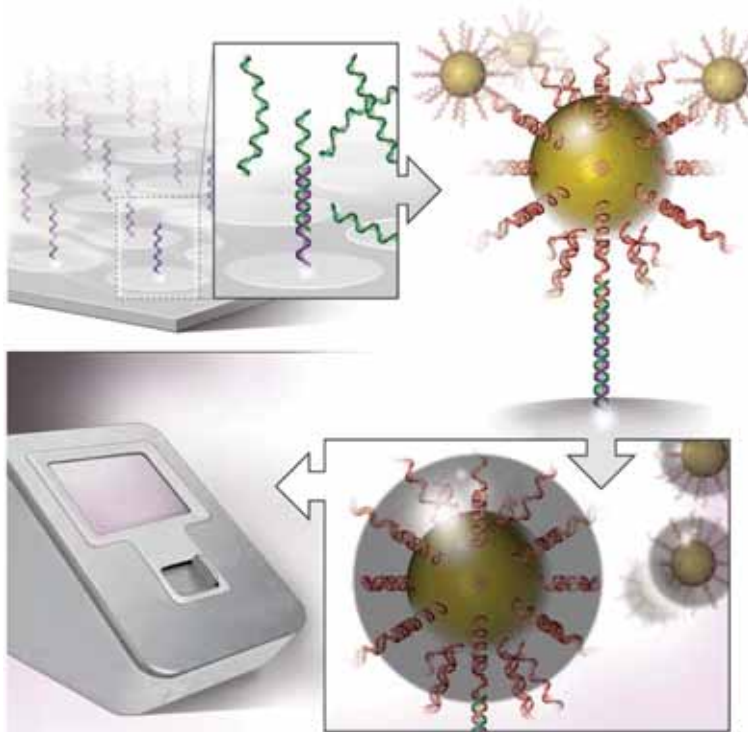


Containment

- Nanomaterial may not be stopped by standard HEPA filters
- Manufacturers must consider the possibility of contaminating the environment or other products lines with their nanomaterial.

Nanotechnology Clearance

Nanosphere – Verigene Platform – 510(k)



Kim, Rutka and Chan., NEJM, 2010, 363, 2434.

<http://www.nanosphere.us/products/verigene-instruments>

Number of FDA-cleared diagnostic tests:

- K140083 Enteric Pathogens
- K132843 Gram-negative Blood Cultures
- K123197 C. Difficile
- K122514 Gram-positive Blood Cultures
- K120466 CYP2C19 Test
- K112424 Staphylococcus Blood Culture
- K083088 Respiratory Virus Plus (additional 510k's)
- K083294 CFTR Test
- K070804 Warfarin Metabolism
- K070597 F5/F2/MTHFR - Thrombophilia



Nanotechnology Clearance

- Given Imaging(CDRH/ODE)
PillCam SB3 Ingestible
Telemetric Gastrointestinal
Capsule Imaging System:
*The PillCam® SB capsule is
intended for visualization of
bowel mucosa.*
- *Cleared Under 510(k) K123864*
- *PillCam® ESO K042960*



-Wikipedia



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Thank you!