FDA Considerations For Regulation Of Nanomaterial Containing Products

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FDA mission

- The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for **advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable**; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

FDA organization

- Agency within the Department of Health and Human Services.
- Consists of 8 Centers/Offices:
  - Center for Biologics Evaluation and Research (CBER)
  - Center for Devices and Radiological Health (CDRH)
  - Center for Drug Evaluation and Research (CDER)
  - Center for Food Safety and Applied Nutrition (CFSAN)
  - Center for Veterinary Medicine (CVM)
  - National Center for Toxicological Research (NCTR)
  - Office of the Commissioner (OC)
  - Office of Regulatory Affairs (ORA)

FDA regulated products

- **Foods**
  - **All interstate domestic and imported, including produce, fish, shellfish, shell eggs, milk (not meat or poultry)**
  - **Bottled water**
  - **Wine (<7% alcohol)**
  - **Infant formula**
- **Food additives**
  - **Colors**
  - **Food containers**
- **Cosmetics**
- **Dietary Supplements**
- **Animal Feeds**
- **Pharmaceuticals**
  - **Human**
  - **Animal**
  - **Tamper resistant packaging**
- **Medical devices**
- **Radiation emitting electronic products**
- **Vaccines**
- **Blood products**
- **Tissues**
- **Sterilants**
- **Counter-terrorism products**

FDA regulates products on a product-by-product basis

- **Pre-market approval**
  - For products that require an FDA approval prior to introduction to the market.
- **Market clearance**
  - For products that are similar to products that were cleared to market previously, or are prepared to approved specifications. FDA review process for these products is more rapid than for pre-market approval.
- **Post-market review**
  - For these products, market entry and distribution are at the discretion of the manufacturer and FDA monitors the behavior of these products. Regulatory action is taken if adverse events occur.

Critical Path Initiative

- Recent analysis of the pipeline problem was conducted by FDA and resulted in the publication of the Critical Path Initiative (March 2004) (http://www.fda.gov/initiatives/criticalpath/)
  - To help reduce existing hurdles in medical product design and development.
  - To take advantage of innovative science and technologies.
- **Nanotechnology is an element under evaluation in FDA's Critical Path Initiative.**

Historically…

- FDA has approved many products with particulate materials in the nanosize range.
- Most drugs are expected to go through a nanosize phase during the process of absorption in the body.
- There have been no safety concerns reported in the past because of particle size.

Application of nanoparticles to drug discovery and biology

- Fluorescent biological markers
- Detection of proteins
- Probing of DNA structures
- Separation and purification of biological molecules and cells
- MRI contrast enhancement
- Tumor destruction via heating
- Tissue engineering
- Drug and gene delivery (Nanomarkets, March 2005)

Possible opportunities for nanotechnology in drug delivery

- Enhanced drug properties such as:
  - Solubility
  - Rate of dissolution
  - Oral bioavailability
  - Targeting ability
- Enhanced dosing requirements:
  - Lower dosed administered
  - Better side effect profile
  - More convenient dosage forms

FDA-regulated products expected to be impacted by nanotechnology

- Drugs (novel NMEs or delivery systems)
- Medical devices
- Biotechnology products
- Tissue engineering products
- Vaccines
- Cosmetics
- Combination products

What are combination products?

- Combination products are made of multiple constituents: drug-device, drug-biologic, device-biologic or drug-device-biologic that are physically or chemically combined, co-packaged in a kit or separate cross-labeled products.
- All components work as a system and are critical to achieve desired therapeutic effect.

Who regulates combination products?

- Office of Combination Products (established in 2002 under Medical Device User Fee and Modernization Act).
- Jurisdiction for regulatory responsibility assigned to a lead Center, based on the “primary mode of action” (most important therapeutic action) of the combination product (proposed rule defining PMOA published in Federal Register on May 7th, 2004).
- www.FDA.gov/oc/combination

Examples of nanotechnology combination products

- Multi-component system that may consist of:
  - Carrier/delivery system (drug or device)
  - Therapeutic agent (drug or biologic)
  - Imaging agent
  - Targeting agent
- Implantable microchip-based delivery systems that deliver different drugs under controlled conditions.
- Injectable delivery systems (transdermal microneedles).

(Nanomarkets, March 2005)

Carriers for “nano-scale” multifunctional therapeutics

- Dendrimers
- Fullerenes
- Quantum dots
- Nanoshells
- Liposomes
- Others

Examples of possible ligands

- Imaging agents (MRI, ultrasound, radioactive marker)
- Therapeutics (small molecule, nucleic acid, protein)
- Targeting agents (receptor ligand, antibody)

Hypothetical Combination Products

- Dendrimer labeled with imaging ligand, receptor targeting, new or approved oncology therapeutic
- Nanoshell with antibody or receptor targeting ligand (for thermal ablation of tumors using external infrared laser)
- Quantum dot with antibody or receptor targeting and new or approved therapeutic

Currently approved “nano-scale” therapeutics

- Gadolinium chelate for MRI imaging (Gd-DTPA Dimeglumine)
- Iron oxide particles for MRI imaging (Feridex)
- Products using NanoCrystal technology (Rapamune, Emend)
- Liposomes (Doxil, DaunoXome)
- Microemulsions (Cyclosporine)
- Albumin-bound nanoparticles (Abraxane)

Currently approved “nano-scale” devices

- Silver nanoparticles (anti-bacterial wound dressing)
- Engineered Calcium Phospahate (NanOss TM, duplicates microstructure, composition and performance of human bone)
- Nanoparticle dental restorative (3M ESPE Filtek)

Other currently approved nanoparticle-containing products

- Cosmetics (containing lipid nanoparticles or “nanosomes” used as delivery systems, for controlled release of active ingredients; L’Oreal, Estee Lauder)
- Sunscreens (containing titanium dioxide and zinc oxide nanoparticles which make the product appear transparent)

Near term applications for multifunctional nanoparticles

- Therapeutics for:
  - Imaging
  - Oncology
- Possible reasons:
  - Injectable formulations
  - Ease of assessment of therapeutic efficacy
  - Risk-benefit aspect
  - Lack of alternative treatments

General considerations for nanotechnology products

- Characterization
- Safety
- Environmental impact

Characterization Considerations

- What are the forms in which particles are presented to host, cells and organelles?
  - Soluble vs. insoluble particles
  - Organic vs. inorganic molecules
  - Nanoemulsions, nanocrystal colloid dispersions
  - Liposomes
  - Nanoparticles that are combination products (drug-device, drug-biologic, drug-device-biologic)

Characterization Considerations (Cont'd)

- What are the standard tools used for characterization of nanoparticle properties?
- What are validated assays to detect and quantify nanoparticles in drug product and in tissues?
- How do we determine long and short-term stability of nanomaterials (in various environments)?

Characterization Considerations (Cont'd)

- What are the critical physical and chemical properties, including residual solvents, processing variables, impurities and excipients?
- How do physical characteristics impact product quality and performance?

Characterization Considerations (Cont'd)

- What are the critical steps in the scale-up and manufacturing process for nanotechnology products?
- How are characterization and manufacturing procedures assessed for "personalized therapies"?
  - What is the level of characterization needed?
  - Preclinical: ADME, toxicology?
  - CMC: extent of physical characterization?

Safety Considerations

- As particle size gets smaller, there may be size-specific effects on activity, such as:
  - Will nanoparticles gain access to tissues and cells that normally would be bypassed by larger particles?
  - Once nanoparticles enter tissues, how long do they remain there?
  - How are they cleared from tissues and blood?
  - If nanoparticles enter cells, what effects do they have on cellular and tissue functions (transient and/or permanent)?
  - Might there be different effects in different cells types?

Safety Considerations (Cont'd)

- Route-specific issues:
  - Inhalation
    - Local respiratory toxicity
    - Distribution in respiratory tissues
    - Systemic bioavailability
  - Sub-cutaneous
    - Sensitization
  - Ocular
    - Intravitreal retention
  - Oral
    - Increased bioavailability

Safety Considerations (Cont'd)

- Route-specific issues (cont'd):
  - Dermal
    - Increased dermal and systemic bioavailability
    - Increased follicule retention
    - Distribution to local lymph nodes
    - Phototoxicity
  - IV
    - Hemocompatibility
    - Sterility
    - Different tissue distribution and half-life of API (with targeted delivery and liposomes)

Safety Considerations (Cont'd)

- ADME
  - What are the differences in the ADME profile, for nanoparticles versus larger particles of the same drug?
  - Are current methods used for measuring drug levels in blood and tissues adequate for assessing levels of nanoparticles (appropriateness of method, limits of detection)?
  - How accurate are mass balance studies, especially if levels of drug administered are very low; i.e. can 100% of the amount of drug administered be accounted for?

Safety Considerations (Cont'd)

- ADME (Cont'd)
  - How is clearance of targeted nanoparticles accurately assessed? If nanoparticles concentrate in a particular tissue, how will clearance be assessed accurately?
  - Can nanoparticles be successfully labeled for ADME studies?

Environmental Considerations

- Can nanoparticles be released into the environment following human and animal use?
- What methodologies would identify the nature, and quantify the extent, of nanoparticle release in the environment?
- What might be the environmental impact on other species (animals, fish, plants, microorganisms)?

Current Preclinical Tests for Safety Evaluation

- Pharmacology
- Safety pharmacology
- Toxicology (including clinical pathology and histopathologic analysis)
- ADME
- Genotoxicity
- Developmental toxicity
- Immunotoxicity
- Carcinogenicity
- Other

Adequacy of Current Preclinical System?

- Existing battery of preclinical tests is currently believed to be adequate.
- Why?
  - High dose multiples used
  - At least 2 animal species used
  - Extensive histopathology on most organs
  - Functional tests (cardiac, neurologic, respiratory, reproductive, immune system, etc/…)
  - Extended treatment periods (up to 2 years for carcinogenicity studies)

Future Testing Considerations

- Types of preclinical screening tests that may be useful in identifying potential risks (Screening IND?):
  - In vitro assays
  - In vivo assays
- Role of new technologies to help identify potential toxicities:
  - Omics
  - Imaging (qualitative/quantitative)
- What is the role of modeling:
  - In predicting exposure?
  - In predicting safety concerns?
  - In helping design of personalized therapies?

Are There Special Testing Requirements for Nanotechnology Products?

- Currently there are no testing requirements that are specific to nanotechnology products.
- CDER/FDA's current requirements for safety testing of products is very rigorous. However if research identifies toxicological risks that are unique to nanomaterials, additional testing requirements may become necessary.

Nanotechnology Product-Specific Guidance Document?

- Guidances are built on precedence from review and on extensive literature data.
- CDER is not anticipating any new preclinical or CMC guidance documents regarding nanomaterials in the near future.

Review Process for Nanotechnology Drugs

- The review process for products containing nanomaterials will be essentially the same as that used for other products that do not contain nanomaterials.

FDA Research in Nanotechnology

- CDER
- CBER
- NCTR
- CFSAN

Examples of CDER Research in Nanotechnolgy

- Particle size determination in marketed sunscreens with TiO_2 and ZnO nanoparticles.
- Development of in vitro assays to assess toxicity of selected nanoparticles.
- Evaluation of safety and efficacy of fullerenes in animal models.
- Manufacture of nanoformulations and characterization of physical and chemical properties.

Examples of CDER Research in Nanotechnolgy (Cont'd)

- Evaluation of the effects of preparation methodology, process and formulation variables (including excipients) on nanotechnology product characteristics (including mathematical modeling of variables).
- Evaluate the stability and pre-clinical bioavailability of certain selected nanotechnology products.

Examples of CBER Research in Nanotechnolgy

- Development of Nanoparticle-Based Bio-Bar Code Amplification Multiplex Assays for Detection of Blood Born Viruses.

- Development of Assays for Testing of Vascular and Blood Cell Compatibility of Nanomaterials.

Examples of CFSAN Research in Nanotechnogy in Cosmetics

Collaboration with NCTR/NTP/Rice U.:

- Evaluating the effects of varying nano-size on the penetration of quantum dots through human and pig skin.
- Evaluating the penetration of TiO_2 and ZnO nanoparticles through human skin.
- Evaluating the photocytotoxicity of TiO_2 nanoparticles using human skin fibroblasts.

Examples of NCTR Research in Nanotechnology

- Evaluating the effect of size and coating on dermal penetration of quantum dots in skin of hairless mice.
- Evaluating the toxicology of nanoscale TiO_2 and ZnO: market survey (size and coating); dermal penetration in vitro & in mice and pigs; PK and toxicogenomics in mice; phototoxicity in vitro & mice; photocarcinogenicity in mice.

Challenges

- New technology: unknown risks
- Limited scientific data available to address public health concerns.
- Timely and accurate reporting of all relevant scientific findings.
- Working in multidisciplinary teams.
- Terminology and Nomenclature (ASTM E56)

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