A FDA Perspective on Nanomedicine
Current Initiatives in the US

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Outline

- Context
- Nanotechnology Task Force report summary
- Identification and considerations for FDA products relevant to nanomedicine
- Current activities within FDA's Center for Drug Evaluation and Research
- New activities across FDA

FDA focus on Nanotechnology

- Increasingly used in products regulated by FDA
  - Drugs, medical devices, cosmetics, dietary supplements
  - Near term/future applications-food applications, targeted medical therapies, device materials
- FDA plays key regulatory role for Nanotechnology in US
- National priority for the US

FDA Development of the Nanotechnology Task Force

- Scientific Issues:
  - Understanding the interaction of nanoscale materials with biological systems
  - Adequacy of testing approaches
- Regulatory Policy Issues:
  - Ability to identify products that contain nanoscale materials
  - Scope of authority regarding evaluation of safety and effectiveness

Science Recommendation: Understanding biological interactions

- More knowledge needed about
  - biological interactions
  - detection and measurement
- In-house expertise and infrastructure should be strengthened
- Agency-wide regulatory-science coordination for nanoscale materials needed.

Science Recommendation: Adequacy of testing approaches

- Current testing approaches to assess safety, effectiveness, and quality of products with nanoscale materials should be evaluated.
- Promote/participate in
  - Development of characterization methods and standards for nanoscale materials
  - Development of models for the behavior of nanoscale particles in-vitro and in-vivo.

Regulatory Policy Issue: Identification and Scope of products containing Nanomaterials

- Requesting submission of data and other information addressing the effects on product safety and effectiveness of nanoscale materials in products subject to FDA premarket authorization.
- Issue guidance requesting submission of information on whether and how the presence of nanoscale materials affects the manufacturing process
- Issue guidance for products
  - Subject to premarket approval
  - Not subject to premarket approval

List of terms applicable to Nanomedicine

- Nanoparticle
- Polymeric nanoparticle platforms
- Dendrimer
- Liposomes
- Micelles
- Nanoemulsions
- Nanocrystal

Platforms	Trade Name	Indication	Approved Date
Liposome	Abelcet	Fungal infections	11/20/1995
	AmBisome	Fungal infections	8/11/1997
	Amphotec	Fungal infections	11/22/1996
	DaunoXome	Antineoplastic	4/8/1996
	DepoCyt	Lymphomatous meningitis	4/1/1999
	Doxil	Antineoplastic	11/17/1995
	Visudyne (verteporfin for injection)	Photodynamic therapy for age-related macular degeneration	4/12/2000
Micelle	Amphotec	Antifungal	11/22/1996
	Estrasorb	Vasomotor symptoms associated with menopause	10/9/2003
	Taxotere	Antineoplastic	5/14/1996
Nanocrystal	Emend	Antiemetic	3/27/2003
	Tricor	Hypercholesterolemia and hypertriglyceridemia	11/5/2004
	Triglide	Hypercholesterolemia and hypertriglyceridemia	5/7/2005
	Megace ES	Anorexia, cachexia or an unexplained significant weight loss in AIDS patients	7/5/2005
	Rapamune	Immunosuppressant; The prophylaxis of organ rejection in patients receiving renal transplants	8/25/2000
Nanoparticle	Abraxane	Metastatic breast cancer	1/7/2005
	Anthelios 20	Sunscreen	10/5/2006
	Helioblock SX Sunscreen Cream	Sunscreen	3/31/2008
Nanotube	Somatuline depot	Acromegaly	8/30/2007
Superparamagnetic iron oxide	Feraheme Injection	Treatment of iron deficiency anemia in patients with Chronic Kidney Disease (CKD)	6/30/2009
	Feridex	MRI contrast agent	8/30/1996
	GastroMARK	Imaging of abdominal structures	12/6/1996

Considerations for nanomaterial-containing drug products

- Product quality assessment
  - Characterization
  - Quality control
  - Manufacturing
- Product safety assessment
  - Biodistribution
  - Clearance
  - Metabolism
  - Toxicology

Characterization Questions

- Identification of products containing nanomaterials
- Identification of critical properties requiring characterization, for optimal product quality and performance assessment.
- Use of appropriate tools and methodologies to:
  - Adequately assess chemistry and any unique characteristics of products containing nanomaterials, using the complete formulation.
  - Use of appropriate quality control measures in order to produce consistent formulations with low batch-to-batch variability.

Safety Questions

- Physico-chemical properties of nanoparticles can impact biodistribution:
  - Size, surface charge, stability, density, crystallinity, surface characteristics, solubility
- Bioavailability of encapsulated and free drug may need to be assessed separately
- Multicomponent constructs may require ADME on each moiety
- Possibility of long term studies

Existing Guidance documents

- As the issues regarding nanoparticle-containing therapeutics are fully identified, all existing Guidance documents are applicable

Topic Area	Guidance Title	Publication Date
CMC	Analytical procedures and methods validation: Chemistry, manufacturing, and controls documentation	2000
	Comparability Protocols- Chemistry, Manufacturing, and Controls Information	2003
	Current Good Manufacturing Practice for Combination Products	2004
	Residual Solvent in Drug Products Marketed in the United States	2009
	Guideline on General Principles of Process Validation	1987
	Good Laboratory Practice Regulations: Questions and Answers	1998
	Liposome drug Products: Chemistry, Manufacturing, and Controls: Human Pharmacokinetics and Bioavailability, and Labelign Documentation	2002
	Process Validation: General Principles and Practices	2008
Imaging	Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessment; Part 2: Clinical Indications; Part 3: Design, Analysis, and Interpretation of Clinical Studies	2004
Procedural	Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies for Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products	1995
	Early Development Considerations for Innovative Combination Products	2006
	Guidance for Reviewers: Pharmacology/Toxicology Review Format	2001
	Guidelines for Submitting Documentation for the Manufacture of and Controls for Drug Products	1987
	Guidelines for Submitting Supporting Documentation in Drug Applications For the Manufacture of Drug Substances	
PK/ADME	Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling	2006
	Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in Vitro	1997
	Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route	2008
	Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients	2005
	Safety Testing of Drug Metabolites	2008
	Single Dose Acute Toxicity Testing for Pharmaceuticals	1996
	Statistical Aspects of the Design, Analysis, and Interpretation for Chronic Rodent Carcinogenicity Studies of Pharmaceuticals.	2001

A few examples of guidance that may be applicable to nanomedicine

- Combination products
- Liposome products
- Comparability protocols

Center for Drug Evaluation and Research
Current Activities

- Development of a MaPP on collection of information on nanomedicines in CMC reviews-completed
- Development of a comprehensive database of approved drugs and drugs under review-in progress

FY2011
FDA Science Budget Initiative and Request

- *1st explicit and dedicated support of science infrastructure and capacity in FDA's budget*
  - ~$25 million across agency
  - Major components

    Nanotechnology, Critical Path, Science Leadership, and others
- **Emerging science**
  - ***Nanotechnology review & safety***
  - **$7.33 million**

Key Components of 2011 Nanotechnology Regulatory Science Initiative

- CORES Program (Collaborative Opportunities for Research Excellence in Science Program)
  - Enhance external and cross-Center activities
  - Support external research programs
- Laboratory Capacity to Assess Nanotechnology Products
  - Equip Core Laboratory Facilities
- Training and staff development

CORES Program

Priorities

Characterization of Nanomaterials

- Define physical/chemical characteristics of nanomaterials that affect potency
- Define characteristics that impact safety

Biocompatibility

- Interaction with biological processes in tissues, fluids
- Pharmacokinetics

Safety

- Toxicokinetics
- *In vitro* toxicity test methods (*e.g.* cytotoxicity, genotoxicity)
- *In vivo* toxicity tests (*e.g.* 90-day, 2-yr)

Staff Training & Professional Development

- Invited Expert Presentations
  - Product Specific
  - Agency Wide
- Day Long Workshops
  - FDA Staff
  - International Experts Meeting
- Center Specific Activities

Nanotechnology Research Laboratory Core Facilities: *Locations*

White Oak Campus and Surrounding Region

- CBER
- CDER
- CDRH
- CFSAN
- CVM

Jefferson Laboratories

- NCTR
- ORA

Summary

- A number of nanomedicine relevant products are approved and currently on the market
- The existing regulatory framework can accommodate the types of nanoparticle therapeutics under development and when needed, adapt to address new challenges
- Current published guidances may be applicable to nanoparticle therapeutics
- Staff are working on addressing the need for guidance documents that address nano-related issues as well as the regulatory science to bring to bear to this emerging technology
- FDA continues to encourage and participate in stakeholder dialogues

Closing Thoughts

International Partnerships

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