NANOTECHNOLOGY: Regulatory Considerations for Drug Development

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What is Nanotechnology?

- Research and technology development at the atomic or macromolecular levels, in the length scale of approximately 1-100 nm range.
- Creating and using structures, devices and systems that have novel properties and functions because of their small or intermediate size.
- Ability to control or manipulate on the atomic scale

The Scale of Things

Object	Size
Width of hair	50,000 nm
Red blood cell	7,000 nm
Bacterium	1,000 nm
Virus	100 nm
Width of DNA	2.5 nm
Aspirin molecule	1 nm

Nanomaterials

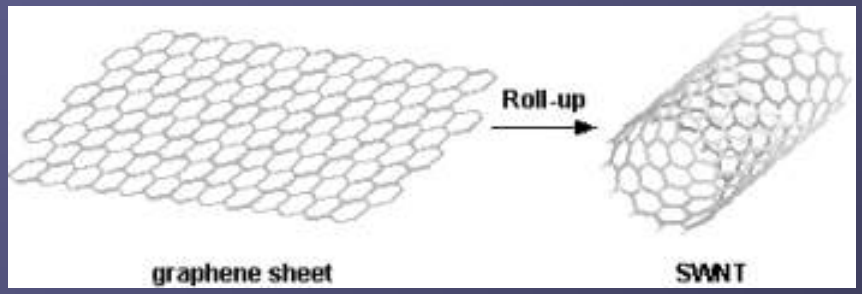
- Multifunctional materials that interact with biological systems in well controlled ways
- Broad class of materials that feed into multiple industries.
- Exhibit unique properties and functions because of their small size.
- Include such structures as:
  - Carbon nanostructures
  - Dendrimers
  - Metal oxides (FeO, TiO2, ZnO)
  - Quantum dots (CdSe)
  - Some liposomes

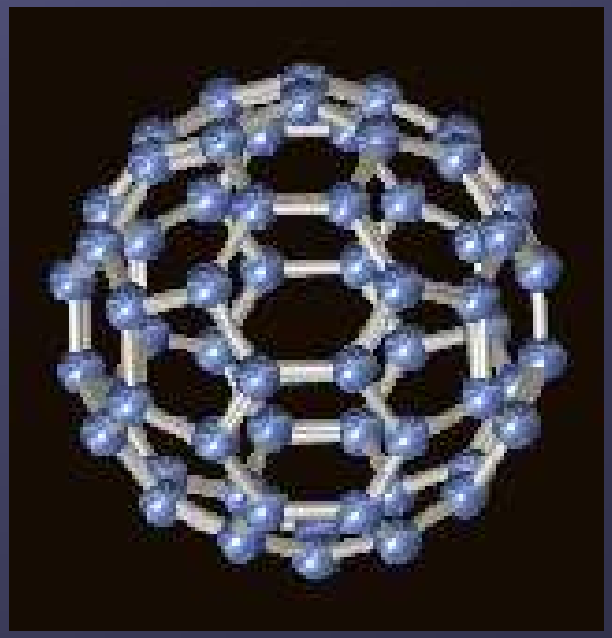
Carbon Nanostructures

- Source of pure carbon (like graphite and diamond).
- Based on fullerene molecules which are closed and convex cage molecules containing only hexagonal and pentagonal faces.
- Examples of carbon nanostructures:
  - Buckyballs
  - Nanotubes
  - Nanowires
  - Nanowhiskers

Carbon Nanotubes and Buckyballs

- Carbon nanotubes
  - elongated fullerenes.
  - resemble graphite sheets wrapped into cylinders
  - Length to width ratio is very high (few nm in diameter and up to 1 mm in length)
- Buckyballs
  - spherical fullerenes (C60 is most stable and symmetrical and resembles a soccer ball).
  - named after architect R. Buckminster Fuller .
  - 1996 Nobel prize in Chemistry awarded for their discovery.

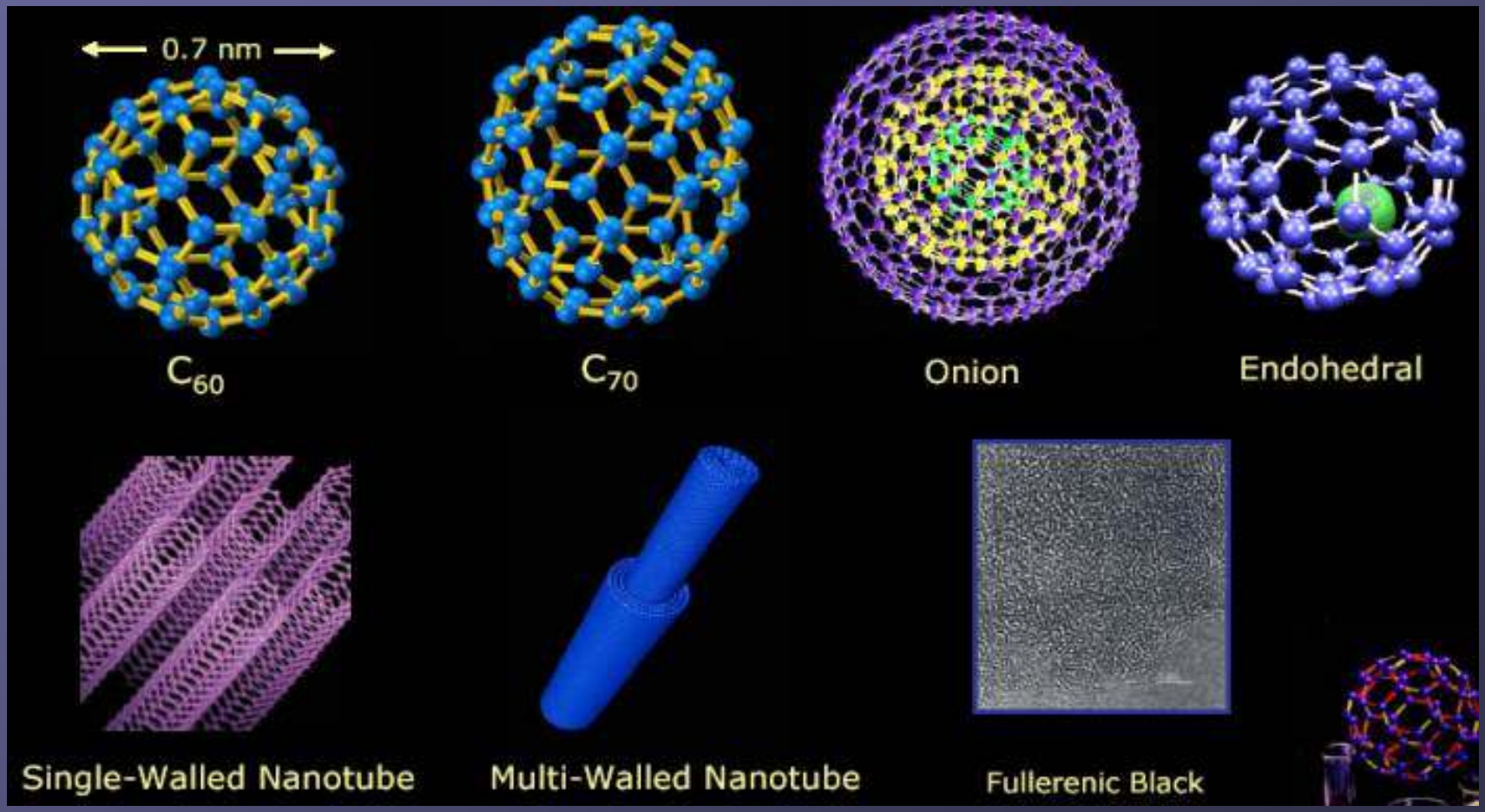




Some Properties of Carbon Nanostructures

- High tensile strength
- Physically stable
- Chemically reactive with free radicals
  - Derivatives can be formed
    - More hydrophilic than fullerenes
    - New organic molecules can be generated
- Other atoms can be placed inside its “cage” (doping with alkali metals)
  - Superconducting properties
  - Optical properties (endohedral fullerenes)

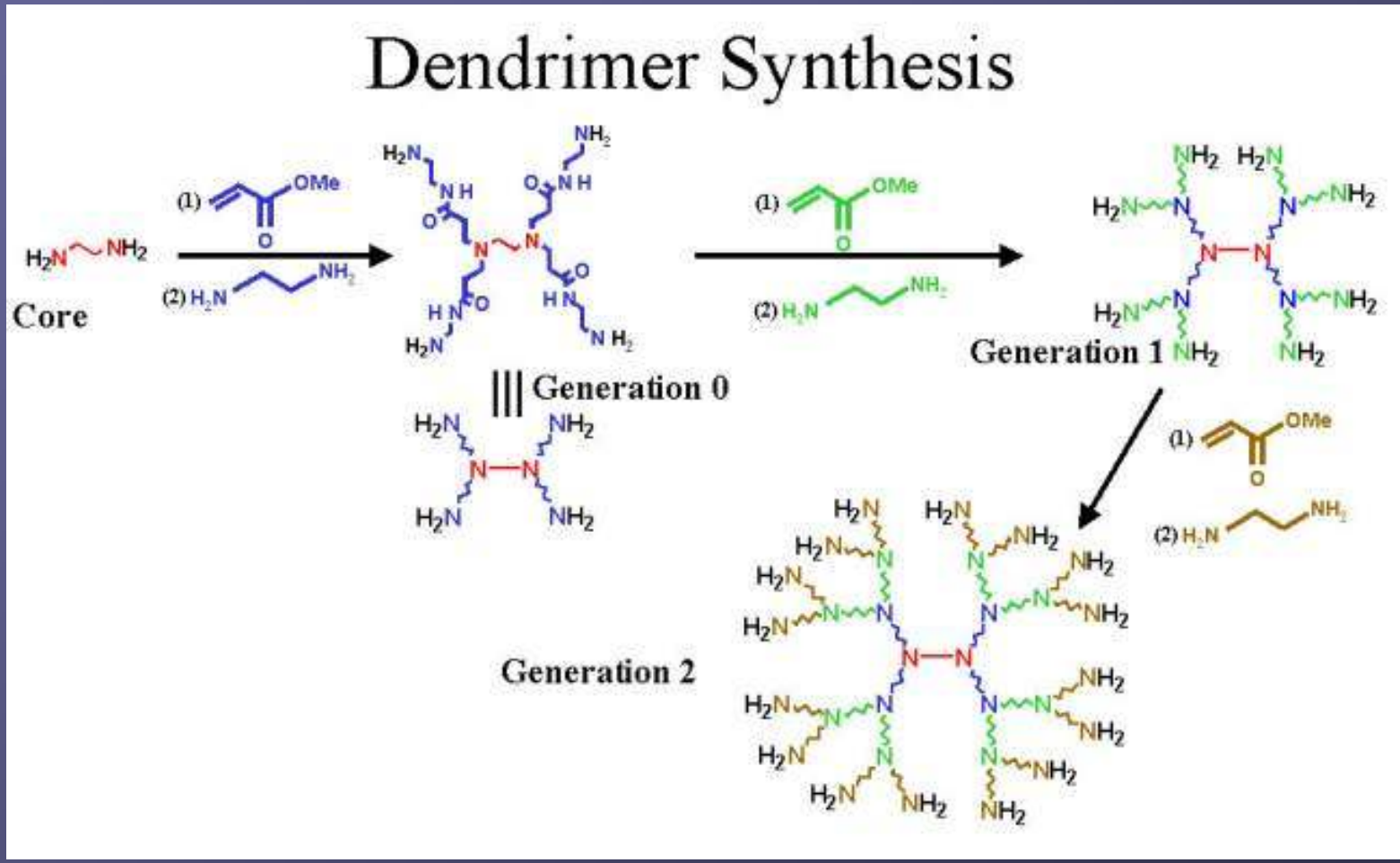
Several Nanocarbon Structures



Dendrimers

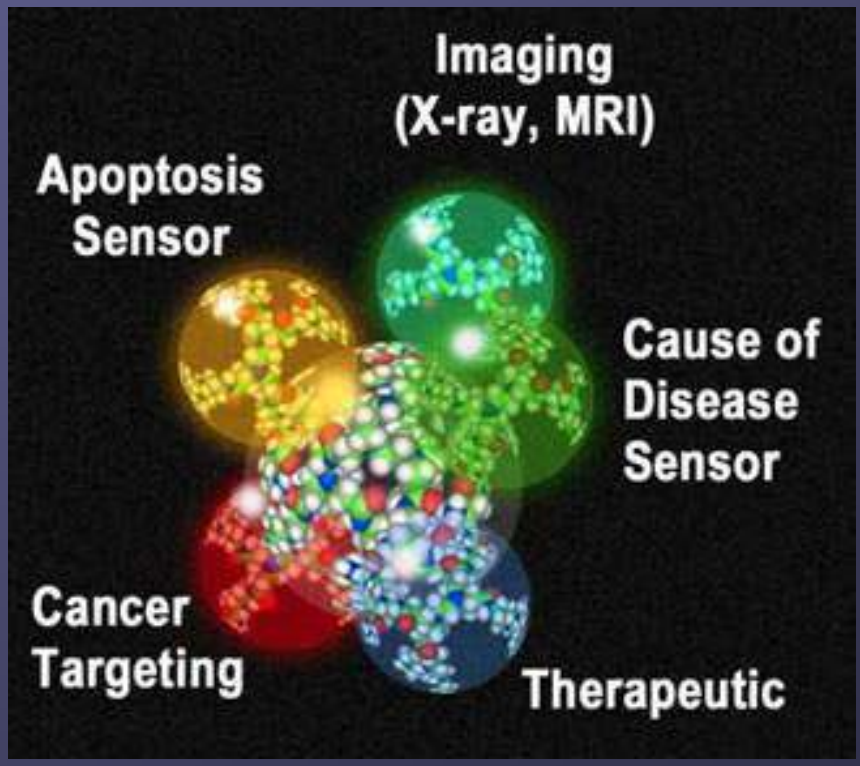
- Spherical polymeric molecules
- Series of chemical shells built on a small core molecule (each shell is called a generation).
- Made from a core and alternating layers of 2 monomers: acrylic acid and diamine.
- Molecular structure has the form of a tree with many branches.
- Can serve as nano-devices for delivery of therapeutics.

Dendrimer Structure



Possible Applications in Drug Development

- Biologic nanodevices based on dendrimers are being developed with the potential to :
  - Recognize Cancer cells
  - Diagnose cause of cancer
  - Delivery of drug to target
  - Report location of tumor
  - Report outcome of therapy (cancer cell death)
  - (http://www.nano.med.umich.edu, James Baker, Univ. of Michigan)



Nanomaterials are not new to FDA

- Many approved products currently on the market with components manufactured in the nanoscale range (drugs, sunscreens, cosmetics…).
- Most drugs act at their site of action as individual molecules that are in the nanosize range.

Reasons for special consideration of nanotechnolgy products

- Rapidly growing area of science
- Anticipated to lead to the development of novel and sophisticated (possibly complex) applications in drug delivery systems
- Private sector, academic centers and federal agencies are developing substantial programs in nanotechnology
- Significant research dollars being invested in nanotechnology

“Nanosizing” of Drugs

- Particle size reductions of drugs has the potential to:
  - Increase surface area
  - Enhance solubility
  - Increase rate of dissolution
  - Increase oral bioavailability
  - More rapid onset of therapeutic action
  - Decrease the dose needed
  - Decrease fed/fasted variability
  - Decrease patient to patient variability

Nanosizing=Nanotechnology ?

- Not necessarily
- Potential nanotechnology applications: Novel drug delivery systems based on nanoparticle carriers (such as dendrimers, carbon nanotubes and buckyballs)

CDER Activities in Nanotechnology

- Creation of a multidisciplinary CDER working group
  - to identify regulatory challenges related to timely scientific assessment of drug and drug-device combination products
  - To propose solutions to overcome challenges
- Participation in FDA Nanotechnology Interest Group and in NCI Cancer Nanotechnology Working Group

Regulatory Considerations for Nanotechnology Drugs

- Nomenclature
- Quality
- Safety
- Environmental Impact

Nomenclature

- Current NNI definition:
  - Research and technology development at the atomic or macromolecular levels, in the length scale of approximately 1-100 nm range.
  - Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size.
  - Ability to control or manipulate on the atomic scale
- Nomenclature may need to be tailored for CDER products
- Procedure:
  - Identify potential nanotechnology drug applications
  - Define nomenclature criteria
  - Develop definition

Quality Considerations

- Critical attributes of nanotechnology products might include:
  - Particle size and size distribution
  - Surface area, surface chemistry, surface coating, porosity
  - Hydrophilicity, surface charge density
  - Purity, sterility
  - Stability (aggregation, protein adsorption)
  - Does in vitro behavior reflect in vivo behavior
- Manufacturing and Controls
- Drug release parameters and bioequivalence testing considerations.

Preclinical Safety Assessment

- Current required studies for drug applications generally include:
  - In vivo short-term and long-term toxicity in rodent and non-rodent species, ADME, pharmacology, safety pharmacology, genotoxicity, developmental toxicity, irritation studies, immunotoxicology, carcinogenicity and other possible studies.
  - Additional studies might be requested based on drug-specific considerations.

Preclinical Safety Assessment (cont'd)

- Our current system is expected to identify possible hazard resulting from drug exposure, due to the extensive pre-clinical evaluation of new drugs.
- For nanotechnology drugs:
  - Are current required studies adequate? YES
  - Are new testing models needed? MAYBE

Examples of Preclinical Considerations for Nanotechnology Drugs

- Studies in In vitro models
  - Absorption (oral, dermal, other route)
  - Cellular uptake
  - Cytotoxicity
- Studies in In vivo models
  - Efficacy/proof of concept
  - Imaging studies
  - Special toxicology studies (functional studies?)
  - Mechanisms of tissue uptake and tissue clearance

Environmental Considerations

- Depend on reported physical characteristics and biological effects of specific nanomaterials.
- 1. Facility design considerations
  - Limiting cross contamination between different products manufactured in the same facility.
  - Limiting contamination by components of machinery used in the manufacturing process
- 2. Impact of nanotechnology products on the environment
  - Disposal of unused/expired products.
  - Potential environmental impact of material entering the environment after administration.

CDER Nanotechnology Working Group

- Goals and Objectives
  - Definition and terminology
  - Develop position papers (White Paper)
  - Identify and propose development of regulatory guidance documents
  - Identify training and research needs
  - Coordination (between Centers/Agencies) and collaboration

Parting Words…

- Maintain open dialogue between academic researchers and scientists/regulators within CDER.
- Timely communication of relevant scientific findings by the research community to regulatory agencies.
- Possible collaborations between academic researchers and CDER researchers.
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