Quality Considerations and Regulatory Perspectives for Drug Products Containing Nanomaterials

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October 5, 2015
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What Qualifies as “nano”??
Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

• Points to Consider
  – Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm);

  – Whether a material or end product is engineered to exhibit 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 (1,000 nm)
Why Apply Nanotechnology to Drugs?
Combination of size and surface effects → novel properties

- Increase bioavailability
- Change biodistribution
- Increased drug action
- Stabilize easily degradable drugs
- Deliver drugs
  - Targeted/controlled/smart delivery of API
- Multifunctional capabilities

Liversidge GG & Cundy KC. International Journal of Pharmaceutics. 1995 125, 91-97

Fig. 2. Effect of formulation on mean ± SE plasma concentrations of danazol following oral administration of three formulations to fasted male beagle dogs.
# Nanomaterials in Drug Products: CDER Examples

<table>
<thead>
<tr>
<th>Platform</th>
<th>Example</th>
<th>NDA Approval</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liposome</strong></td>
<td>DOXIL® (Doxorubicin)</td>
<td>1995&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cancer</td>
</tr>
<tr>
<td><strong>Inorganic nanoparticle</strong></td>
<td>FERRLECIT® (Sodium ferric gluconate complex)</td>
<td>1999&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Anemia</td>
</tr>
<tr>
<td><strong>Protein nanoparticle</strong></td>
<td>ABRAXANE® (Paclitaxel)</td>
<td>2005</td>
<td>Cancer</td>
</tr>
<tr>
<td><strong>Polymer nanoparticle</strong></td>
<td>MACUGEN® (Pegaptanib sodium)</td>
<td>2004</td>
<td>Macular degeneration.</td>
</tr>
<tr>
<td><strong>Emulsion</strong></td>
<td>RESTASIS® (Cyclosporine)</td>
<td>2002</td>
<td>To increase tear production</td>
</tr>
<tr>
<td><strong>Lipid complex</strong></td>
<td>AMPHOTEC® (Amphotericin B)</td>
<td>1996</td>
<td>Invasive aspergillosis</td>
</tr>
<tr>
<td><strong>Nanotube</strong></td>
<td>SOMATULINE DEPOT® (Lanreotide acetate)</td>
<td>2007</td>
<td>Acromegaly</td>
</tr>
<tr>
<td><strong>Nanocrystal</strong></td>
<td>TRICOR® (Fenofibrate)</td>
<td>2004&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td><strong>Micelle</strong></td>
<td>TAXOTERE® (Docetaxel)</td>
<td>1996</td>
<td>Cancer</td>
</tr>
</tbody>
</table>

<sup>1</sup> First ANDA approval in 2013  
<sup>2</sup> First ANDA approval in 2011  
<sup>3</sup> First ANDA approval in 2011  

Tyner KT et al. WIRES Nanomedicine and Nanotechnology 2015.
Evolution of Drug Products Containing Nanomaterials

Reformulations to increase bioavailability and biodistribution
- Liposomes
- Nanocrystals
- Iron colloids

Multifunctional, multicomponent
- Complex microstructures
- ANDAs

CDER’s questions and understanding has evolved with the technology

- Liposome: 26.68%
- Nanocrystal: 3.68%
- Iron-Polymer Nanocomplex: 6.74%
- Nanoemulsion: 6.44%
- Drug-Lipid Nanocomplex: 11.04%
- Micelle: 14.41%
- Drug-Polymer Nanocomplex: 18.40%
- Polymeric NP: 0.92%
- Dendrimer: 0.61%
- Nanobubble: 0.30%
- Drug-Metal Nanocomplex: 0.30%
- Protein NP: 0.30%
- Drug NP: 0.30%
- Solid Lipd NP: 0.30%
- Nanotube: 0.30%
- Silica NP: 0.30%
- Metal-Protein Nanocomplex: 0.30%
- Metal-Nonmetal Nanocomplex: 0.30%
- Metal-Polymer Nanocomplex: 0.30%
What are the Nano Issues?

- CDER current regulatory framework and review process can adequately identify and manage potential risks associated with the use of nanomaterials in drug products
  - So what is different?

- Physicochemical properties (such as particle size) can significantly affect product performance and safety

- Specialized analytical methods are needed to characterize nanomaterials appropriately
Common Challenges and Potential Risks

- PK profiles of the parent drug and the drug encapsulated in the nanoparticles are often different.

- Nanomaterials may also enhance the delivery of drugs to certain tissues and thus, cause new side effects.

- Nanomaterials may have physical and chemical stability challenges.

CHARACTERIZATION
Appropriate Characterization

- Characterization is fundamental
  - Need to know what you have administered before you can discuss any observations

- Regulations and Law do NOT separate nanotechnology products
  - "nano" products are not treated differently
  - Look to Regulations and Guidances

- 21 CFR 314.50(d) requires a full description of physical and chemical characteristics and stability for the drug substance
  - Particle size, crystalline form, surface area/volume, etc...
  - Identity, strength, quality, purity, etc.
  - Manufacturing Process and Controls
  - Analytical procedures

FDA Guidances may be found at: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm
## What to Characterize?

<table>
<thead>
<tr>
<th>Characterization Area</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Agglomeration/aggregation</td>
<td>Stability</td>
</tr>
<tr>
<td>Chemical composition</td>
<td>Concentration</td>
</tr>
<tr>
<td>Crystal structure/crystallinity</td>
<td>Zeta potential</td>
</tr>
<tr>
<td>Particle size/size distribution</td>
<td>Surface energy</td>
</tr>
<tr>
<td>Purity</td>
<td>Catalytic properties</td>
</tr>
<tr>
<td>Shape</td>
<td>Dustiness</td>
</tr>
<tr>
<td>Surface area</td>
<td>Oleophilicity/hydrophilicity</td>
</tr>
<tr>
<td>Porosity</td>
<td>Grain size</td>
</tr>
<tr>
<td>Surface charge</td>
<td>Photocatalytic activity</td>
</tr>
<tr>
<td>Surface chemistry (composition and reactivity)</td>
<td>Octanol-water partition coefficient</td>
</tr>
<tr>
<td>Endotoxin content</td>
<td>Redox potential</td>
</tr>
<tr>
<td>Solubility</td>
<td>Radical formation potential</td>
</tr>
</tbody>
</table>

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**Card and Magnuson, J. Food Sci., 74, vi-vii, 2009; MinCHAR project; www.characterizationmatters.or; http://www.toxicology.org/isot/ss/nano/docs/Ostraat_guest_presentation.pdf**
What to Characterize?

- There are usually specific reasons why a product is being developed to include nanoscale materials.

- The nanomaterial properties that are being exploited for the drug product will often translate into CQAs, which will, in turn, have to be further characterized and controlled.

- Changes in nanomaterial properties may change pharmacokinetics, biodistribution and toxicity, affecting the therapeutic effect
  - Particle size & shape
  - Charge
  - Surface coating
  - Encapsulation efficiency (e.g. liposomes)
  - Drug release rate
  - Stability (chemical and physical)

How to Characterize?

• Specialized analytical methods
  – Traditional methods may not be adequate for characterization of nanomaterials
    • Example: Chromatography for molecular weight (may also need particle size and size distribution)
  – Common methods may break down or not be suitable for this size range
    • Example: Laser diffraction methods used for micron-sized particles applied to nanomaterials
  – Techniques may be new, or applied differently
    • Example: Nanoparticle tracking analysis (new)
    • Example: XRD for particle size vs crystal structure (old)

• Method/system suitability
  – A dissolution method with a 0.2 \( \mu \text{m} \) (200 nm) filter will not be suitable to discriminate dissolution of 100 nm particles
  – Even small particles may interact with filters (robustness)
An Example of Size

**Stock Solution**

- **DLS**
  - Zave: $51.0 \pm 0.5$ nm

- **TEM**

**Dosing Solution Week 1**

- **DLS** – Zave: $51.8 \pm 0.5$ nm

**Dosing Solution Week 7**

- **DLS** – Zave: $50.6 \pm 0.7$ nm
An Example of Size

**Stock Solution**
- **DLS**
  - Zave: 51.0 ± 0.5 nm
  - pdi: 0.141 ± 0.004
- **TEM**
  - Feret diameter: 50 ± 4 nm
- **NAA**
  - 1.12 g/L
  - 1.0 g/L (theoretical)

**Dosing Solution—Week 1**
- **DLS**
  - Zave: 51.8 ± 0.5 nm
  - pdi: 0.231 ± 0.005
- **TEM**
  - Feret diameter: 42 ± 6 nm
- **NAA**
  - 0.36 g/L
  - 0.46 (theoretical)
An Example of Size

**Stock Solution**

![Graph showing distribution of particle size for Stock Solution](image1)

- **Zave**: 51.0 ± 0.5 nm
- **Pdi**: 0.141 ± 0.004

**Dosing Solution—Week 1**

![Graph showing distribution of particle size for Dosing Solution](image2)

- **Zave**: 51.8 ± 0.5 nm
- **Pdi**: 0.231 ± 0.005
What about Generics?

- **Examples of approved generic drug products containing nanomaterials**
  - Sodium ferric gluconate injection
  - Doxorubicin HCl injection

- **FDA product-specific equivalence guidances developed:**
  - Doxorubicin HCl liposome injection
  - Verteporfin liposome injection
  - Amphotericin B liposome injection
  - Daunorubicin liposome injection
  - Sodium ferric gluconate injection
  - Ferumoxytol injection
  - Iron sucrose injection
  - Paclitaxel albumin-bound particles for injectable suspension

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
How does this fit into the rest of the world?

- **Definitions**
  - 1-100 nm
  - Nanomedicine
  - Nanosimilars

- **Platforms**
  - Drug/Device/Cosmetic
  - Liposomes
  - Nanocrystals
  - SPIOs
  - Protein-drug complexes

- **International Pharmaceutical Regulator’s Forum**
  - US, EMA, Japan, Health Canada, TGA Australia
Advice to the Review Side

• Have all the critical quality attributes been identified and controlled?

• Have the potential risks to quality been identified?

• Is there an adequate level of process knowledge and understanding to address the potential risks and to justify the proposed controls?

• Are the proposed controls sufficient to assure product quality during routine production?
Advice to Industry

• Communicate early (PIND, IND and EoP2b) and discuss characteristics and characterization of the formulation and any impact of nanomaterial quality attributes on safety and efficacy.

• Follow the principles of ICH Q8, Q9, and Q10 which are based on the link of critical quality attributes (characterization) and a risk-based approach to development.

• Discuss challenging methods early in the development, so that non-clinical studies and pivotal clinical batches are adequately characterized and relevant to the final control strategy.
Conclusions

- The state of nanotechnology in drug products has evolved and matured
  - First generation: nanocrystals, liposomes, iron colloids
  - New generation: complex, multicomponent, multifunctional

- Despite the diversity in drug products containing nanomaterials, there are still common issues

- FDA and CDER continue to foster innovation and the responsible development of drug products containing nanomaterials

- Current review practices and regulatory framework are capable of detecting and managing the potential risks to quality, safety and efficacy due to nanomaterials in drug product

- As the nanotechnology field continues to mature, the complexity of nanomaterials within drug products is expected to increase

- Characterization plays a critical role in establishing the quality of the drug product
Acknowledgements

- Celia Cruz, OPF/OPQ/CDER
- Sau (Larry) Lee, OPQ/IO
- Wenlei Jiang, OGD
- Sheetal D’Mello, OPQ/IO
- CDER Nanotechnology Working Group