Measuring Exposure Levels of Drug Products Containing Nanomaterials

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Agenda

- Considerations for intentional exposure studies
- In vitro examples
- In vivo examples
Agenda

• Considerations for intentional exposure studies

• In vitro examples

• In vivo examples
An Intentional Discussion

• In the majority of instances, the administration of drug products containing nanomaterials means an intentional exposure
  – Unintentional exposure is possible and is part of a robust risk assessment

• Know the exposure has occurred
  – Material
  – Dose
  – Pharmacokinetics/Toxicity (PK/TOX)
  – ADME (adsorption, distribution, metabolism, elimination)

• Detection is still key
  – In vitro
  – In vivo models
  – Clinical
## 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>1995¹</td>
<td>Cancer</td>
</tr>
<tr>
<td><strong>Inorganic nanoparticle</strong></td>
<td>FERRLECIT® (Sodium ferric gluconate complex)</td>
<td>1999²</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>2004³</td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td><strong>Micelle</strong></td>
<td>TAXOTERE® (Docetaxel)</td>
<td>1996</td>
<td>Cancer</td>
</tr>
</tbody>
</table>

¹ First ANDA approval in 2013
² First ANDA approval in 2011
³ First ANDA approval in 2011

Tyner KT et al. WIRES Nanomedicine and Nanotechnology 2015.
Analytical Methods for Detecting Nanomaterials in Biological Systems

- Non-carbon nanomaterials have methodology for quantification and characterization
  - Detection of elemental signal & visual confirmation
  - Example: ICPMS, TEM/EDS
Untreated animal
PK/ADME/Toxicity

• Pharmacokinetics (PK) is the study of the kinetics of absorption, distribution, metabolism and excretion of drugs and their pharmacologic, therapeutic or toxic response in animals and man.

• ADME
  - Adsorption
    • How it gets in the body
  - Distribution
    • Where it goes in the body
  - Metabolism
    • How the body breaks it down
  - Elimination
    • How the body gets rid of it
PK/ADME Methods & Nanomaterials

• Analytical methods
  – Most popular techniques for small molecules are radiolabeling and bioanalytical techniques
  – Radiolabeling or fluorescently tagging nanomaterials may alter biodistribution

• Common bioanalytical techniques are not always valid for nanomaterials
  – Example: Nanomaterials interacting with filtration step or chromatography columns

• Variety of matrices
  – Blood, urine, feces, on and off-target tissues

• Questions/considerations
  – What is being measured/labeled (drug vs carrier)?
  – Does the nanomaterial remain intact?
    • How are the constituents being identified
  – Is the bioanalytical method appropriate?
    • Controls
    • Testing conditions
Detection and Quantitation of Nanomaterials in Biological Matrices

- **HPLC-MS**
  - Dendrimers, Polymers, Drugs, Metabolites, Fullerenes

- **Capillary Electrophoresis**
  - Fullerenes

- **Radiolabeling**
  - Liposomes, Dendrimers, Polymers

- **ICP-MS & Neutron Activation Analysis**
  - Metallic Nanoparticles (e.g., Gold)
  - Metal Oxides

- **Electron Microscopy**
  - EDS, EELS (Detection and confirmation of composition)

- **Optical Microscopy**
  - Raman, Hyperspectral imaging (Detection)
Agenda

• Considerations for intentional exposure studies

• In vitro examples

• In vivo examples
In Vitro Examples: Is the Method Appropriate? Controls

Naïve cells

Hyperspectral Imaging

Positive id
In Vitro Examples: Is the Method Appropriate? Design Considerations

- Mass balance & control of exposure
- Cell culture conditions influence assay results
- Artificial constraints and/or parameters may influence results
Agenda

• Considerations for intentional exposure studies

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In Vivo Examples
In Vivo Example: What is Being Measured? Complementary Analysis

% ID/mL

0 500 1000 1500

TNF-Au NP PK in rats, [TNF] by ELISA; [Au] by ICP-MS

In Vivo Example: Does the Nanomaterial Remain Intact? Dual Labeling

<table>
<thead>
<tr>
<th></th>
<th>V_d (mL/kg⁻¹)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceramide</td>
<td>1020 ± 478</td>
<td></td>
</tr>
<tr>
<td>Liposome</td>
<td>63 ± 19</td>
<td></td>
</tr>
</tbody>
</table>

Zolnik, B.S. et. al. Drug Metab Dispos, 2008, 36, 1709-1715
In Vivo Example: Is the Method Appropriate? Capillary Electrophoresis

In Vivo Example: Is the Method Appropriate? Testing Considerations

- Detection
- Limits of detection
- Limits of quantification
- Nanomaterial interference
- Appropriate controls
- Well-designed studies
Conclusions

- PK/ADME determination for drug products containing nanomaterials is an evolving area

- Techniques & methods exist to detect nanomaterials within biological tissues
  - Multiple endpoints/methods

- Multiple issues and/or considerations may confound method development and analysis
  - Appropriate controls
  - Well designed studies

- Regulatory science projects continue to address these issues
  - Collaboration opportunities!
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