CDER Risk Assessment to Evaluate Potential Risks from the Use of Nanomaterials in Drug Products

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Outline

• Background
  – Nanomaterials in drug products
  – Drivers for risk assessment exercise

• CDER Risk Assessment
  – Methodology
  – Findings

• Risk Management:
  – Interdisciplinary Review Considerations
  – CDER Guidance development
  – Regulatory Research Priorities
FDA Draft Guidance

Points to consider a material as a nanomaterial from a review perspective:

– Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or

– Whether an engineered material or end product exhibits 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.
Diversity of Nanomaterials

Diversity in chemistry, structure, morphology and function

- Nano: crystals, composites, micelles (varying complexity), liposomes, dendrimers, tubes, and coatings
- Organic and inorganic
- Designed as carriers, depot-forming, and/or self-assembling structures
- Active and inactive (excipient)
What are some unique chemical and biological properties of nanomaterials?

- Particle attributes can be manipulated and enhanced compared to bulk materials, to interact with biological systems.
  - Dissolution rate
  - Size
  - Shape and structure
  - Charge
  - Surface Modifications: hydrophobicity and hydrophilicity

- Biological activity will depend on these physical and chemical characteristics
  - E.g. absorption, phagocystosis, penetration into tissue, selectivity interaction with tumor cells, time in body.
What may be some common challenges of nanomaterials?

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

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

• Nanomaterials may have physical and chemical stability challenges.
CDER Risk Assessment Goals

Multidisciplinary working group

• **Technical**
  – To identify potential risks to safety, quality and efficacy from the use of nano-sized materials in drug products.

• **Regulatory**
  – To identify areas where CDER may need to develop a new guidance, policy, or internal procedures to address these risks (i.e. gaps in our current review or regulatory practices).
Risk Assessment Scope

• Nanomaterial active ingredient, per common routes of administration
  – Oral (considering local and systemic)
  – Topical
  – Transdermal
  – Inhalation
  – Parenteral

• Nanomaterial inactive ingredient
  – Excipients
Systematic Approach Used

1. Ishikawa Diagram
   - Used tool to identify the potential risk factors and map them by category
   - Identified factors that may lead to an effect on quality safety and/or efficacy, if drug product component is a nanomaterial

2. Gap Analysis
   - Identified any areas for improvement in our current approaches (e.g., policy, review procedure, or data requirements)
   - Documented whether current approaches can evaluate the potential risk or whether additional work is necessary
   - Developed recommendations

Publication on risk assessment methodology
Example: Identification of Potential Risk Factors to Safety, Quality & Efficacy from Nanomaterial API

Oral Route of Administration

Product manufacture → Ingestion and dissolution → Absorption and distribution → Elimination
O2: Oral Administration, Potential Effects on Safety and Efficacy of Nanomaterial API at the Ingestion and Dissolution Phase

Dosage form properties

- Unintended exposure: Inhalation or skin
- Oral solid immediate release profile (IR): tablet, capsule, granules
- Oral solid controlled release/modified release profile (CR/MR): tablet, capsule, granules
- Oral liquid IR suspension
- Oral liquid CR/MR suspension

Particle dissolution rate

- Solubility
- Re-precipitation
- Particle aggregation
- Particle size distribution (PSD)

Analytical methods

- Dissolution/release rate
- Particle sizing

Interactions in the stomach

- Excipients
- Food
- Other drugs
- Combination drug products

Local toxicity

Irritation/adverse reactions

Gut pH

Local degradation

Ingestion and Dissolution Phase (Safety & Efficacy)
## Gap Analysis ➔ Areas of focus for review and research

<table>
<thead>
<tr>
<th>Risk Identified: Risk Factor Category</th>
<th>Sub Risk Factor, Primary and/or Secondary Cause</th>
<th>What do we do or require currently to address this risk?</th>
<th>Is this sufficient to address nanomaterial API effects and/or causes?</th>
<th>Potential approach to gap, e.g. proposed solution, references to future or proposed work, if any.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analytical Methods</strong></td>
<td>Dissolution/Release Rate Method</td>
<td>Evaluate dissolution/release rate method development report for discrimination and justification of parameters.</td>
<td><strong>Identified Area for Improvement</strong></td>
<td><strong>Area of Focus</strong></td>
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<td>Evaluate method against changes in formulation or IV/IVR</td>
<td></td>
<td>Reminder that for nanomaterials to focus on understanding the effect of particle size distribution on bioavailability and dissolution for Immediate Release, particularly for BCS II and IV, where API PSD may have impact on dissolution</td>
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<td>Methods are reviewed following the same requirements for discrimination, development information, etc., regardless of Case A, B, C, or D.</td>
<td></td>
<td>Request studies to show API PSD impact on dissolution, a dissolution specification is requested that covers ranges in dissolution may need to show in vivo data (“clinically relevant specs”).</td>
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<td>For OTC, methods are compendial and evaluation is done against compendial methods.</td>
<td></td>
<td>Conventional methodology involving filtration of materials in in-vitro analytical methods (e.g. Dissolution, Assay) may need to be reevaluated when applied to nano materials.</td>
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<td>BE data would also catch differences in modified release formulations and could trigger more work on method development information.</td>
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</table>

Guidelines, Policies, Submitted Data, or Research that currently address this risk
Risk Assessment Results

• CDER current regulatory framework and review process can adequately identify and manage potential risks associated with the use of nanomaterials in drug products
• The key areas for improvement can be addressed by a combination of reviewer training, industry guidance, and additional research

Presentation to the August 2012 OPS Advisory Committee
Risk Assessment Results

• Analysis generated 20 gaps and areas of focus that centered on the following themes:
  – Material characterization and analytical methods
  – In-vitro equivalence methods, Biopharmaceutics
  – Unintended exposure and safety
  – Nanomaterial excipient changes and properties
  – Impactful changes in nanomaterial drug product properties later in the product lifecycle.

• After prioritization exercise → top 3 key interdisciplinary findings
Risk Assessment Results: Key interdisciplinary findings

1. Specialized analytical methods are needed to characterize nanomaterials appropriately

2. Particle size (properties) changes can affect product performance, including product quality

3. Particle size (properties) changes can affect safety and may result in unintended exposure
Risk Management: Review Considerations (training)

- **CMC:**
  - Adequacy of analytical methods for structural and physicochemical characterization
  - Process risks and control strategy for nanomaterial products
- **Biopharmaceutics:**
  - In vitro comparison of formulation is key to determine the impact of particle size on product performance
  - Adequacy of analytical methods for performance characterization
- **Pharm Tox**
  - Degree of evaluation of nanomaterial in nonclinical studies
  - Bridging studies needed for products in which there is a switch from non-nanomaterials to nanomaterials
- **Clinical Pharmacology**
  - Mechanistic understanding of role of nanomaterial in PK and ADME (e.g. carriers vs. non-carriers)
  - Adequacy of analytical methods
CDER Priorities in Nano Regulatory Research
Top 3 Research Priorities Identified from Risk Assessment

1. Dissolution Testing
   • Research to determine appropriate methodology and controls, addressing filtration issues

2. Alternate *In Vitro* Release Testing Methods
   • Research to develop/validate current methods
   • Determine if dissolution testing can serve as a surrogate for bioavailability for nanomaterial APIs

3. Permeability/Systemic Absorption (API and/or excipients)
   • Research to determine the effect of reducing the particle size (and other nano-particle properties) on permeability and/or systemic absorption
CDER Nano Regulatory Research Priorities

• Previously
  – Nanomaterials in sunscreens
  – Stability of nano-particle formulations
  – Effects of aggregation and agglomeration on product performance
  – Liposomes

• Ongoing
  – Nano-particle bioaccumulation and macrophages function
  – In Vivo Inhalation Safety Study and Characterization of Nanomaterials in Over-the-Counter Sunscreen Drug Products.
Risk Management: Future Planned CDER Guidance for Industry on Nanomaterials in Drug Products

• Key principle: risk based approach focused on (a) intended nanomaterial function in drug delivery and (b) nanomaterial potential persistence in the body.

• Potential Guidance elements:
  – Structural characterization requirements for nanomaterials
  – Establishing the intended function of the nanomaterial in the drug product
  – Understanding of the contribution of the nanomaterial to drug delivery (efficacy) and to safety
  – Expectations on information and adequate communication of changes of a nanomaterial attribute or component that may impact safety and efficacy.
Risk Management: Future Planned CDER Guidance for Industry on Nanomaterials in Drug Products

– Recommendations for in-vitro comparisons
– Recommendations for complementary non-clinical studies that address potential changes in safety/efficacy of the nano-drug

• Seeking input on elements to consider for the guidance.
Conclusions

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

- Reviewer training, targeted regulatory research, and a guidance for industry will improve management of potential risks and inform the responsible development of this emerging technology.
Thank you!