Research needs in pharmaceutical excipients: implications of a global supply chain

FY 2015 GDUFA Regulatory Science Initiatives
Part 15 Public Meeting
June 5, 2015
Silver Spring, MD

Stephen W. Hoag, Ph.D.
University of Maryland, Baltimore; School of Pharmacy
A NIPTE Institution
Email: shoag@rx.umaryland.edu
Topic #6. Strategies for enhancing quality and equivalence risk management during generic drug product development, during regulatory review, and/or throughout the drug product's lifecycle following initial approval.
Dosage Form Variability

\[ \sigma_{Tot} = \sigma_{Exc} + \sigma_{API} + \sigma_{PC} + \sigma_{Int} + \sigma_{Mes} \]
Excipient Property Relations

Material Properties
• Particle size
• Molecular weight
• Degree of substitution
• Bulk, true density
• Etc.

QTPP
• Clinical use factors
• USP specs.
• PK/PD performance
• Bioavailability
• Misuse risk minimization
• Shelf life

Lack of knowledge makes risk management difficult & empirical
• Empirical analysis is only as good as studies done to develop risk models
• Excipient variability complicates studies that need to be done
  • Lot-to-lot, grade, manufacturing site, manufacturer, etc.
• Makes change control difficult
Determining material properties and material variation is essential to reach desired end point.

FDA should partner with other agencies to support this research.
Identifying Performance Metrics

• By nature excipients are highly variable materials
  – Thus, material science is key to process understanding
  – For each dosage form type: need to identify properties that affect QTPP
    • For some properties this is well known
      – E.g., particle size and flow
    • For most properties this is not well known
      – E.g., water activity and stability
      – Degree of substitution on a polymer and bioavailability
  – Should develop risk evaluation scheme for excipients section of the CMC
    • Should be open to public and built with input from FDA, industry and academics
Global Supply Chain

• With globalization of the supply chain there has been a dramatic increase in the kinds and sources of excipients
  – Excipient vendors from all over the world now sell excipients in many markets
    • Products are now manufactured all over the world and imported to the USA, often using local excipient suppliers
  – In an effort to meet drug manufacturers needs excipient vendors have developed many new excipients
    • E.g., new excipients for low solubility drugs
Comparison of different grades of MCC

- Decrease moisture content
- Increase stability of moisture-sensitive drugs
- Increase flow
- Increase batch size
- Loose bulk density

Particle size:
- 180 um
- 150 um
- 100 um
- 50 um
- 20 um

FMC
- NMT 1.5%
- NMT 2%
- NMT 3%
- NMT 5%

Comparison grades:
- PH-102 SCG
- PH-102
- PH-101
- PH-105
- PH-302
- PH-301

NMT = not more than
## Comparison of different grades from different manufacturers--MCC

**FMC = FMC BIOPOLYMERS**  
**JRS = J Rettenmaier & Söhne GmbH and Co.KG**  
**AKC = Asahi Kasei Corporation**

<table>
<thead>
<tr>
<th>Manufactures</th>
<th>Grades</th>
<th>Particle Size, µm</th>
<th>Moisture, %</th>
<th>Loose Bulk Density, g/cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMC</td>
<td>Avicel PH101</td>
<td>50</td>
<td>3.0-5.0</td>
<td>0.26-0.31</td>
</tr>
<tr>
<td>JRS</td>
<td>Vivapur 101</td>
<td>65</td>
<td>--</td>
<td>0.26-0.31</td>
</tr>
<tr>
<td></td>
<td>Emcocel 50M</td>
<td></td>
<td></td>
<td>0.25-0.37</td>
</tr>
<tr>
<td>AKC</td>
<td>PH-101</td>
<td>50</td>
<td>2.0-6.0</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>UF-711</td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>KG-802</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>KG-1000</td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>FMC</td>
<td>Avicel PH-102</td>
<td>100</td>
<td>3.0-5.0</td>
<td>0.28-0.33</td>
</tr>
<tr>
<td>JRS</td>
<td>Vivapur 102</td>
<td>100</td>
<td>--</td>
<td>0.28-0.33</td>
</tr>
<tr>
<td></td>
<td>Emcocel 90M</td>
<td></td>
<td></td>
<td>0.25-0.37</td>
</tr>
<tr>
<td>AKC</td>
<td>PH-102</td>
<td>90</td>
<td>2.0-6.0</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Change Control in a Global Supply Chain

• Often excipients are considered an interchangeable commodity item
  – In addition to the Certificate of Analysis, one needs to identify critical material attributes that need to be the same for a change not affect the patient
    • Key material attributes depends on the type of dosage form
  – Given our knowledge of excipient properties, assessing what changes won’t affect the patient can be difficult

• Industry, FDA and academics should develop a set of metrics for assessing excipient changes
Cataloging Material Properties

- Risk assessment methods are expensive and time consuming to develop
  - It would be very beneficial if all these efforts could be cataloged into a central location
- This information should be cataloged into a database that can track excipient properties:
  - Different vendors
  - Lots
  - Grades
  - Etc.
- The database should have tools to take information from the database and use it in a risk analysis
- Also, we are entering the area of “Big Data”
  - It would go a long way to improve product quality to be able to data mine excipient properties to identify unknown properties that affect product performance
  - Data mining can be used to guide theoretical studies on excipients
Nomenclature
- Compendial Name
- CAS Number
- Chemical structure
- Common & Product Name
- Description & Functional Category

Property Measurements
- Traceable
- Searchable
- Sortable
- Organized data into families by
  - Measurement type or chemical class
Summary

• Greatest needs
  – Fundamental material science research on excipient performance
  – For each dosage form type identifying performance metrics that relate to product efficacy and can be used in a risk analysis
  – Develop risk analysis schemes for excipient change control for excipients coming from different sources
  – Cataloging excipient information in a database or knowledge management system