Excipient Nomenclature Development - FDA Draft IID Guidance Comments

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Excipient Nomenclature Joint Subcommittee

- Understanding Excipients that helps develop an Excipient Nomenclature Guideline

- Being responsible for
  - recommending an appropriate title for a new excipient monograph
  - recommending a change to an official monograph title

- Working on a *Stimuli* article based on discussions for PLGA ([ID name: Poly(DL-Lactic-co-Glycolic Acid), (50:50; 12000 MW)] new monographs)
Published a *Stimuli* article in *PF 44*(3)[May – June 2018]

The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities
Understanding Excipients

The *Stimuli* article in *PF 44*(3) defines

- **Nominal component**: Substance typically found in the excipient that is expressed by the official name and definition and/or assay provided in the USP monograph.

- **Minor component**: A component of an excipient which is not the nominal component or, where the official name does not relate to the excipient components, not the major component.

- **Simple excipient**: An excipient composed of a single main substance with a well-defined chemical structure that can be characterized well analytically.

- **Complex excipient**: Any excipient that does not fit the definition of a simple excipient.

- **Concomitant component**: please refer to the *Stimuli* article.

- **Added substances in official substances**: please refer to the *Stimuli* article.

- **Excipient impurity**: please refer to the *Stimuli* article.
Understanding Excipients

The *Stimuli* article in *PF 44*(3) presents excipient classification.

![Excipient Classification Diagram]

Figure 1. Classes of substances used as excipients.
Isostearyl Isostearate

- Simple excipient – organic, synthetic ester (mixture), new monograph
- Title was approved in Nov. 2016
- The assay based on the HPSEC technique determined the content of nominal component, isostearyl isostearate, to be NLT 85.0%
- From the approved title, we may be able to propose *nominal component* to be monograph title
Neohesperidin Dihydrochalcone

- Simple excipient – organic, a purified excipient, new monograph
- Title was approved in June 2017
- The assay based on the HPLC determined the content of nominal component, neohesperidin dihydrochalcone, to be NLT 96.0% and NMT 102.0%.
- Product’s impurity profile is provided and specifications are established
- From the approved title, we may be able to propose *nominal component* to be monograph title
Methyl Acrylate, Methyl Methacrylate and Methacrylic Acid (7:3:1) Copolymer 280000 Dispersion

- Complex excipient – organic, synthetic polymer, new monograph
- Title was approved in January 2018
- From the approved title, we may be able to propose a title for a new copolymer

Monomer 1 and Monomer 2 (monomer ratio) Copolymer xxxx
[xxxx – weight-average molecular weight value]

Monomer 1, Monomer 2, and Monomer 3 (monomer ratio) Copolymer xxxx
Polypropylene Glycol 11 Stearyl Ether

- Complex excipient – organic, synthetic polymer, new monograph
- Title was approved in March 2018
- The prefix term “Polyoxyl” cannot be continually used due to its non-specific nature
  - If polymerization with ethylene oxide, the prefix term “Polyethylene Glycol … …” will be used.
  - If polymerization with propylene oxide, the prefix term “Polypropylene Glycol … …” will be used.
Polypropylene Glycol 11 Stearyl Ether (Continued)

- For a derivative of Polypropylene Glycol and/or of Polyethylene Glycol, use monomer repeating unit number after the prefix term
  Polypropylene Glycol xx … End Cap Group
  [xx – monomer repeating unit]
  Polyethylene Glycol xx … End Cap Group

- For Polyethylene Glycol, use weight-average molecular weight after the prefix term
  Polyethylene Glycol xxxx
  [xxxx – weight-average molecular weight]

Examples: official monographs
  Polyethylene Glycol 3350
  Polyethylene Glycol 3350 and Electrolytes for Oral Solution
Sucrose Diacetate Hexaisobutyrate

- Complex excipient – organic, semi-synthetic mixture, new monograph
- Title was approved in July 2018
- Food Chemicals Codex has a monograph entitled:
  - Sucrose Acetate Isobutyrate
- The numbers of substituting groups (acetate and isobutyrate) are included within the *NF* monograph title
  - Sucrose *Di*acetate *Hexa*isobutyrate
Myristyl Lactate

- Complex excipient – organic, semi-synthetic mixture, new monograph
- Title was approved in October 2018
- Myristyl Lactate in FDA inactive ingredient database – used in topical formulation, functional category: emollient
- Myristyl Lactate may contain NLT 70% of myristyl lactate (C\textsubscript{17}H\textsubscript{34}O\textsubscript{3}) and NMT 20% of myristyl alcohol (C\textsubscript{14}H\textsubscript{30}O)
Recent Updates: Excipient Nomenclature

- **Glyceryl Monocaprylate NF, USP 41-NF 36**
  - **Contents of Monoglycerides, Diglycerides, and Triglycerides** in the Assay are determined by GC/FID

<table>
<thead>
<tr>
<th>Content of Monoesters (%)</th>
<th>Content of Diesters (%)</th>
<th>Content of Triesters (%)</th>
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<tbody>
<tr>
<td>Type I</td>
<td>40.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Type II</td>
<td>75.1</td>
<td>—</td>
</tr>
</tbody>
</table>

- Based on FDA’s *Request for Revision*, USP split the monograph and proposed these changes in *PF 44(5)[Sept.-Oct 2018]* for public comment
  - Type I – included in a new monograph entitled **Glyceryl Mono and Dicaprylate**
    - The new title, **Glyceryl Mono and Dicaprylate**, was approved in March 2018
  - Type II – represented by the existing monograph, **Glyceryl Monocaprylate**
Recent Updates: Excipient Nomenclature

- Glyceryl Monocaprylocaprate NF, USP 41-NF 36
  - Contents of Monoglycerides, Diglycerides, and Triglycerides in the Assay are determined by GC/FID

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<td>Max.</td>
<td>Min.</td>
</tr>
<tr>
<td>Type I</td>
<td>40.0</td>
<td>75.0</td>
<td>20.0</td>
</tr>
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  - Type II – represented by the existing monograph, Glyceryl Monocaprylocaprate
Since Sept. 2019, the Excipient Nomenclature working group is formed
- Developing a *Stimuli* article or a positional paper
- Drafting the excipient nomenclature guideline

FDA published the draft IID guidance in July 2019
- Excipient PUT worked with Global External Affair dept. and submitted FDA USP comments on the draft IID guidance
- Analyzing inconsistency between *USP/NF* official titles, GSRS preferred names, and IID naming
- Preparing further discussions with FDA on this topic
Thank You

Empowering a healthy tomorrow
Discontinuation

Due to limitations in excipients, 28 percent of respondents experienced a discontinuation of a drug’s development for the U.S. market. The phases at which the discontinuation occurred were most commonly Pre-IND and IND.

36% experienced a discontinuation (excluding DKs)

<table>
<thead>
<tr>
<th>Discontinuation Phase</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-IND</td>
<td>40%</td>
</tr>
<tr>
<td>IND</td>
<td>37%</td>
</tr>
<tr>
<td>NDA/ANDA/BLA</td>
<td>32%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
</tr>
</tbody>
</table>

Q8 Have you experienced a discontinuation of a drug’s development for the U.S. market because you were limited to using excipients used in approved drugs in the U.S? n=264, all responses, n=208, excluding DK responses. Q8A Again, consider the dosage form you have the most experience formulating: $Q3/SelectedChoices$. Please select the phase at which the discontinuation occurred. Please select all that apply. N=75.
The most commonly cited reason for the discontinuation of drug development was the inability to formulate a stable delivery of API and to overcome insolubility/permeability of API using the available excipients.
4. Challenges faced with using Novel/New excipients
New/Novel Excipients: Challenges

More than three quarters of respondents (77 percent) have experienced challenges using novel excipients in advancing formulation through drug development for the U.S. market.

- Regulatory issues are the most common challenges.

 Respondents who work in companies with greater than 500 employees were more likely to experience challenges: 84% vs. 67% for those with 500 or less employees.
5. Cross Tabulations of Results

By Manufacturer
Cross Tabulation

<table>
<thead>
<tr>
<th>By Drug Manufacturer</th>
<th>By Excipient Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>▸ Generic Drugs (small molecule)</td>
<td>▸ Excipient Manufacturer</td>
</tr>
<tr>
<td>▸ Branded Drugs (small molecule)</td>
<td>▸ Excipient Distributor</td>
</tr>
<tr>
<td>▸ Branded Biologics</td>
<td></td>
</tr>
<tr>
<td>▸ Branded Biosimilars</td>
<td></td>
</tr>
</tbody>
</table>

Questions:

Q 5 For dosage form [XXX], which you indicated having the most experience formulating, please rate the importance of excipients in advancing a formulation through drug development. [Likert scale used: Critical, Somewhat important, Very important; Aggregate by Critical, Very Important: By Manufacturer – Responding as Yes]

Q 6 How often have excipients used in approved drugs in the U.S. limited your ability for drug development for the U.S. market? [Likert scale used: Always, Never, Often, Sometimes; Responses are an aggregate of Always/Often/Sometimes]

Q 7 Have you or your organization reformulated a drug product for the U.S. market because you were limited to using excipients used in approved drugs in the U.S.? [Likert scale used: Yes/no; Responses are Yes]

Q 8 Have you experienced a discontinuation of a drug’s development for the U.S. market because you were limited to using excipients used in approved drugs in the U.S.? [Likert scale used: Yes/no; Responses are Yes]

Q 10 Have you or someone you have supervised experienced challenges using novel excipients for the U.S. market in advancing a formulation through drug development? [Likert scale used: Yes/no; Responses are Yes]
## Cross Tabulation Summary

<table>
<thead>
<tr>
<th>Question</th>
<th>Drug Manufacturer*</th>
<th>Excipient Manufacturer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 5 For dosage form [XXX], which you indicated having the most experience formulating, please rate the importance of excipients in advancing a formulation through drug development</td>
<td>95%</td>
<td>97%</td>
</tr>
<tr>
<td>Q6 How often have excipients used in approved drugs in the U.S. limited your ability for drug development for the U.S. market?</td>
<td>81%</td>
<td>92%</td>
</tr>
<tr>
<td>Q 7 Have you or your organization reformulated a drug product for the U.S. market because you were limited to using excipients used in approved drugs in the U.S.?</td>
<td>45%</td>
<td>73%</td>
</tr>
<tr>
<td>Q8 Have you experienced a discontinuation of a drug's development for the U.S. market because you were limited to using excipients used in approved drugs in the U.S.?</td>
<td>25%</td>
<td>67%</td>
</tr>
<tr>
<td>Q10 Have you or someone you have supervised experienced challenges using novel excipients for the U.S. market in advancing a formulation through drug development?</td>
<td>71%</td>
<td>87%</td>
</tr>
</tbody>
</table>

* See slide 26 “Cross Tabulation” for definition and scales