Novel Excipients - Update on Recent Survey Findings

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Objectives & Methodology

Research Objectives:

- Identify, if any issues being experienced by stakeholders related to Novel Excipients
- Better understand views of stakeholders on the current state of innovation in excipients.
- Determine the extent to which excipients are a factor in advancing API selection through early stages of the formulation process.
- Identify specific issues with using novel excipients.

Survey Fielding:

Quantitative survey fielded online February 1-March 22, 2019. Conducted through Qualtrics.

Target Audience:

Qualified respondents had to have 1-formulated medicines or 2-supervised others who formulate medicines in the past five years.
Respondents are formulators for generic and branded; Biologics and biosimilars; Solid dosage, liquids and specialty dosage forms, including Injectables.

264 respondents qualified for and completed the survey

Overall margin of error is +/-6% at a 95% level of confidence.

Sample sources & distribution:

Included: Internal USP contact lists of Excipients stakeholders, IPEC Federation, Social Media sites, USP websites, and other internal and external sources.
The vast majority of respondents who formulate medicines—or supervise others who formulate—report that drug development had been limited, at least some of the time, due to excipients currently used in approved drugs.

- Most common reason for this limitation relates to the current excipient not used in the selected dosage form.

The concept of new/novel excipients is well-known, as 85 percent of formulators or formulator supervisors expressed familiarity.

- About half of respondents have used novel excipients in the U.S. for advancing formulation through drug development. While more than half of respondents expressed a likelihood to use novel excipients in the future—assuming no change in the current U.S. regulatory landscape—nearly a third do not expect to use them.

Reformulation of a drug product was a consequence of excipients limitations, according to two in five respondents.

28 percent of respondents experienced a discontinuation of drug development as a result of excipients limitations.

Challenges in using novel excipients are common.

- More than three-quarters of users have faced challenges in using novel excipients.
- Regulatory issues represent the most frequently cited challenges, followed distantly by safety concerns.
- Respondents who work in large companies were more likely to experience challenges using novel excipients.
New/Novel Excipients

Please review the following descriptions:

According to FDA Excipient Guidance (May 2005): “new excipients means any inactive ingredients that are intentionally added to therapeutic and diagnostic products, but that: (1) we believe are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.”

According to the 2002 FDA publication of the Step 4 ICH Tripartite guideline (eCTD Module 3 Quality):

Control of excipients: Novel Excipients (name, dosage form) as:
“For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format.”
Respondent Profile
Nearly two-thirds of respondents work for companies that manufacture or supply branded small molecule drugs.

- Generic Drugs (small molecule): 50%
- Branded Drugs (small molecule): 64%
- Branded biologics: 48%
- Biosimilars: 27%

Q15 Does your organization/company manufacture or supply the following: n=264
Respondent Profile: Organization Type

Pharmaceutical manufacturer: 49% (129)
Exipients manufacturer: 22% (59)
Pharmaceutical Contract Manufacturing Organization/Contract development and manufacturing organization (CMO/CDMO): 9% (23)
Pharmaceutical Excipient Distributor (Packagers, Repackagers, Blending or Labeling): 6% (15)
Academia: 5% (12)
Pharmaceutical Contract Research Organization (CRO): 4% (11)
Government: 0% (1)
Other (please specify): 5% (14)

Q14 Which of the following best describes the organization/company for which you currently work? *Select one* n=264
**Respondent Profile: Primary Role**

**Q16 What is your primary role at your organization/company? (Select one) n=n=264**

- **Formulator**: 29%
- **R&D Scientist (Pharmaceutical/Industry manufacturing)**: 25%
- **Quality Assurance (QA/QC)**: 14%
- **Regulatory Affairs Manager**: 6%
- **Academic Scientist**: 4%
- **Consultant**: 3%
- **Executive/CEO**: 3%
- **Manufacturing Manager**: 3%
- **Pharmacologist**: 3%
- **Regulatory Scientist**: 3%
- **Medicinal Chemist**: 2%
- **Toxicologist**: 1%
- **Government Scientist**: 0%
- **Other (please specify)**: 5%
Qualiﬁed respondents were more likely to work for large companies:

- More than 500 employees: 59%
- 500 or less employees: 41%
Please select the country in which you work. (n=264)
Overall Respondent Profile: Formulation Experience and Dosage Forms

Q1a In the past five years, have you formulated medicines or supervised others who formulate medicines? Please select one response only. N=264

- Yes, I have personally formulated medicines and supervised others who formulate medicines: 40%
- Yes, I have supervised others who formulate medicines: 32%
- Yes, I have personally formulated medicines: 28%

Q3. Please select the dosage form you have the most experience formulating. N=264

- Tablets: 37%
- Injections: 17%
- Capsules: 11%
- Liquids: 4%
- Powders: 4%
- Emulsions: 3%
- Granules: 3%
- Solutions: 3%
- Suspensions: 3%
- Pils: 2%
- Creams: 2%
- Lotions: 2%
- Aerosols: 2%
- Others-Foams, Gels, Implants and 10 more Others: 8%
1. Familiarity with and Use of Novel/New excipients
The vast majority of respondents—85 percent—reported being familiar with new/novel excipients. Among those familiar, more than half used or supervised others who used new/novel excipients in advancing a formulation through drug development.

U.S. respondents were more likely to be familiar with novel excipients: 93 percent vs. 84 percent for ex-U.S. respondents.
New/Novel Excipients: Expected Use

- In the next five years, more than half of respondents (55 percent) expect to use novel excipients for the U.S. market, assuming there is no change in the current U.S. regulatory landscape.
- Nearly a third (29 percent) of respondents are not likely to use novel excipients in the next five years.
- Among companies with greater than 500 employees, more than two in five (43 percent) are not likely to use new/novel excipients.

Q10b Assuming no change in the current U.S. regulatory landscape in the next five years, how likely are you to use novel excipients for the U.S. market in advancing a formulation through drug development? N=258
The overwhelming majority of respondents (96 percent) believe that excipients are at least *very important* in advancing a formulation through drug development.

**Importance: Top Reasons**

- Quality of drug product/Efficacy: 26%
- Stability: 23%
- Impact on the formulation: 15%
- Impact on drug release: 14%
- Bioavailability: 10%

Q4 For dosage form [Q3/SelectedChoices], which you indicated having the most experience formulating, please rate the importance of excipients in advancing a formulation through drug development. (n=253). Q4A Please elaborate on why you believe excipients are [Q4/SelectedChoices] in advancing a formulation through drug development?
Phases of Drug Development

Key decisions are made regarding excipient selection across all phases of drug development.

Q5 For the dosage form you have the most experience formulating, please choose the phase(s) of drug development where key decisions were made regarding excipient selection. Please select all that apply. n=264

- NDA/ANDA/BLA: 46%
- IND: 46%
- Pre-IND: 41%
- Other (please specify): 7%
2. Limitations of current excipients
Limitations of Current Excipients

Current excipients have imposed limitations on drug development for the majority of respondents (84 percent). The most common reason is that the excipient is not used in an approved drug in selected dosage form.

Top Reasons for Limitations

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient not used in an approved drug in selected dosage form</td>
<td>54%</td>
</tr>
<tr>
<td>Unable to maintain stability of final drug product</td>
<td>36%</td>
</tr>
<tr>
<td>Unable to overcome bioavailability issues</td>
<td>33%</td>
</tr>
<tr>
<td>Unable to overcome solubility/permeability issues</td>
<td>32%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
</tr>
</tbody>
</table>
3. Types of Limitations and Reasons
Reformulation

Due to limitations in excipients, two in five respondents were compelled to reformulate a drug product for the U.S. market. For the majority of those who had to reformulate, the delay was 1-5 years. The most commonly cited reason was the inability to formulate a stable delivery of API.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unable to formulate a stable delivery of API</td>
<td>57%</td>
</tr>
<tr>
<td>Unable to overcome insolubility/permeability of API</td>
<td>51%</td>
</tr>
<tr>
<td>Other reasons</td>
<td>12%</td>
</tr>
</tbody>
</table>

Length of Delay

- 1-5 years: 64%
- < 1 year: 34%
- > 5 years: 2%

Q7 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.? n=264-all responses / n=201-excluding DK values. Q7A On average, how long was the delay to reformulation? Please select one response only. n=106. Q7B Please indicate why the drug product development was delayed. Please select all that apply.
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.

Discontinuation Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Percentage</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>
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
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
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]

Q6 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]

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.? [Likert scale used: Yes/no ;Responses are Yes]

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? [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 <strong>importance of excipients</strong> 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 <strong>reformulated a drug product</strong> 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 <strong>discontinuation of a drug’s development</strong> 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
Thank You

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