USP Excipients Stakeholder Forum
Wednesday, November 13, 2019

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 [IID name: Poly(DL-Lactic-co-Glycolic Acid), (50:50; 12000 MW)] new monographs**

Understanding Excipients

Excipient Expert Committees

- 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

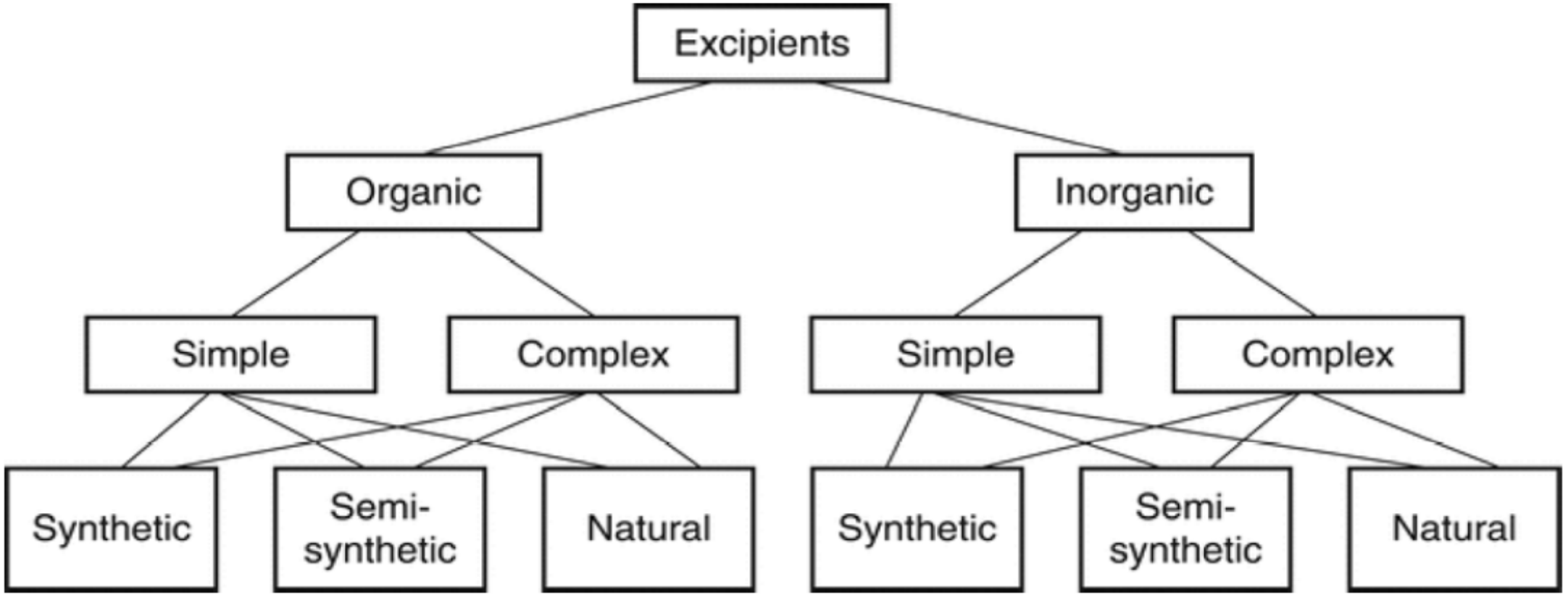

Figure 1. Classes of substances used as excipients.

New Monograph Titles Worked and Approved

- **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

New Monograph Titles Worked and Approved

- **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

New Monograph Titles Worked and Approved

- **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

New Monograph Titles Worked and Approved

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.

New Monograph Titles Worked and Approved

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

New Monograph Titles Worked and Approved

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

New Monograph Titles Worked and Approved

- **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 ($C_{17}H_{34}O_3$) and NMT 20% of myristyl alcohol ($C_{14}H_{30}O$)

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

	Content of Monoesters (%)		Content of Diesters (%)		Content of Triesters (%)	
	Min.	**Max.**	**Min.**	**Max.**	**Min.**	**Max.**
Type I	40.0	75.0	20.0	50.0	—	15.0
Type II	75.1	—	—	24.9	—	5.0

- 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

	Content of Monoesters (%)		Content of Diesters (%)		Content of Triesters (%)	
	Min.	**Max.**	**Min.**	**Max.**	**Min.**	**Max.**
Type I	40.0	75.0	20.0	50.0	—	15.0
Type II	75.1	—	—	24.9	—	5.0

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Excipient Nomenclature Working Group

- 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 inconsistence between *USP/NF* official titles, GSRS preferred names, and IID naming
  - Preparing further discussions with FDA on this topic

Thank You

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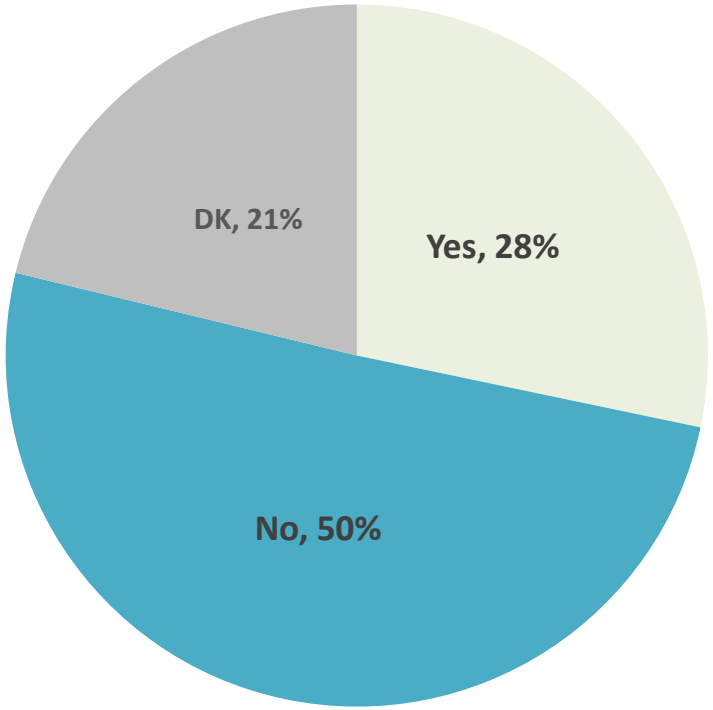
Discontinuation

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.



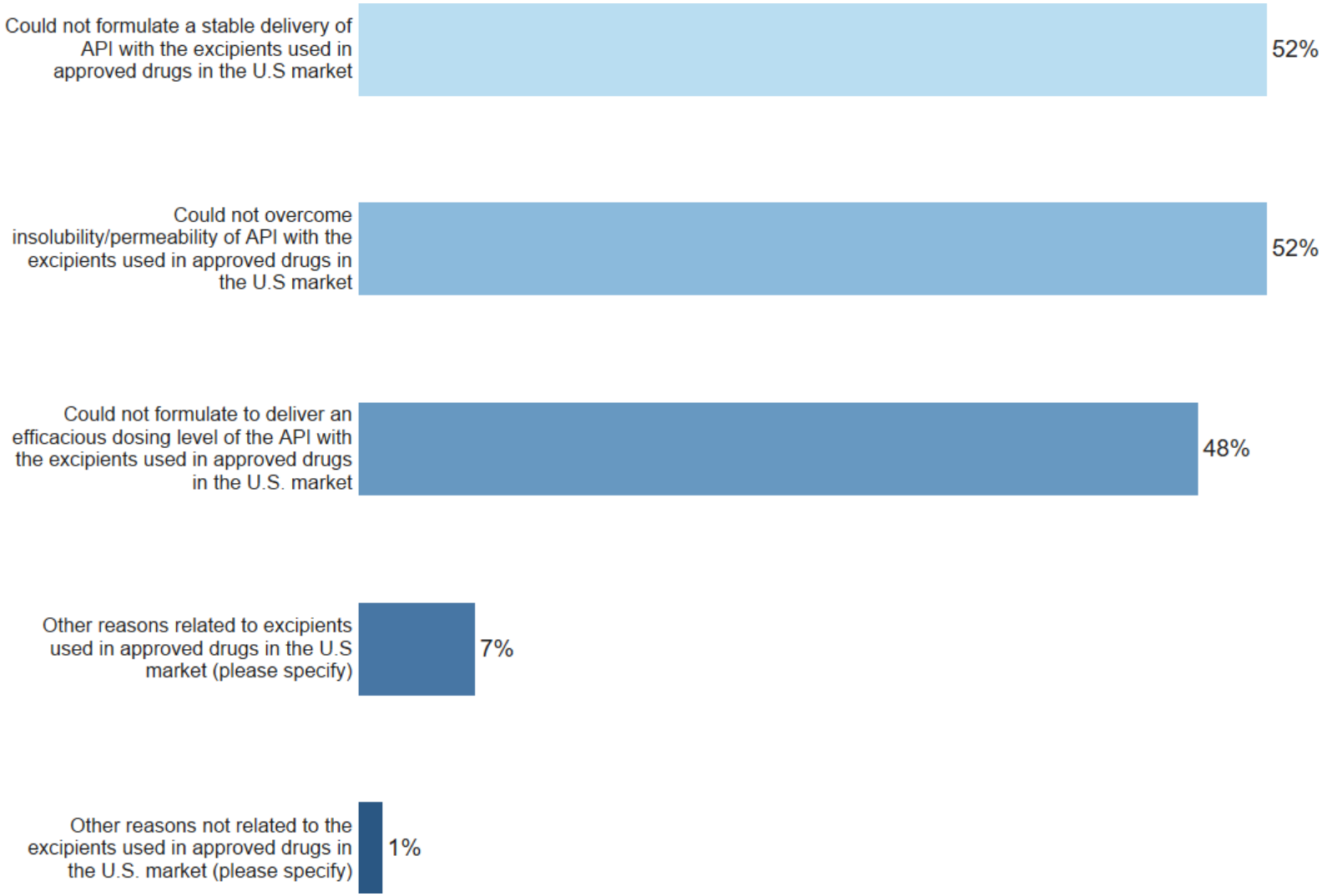
36% experienced a discontinuation (excluding DKs)

Discontinuation Phase	
Pre-IND	40%
IND	37%
NDA/ANDA/BLA	32%
Other	4%

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.

Discontinuation: Reasons

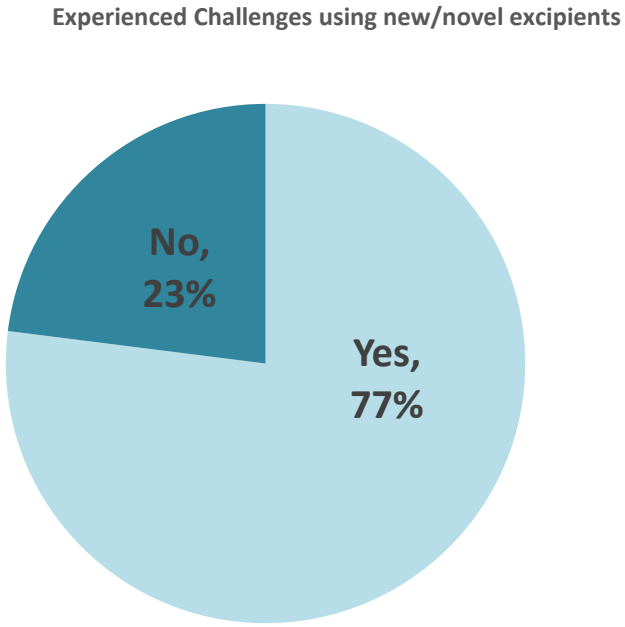
The most commonly cited reason for the discontinuation of drug development was the inability to formulate a stable delivery of API and to overcome insolubility/permeability of API using the available excipients.

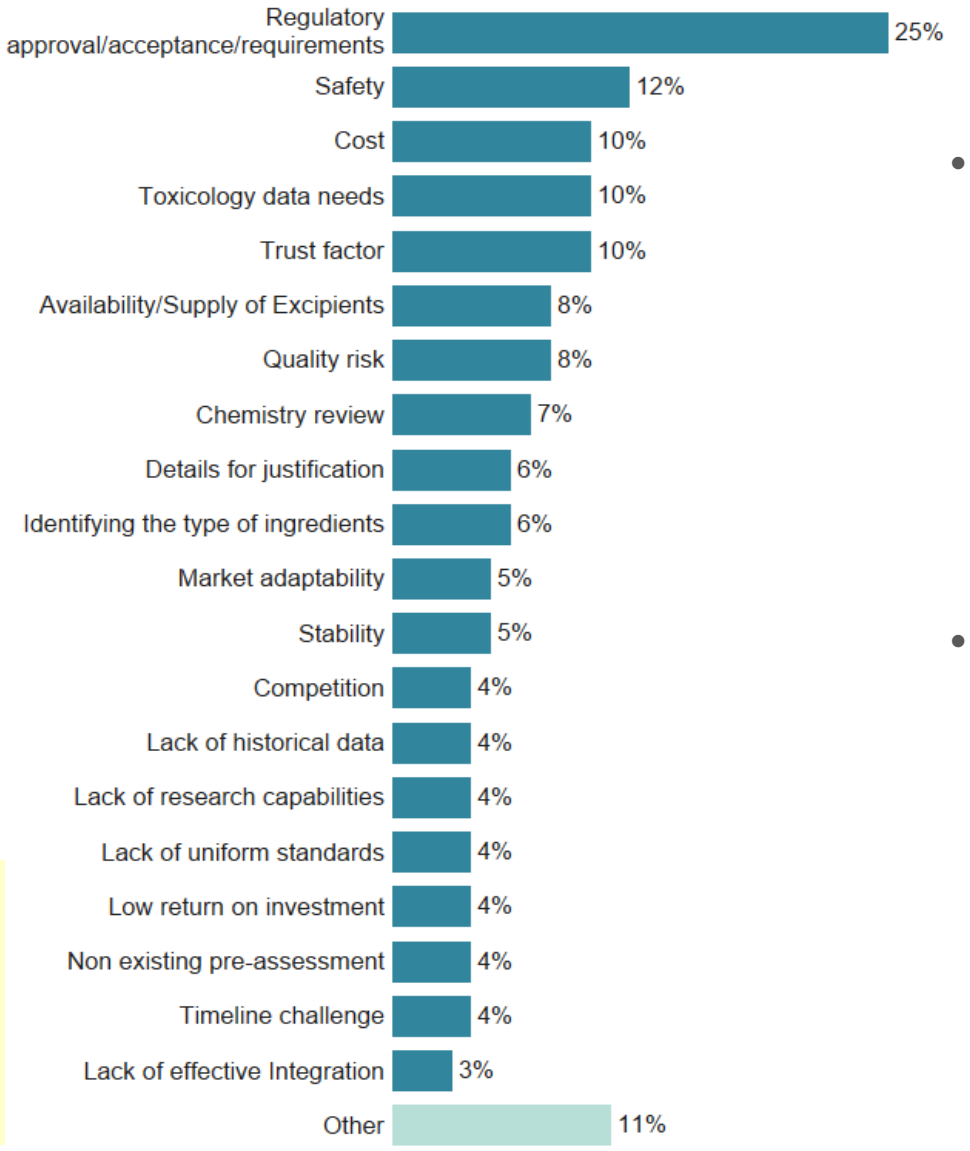


Q8B_For the Pre-IND/NDA/ANDA/BLA/Other phase (s) selected, please select the reasons for the discontinuation. (Select all that apply). N=75 (all phases combined)

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.

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? N=134. Please describe the challenges using novel excipients for the U.S. market in advancing a formulation through drug development. N=103 *Note: n/a & none responses have been excluded. Single responses have been grouped in Other.*

Data Findings

5. Cross Tabulations of Results

By Manufacturer

Cross Tabulation

By Drug Manufacturer

- Generic Drugs (small molecule)
- Branded Drugs (small molecule)
- Branded Biologics
- Branded Biosimilars

By Excipient Manufacturer

- Excipient Manufacturer
- Excipient Distributor

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

Question	Drug Manufacturer*	Excipient Manufacturer*
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	95%	97%
Q6 How often have excipients used in approved drugs in the U.S**. limited your ability for drug development** for the U.S. market?	81%	92%
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.?	45%	73%
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?	25%	67%
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?**	71%	87%

* See slide 26 "Cross Tabulation" for definition and scales

Thank You

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