

USP Excipients Stakeholder Forum
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Novel Excipients - Update on Recent Survey Findings

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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.

Summary



- **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.”

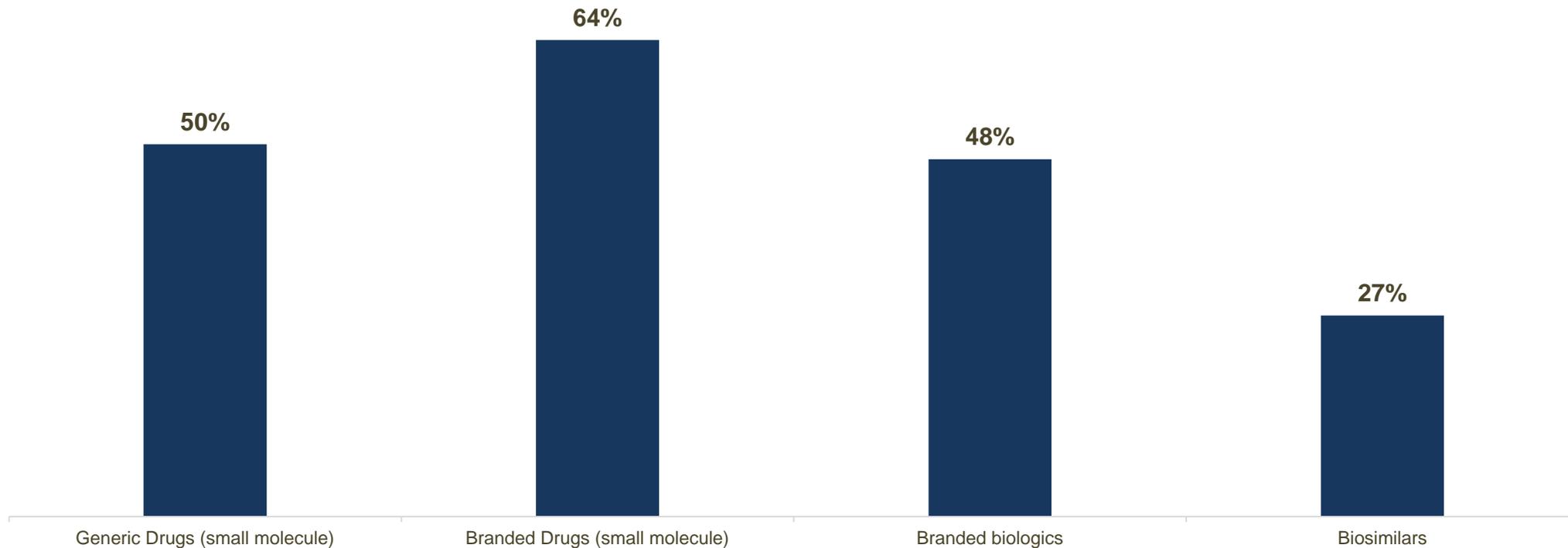


Respondent Profile

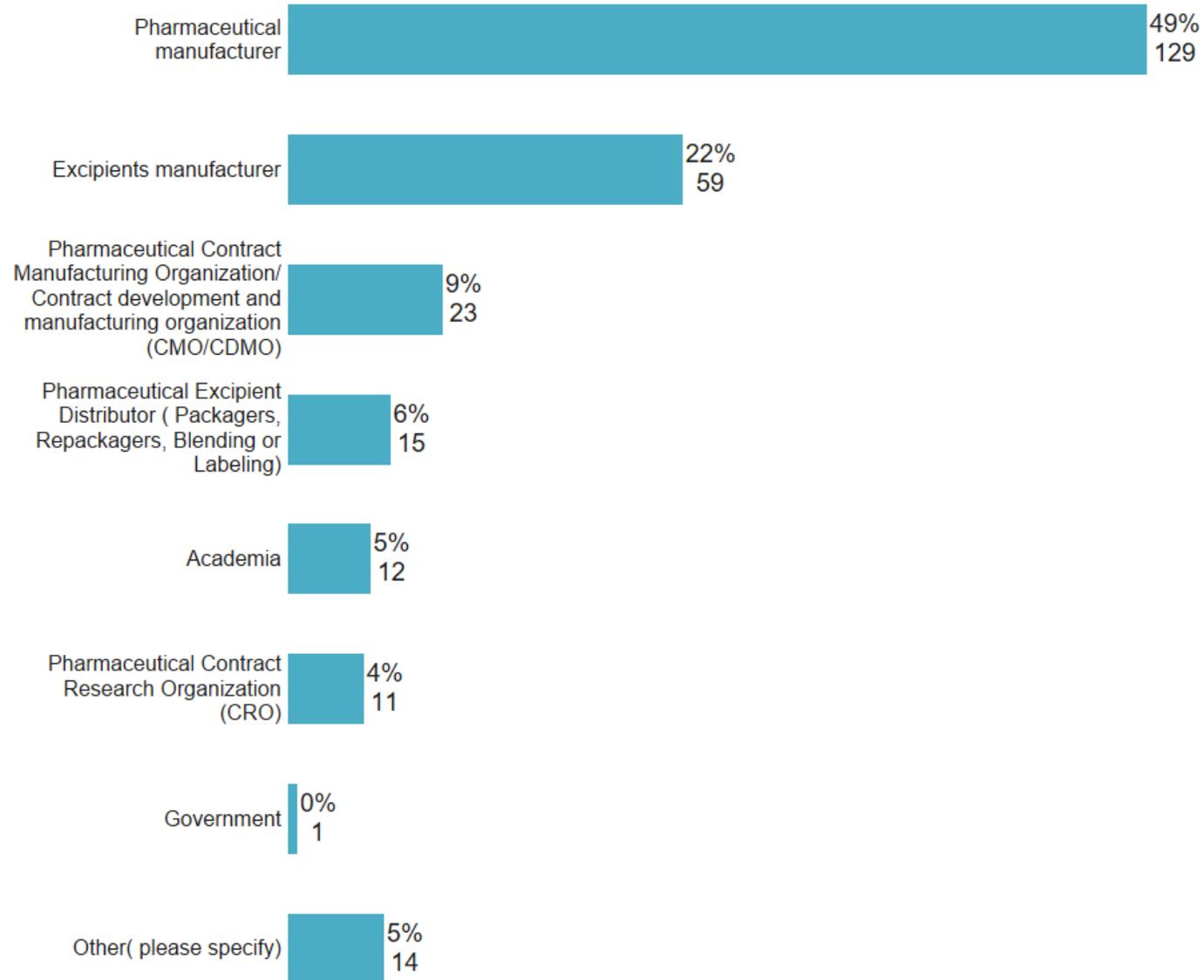
Respondent Profile: Manufacturer/Supplier Type



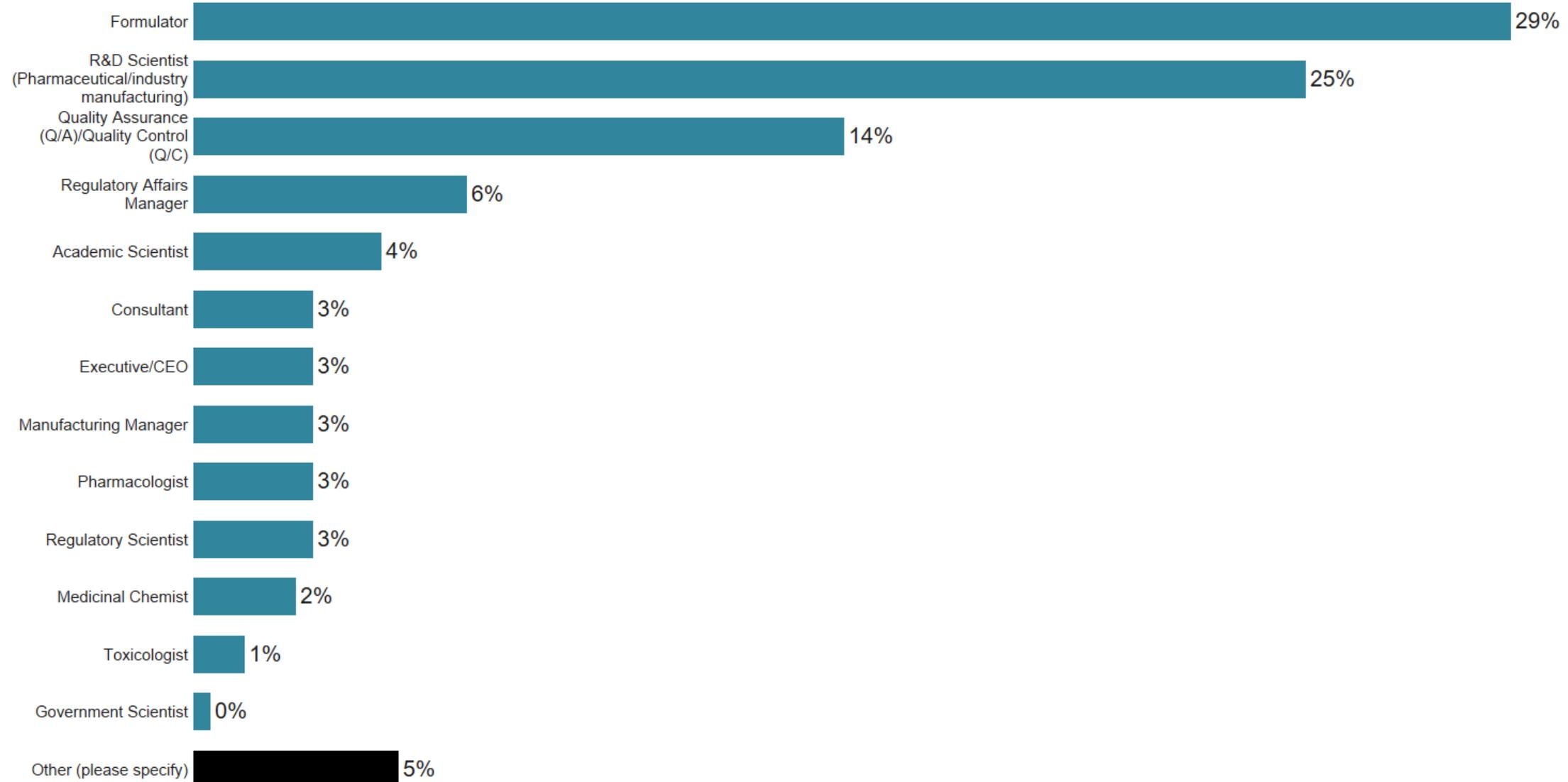
Nearly two-thirds of respondents work for companies that manufacturer or supply branded small molecule drugs.



Respondent Profile: Organization Type

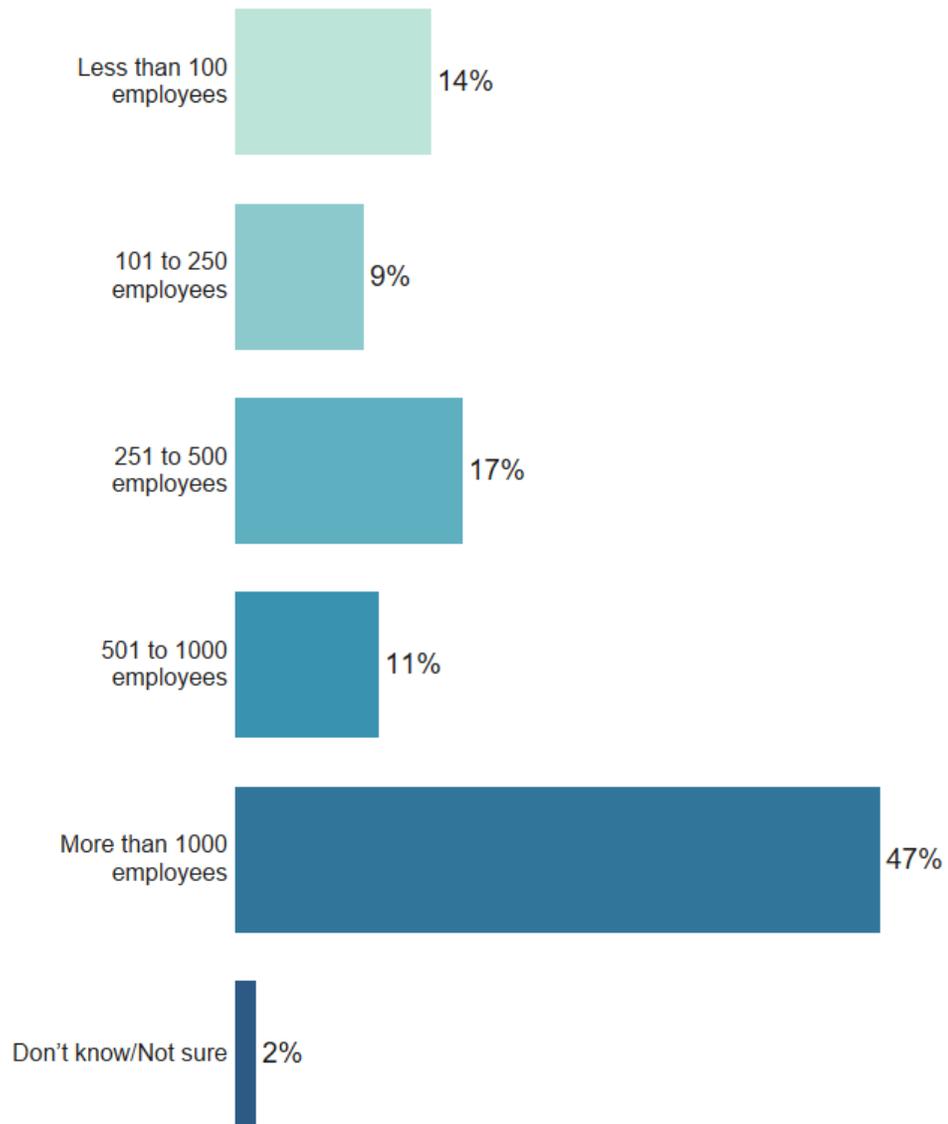


Respondent Profile: Primary Role



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

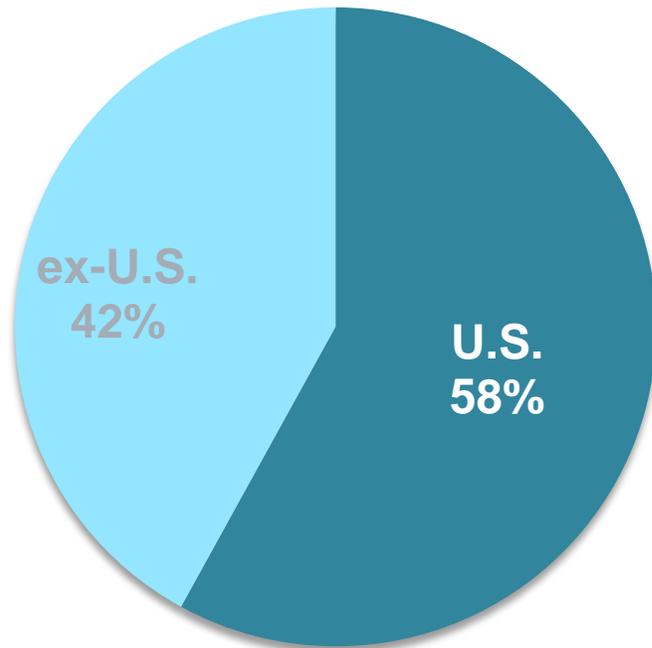
Respondent Profile: Company Size



Qualified respondents were more likely to work for large companies*:

- More than 500 employees 59%
- 500 or less employees 41%

Overall Respondent Profile: Regions



Geographic Regions		
	Count	%
United States	153	58%
Europe	47	18%
India	33	13%
Others	31	12%

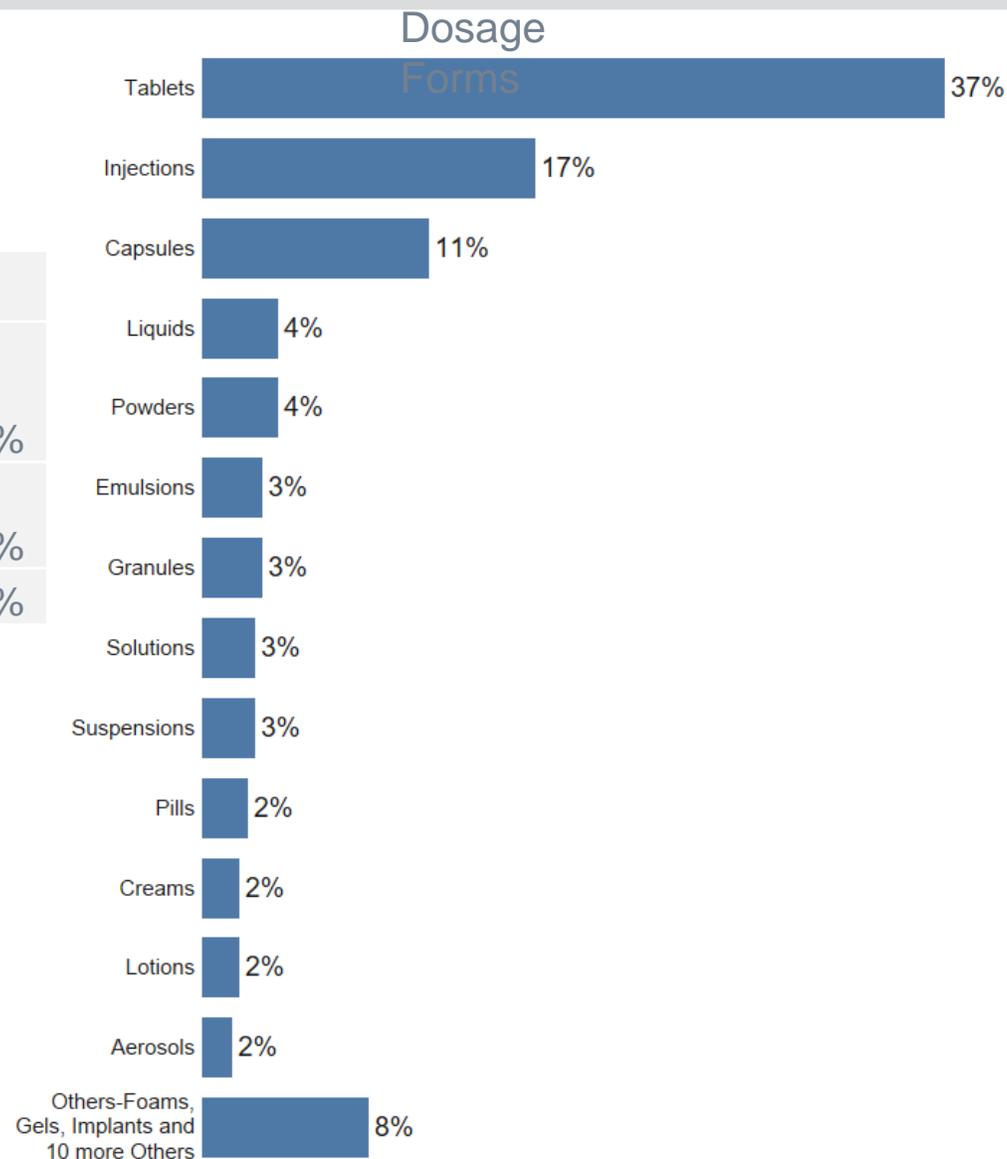
Please select the country in which you work. (n=264)

Overall Respondent Profile: Formulation Experience and Dosage Forms



Formulation Experience

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%



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

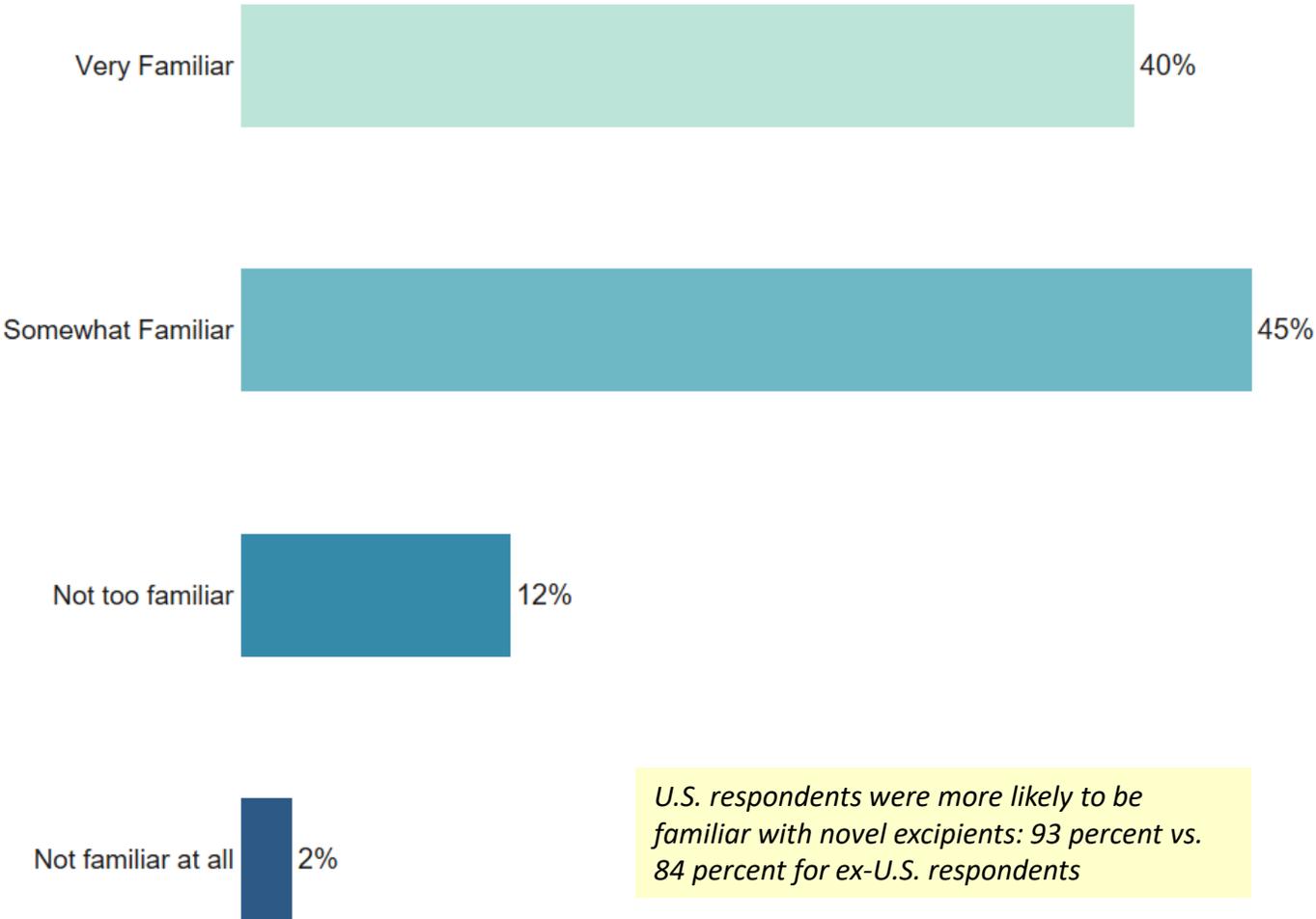
Q3. Please select the dosage form you have the most experience formulating. N=264

1. Familiarity with and Use of Novel/New excipients



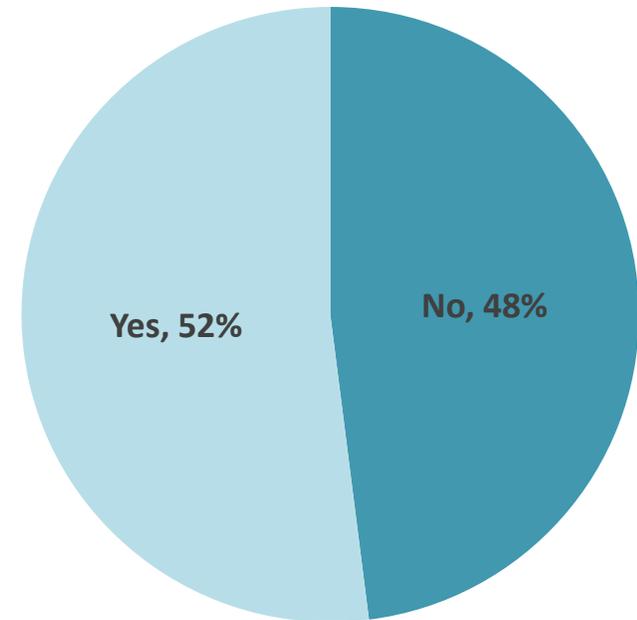
New/Novel Excipients: Familiarity & Use

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

Used new/novel excipients in the past five years

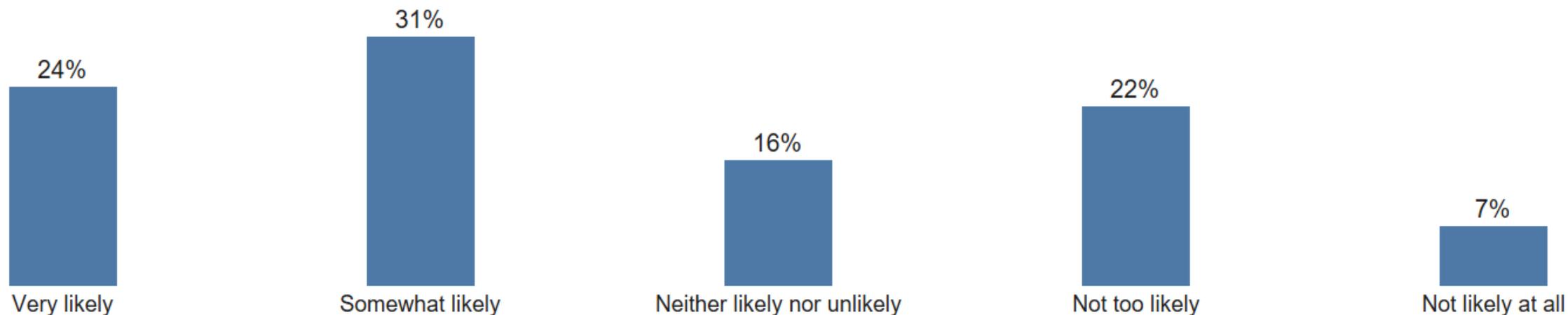


Q9a Prior to this survey, how familiar were you with New/Novel Excipients? n= 264. Q9 In the past five years, have you or someone you have supervised used novel excipients for the U.S. market in advancing a formulation through drug development? N=258

New/Novel Excipients: Expected Use



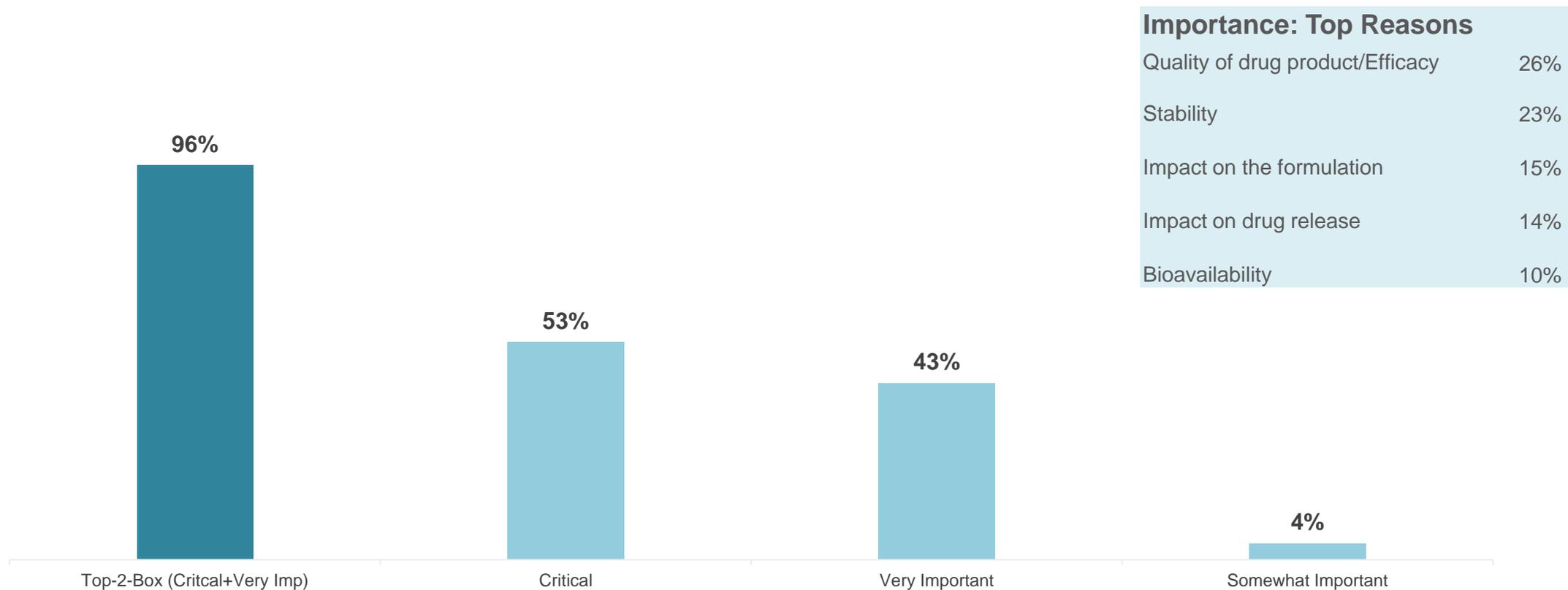
- In the next five years, more than half of respondents (55 percent) expect to use novel excipients for the U.S. market, assuming there is no change in the current U.S. regulatory landscape.
- Nearly a third (29 percent) of respondents are not likely to use novel excipients in the next five years.
-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



Importance of Excipients in Advancing Formulation



The overwhelming majority of respondents (96 percent) believe that excipients are at least *very important* in advancing a formulation through drug development.

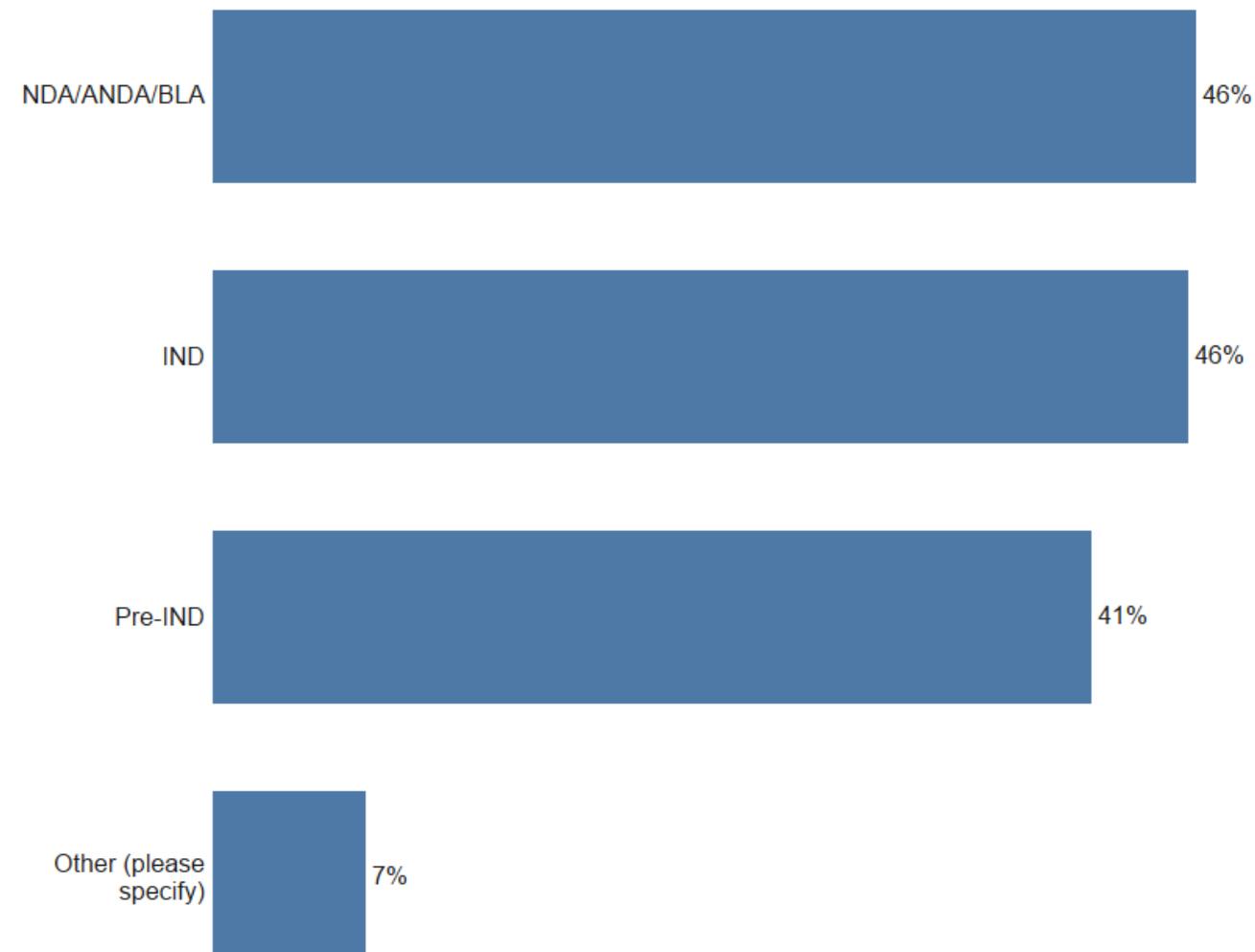


Q4 For dosage form {Q3/SelectedChoices}, which you indicated having the most experience formulating, please rate the importance of excipients in advancing a formulation through drug development. (n=253). Q4A Please elaborate on why you believe excipients are {Q4/SelectedChoices} in advancing a formulation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

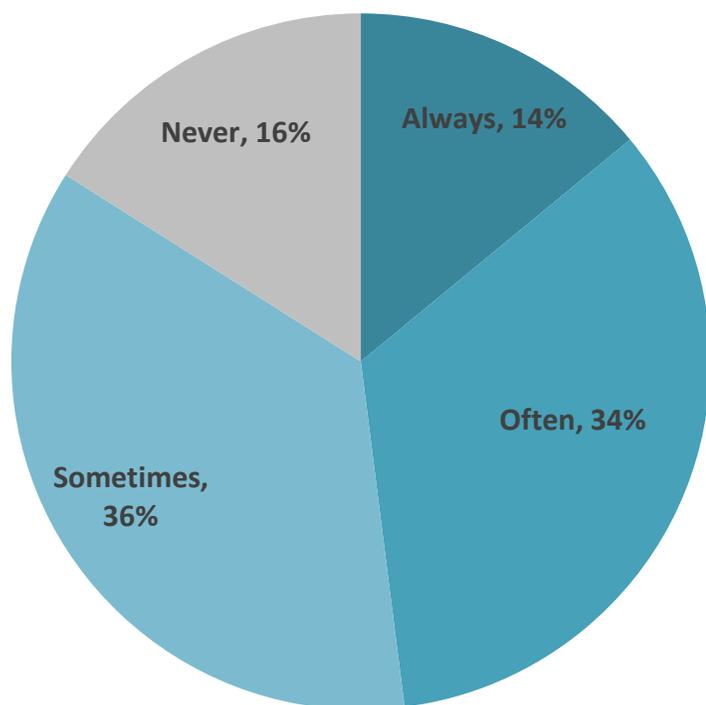


2. Limitations of current excipients



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	
Excipient not used in an approved drug in selected dosage form	54%
Unable to maintain stability of final drug product	36%
Unable to overcome bioavailability issues	33%
Unable to overcome solubility/permeability issues	32%
Other	6%

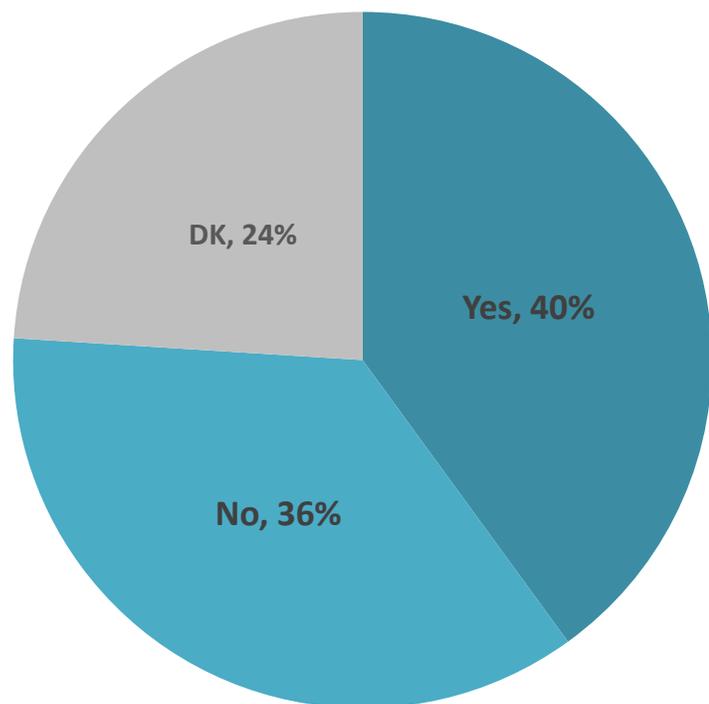


3. Types of Limitations and Reasons

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.



53% had to reformulate (excluding DKs)

Reasons for drug development delay	
Unable to formulate a stable delivery of API	57%
Unable to overcome insolubility/permeability of API	51%
Other reasons	12%

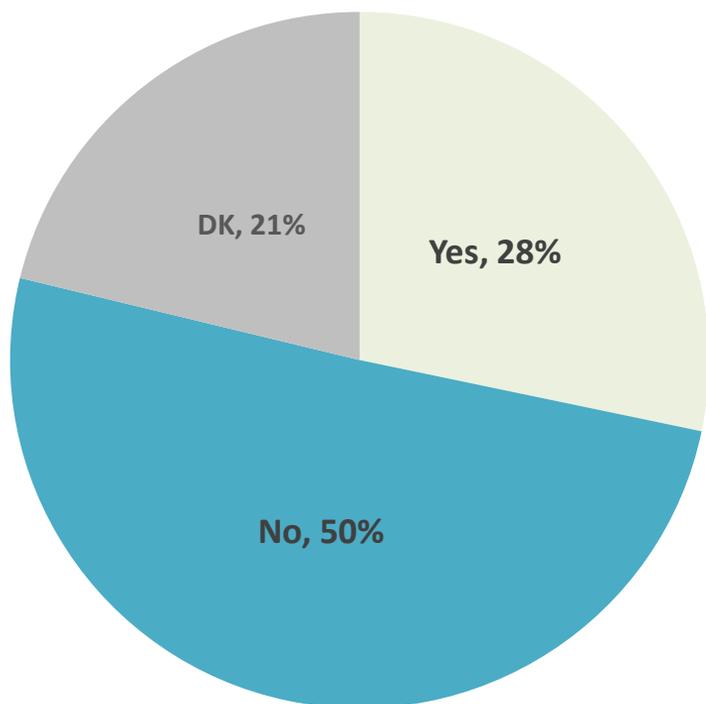
Length of Delay	
1-5 years	64%
< 1 year	34%
> 5 years	2%

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.



36% experienced a discontinuation (excluding DKs)

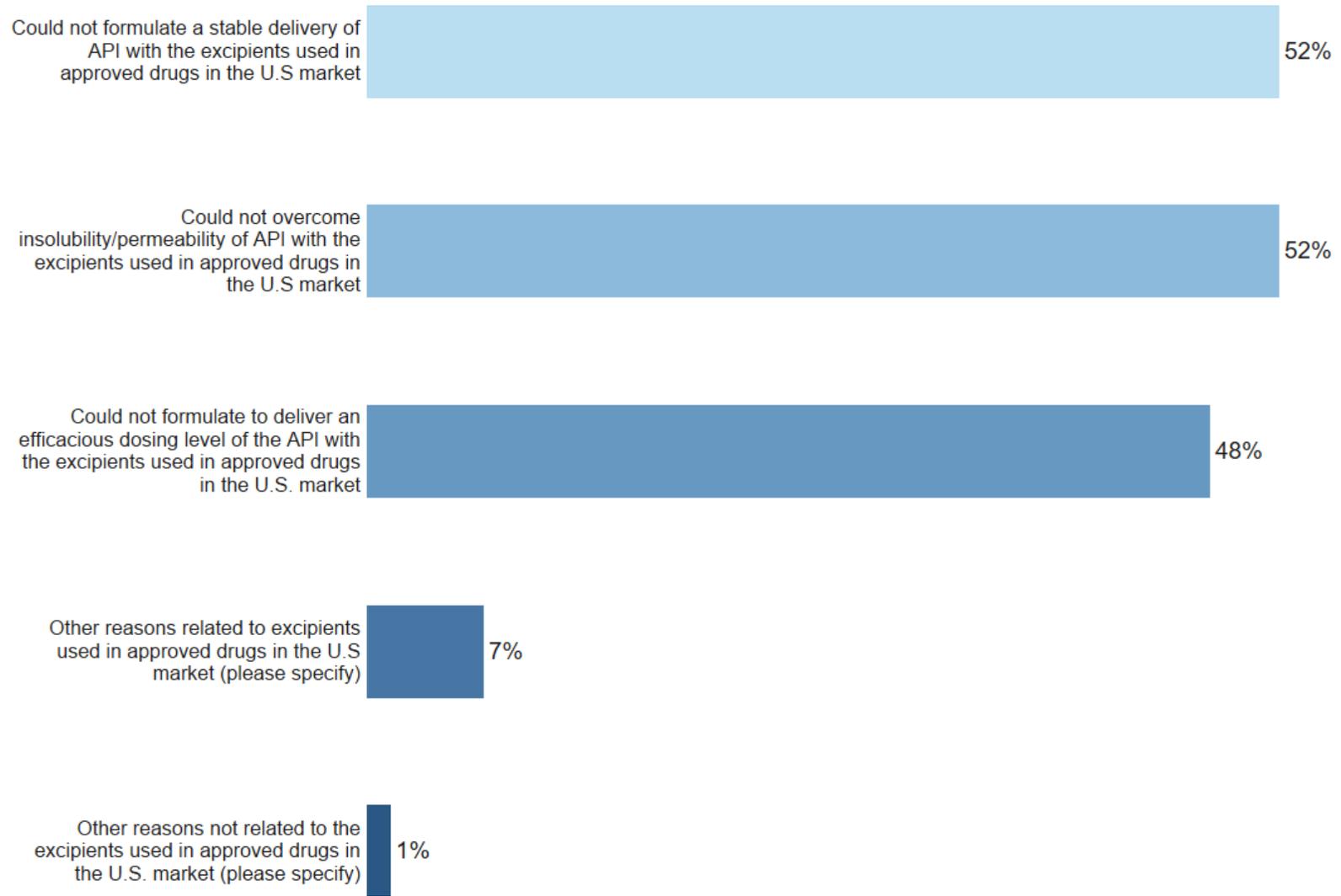
Discontinuation Phase	
Pre-IND	40%
IND	37%
NDA/ANDA/BLA	32%
Other	4%

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/Selected Choices}. 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.



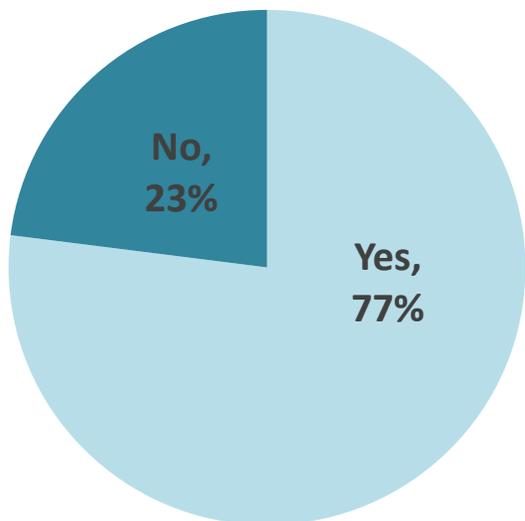


4. Challenges faced with using Novel/New excipients

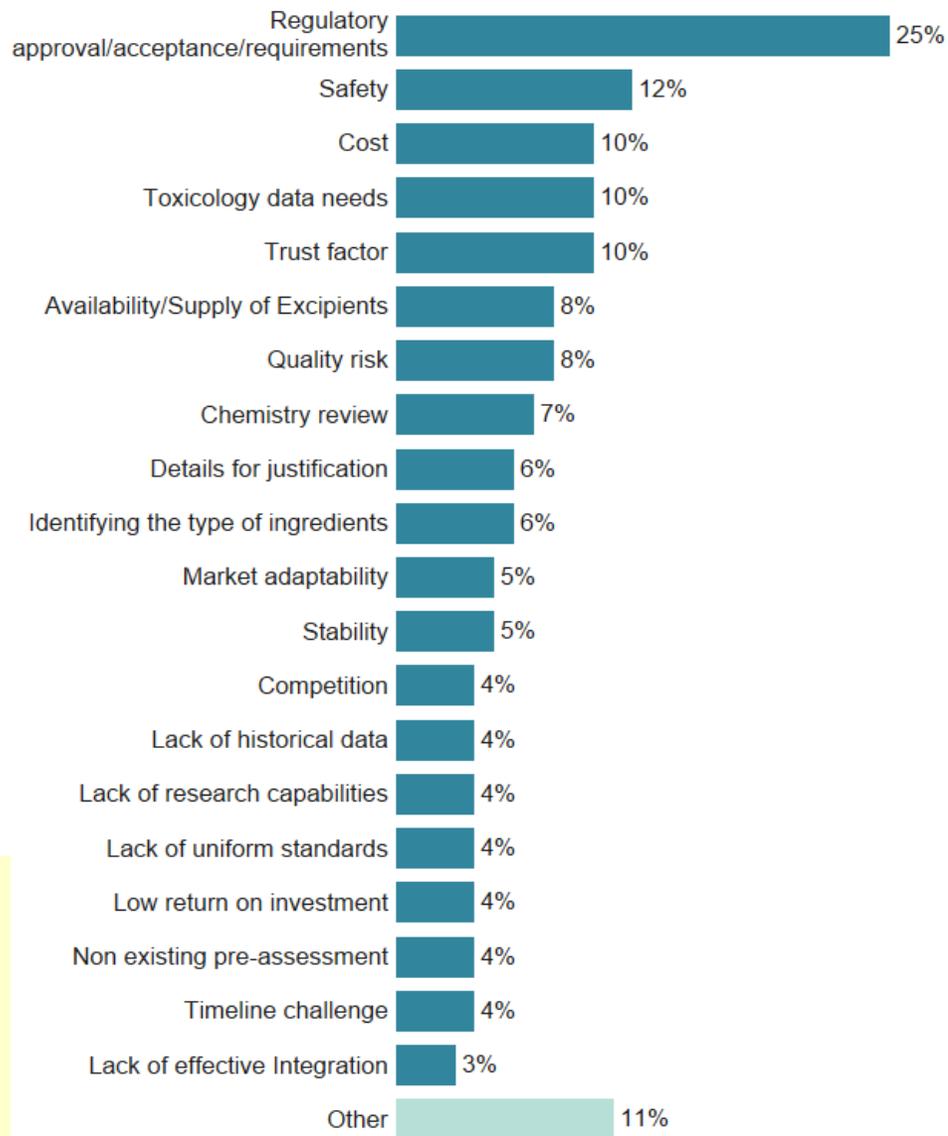
New/Novel Excipients: Challenges



Experienced Challenges using new/novel excipients



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.



- 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.

5. Cross Tabulations of Results

By Manufacturer

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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