Excipient Impurities Research

Excipient Impurities 2018 Survey
Final Summary

October 2018

Objectives & Methodology

- Survey feedback will guide the USP Excipients PUT on development of written standards for Excipient Impurities. Specific research objectives are to:
  - Collect stakeholder feedback on technical issues related to setting specifications for impurities in excipients.
  - Better understand current industry practices around specifying components and impurities of excipients.
- Quantitative survey fielded online August-October of 2018.
- **42 respondents qualified for and completed the survey** (as of Sept. 28, 2018). As the base size is relatively small, results should be interpreted with caution. *Note: The survey will remain active until the end of October 2018.*
- Qualified respondents had to have 1-conducted or supervised testing organic impurities in excipients used as a component in drug products in the past five years and 2-read the USP Stimuli article, “The Complexity of Setting Specifications for Excipient Composition and Impurities” published in Pharmacopeial Forum (PF) 44(3) [May-June 2018].
- Sample sources included: 1-Contact list of Excipients stakeholders from PF (approx. 4,700), 2-PharmTech subscriber lists (approx. 10,000), 3-Social Media (i.e. survey posted on Twitter/Facebook/LinkedIn), 4-USP.org website and 5-GMI contacts.
- As an incentive, qualified respondents had the option to enter into a drawing for one of five $50 virtual gift cards.

Excipient Impurities 2018 Survey
Summary (Updated 4/21/20)

1. The vast majority of respondents (87%) believe that updating USP specifications for excipient composition and impurities is important.

2. Specific impurities tests in monographs are the most commonly used USP-NF resources for testing impurities in excipients (by nearly 8 in 10).
    - About a quarter “never use” General Notices 5.60 on Impurities and Degradation Products.

3. Nearly all respondents agreed with the proposed definitions in the *Stimuli* article for “Simple Excipient”, “Nominal Component”, and “Added Substances in Official Substances”.

4. More than 6 in 10 respondents said that General Notices 5.60.10 *Other impurities* in USP and NF articles should be updated/clarified.

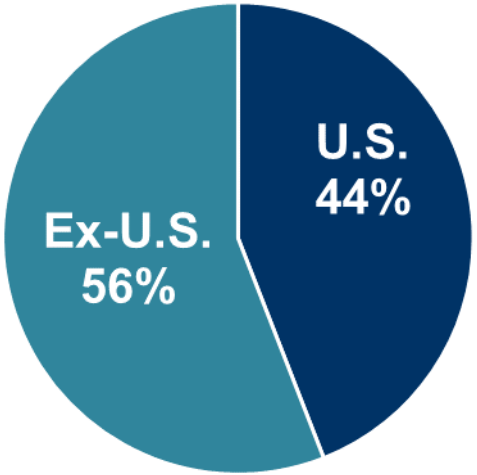
5. Pharmacopeial methods are most commonly used by respondents to test excipients for specific impurities specifications, followed by in-house procedures.
    - COAs and Outsourced Testing are less frequently used.

6. Nearly all respondents would support updating USP-NF to allow use of alternative testing options in the monograph, when one standard cannot be used for a particular material.

7. Three quarters of respondents would be interested in training from USP if a USP-NF general chapter on impurities for excipient were developed.

Quantitative survey fielded online August-December 2018. 47 respondents qualified for and completed the survey. Note, the initial reporting of the survey results was in early October 2018. This updated summary represents results from a small number of additional surveys received after reporting and until the survey officially closed on 12/4/18. ***As the base size is relatively small, results should be interpreted with caution.***

Overall Respondent Profile: Regions

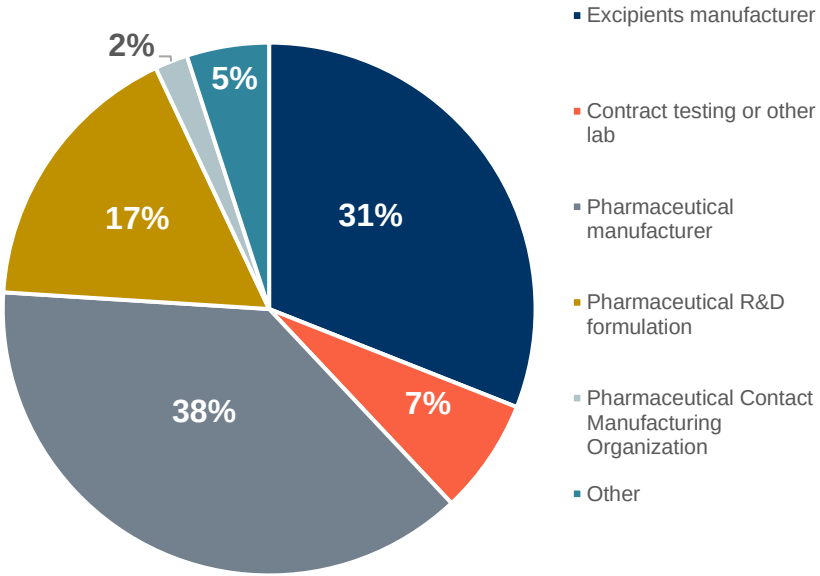


Top Geographic Regions By Frequency of Survey Response		
	Count	%
United States	15	44
China/Taiwan	1	3
India	8	24
Brazil	2	6
Germany	3	9
South Korea	1	3
United Kingdom	2	6
Other	2	6

Please select the country in which you work. (n=34)

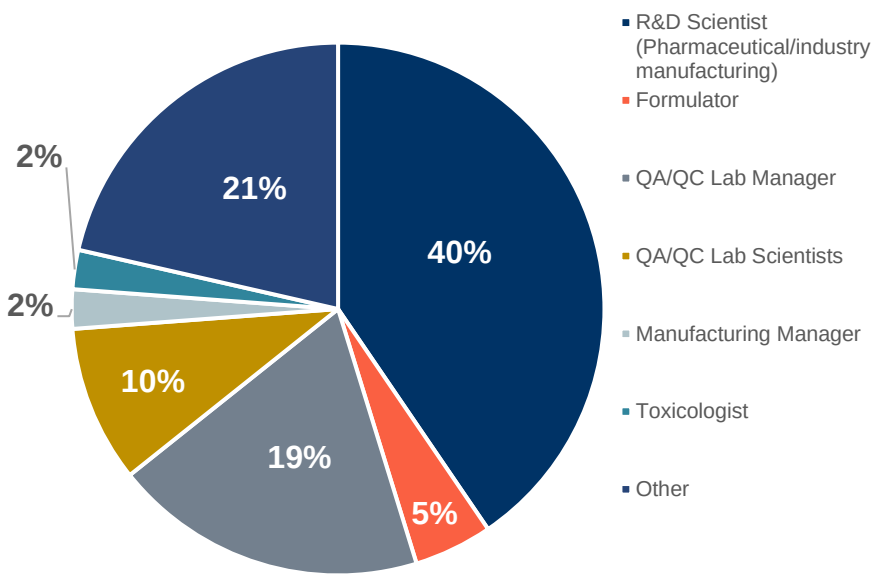
Overall Respondent Profile: Company Type and Role

Type of Company for Which Respondent Works



Q5 Please describe your organization/company for which you work (n=42)

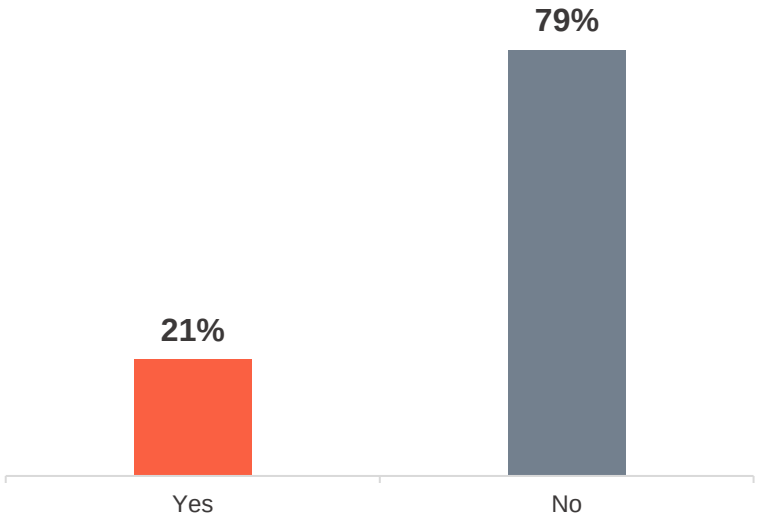
Primary Role at Company



Q6 What is your primary role at your company? (n=42)

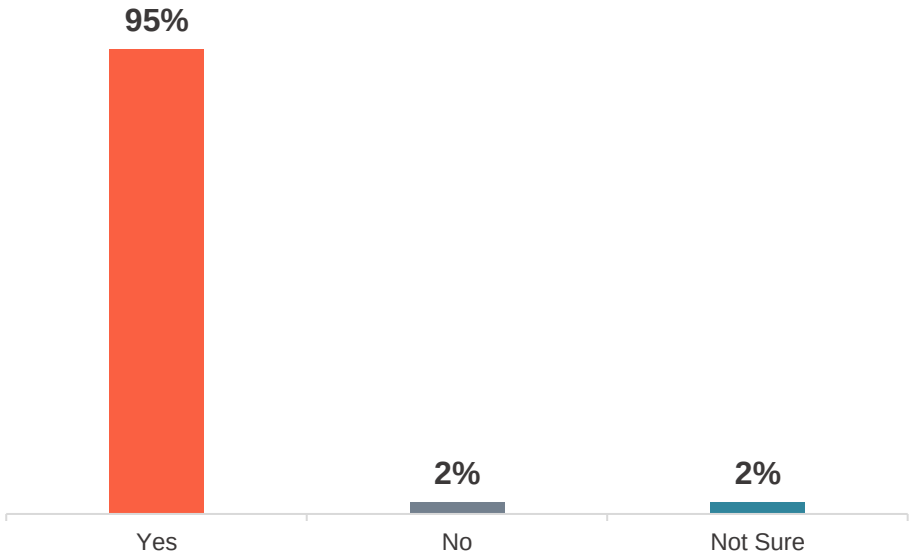
Overall Respondent Profile: Interaction with USP

Whether is or Served as Committee/Working Group Member for USP or other pharmacopeia?



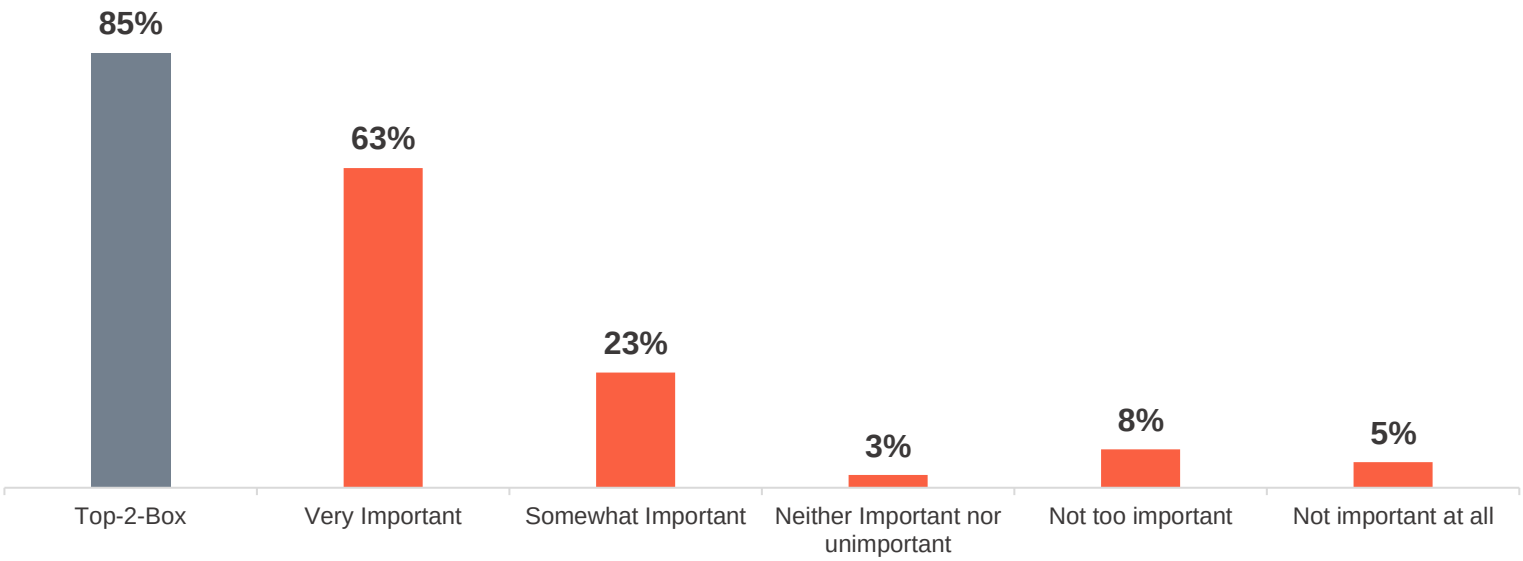
Q7 Are you or have you served as a Committee/Working Group Member for USP or other pharmacopeia? (n=42)

Whether Use –at Least Once a Year- USP-NF for purposes of excipient impurity testing



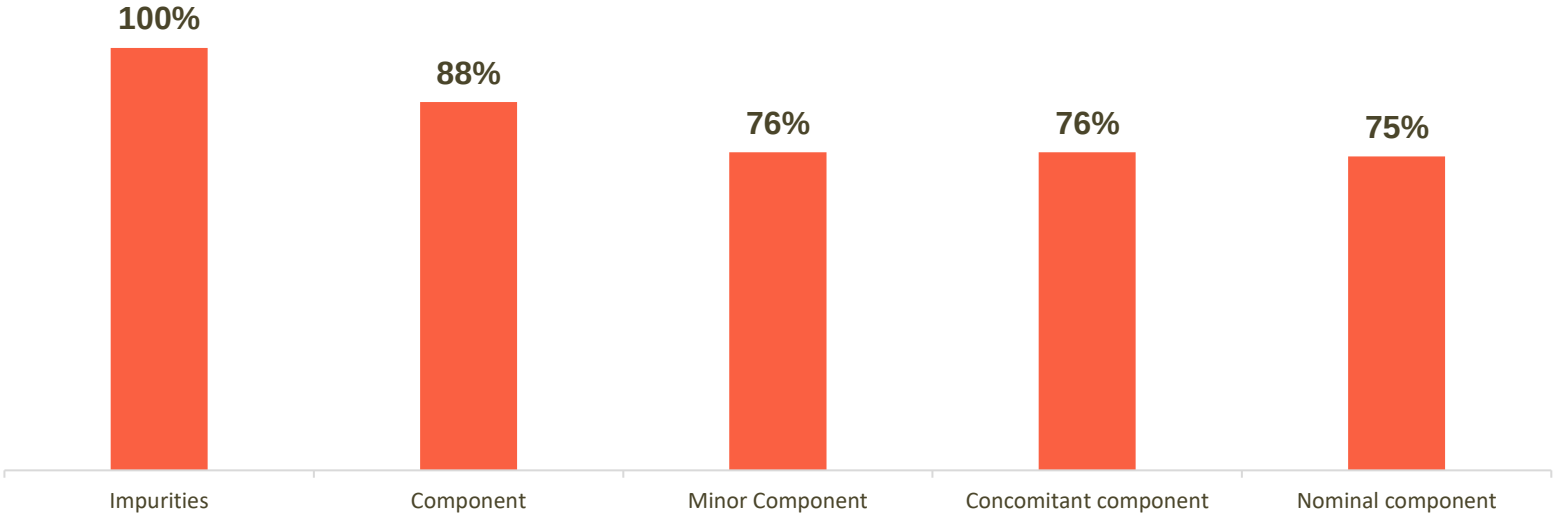
Q8 In the past 5 years, have you used--at least once a year--the USP-NF, the United States Pharmacopeia (USP) and the National Formulary (NF) (including monograph /general chapter test procedures and associated reference standards) for purposes of excipient impurity testing? (n=41)

Finding 1. 85% said it is very/somewhat important to update USP specifications for excipient composition and impurities



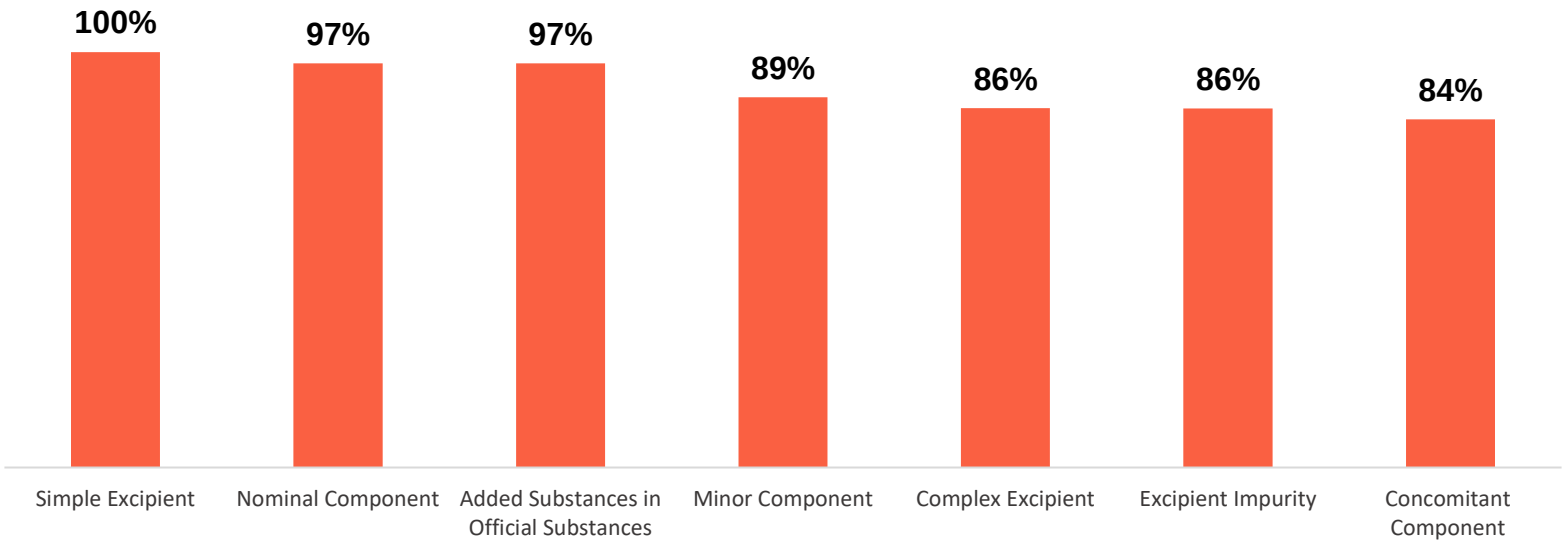
Q9 In your opinion, how important is updating USP compendial specifications for excipient composition and impurities for determining the quality of pharmaceutical excipients? ***"Top-2-Box" percent reflects top-two scores (5 & 4) on a 5-point "Importance" scale.*** *(n=40)*

Finding 2. 88% or more were very/somewhat familiar with the terms "component" and "impurities" for describing excipient composition



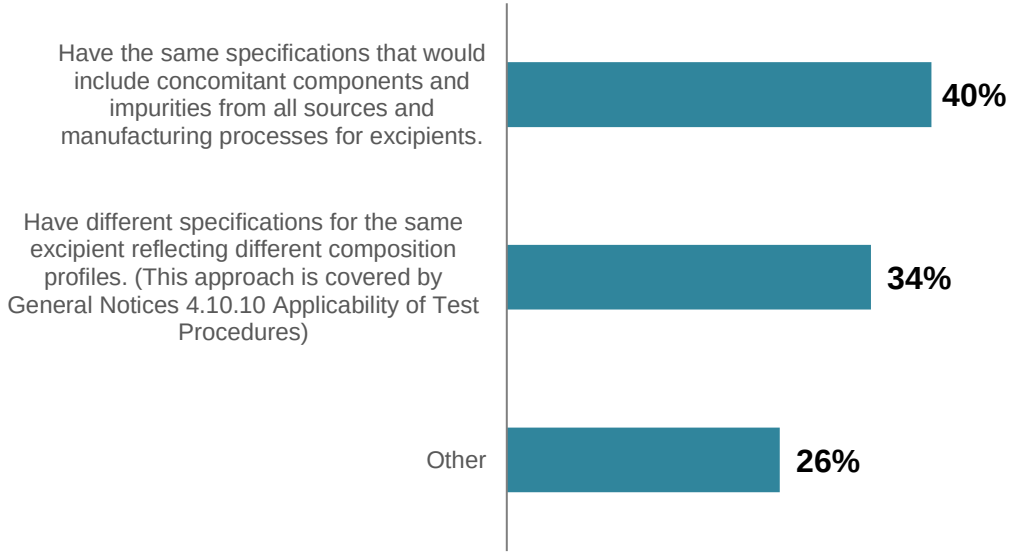
Q10 To what extent are you familiar with the following terms, component, nominal component, concomitant component, impurities, and minor component for describing excipient composition? ***Findings reflect top-two scores (4 & 3) on a 4-point "Familiar" scale.*** *(n=40)*

Finding 3. Nearly all respondents agreed with the proposed definitions for Simple Excipient, Nominal Component, and Added Substances in Official Substances



Q11 Please indicate your level of agreement with the following USP Pharmacopeial definitions for a pharmaceutical excipient proposed in the Stimuli article published in Pharmacopeial Forum (PF) 44(3). ***Findings reflect top-two scores (4 & 3) on a 4-point "Agree" scale.*** *(n=37)*

Finding 4. There is no clear preference on the proposed approaches to resolve differences in sources and manufacturing processes



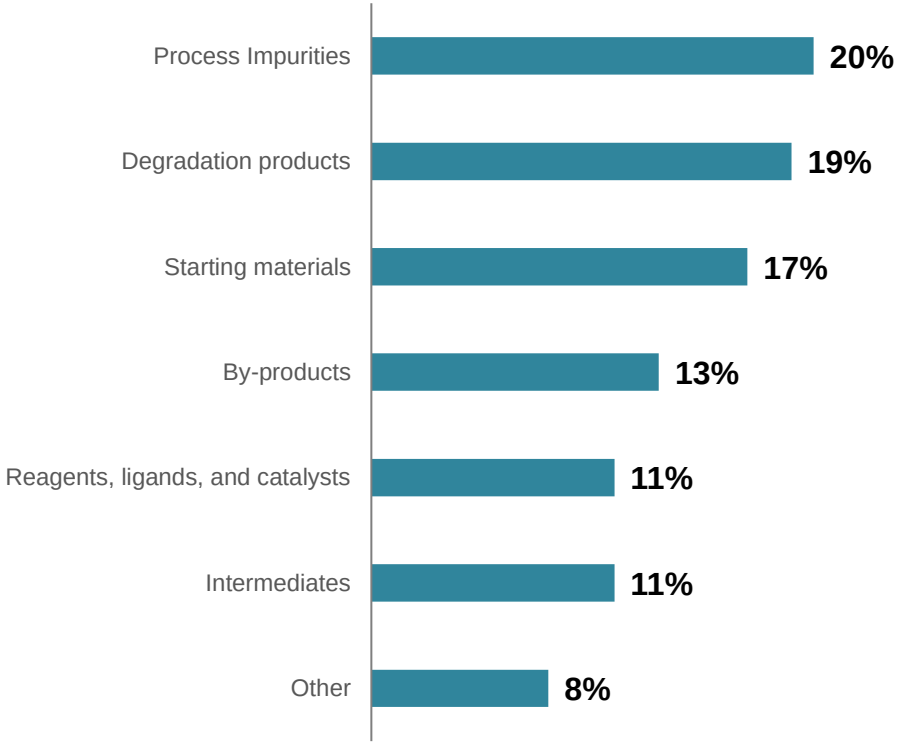
Q12 In your opinion, which is the best approach that USP should take in order to resolve differences in sources and manufacturing process potentially leading to different composition and impurities profiles…? Please select one. (n=35)

Finding 4. "Other" approaches: Respondent Verbatims

- *Alternate method, under same monograph (Flexible monograph approach)*
- *USP should not try to cover all potential concomitant components or impurities in monographs.*
- *A very good question. I'm not 100% sure...it sounds like different specifications right now...if compositions are different.*
- *Same NF specifications should be applied; however, I do not believe each potential concomitant component or impurity must be included. It is the pharmaceutical developer's role to identify which parameters of an excipient are critical and to provide the supportive data to health authorities for evaluation. Having additional non-relevant information leads individuals to think excipient quality evaluation is unnecessary.*
- *Flexible monograph approach*
- *Both approaches may be used depending on the overall difference in the excipient quality due to differences in source/manufacturing process. Smaller deviations: one monograph, totally different impurity profiles (natural vs. synthetic): separate monographs*
- *Do not attempt to control, unless the presence of those substances are a risk to health and safety.*
- *Both. Use one or the other on a case by case basis. It depends on the complexity of the excipient and the situation.*
- *For plant and animal derived substances it does not make sense to define impurities like herbicides, environmental contaminants, antibiotics in the USP. In this case reference to the food law taking into account global acceptance (Codex Alimentarius) is the way forward. Only when considering non oral routes of administration it might be considered to set up compendial tests plus limits.*

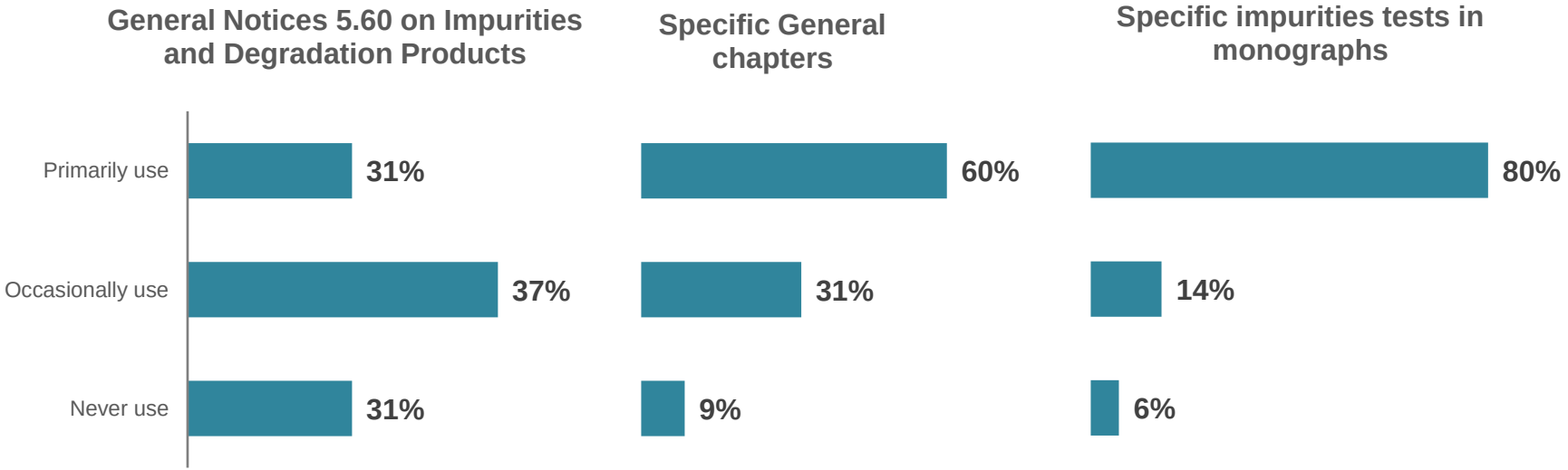
Q12 In your opinion, which is the best approach that USP should take in order to resolve differences in sources and manufacturing process potentially leading to different composition and impurities profiles…? Please select one. (n=35)

Finding 5. USP-NF is most frequently used for testing degradation products and process impurities



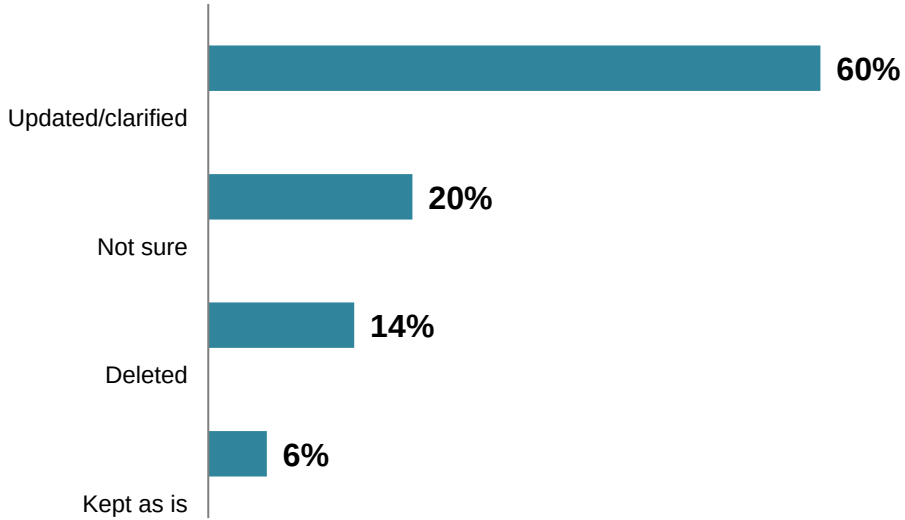
Q13 Do you use the USP-NF for testing the following impurities in pharmaceutical excipients? (Please select all that apply.) (n=17 for starting materials; n=13 for by-products; n=11 for intermediates; n=20 for process impurities; n=19 for degradation products; n=11 for reagents, ligands, and catalysts; n=8 for other)

Finding 6. Specific impurities tests in monographs are the most commonly used USP-NF resources for testing impurities in excipients



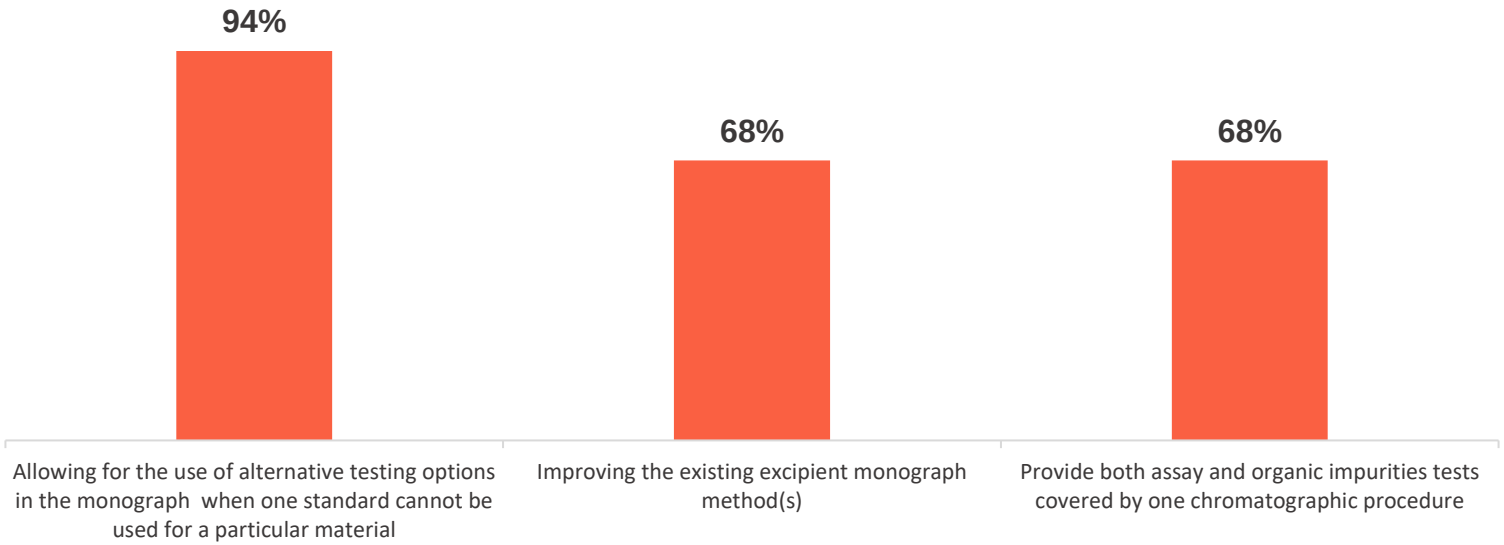
Q14 To what extent do you use each of the following USP-NF resources primarily for testing impurities in pharmaceutical excipients? (n=35)

Finding 7. 60% said that general notices 5.60.10 *Other impurities* in USP and NF articles should be updated/clarified



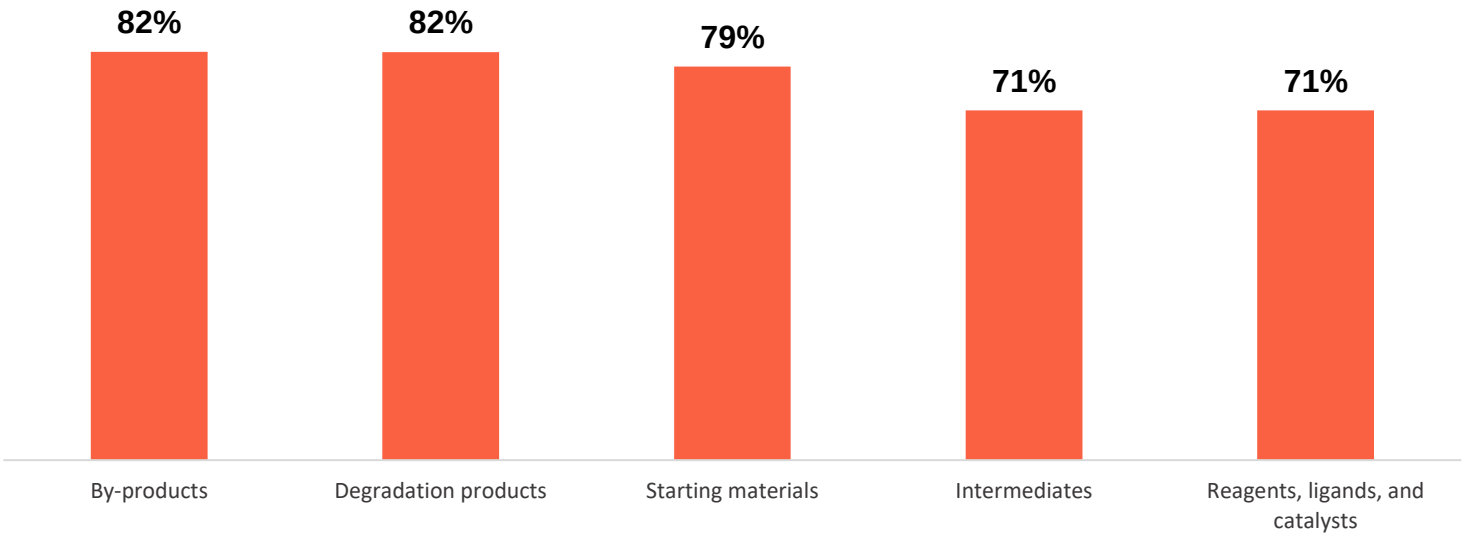
Q15 General notices 5.60.10 Other impurities in USP and NF articles contains a requirement for other impurities, not detected by the compendial chromatographic procedures, that is applicable to excipients. Please provide your opinion whether this section needs to be: (Select one) (n=35)

Finding 8. Almost all (94%) would support updating USP-NF to allow use of alternative testing options when one standard cannot be used for a material



Q16 How supportive would you be of adding or updating USP-NF (to include monograph test procedures and reference standards) on impurities for pharmaceutical excipients from the following options. ***Findings reflect top-three scores (7, 6 & 5) on a 7-point "Supportive" scale.*** *(n=34)*

Finding 9. Approximately 8 in 10 said it would be helpful to add standards for starting materials/by-products/degradation product tests



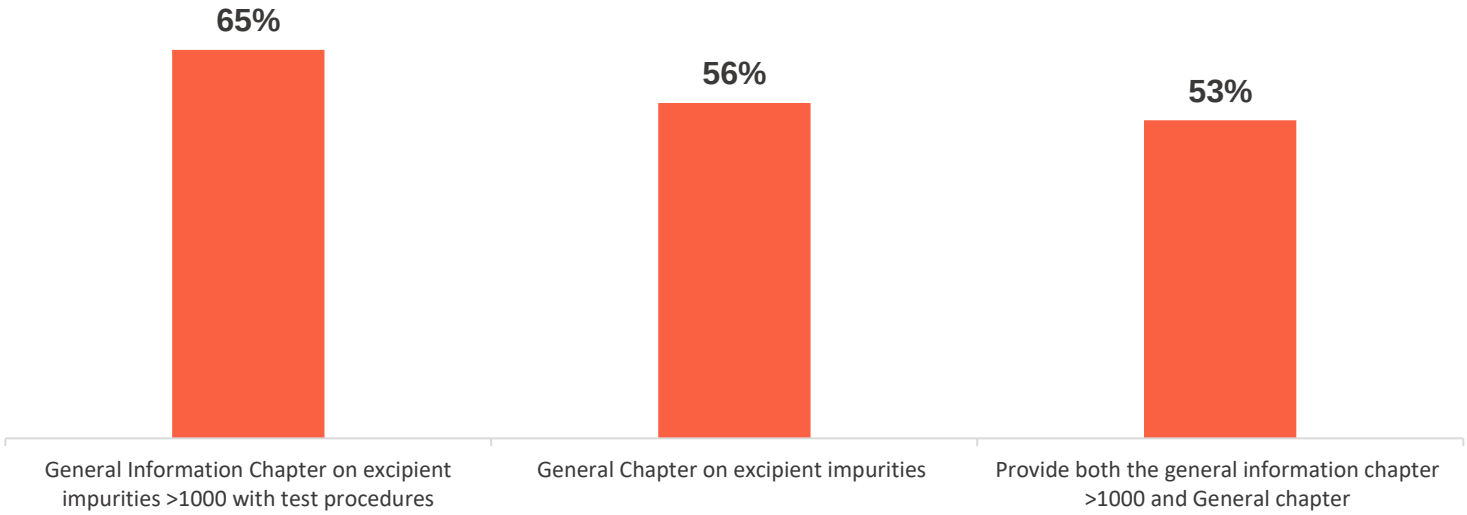
Q17 How helpful would the introduction of standards into USP-NF (including monograph test /general chapter test procedures and reference standards), be to the following impurities tests? ***Findings reflect top-two scores (4 & 3) on a 4-point "Helpful" scale. (n=34)***

Finding 9. “Other” Tests: Respondent Verbatims

- *Old methods related to residual solvents can be updated*
- *Impurities in excipient should be carefully considered as the level of the excipient in the finished product can greatly change the risk. What may be high risk to one finished product may be extremely low risk to another product. One test to much one tested unnecessarily. One test not enough one tested adequately.*
- *USP should focus on specs and methods that are applicable to all grades of the official article and not try to differentiate between grades or manufacturers unless there are known issues that impact safety or quality.*
- *Light and heat degradants*
- *As indicated previously the critical quality parameters are specific to the drug product under evaluation. The addition of any test or reference standard may or may not be a benefit or hindrance depending on the specific needs of the drug product in development.*
- *We were not quite sure what you mean by this question. We assume you mean reference standards when you mention 'standards'.*
- *Impurities*
- *Element impurities*
- *concomitant materials*
- *Maybe water content*
- *Only consider addition of content around substances with known human health and safety risks. (melamine in Lactose, gelatin). There should be no impurities testing expectations for pharmaceutical excipients unless a known safety risk exists.*

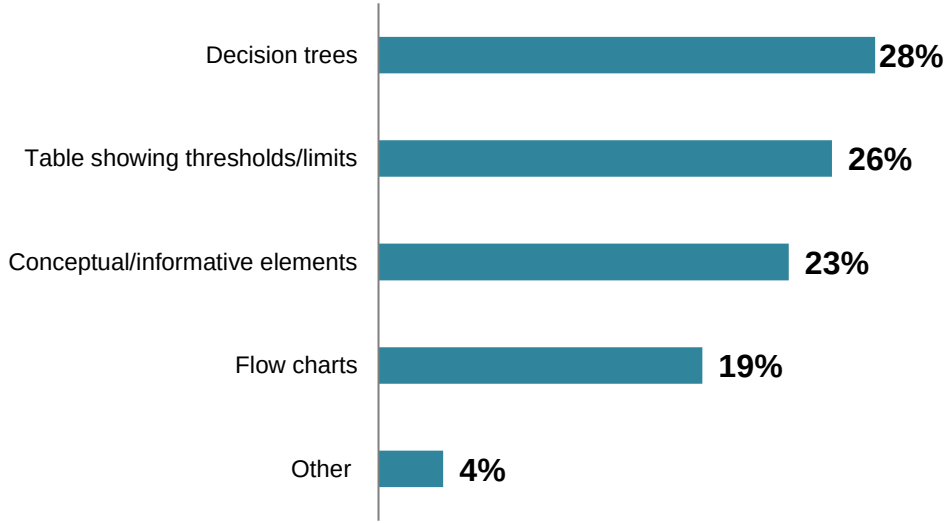
Q29 - Are there any other tests that would benefit with the introduction of standards into USP-NF? Please be as specific as possible. If you don't have anything, please type 'NA'.

Finding 10. 65% supported the development of a general chapter on excipient impurities >1000 with test procedures



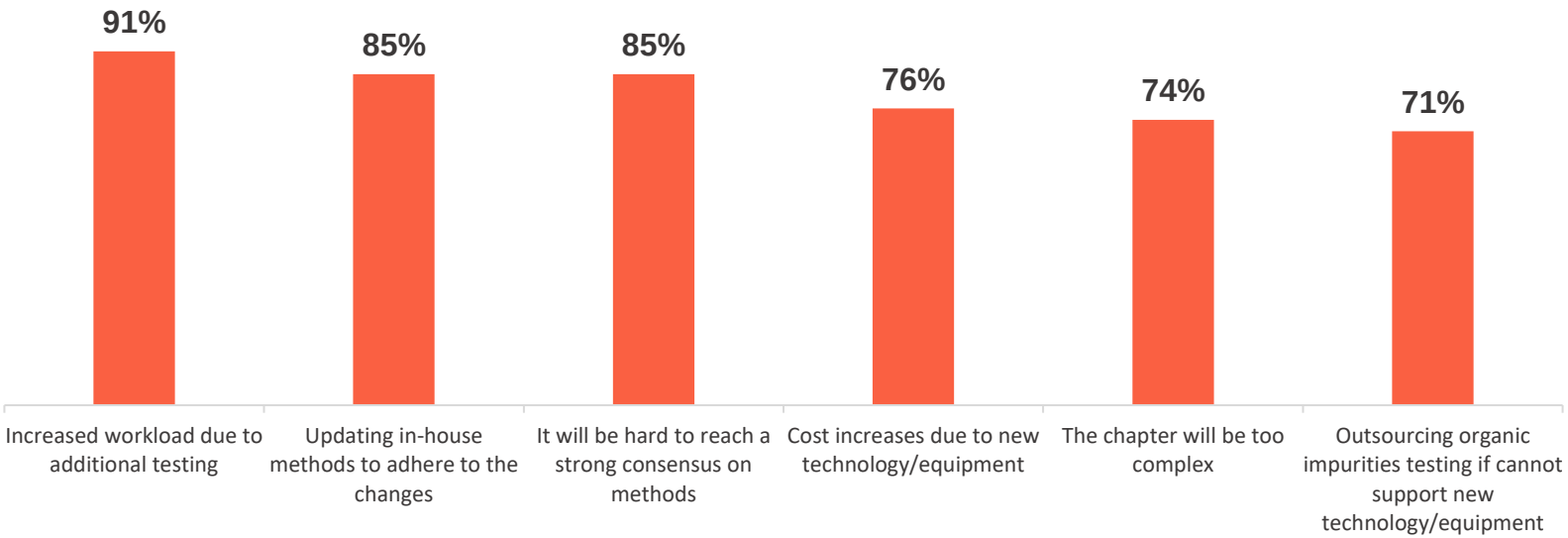
Q18 Please indicate your level of support for USP's development of a General Chapter on Impurities in Pharmaceutical Excipients from the following options. ***Findings reflect top-three scores (7, 6 & 5) on a 7-point "Supportive" scale.*** *(n=34)*

Finding 11. More than half would like to see decision trees and a table showing thresholds/limits in the chapter on Impurities



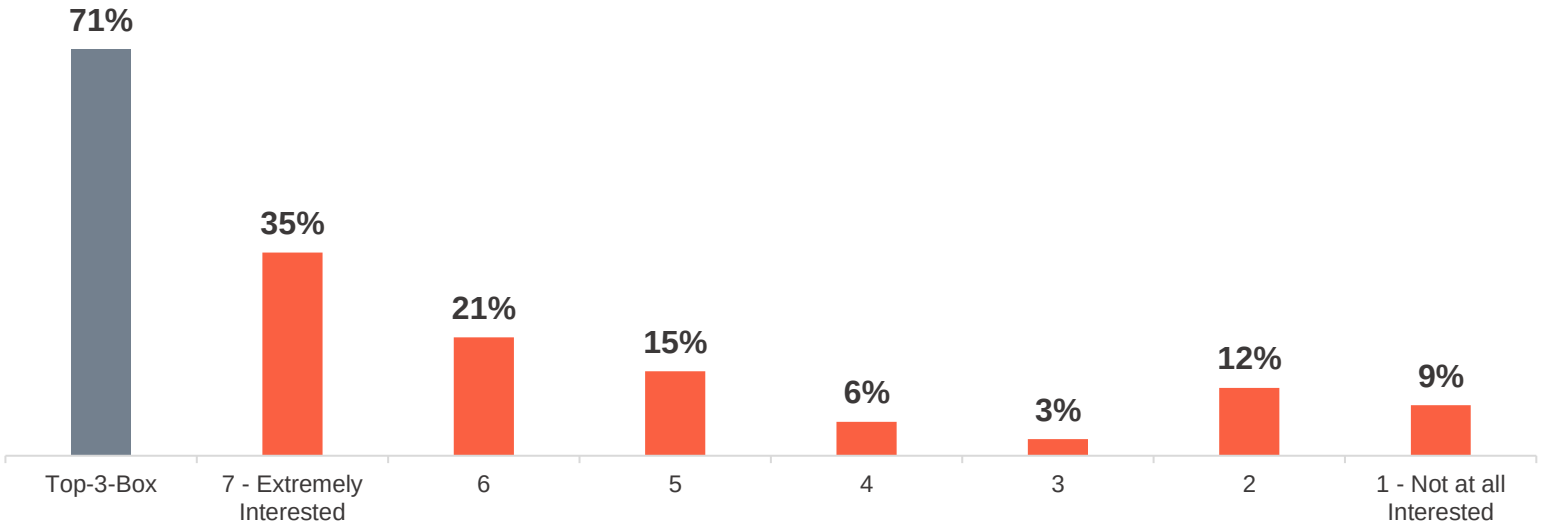
Q19 If supportive, which of the following items would you like to see in a future General Chapter on Impurities in Pharmaceutical Excipients? (n=15 for flow charts; n=23 for decision trees; n=21 for table showing thresholds/limits; n=19 for conceptual/informative elements; n=3 for other)

Finding 12. Increased workload was a concern by nine in 10 respondents, if a chapter on impurities for excipients were developed



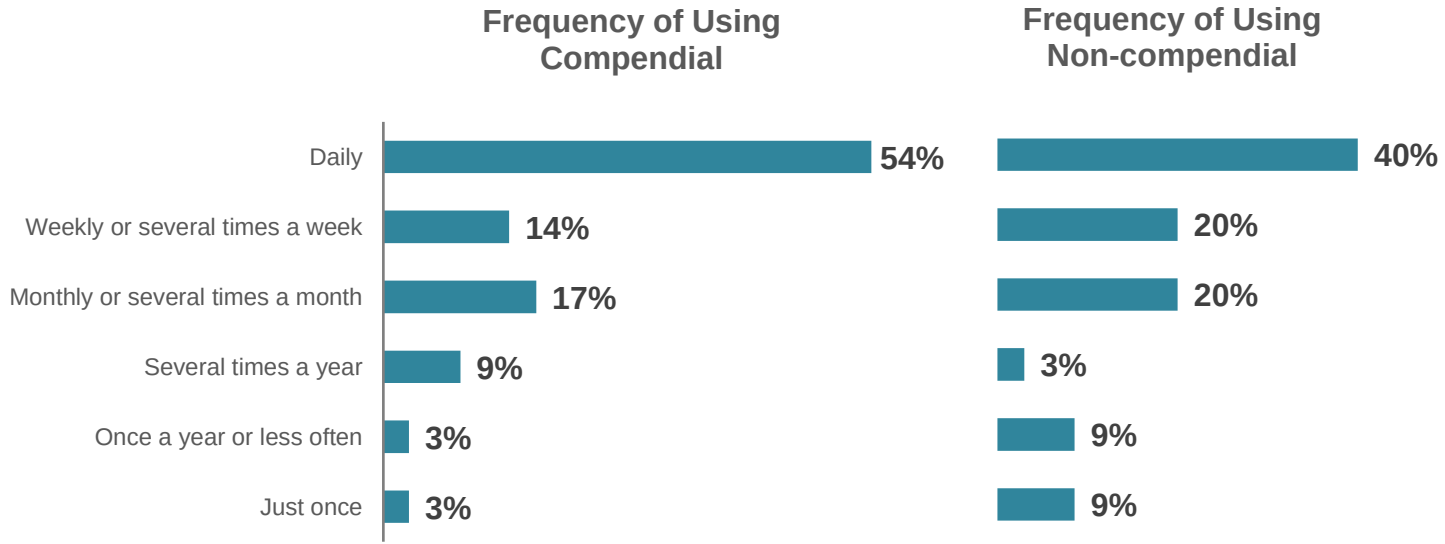
Q20 If a USP-NF general chapter on impurities for excipient is developed, how concerned would you be about the following. ***Findings reflect top-three scores (7, 6 & 5) on a 7-point "Concerned" scale.*** *(n=34)*

Finding 13. 71% would be interested in training from USP if a USP-NF general chapter on impurities for excipient were developed



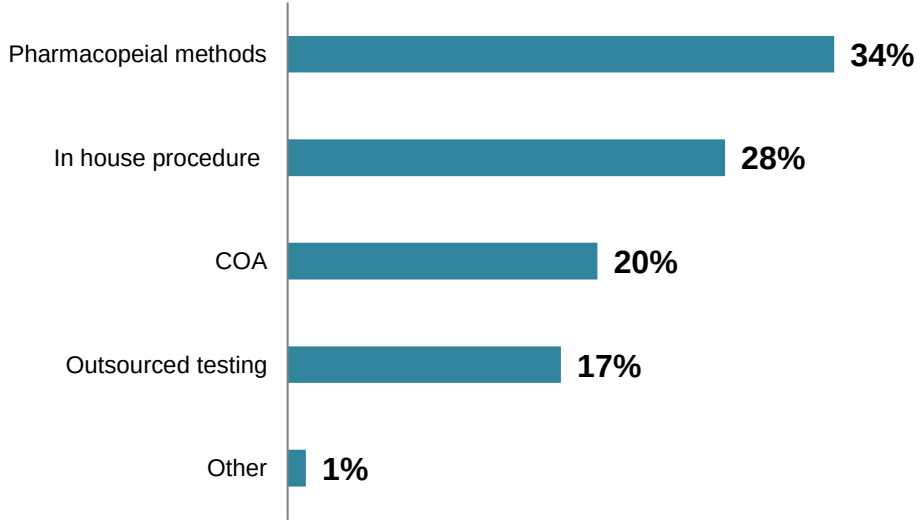
Q21 If a USP-NF General Chapter on impurities for excipient is developed, how interested would you be in taking training from USP on the new standard? ***"Top-3-Box" percent reflects top-three scores (7, 6 & 5) on a 7-point "Interested" scale.*** *(n=34)*

Finding 14. A greater percent of organizations uses compendial (54%) vs. non-compendial (40%) test for pharmaceutical excipients daily



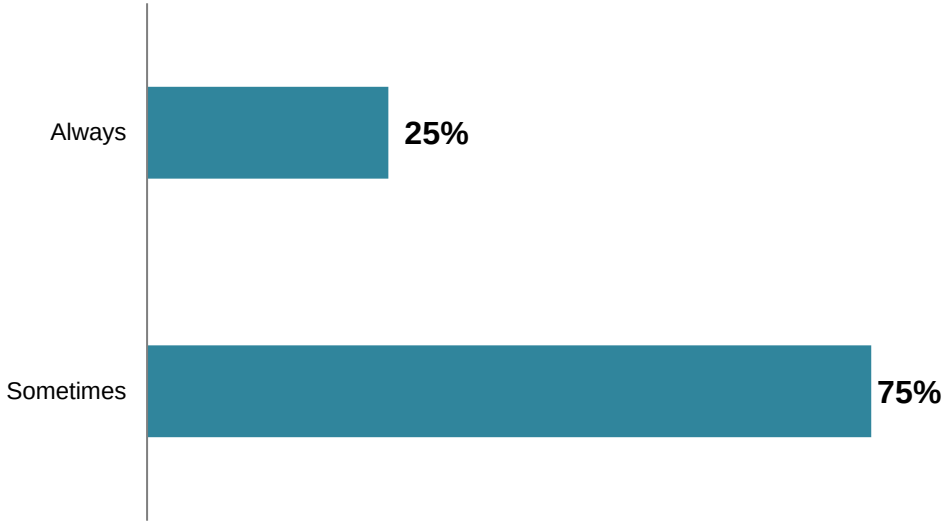
Q22 How often does your organization use assays/impurities test for pharmaceutical excipients? ***Combined "Weekly" and "Several times a week," "Monthly" and "Several times a month," "Once a year" and "Less than once a year"*** *(n=35)*

Finding 15. Pharmacopeial methods (34%), followed by in-house procedures (28%) are most commonly used to test excipients for specific impurities specifications



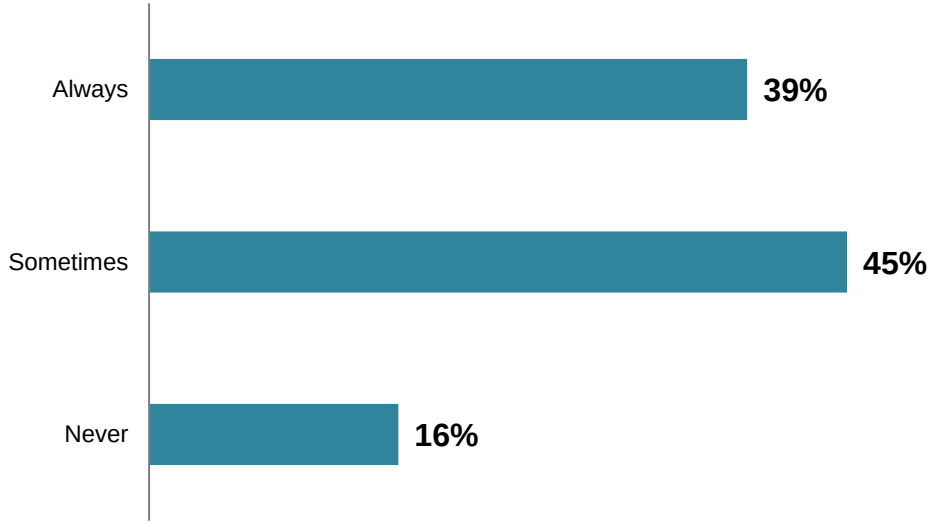
Q23 How does your organization/company TYPICALLY test excipients for specific impurities specifications? (n=17 for COA; n=24 for in house procedure; n=30 for pharmacopeial methods; n=15 for outsourced testing; n=1 for other)

Finding 16. Only a quarter of respondents said they always use COA to confirm impurities in pharmaceutical excipients



Q24 My company uses the information from the COA to confirm Impurities in pharmaceutical excipients: Never, Sometimes, Always (n=16)

Finding 17. Almost 40% said their company always tests incoming excipients to confirm impurities in pharmaceutical excipients



Q25 My company tests incoming Excipients to confirm impurities in pharmaceutical excipients: Never, Sometimes, Always (n=31)

Verbatims: Respondent Views on Setting Specifications for Excipient Composition and Impurities *(Sample)*

The stimuli article is a milestone forward - thank you! But still only a starting point to address the complexity of excipients. Note that the term "by-products" is introduced in the article but not defined. Note that some polymeric excipients need USP-NF grades emulsifiers to be manufactured. These emulsifiers remain (and have to remain) in the excipients commercial forms. I would consider them concomitant components, but they are not identified in the title or definition of the respective monographs, but are to be indicated in the labelling. Note also that for example in the title "Methacrylic acid ethyl acrylate copolymer" the names of the leading impurities show up: namely the monomers. That could be understood as a contradiction to the suggested definition for "Excipient impurity".

1.Element impurities could be taken in account. 2.When one excipient can be used in different routes of administration, for example, can be used in the both oral and injection preparation, the requirement of impurities could be different.

Setting meaningful specifications for excipients requires both understanding of the critical qualities of the excipient and the drug product itself. Therefore, trying to set specifications for an excipient without a corresponding drug product results in a list of tests that may or may not provide meaningful information.

There is some confusion as to the wording of specification between 4.1 and 4.5. The confusion is if a value of 4.1 or 4.5 is acceptable, and between, or not acceptable because it is not between. Please consider different wording of these criteria, NLT 4.1 and NMT 4.5 or "4.1 to 4.5"

Any manufacturing ingredient of an excipient that does not impart functionality should be considered an impurity. This would not apply to additives, which are added for a specific purpose. As a toxicologist, impurities do not denote toxicity.

Q26 Please feel free to provide any additional information or comments that you feel will contribute to USP's understanding of your views on Setting Specifications for Excipient Composition and Impurities.

Verbatims: Respondent Views on Setting Specifications for Excipient Composition and Impurities *(Sample)*

Using a risk based approach would be very helpful in any complex situation like this. an informative general chapter <1000 would be a good start to get the concepts understood and on a wider agenda.

USP needs to stop trying to get so prescriptive. There will be differences between manufacturers and sometimes grades. Unless these impact safety or quality it is outside of USP's scope and has been effectively managed by industry and should continue to be.

The USP should ensure information is gathered from major manufacturers of excipients.

Work with IPEC and use the existing guide lines IPEC has established.

Before the setting of specification for excipient composition and impurities, please set such method, which can be analyst friendly and should not be complicated. Sources should be available easily.

Q26 Please feel free to provide any additional information or comments that you feel will contribute to USP's understanding of your views on Setting Specifications for Excipient Composition and Impurities.

Thank You

Empowering a healthy tomorrow