USP Open Forum – Excipients

Setting Compendial Specifications for Excipient Composition, Organic and Inorganic Impurities

February 11 – 12, 2021

Q & A Summary – Unanswered Questions

The following questions from attendees were not answered at the Open Forum due to time limitations. USP has divided the questions into groups based on similarity to provide brevity and clarity. Please do not hesitate to contact USP if you wish to obtain a more detailed response to your question.

Open Forums and Stakeholder Forums

1. We are concerned that the new Open Forum format does not provide an opportunity for sufficient stakeholder input, as compared to the Stakeholder Forums. What role will stakeholders play in the development of future Open Forum agendas?
    - A1: Open Forums, focus on a timely topic (suggested by USP, Industry, or Regulators) complement other flexible approaches. This was the first Excipient Open Forum open to all stakeholders where USP shared focused-specific content on one topic intended to help inform USP work.
        - We encourage stakeholders to submit topics for discussion on the Stakeholder Forum landing page under (Submit Topic Suggestions). The agenda is derived from the Open Forum event topic.
    - Open forums generally focus on one topic, are 1-2 hours in duration, and about 60% of the scheduled time is allocated for stakeholder dialogue.
    - Open Forums do not have a Planning Committee; they are facilitated by an Expert Committee member or a USP Facilitator.
    - Proactive, issue-driven, intended to help inform USP's work.

2. As this is an Open Forum, will all questions and responses be made available (while keeping the requestor anonymous)?
    - A2: Yes, they will be made available upon completion.

3. Stakeholder forums have a planning committee that includes industry, so why don't you do this for Open Forums? Even though they are topic-focused, stakeholders should have input on content.
    - A1: Open Forum events focus on one topic and are one to two hours long. The focus is presenting the topic, and 60% of the event focuses on listening to gather information. Each Open Forum is initiated based on feedback from stakeholders, and significant time at each Open Forum is focused on hearing

from stakeholders. Planning these events allows USP to react quickly when a topic arises and gain stakeholders' input.

Stakeholder Engagement Tools in General

1. Will Project Teams (PT) be continued on key topics like General Notices and Compendial process improvement (CPI)? If so, when will they get started? These groups should be continued.
    - We want to keep engaging stakeholders on important topics like compendial processes and GN, but some engagement will look different.
2. When can we expect USP to implement these new project teams, etc., to get stakeholders' input?
    - There is not a timeline currently. USP is engaging stakeholders through a variety of tools; at this time, project teams may be formed by the Council of Experts (CoE) Chairperson to address a specific compendial topic. Please see the Rules and Procedures of the 2020-2025 Council of Experts, section eight (External Stakeholder Engagement Activities).

USP Documentary Standard Revision Process and Stakeholder Engagement

The USP Open Forum aimed to level set global stakeholders' understanding of the USP standard-setting process and stakeholder engagement to understand the complexity of setting specifications for excipient composition and impurities. USP hopes that the Open Forum will further engage global stakeholders to help USP determine the next steps. Below are answers to questions and comments.

Q1: USP should be working closely with stakeholders on setting any limits for simple excipients as well as complex excipients. Why would USP handle this differently?

A1: It's not clear from the original question how the approach is viewed as different. USP welcomes a follow-up question for further clarification.

Q2: Will a Working Group be formed for the implementation of Excipient Impurities? What is the strategy and timing for the creation of this Team?

Q3: How will USP determine which experts to reach out to for these Joint Subcommittees?

A2-3: Before USP can consider these activities, the Open Forum served to communicate the questions & comments collected after the publication of the 2018 Stimuli and during the Open Forum to the Excipient Composition and Impurities Joint Subcommittee (JS), who will discuss and plan how to engage further with stakeholders through our existing Stakeholder Engagement

Model. Subsequently, the JS may recommend to the Excipients Expert Committees (ECs) the formation of a Project Team and/or call for candidates for Expert Advisors. Stakeholders' expertise and experience will be the main criteria for the selection of Project Team members and Expert Advisors.

Additionally, volunteers are requested from the governing ECs to serve on the JS. Expert Advisors may be engaged to provide additional expertise and assist in the development of a standard.

Q4. Previously, USP agreed that a mechanism is needed to support collaboration between USP, FDA, and industry on excipient topics. USP proposed the formation of an advisory panel or similar way to bring stakeholders together. When can USP commit to industry to establish a focus group for excipient stakeholders?

A4: USP continues to collaborate with its stakeholders through the existing engagement model to convene the right experts at the right time, focused on defining and solving a problem. The Open Forum serves as USP's commitment to engage global stakeholders on this important excipient topic.

Q5: The Stimuli article sought early stakeholder input on impurities. Industry responded and requested further discussion. USP/PDG proposed monograph changes in PF before getting that input. How can industry provide that input before the PF?

A5: The USP PDG landing page provides information on how USP engages its stakeholders through each step in the PDG process and working procedures. Please also see information on the EDQM and JP website for PDG activities.

Q6: Is a stimuli article the first step before publication in PF, or can the chapter then be immediately published as an official chapter?

A6: USP utilizes the Prospectus notice and Stimuli articles as part of the early stages of engagement with stakeholders on standards development. A Stimuli article is not a direct precursor to PF or official publication. New and revised standards must go through PF as an "In Process Revision," which is the marked-up proposal before going to *USP-NF* (except Accelerated Revisions). If comments received on the original PF proposal request the introduction of additional substantial changes, the proposal will be republished in *PF*, potentially more than once.

Q7: As indicated that there would be a PNP for excipients, could a topic for that be the submission guidelines that Hong and Peng mentioned?

A7: The Excipient Stakeholder Forum (Excipient SF) allows excipient stakeholders to meet with USP, similar to the way pharmaceutical stakeholders meet at a PNP stakeholder meeting. The Excipient SF allows

excipient makers, users, and distributors to collaborate with FDA and USP on excipient-related issues for quality, manufacturing, and supply chain topics. It allows for more in-depth discussions that were not primarily the focus of the PNP SF. Updating the USP Guideline for Submitting Requests for Revision to *USP-NF*, Submission Guideline for Excipients could be added as a topic to either an Excipient SF or USP Excipient Open Forum.

Q8: Discussions on composition and impurities should occur with the excipient manufacturers long before anything shows up in the PF for further discussion. When does USP ask the major excipient manufacturers for feedback before PF publication?

A8: USP stakeholder engagement begins with sharing a list of priority excipient monographs for update, followed by outreach to potential sponsors to support a revision. Many companies (both excipient manufactures and pharmaceutical users) are contacted by USP. The PF publication is the primary vehicle for the EC to receive stakeholder feedback and comments from those stakeholders who are not the sponsors. See **USP Guideline for Submitting Requests for Revision to *USP-NF*, General Information for All Submissions** and **USP Guideline for Submitting Requests for Revision to *USP-NF*, Submission Guideline for Excipients** posted on USP website, see below:

- USP Guideline for Submitting Requests for Revision to USP–NF General Information for All Submissions: https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/general-information-for-all-submissions.pdf
- USP Guideline for Submitting Requests for Revision to USP–NF Submission Guideline for Excipients: https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/excipients_rfr_guideline-28apr16.pdf

You can support Excipient standard-setting activities by providing methods and specifications for new and existing monographs (revisions) in *USP-NF*. If interested, please reach out to anyone below.

- Chuck Bates, Consultant, RPO Excipients, chuck.bates@usp.org
- Scientific liaison whose name is listed at the bottom of a monograph (for revisions to existing monographs) in the online USP-NF
- Your local Strategic Customer Development Manager
- USP's authorized distributors in your region/your supplier of USP RS

You can also support excipient standard-setting activities by donating bulk materials, which USP could use to develop reference standards. If interested, please reach out to anyone from below

- Gregory Agoston, Senior Manager, Raw Material Acquisition, GEA@usp.orgGEA@usp.org
- Chuck Bates, Consultant, RPO Excipients, chuck.bates@usp.orgchuck.bates@usp.org
- Scientific liaison listed at the bottom of the monograph (for revisions to existing monographs)
- Your local Strategic Customer Development Manager
- USP's authorized distributors in your region/your supplier of USP RS

Q9: Is there an expectation that manufacturers of excipients provide fully validated methods, or will USP support the costs involved?

A9: See **USP Guideline for Submitting Requests for Revision to *USP-NF*, General Information for All Submissions** and **USP Guideline for Submitting Requests for Revision to *USP-NF*, Submission Guideline for Excipients,** the links to which are provided in A8. For monograph donation or discussion, any relevant information regarding validation and stakeholders' involvement, as well as your topics of interest, contact USP staff whose contact information is provided in A8.

Q10: Is there a database at USP where excipient manufacturers can register for type of products, where we would be open to donate samples and participate in stakeholder workgroups?

A10: You can support Excipient standard-setting activities by donating samples/submitting procedures and specifications in support of a new and/or existing monographs (revisions) in *USP-NF*. If interested, please reach out to anyone from USP staff listed in A8.

Impurities and their limits

Q11. Where does the 0.1% limit come from for unknown impurities for simple excipients? Excipients are not covered by ICH impurity guidelines, and this should not be a standard applied across the board, only when there is a rationale showing this is necessary.

Q12. What is the basis for the NMT 0.1% limit for unknown impurities in simple excipients listed in the USP submission guideline for excipients? How was the limit developed to be applicable to all simple excipients?

Q13: I have the same concerns about using the 0.1% impurity limit for all the other excipients that Dr. Wang talked about in her presentation. You should not use them to set a precedent without a good rationale about the need.

A11-13: For unknown impurities, 0.1% was chosen as a starting point for initiating analytical work on determination of their structures. This limit aligns with the current official **5.60.10. Other Impurities in *USP* and *NF* Articles** that states: "The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater." 5.60.10. Other Impurities in *USP* and *NF* Articles will be considered for revision in the future. As part of USP standard-setting process, USP conducts further evaluation of impurity levels by analyzing commercially available pharmaceutical and food-grade samples and proposes limits for impurities based on the results of statistical tests. For simple excipients that typically exhibit levels of impurities well below 0.1%, a presence of an unknown impurity at 0.1% or higher is considered a starting point for determining a cause for change in an impurity profile. Because the source and toxicity of that unknown impurity are not known, setting a limit higher than 0.1% may be inappropriate; thus, collaboration with appropriate material manufacturers is necessary as their materials are used in FDA-regulated and approved medicinal products. In Dr. Wang's presentation, in addition to the Propanediol, Butylated Hydroxytoluene, and Hexylene Glycol monographs that have a limit for any individual impurity of not more than 0.1%, she also provided examples of monographs such as Sodium Caprylate, Isomalt, and Inositol that have a limit for any individual impurity of not more than 0.3%, 0.5%, and 0.3%, respectively.

USP seeks to engage manufacturers in identifying the appropriate excipient impurity limits and setting acceptance criteria. USP welcomes input from stakeholders on defining the starting point and level at which unknown impurities would require identification and characterization. There are multiple ways to engage with USP in the standard-setting process, which are listed in A8.

Q14: We appreciate the examples shared by Dr. Wang and Dr. Zhang for organic impurities and the comments received from stakeholders. We observe that limits adopted for the various examples differ widely for individual impurities and total impurities:

% Individual Impurity /% Total Impurities:

Isomalt 0.5/2.0
Inositol 0.3/1.0
Propoanediol 0.1/0.3
BHT 0.1/0.7
Maltol 0.1/1.0

The rationale for these differences has NOT been clearly provided, except for saying that 'impurities observed in USP validation of these methods are below these limits.'

It does not appear that the concerns and objections expressed by stakeholders and industry groups have been seriously considered.

> A14: USP closely works with excipient manufacturers whose products are used in FDA-regulated and approved drug products and formulations to set specifications, including the specifications for impurities. The Excipients Expert Committees and USP staff work closely with monograph sponsors to develop and update *USP-NF* standards by following USP Request for Revision submission guidelines that are posted on the USP website. Those limits were proposed and developed based on sponsors' rationale, data, and supporting documents and were open for *PF* public review and comment, a critical step in stakeholder engagement on a revision to the official USP-NF standard. During that time, stakeholders evaluated *PF* proposals and shared their concerns and recommendations with USP. USP staff worked with Expert Committees and monograph sponsors, reviewed public comments and reports, addressed any concerns about the *PF* proposals and modified and republished the proposals as needed.

Q15. How many samples from each of the Maltol manufacturers were tested, and did you ask those manufacturers if the 0.1% impurity limit would be OK?

Q16. With Maltol, if all you looked at were three lots from each supplier, how can USP say that they did any type of statistical analysis to determine impurity limits, etc.?

> A15-16: Development and revision of an excipient standard are conducted in collaboration between stakeholders and USP staff and Excipient ECs as described in A11-13 and A14. In addition to monograph sponsors' participation in USP standard-setting process, USP Expert Committees and staff use Pharmacopeial Forum and other stakeholder engagement/collaboration/communication tools to publicize any excipient standard revision/development proposals and seek stakeholders' comments, including any Maltol manufacturer that is not a sponsor.

Q17. Three lots are not nearly enough to set limits like <0.1% unless you had a detailed discussion with each excipient supplier, and they are in total agreement!

Q18: Limits based on less than statistically significant data sets are unlikely to reflect all the material currently being used. Can USP share the number of samples and sources used for each standard developed?

Q19: Three samples are neither representative of multiple manufacturers nor statistically significant. How is this number justified?

A17-19: See response in A11-13, A14, and A15-16. To initiate a new monograph or to revise a current official monograph, the USP Excipient Expert Committees and staff begin with a Request for Revision from the public stakeholder. Please see the links to USP Request for Revision submission guidelines in A8. By working with monograph sponsors, USP Excipient Expert Committees ensure that specifications represent the quality of excipients that are used in FDA-regulated and approved drug products and formulations.

According to the USP Request for Revision submission guideline, USP requests manufacturer's original Certificate of Analysis (CoA) for at least three production-scale lots/batches and from at least three different manufacturers. If CoAs are not available, data can be submitted in a summary table or other convenient formats. Historically, based on years of collaboration with USP monograph sponsors, supporting data from at least three lots are used from each monograph sponsor.

Q20. The principles and approaches adopted by the Expert Committee do not include consideration for patient safety when setting limits for impurities. Can you please comment on this?

Q21. How are you defining a safety risk when determining the impurities limits in Maltol? It should be related to real patient safety risk from the use of the Excipient, not just on the tox profile of the specific impurity on its own.

A20-21: FDA establishes safety and efficacy for legally marketed US drug products. USP standards focus on quality specifications. USP standards for an article recognized in the compendia (*USP–NF*) are expressed in the article's monograph, applicable general chapters, and General Notices. The identity, strength, quality, and purity of an article are determined by the official tests, procedures, and acceptance criteria, and other requirements incorporated in the monograph, in applicable general chapters, or in the General Notices (General Notices 3.10. Applicability of Standards). To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity unless labeled to show all respects in which the drug differs. See, e.g., FDCA § 501(b) and 21 CFR § 299.5(c). In addition, to avoid being deemed misbranded, drugs recognized in *USP–NF* must also be packaged and labeled in compliance with compendial standards. See FDCA § 502(g). See link to a standard-setting process.

USP closely works with excipient manufacturers whose products are used in FDA-regulated and approved drug products and formulations to set specifications, including the specifications for impurities.

Additionally, USP looks at LD50, available tox data, and reaches out to FDA government liaisons and toxicologists when necessary, to establish an appropriate limit for an impurity.

If a manufacturer that produces/claims NF grade Maltol has any issue with releasing their products according to the official NF monograph, please feel free to contact USP directly.

Q22. If I cannot decide whether a substance in our product belongs to the concomitant component category or impurity category, who should I contact at USP to discuss? Also, we want to keep the information discussed confidential.

A22: Please contact the monograph liaison directly. USP staff keep all communication with stakeholders confidential. Please also refer to the proposed definition for concomitant component in the 2018 Stimuli article "The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities."

Q23. We saw two excipient examples with a toxic impurity, i.e., Japanese star anise oil and hydroxypropyl betadex. Did the other examples have toxic impurities?

A23: Not all excipients, the composition of which was discussed in the Open Forum presentations, have toxic impurities; however, many excipients do. For example, *USP* General Chapter <469> *Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Ethoxylated Substances* address toxic impurities, ethylene glycol, and diethylene glycol in 17 excipients including Polysorbate, PEG, and PEG derived products. *USP* General Chapter <228> *Ethylene Oxide and Dioxane* also addresses impurities such as ethylene oxide and dioxane in many excipients. Many monomers that are used in production of polymers (Polyvinyl Acetate, PEG, and Povidone) are toxic, for example, vinyl acetate, ethylene oxide, vinylpyrrolidone, etc. Formaldehyde is also limited in many excipients (Polyethylene glycol 3350, Tyloxapol, Propanediol, Sorbic acid, Potassium sorbate, etc.) due to its toxicity.

Q24: We heard from USP that this is a long journey. Will USP continue revising excipient monographs and implementing new impurities testing requirements while the information chapter is being developed?

A24: Yes, as documented in USP Guideline for Submitting Requests for Revision to *USP-NF*, Submission Guideline for Excipients, Section 2.2 General requirements, and considerations. USP staff and the Excipient Expert Committee have been actively working to develop and update excipient standards (monographs and chapters) upon requests from public stakeholders. USP will continue revising excipient monographs based upon stakeholder/public requests. Concurrently, through the stimuli article, surveys, and this Open Forum, the Excipient Composition and Impurities Joint

Subcommittee (JS) is seeking feedback to help identify a pathway forward to capture the general principles and approaches utilized by the Excipient Expert Committees in setting specifications for excipient composition and impurities. The feedback received will be considered as part of the JS's next steps and possible approaches, e.g., formation of a Project Team, JS call for expert advisors, potential development of a general chapter, etc.

Q25: If no final guidance yet, why make updates to monographs? Why not wait?

Q26: It appears that a final strategy/guideline is not yet established, and USP is already acting on it - see examples of monographs related updates that have been published (e.g., Maltol and others).

Q27: The same trend is also being observed for individual element-specific test updates in excipient monograph ahead of a defined/finalized policy (Roadmap is still being discussed).

Q28: There should be no monograph update until the related policy is established (i.e., finalized and communicated). Is there a reason why USP is doing this in parallel?

A25-28: USP staff and Excipient Expert Committees develop and update excipient standards (monographs and chapters) based upon public requests for revisions and according to USP Request for Revision submission guidelines. This guideline has existed for decades; the most recent update occurred in 2016. The Excipient Expert Committees apply a set of general principles and approaches as described in the 2018 stim article and Open forum presentations in setting specifications for excipient composition and impurities.

As reported in Dr. Hong Wang's presentation, USP staff and Excipient Expert Committees apply the strategy and guidelines to address USP standard-setting processes as follows:

- Begin with using the Request for Revision Submission Guidelines posted on the USP website
- USP Expert Committees and staff work closely with sponsor(s) of excipient standards to
    - Continually develop, improve, update and harmonize excipient standards (monographs and chapters);
    - Respond to the public needs for a better understanding of excipient composition;
    - Introduce tests and limits for assays, impurities, and other excipient components that are needed to define or assure the excipient quality and/or safety.
- Introduce tests and specifications into an excipient standard by rationale and supporting data/documents from standard sponsors to

address requests from sponsors and FDA, adulteration and/or contamination issues, and safety/toxicological concerns.

One of three goals for the 2018 Stimuli article "The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities" was to introduce definitions for "simple excipient," "complex excipient," "excipient composition," and "excipient impurity." The public comments on the definition for simple Excipient, complex Excipient, excipient composition, and excipient impurity will help USP to update the 2016 Guideline for Submitting Requests for Revision to *USP-NF*, Submission Guideline for Excipients, 7. Impurities.

As described in the USP Guideline for Submitting Requests for Revision to *USP-NF*, Section 2.2 General requirements and considerations, since 2000, USP staff and Excipient Expert Committees have been actively working to develop and update excipient standards (monographs and chapters) upon requests from the public/stakeholders. USP staff subsequently work with the expert committees to address requests from the public/stakeholders.

Elemental impurities

Q29: Should an excipient that has a specific chapter with limits for Elemental Impurities (IE), such as titanium dioxide, be evaluated according to its monograph or chapter <232>?

A29: Because <232> only applies to drug products, the limits and procedures in the Titanium Dioxide monograph should be followed. Additionally, General Notices *3.10. Applicability of Standards* states: "Where the requirements of a monograph differ from the requirements specified in these General Notices or an applicable general chapter, the monograph requirements apply and supersede the requirements of the General Notices or applicable general chapters, whether or not the monograph explicitly states the difference."

Q30: Why is USP proposing new EI tests in monographs? What is the rationale for this?

Q31: You have proposed adding certain EI tests in monographs that were not there before. What justification do you have for this?

A30-31: USP is not proposing new EI tests in monographs. USP is currently seeking collaboration with stakeholders on identifying excipients that may benefit from additional EI tests. USP also collects stakeholder input on possible harmonization of element-specific tests in monographs of excipients of natural origin with those in the corresponding *Ph.Eur*. Monographs. This effort, where Carrageenan was presented as an example, may lead to increasing the number of EI tests in a monograph. Additionally, USP is

assessing whether, with the removal of <231> from excipient monographs, some excipients are missing control of a critical quality attribute.

Q32: IPEC-Americas commented that specific EI limits in existing excipients should not be reduced. Dr. Holloway did not mention this important input in her summary of stakeholder comments.

A32: The presentation did not contain a list of all comments on the *First Draft of the Roadmap.* However, all comments will be reviewed and taken into consideration by the Elemental Impurities in Excipients Joint Subcommittee for preparation of the final *Roadmap.*

Q33: The Lhasa database only contains a very limited dataset and should never be used to reduce any limits unless there is careful discussion with ALL global manufacturers of an existing excipient. Again, there is no reason to reduce limits given <232> control.

Q34: For excipient monographs with element-specific tests, will any of the currently established limits be reduced? What is the rationale, if so, considering that ICH Q3D is not applicable to excipients?

Q35: One of the main comments that industry submitted to USP previously about the *Roadmap* was that EI limits should not be reduced for existing excipients. Why did you not even mention this important topic when you discussed stakeholder input?

Q36: Revising the test procedures for EI is one thing, but no limits for existing excipients should be reduced based on the results from a limited number of samples unless there is some dramatic safety concern, which is not normally going to be the case!!!

Q37: What justification does USP use to reduce EI limits on existing excipients when any safety concerns are already handled through ICH Q3D and <232>? There appears to be no justification for reducing any EI limit for existing excipients.

A33-37: USP does not intend to reduce limits provided in <232>. Neither did USP propose reducing the existing EI- limits in excipient monographs in the presentation on the *Roadmap.* As stated in the General Announcement, the Lhasa database may be used for making recommendations for setting new acceptance criteria due to the implementation of advanced analytical technology for testing EIs in excipient monographs. A decision for each monograph will be made on a case-by-case basis.

For clarification, the goal of the presentation was to familiarize global stakeholders with the draft *Roadmap* and not as much to discuss comments received.

Q38: When you say that element-specific general chapters can be deleted, do you mean deleted from the *USP* or just no longer referenced in the excipient monographs? These general chapters are still referenced in some API monographs.

A38: *The First Draft of Roadmap* identified element-specific general chapters where deletion from *USP-NF* will not impact excipient monographs. The deletion of these general chapters can only be done when none of the monographs in *USP-NF*, including monographs for drug substances, reference those general chapters.

Toxicology

Q39: Is toxicological assessment being considered as part of the USP principle/approach for monograph modernization?

A39: When proposing a limit for a newly identified impurity that is not included in an official monograph, toxicological assessment data and reports are required by USP Excipient Expert committees. USP has examples of PF proposals for Methyl Salicylate in PF 40(2) [Mar.-Apr. 2014] and Octyldodecanol in PF 42(4) [Jul.-Aug.2016]. USP Excipient Expert Committees requested and obtained toxicological data and reports during updating Methyl Salicylate and Octyldodecanol monographs.

Q40: With BHT, why did the organic impurities limit go from 0.5% to 0.1%? Why is this reduction needed? What is the patient safety risk here? 0.1% should not be used across the board unless absolutely needed for safety reasons.

A40: USP worked with a BHT manufacturer on setting acceptance criteria for individual and total impurities in addition to conducting analysis of other manufacturers' samples.

Q41: Are the impurities shown for maleic acid a safety concern, i.e., toxic?

A41: Impurities specified in the Maleic Acid monograph are not considered toxic.

Identity Tests

Q42: In the batches of raw materials for excipients, is it necessary to do an identity test on each container, or is the test on a representative sample of the batch enough?

A42: Please follow the requirements in USP General Notices. See also CFR (Code of Federal Regulations) 21CFR211.84.

Q43: Is it necessary to have two identification tests for excipients?

A43: For a simple excipient, identification by an orthogonal approach is often utilized. For example, an HPLC analytical procedure alone, depending on the separation mechanism of the compounds studied, does not provide information about the chemical structure of the components separated, whereas IR provides information about the basic chemical structure of the components or their functional groups. In general, spectroscopic and separation methodologies are complementary. Separately, neither spectroscopic nor separation procedure is likely to be sufficient for unique identification, but when used together, they provide greater assurance of uniquely identifying an excipient. In USP Guideline for Submitting Requests for Revision to USP-NF, Submission Guideline for Excipients (https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/excipients_rfr_guideline-28apr16.pdf), pages 9 – 12 of 26, detailed guidelines on how to establish appropriate identifications for an excipient are documented.

Oleyl Alcohol

Q44: Will there be two monographs for Oleyl Alcohol, one for Purified Oleyl Alcohol and one for the regular (mixture type) Oleyl Alcohol?

A44: USP Excipient Expert Committees have incorporated Purified Stearic Acid into a harmonized monograph for Stearic Acid, as one of three grades of Stearic Acid, "Stearic Acid 95." The Excipient Expert Committee in the 2020-2025 revision cycle will be investigating how many pharmaceutical grades of Oleyl Alcohol are used in FDA-regulated and approved drug products and formulations and will consider following the Stearic Acid monograph approach to update oleyl alcohol in the future.

Q45: How USP handles minor components should not be determined by what drug manufacturers would like to see, as stated with Oleyl Alcohol. The excipient manufacturers need to be the primary ones determining this and then working with their users on other issues.

A45: For Oleyl Alcohol PF 40(2) [Mar.-Apr. 2014], the manufacturers initiated the monograph revision process. Excipient manufacturers were willing to work with USP Expert Committees to update the *Assay* and *Related Substances* for oleyl alcohol. They believed that their collaboration with USP would help them to communicate with their users, regulators, and other key stakeholders.

Excipients for injection application

Q46: Would it be possible, in the future, to implement additional monographs for excipients intended for injection application with additional HPLC testing (as the ChP does, for example, for Polysorbate 80)?

A46: Currently, the USP Expert Committees are continuing to use the labeling, additional requirements, and specific tests sections of the USP monograph to support excipients intended for different routes of application, including injection. As background, the 2015-2020 USP Polysorbate Joint Subcommittee published a Stimuli article titled "Understanding the Composition and Quality of Polysorbates to Strengthen *USP–NF* Compendial Standards" in PF47(1). USP Complex Excipients Expert Committee (CE EC) received a Request for Revision from an external stakeholder/sponsor to develop a direct assay for Polysorbate 20 with supporting data that includes HPLC procedure and validation reports. Currently, USP staff and CE EC are working on this request. The Polysorbate 20 *NF* monograph indicates multiple applications in drug formulations, including injection application using the above approach.

Adulteration

Q47: Analytical methods developed for assay and related substances are unlikely to detect potential adulterants. Supply chain control and supplier qualification are more effective for preventing adulteration.

A47: The commenter brings up good points in that supply chain control and supplier qualification is effective risk-based approaches in controlling and preventing adulteration. However, neither one of these together nor alone are entirely effective for preventing adulteration. Testing measures to prevent adulteration should be viewed as an integral part of a holistic approach, as no individual measure is completely effective. The effectiveness of a combination of approaches creates synergy, which increases trust between the excipient manufacturers and users. USP's role in preventing adulteration stems from the standards and methods published by USP and enforced by the FDA and other regulatory agencies that recognize USP.

More specifically, the USP standards and methods are designed to detect potential adulteration. In drafting and proposing new or revised monographs for excipients, USP seeks input from stakeholders, including

regulatory authorities, manufacturers, and users. The stakeholders are sources of information about what could be used as potential adulterants. Updated monograph tests provide new insight into the composition of the Excipient. An example used in the presentation pertained to Anise Oil and Star Anise Oil. The test can distinguish between Anise Oil, Star Anise Oil, and Japanese anise, especially for the impurities of *trans*-anethole, safrole, foeniculin, and pseudoisoeugenyl 2-methylbutyrate. It should be recognized that Anise Oil and Star Anise Oil are used in very small quantities for flavoring. Therefore if a very small quantity of Japanese anise is present and could not be detected, the levels of the toxic compounds would be very low. This is also an example of where supply chain control and supplier qualification could fail because the anise botanical parts used for oil extraction are indistinguishable after harvesting and drying.

Also, the USP Expert Committees carefully consider the potential ways of adulteration for each Excipient when a monograph is proposed or updated. The Expert Committees weigh a number of factors, including those mentioned above, and assess the risk associated with the likely level of adulteration, along with the other risks that need to be considered.

Q48: This seems to be a trend that the reporting threshold policy is not yet established, but monograph updates were way ahead of a defined policy.

A48: USP staff and Excipient Expert Committees do not apply the ICH Q3 term "reporting thresholds" in excipient monographs.

Quality testing and release procedures – General Notices

Q49: About the end users' responsibility to ensure the quality of excipients used in testing: What is the scope of testing or the acceptable practice/approach for end users' internal release procedures? (full monograph testing? identity testing only? Other?)

A49: That is a question for the FDA in terms of enforcement and compliance.

General Notices

Q50: We didn't get an update for the General Notices Team. What is the plan going forward for this Team?

Q51: We see additives are not listed in Dr. Holloway's slide ~ #30. Yet they are in GN 5.20.10, so we think section 5.20.10 needs to change.

A41-51: The submitter needs to provide additional context and clarity to the comment.

Request for product testing

Q52: Can I request that USP test my product that has been used in many important drugs? We may have some minor components. If USP classified those as impurities, those drugs will be impacted, and ultimately this could cause a drug shortage.

A52: You can support Excipient standard-setting activities by providing methods and specifications for the development of new and update of existing monographs (revisions) in *USP-NF*. If interested, please reach out to anyone mentioned in A8. Please also refer to A 11-13, 5.60.10. Other Impurities in USP and ***NF*** Articles.

USP received public comments on the 2018 USP Stimuli article *"The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities,"* including FDA's recommendations on defining an excipient impurity.

USP considers an excipient "impurity" as a technical term related to a substance not intended to be in the material/excipient (e.g., a process residual material or a degradant). An impurity should be identified, quantified, and analyzed for safety, as appropriate.
The JS currently considers an impurity as a substance that is not intended to be in an excipient, it could be toxic or non-toxic, and it could be

- Residual starting material(s)
- Process residual material(s) (reagent(s), solvent(s), and catalyst(s))
- Intermediate(s)
- By-product(s)
- Degradation product(s).

Co-processed excipients

Q53: Do you consider co-processed excipients to be a separate component going into the finished product manufacture, or more like a finished product intermediate?

A53: In USP Guideline for Submitting Requests for Revision to *USP–NF*, Submission Guideline for Excipients (https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/excipients_rfr_guideline-28apr16.pdf), Section 2.2 General requirements and considerations discusses the rationale for including co-processed excipients in *NF*. A Request for Revision for a co-processed excipient monograph should consider the criteria appearing in section C. Co-processed Excipients.

Miscellaneous. Need further clarification

Q54: Are the decision of removal based on theoretical approach only or also based on supportive data? Will rationale be available in the briefing of the revision?

Q55: Who can request? Individual company? Industry group? Perhaps, if USP can develop and publish/post a process/guideline/FAQ on the USP website, that would be helpful.

Q56: I have a doubt in the case that we perform the impurity test and we found that the results are always below of the specifications established, we have to perform the elemental impurities in each batch, or it is possible to justify by an assessment of risk?

Q57: Is there a forecast for when the chapter with IE specifications for excipients will come into effect?

A54—57: USP needs more clarification to respond.

Stakeholders' Recommendations and comments

Q58: Dr. Holloway's presentation was very heavy on content and moved at a brief pace. I know additionally some individuals did not have schedule availability to log-in the second day for the run-over content.

Q59: Some ideas for providing clear rationale have been proposed (e.g., a new General Notices section, a Working Group to involve stakeholders), and we welcome the openness of USP to these ideas. Thank you.

Q60: Stakeholders would LOVE to get involved BEFORE USP proposes things in PF, but they typically do not know anything about what you are discussing until you put it in PF. Discussions with manufacturers should occur FIRST!

Q61: The excipient manufacturers will be able to tell you if the minor components have been historically present. No additional requirement for minor components should be proposed without FIRST discussing this with the manufacturers!

Q62: USP should establish a project team for EI issues as well. This is very important that all stakeholders are involved in how this will proceed on a detailed basis!

Q63: The JS Project should be utilized to discuss feedback on the correct definitions before anything is finalized. The appropriate experts could be involved.

A60-62: Please see A11-13.

Q64: IPEC requests additional interactions with USP to refine the definitions listed in the Stimuli article and Dr. Holloway's presentation.

Q65: IPEC-Americas does not agree with many of the concepts being used by USP to handle composition and impurities; we request a telecon mtg. to discuss this ASAP! We have significant concerns!

A63-64: Please submit your recommendations and concerns to USP in writing.

Q66: I agree that it is critical that there be much more discussion about how USP plans to address composition and impurities. Before the JS goes very far, it is absolutely critical that they get input from a project team and appropriate advisors from industry.