USP Open Forum | Excipients

USP Addressing Maltol PF 46 (2) comments

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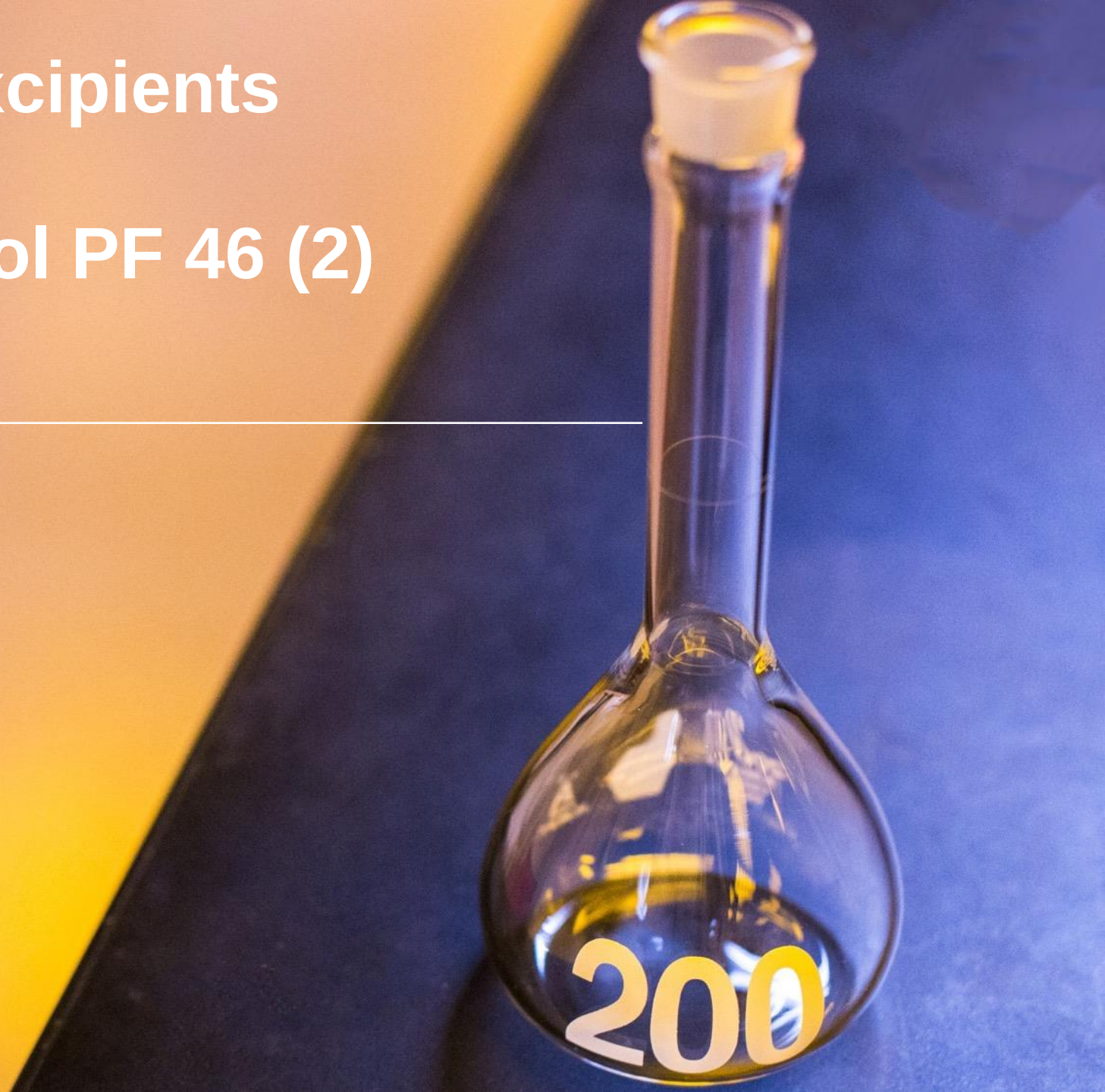

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Presentation Overview

Updates on USP's Continuous stakeholder engagement from USP PNP Stakeholder Forum, Apr 2020:

- An overview of the Maltol excipient monograph's recent revision/modernization proposed in PF 46 (2).
- Update stakeholders on addressing public comments on the Maltol revision proposal of PF 46 (2).
- Update stakeholders on ***Next Steps***.

Background

- Maltol modernization proposal was published in PF 46 (2) in March 2020. This included:
  - Replacement the UV based unspecific Assay method with a GC specific assay method and addition of a GC organic impurity method.
  - USP developed and validated both the assay and organic impurity methods successfully.
  - Multiple NF grade or FCC grade samples from 3 manufacturers (US and Asian markets) were procured and analyzed using the new methods. A statistical evaluation was performed for the assay results.
- **All the samples are very clean and no Individual impurity ≥ 0.10% is detected in any of the sample lots.**
- Based on the statistical evaluation and sample analysis results, our Expert Committee (EC) agreed to set the limit for:
  - **assay at 98.0-102.0%,**
  - **any unspecified impurity at NMT 0.1%, and the limit for the total impurities at NMT 1.0%.**

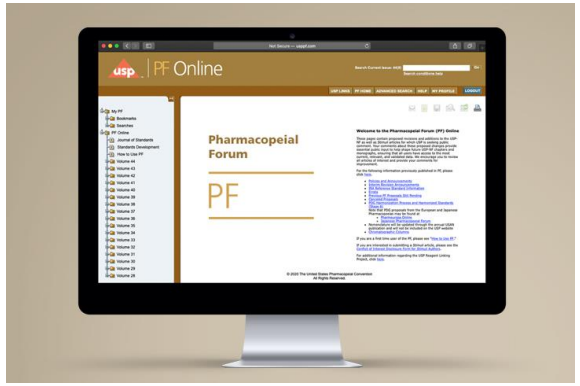
Summary of Comments

Name of monograph (Proposed in PF)	Comments (from stakeholders (commenters) on PF proposal)	Commenters (the number of individual stakeholders submitting comments)	Category
Maltol	6	4	Organic impurities

PF *comments*- Commenter 1

- In Apr 2020, **Commenter 1** sent their ***comments*** on Maltol-PF 46(2), which are summarized below:

- Recommended making a distinction between impurities and concomitant components in excipient monographs
- Recommended setting impurity/component specifications based on toxicological assessment.
- Recommended forming an advisory panel for excipient impurities.
- Requested **not** applying an approach intended to address impurities in APIs, such as ICH Q3A, to excipients.



PF comments –Other Commenters- Summaries

- The next two commenters echo Commenter 1:
  - On 24 July 2020, Commenter 2 sent comments on Maltol- PF 46(2) to echo Commenter 1's comments. Additionally, they requested forming a collaborative USP-industry working group to more thoroughly discuss excipient impurities.
  - On 30 July 2020, Commenter 3 sent comments on Maltol- PF 46(2) to echo Commenter 1's comments. Additionally, they suggested that USP adds an additional section to the General Notices that would address excipient composition and impurities.
- On 31 July 2020, Commenter 4 sent comments on Maltol- PF 46(2), which included suggestions similar to the 2nd *comment* from Commenter 1. Additionally, they suggested including a rationale for the proposed organic impurity specifications in the briefing. They requested USP not to include the organic impurities test to the monograph.

USP Follow-up Communications with Stakeholders to Address PF Comments

- USP continued the communications and follow-up with stakeholders as follows:
  - PNP Stakeholder Forum, Apr 2020: USP presented Excipient Impurities highlighting the maltol modernization case.
  - 30 July 20 to 04 Aug 20: USP communicated with Commenter 1 by emails about their comments on Maltol.
  - 04 Aug 20: USP communicated with Commenter 2 on their comments on Maltol by email.
  - 05 Aug 20: USP communicated with Commenters 3 and 4 on their comments on Maltol by email, respectively.

Comment Summary and Points for Consideration

Comment 1 Summary : Commenter recommended making a distinction between impurities and concomitant components in excipient monographs.

➢USP points for consideration:

- In the ***2018 USP Stimuli article on Excipient Composition and Impurities***, the USP Excipient expert committees (ECs) proposed *definitions for impurities and concomitant components*.
- During 2018 – 2019, USP also launched a ***survey*** on Excipient Impurities to solicit comments and input from stakeholders.
- In September 2020, the USP Excipient Expert Committees and staff published a ***second stimuli article on excipient impurities: "USP Responses to Comments on Stimuli Article: The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities***" to address stakeholders' comments.

Comment Summary and Points for Consideration (cont'd)

Comment 2 Summary: Commenter recommended setting impurity/component specifications based on toxicological assessment.

➢USP points for consideration:

- USP Excipient ECs have engaged toxicologists into the Excipient standard-setting processes and will continue this practice during the COE revision cycle 2020-2025.
- The processes involving toxicological evaluation have been incorporated and documented in our *2018 Stimuli article – Excipient Composition and Impurities* PF 44(3). For examples:
  - The case study 1 (Fumaric acid): EC performed a review of safety/toxicological data for the two impurities (Maleic acid and Malic acid) and set their limits.
  - The case study 2 (Methyl Salicylate): EC engaged FDA in providing feedback in setting limit for a proposed impurity (dimethyl 4-hydroxyisophthalate).
- The term of “unspecified impurity” will be changed to “unidentified impurity” in the Organic Impurities test.

Comment Summary and Points for Consideration (cont'd)

Comment 3 Summary: Commenter requested **not** applying an approach intended to address impurities in APIs, such as ICH Q3A, to excipients.

➢USP points for consideration:

- For any excipient monograph modernization, the Excipient ECs followed the USP Request for Revision guideline, https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/excipients_rfr_guideline-28apr16.pdf as well as the Excipient EC practices that were documented in the 2018 *Stimuli* article.
- ***The Excipient ECs do not apply an approach intended for impurities in APIs to any excipient standard studied, including Maltol.***
- The same individual impurity limit for Maltol was used in other monographs. Previously included in revisions to both **Propanediol**, **Butylated Hydroxytoluene (BHT),** and **Hexylene Glycol** as discussed in Hong's prior presentation, today.

Comment Summary and Points for Consideration (cont'd)

Comment 4 Summary: Commenter suggested including a rationale for the proposed organic impurity specifications (i.e., NMT 0.1% for any individual unspecified impurity and NMT 1.0% total impurities) in the briefing.

➢USP points for consideration:

- In the Maltol modernization case, multiple NF grade or FCC grade samples/products from multiple manufacturers (US and Asian markets) were studied. **No** individual impurity ≥ 0.10% was detected in any of the samples/products.
- USP will provide more clarity in the briefing section of the PF proposal for similar cases, in the future.

Comment Summary and Points for Consideration (cont'd)

Comment 5 Summary: Commenter recommended adding an additional section to the General Notices that would address excipient composition and impurities.

➢USP points for consideration:

- Excipient Composition and Impurities Joint Subcommittee (JS) will work on developing a policy/strategy on setting specifications for excipient composition and impurities. USP has been actively engaging stakeholders through our stimuli articles, survey, PNP stakeholder presentation, commentary, etc.
- Excipient ECs and staff will work closely with USP's General Notices Project Team to address stakeholders' comments on sections of USP's General Notices (including 5.20.10 *Added Substances in Official Substances and* 5.60.10 *Other Impurities in USP and NF Articles*).

Comment Summary and Points for Consideration (cont'd)

Comment 6 Summary: Commenter recommended forming an advisory panel or collaborative working group for excipient impurities.

➢USP points for consideration:

- USP has formed the Excipients Composition and Impurities JS in this new COE revision cycle to continue the work from the previous revision cycle.
- The JS will consider the questions and discussions from today's Open Forum and form a Project Team to determine the best approach. This is discussed previously by Galina.
- During this revision cycle, the JS has the ability to call for expert advisors.

USP's next steps

- USP will change the term of "unspecified impurity" to "unidentified impurity" in the Maltol monograph.
- Through this open forum, USP will collect feedback and input from stakeholders on excipient composition and impurities and provide them to the JS for further consideration.
  - USP will form the Excipients Composition and Impurities project team to work directly with this JS.
- Excipients Composition and Impurities JS will consider development of an information general chapter on composition and impurities of excipients.

Thank You

Stay Connected

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