“Excipient “Impurities”: Current Excipient Expert Committees’ Practices” Update on PF 46(2) Revision Proposal for Maltol

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Agenda

- USP Up-to-Date Initiatives
- Address Stakeholders’ Topic on Excipient *Impurities*
  - Update on Excipient Composition and Impurities work to date
    - USP Excipient Expert Committees’ *Stimuli* Article:
      *PF 44(3): The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities*
- Excipient Expert Committees’ Practices for Updating Impurities in Monographs
- Summary
USP Up-to-Date Initiatives

- **Monograph Modernization** – Bringing monograph up to date
  - Develop standards (monographs and general chapters) that reflect “state-of-the-industry” techniques for sufficiently monitoring drug and excipient quality, purity, and strength, and evaluating excipient performance.
  - Ensure that all monographs in the USP–NF are current and suitable for their intended use.
Address Stakeholders’ Topic on Excipient Impurities

Current Status on Expert Committees’ (ECs) Strategy: USP Excipient (ECs) Stimuli Article and Survey 2018

- Published Stimuli article in PF 44(3)[May-June 2018]: THE COMPLEXITY OF SETTING COMPENDIAL SPECIFICATIONS FOR EXCIPIENT COMPOSITION AND IMPURITIES

- Presented at the Excipients Stakeholder Forum on Dec. 11, 2018
  - Questions: How many have read the Stimuli article? Completed the survey?

- USP Excipient Stakeholder Forum planned for Fall 2020
  - Discuss details on the USP strategy for developing specification for Excipient Composition and Impurities
The following projects also in progress will impact excipients strategy

- Revision to USP General Chapters on Impurities in drug substance and drug products (<476> and <1086>)
- Revision to General Notices 5.60.10
- Planned revision strategy for Excipient Composition and Impurities
- Proposed a *Stimuli* article (response to public comments on the *Stimuli* article in PF 44(3))
- Alignment is key between strategies (Glossaries, terminologies)
The *Stimuli* Article in *PF* 44(3) Proposes the Following Definitions

- **Nominal component:** Substance typically found in the excipient that is expressed by the official name and definition and/or assay provided in the USP monograph.
- **Minor component:** A component of an excipient which is not the nominal component or, where the official name does not relate to the excipient components, not the major component.
- **Simple excipient:** An excipient composed of a single main substance with a well-defined chemical structure that can be characterized well analytically.
- **Complex excipient:** Any excipient that does not fit the definition of a simple excipient.
- **Excipient impurity:** Any substance that detracts from the quality of the excipient (i.e., that is not the substance appearing in the official name, or a concomitant component or added substance as defined above).
When an impurity profile or a composition of an excipient is revealed by a more specific procedure, all minor components are initially investigated as potential impurities unless it can be otherwise justified.

Simple Excipients
- When minor components exceed 0.1%, the Expert Committee’s (EC’s) general approach is to identify what those components are, if possible. (As per current USP General Notices 5.60.10)

Polymeric and mixture type excipients,
- USP closely works with the sponsors/stakeholders to address composition, concomitant components, and/or impurities.
During impurity studies, the ECs and USP staff perform

- monograph sponsor engagement for submitting the up-to-date methods/validations, providing information for excipient manufacturing processes, and briefing potential impurities
  - a limit used by manufactures to control variability of the excipient can be proposed for adoption
- FDA Government Liaisons (GLs) consultation to weigh in on newly identified components (including toxicology input)
- other Pharmacopeial consultation if no pertinent information on safety or toxicity of a minor component is available
  - a limit specified in another Pharmacopeia can also be proposed for adoption
During impurity studies, the ECs and USP staff perform

- a review of the safety data and toxicological data (LD50s for the nominal and all other components and data from TOXNET)
- a review of process capability
- a statistical evaluation of the impurity levels of the currently marketed pharmacopeial excipients
  - a set of samples representative of the excipient U.S., European, Asian markets
  - a large range of samples needed to ensure that they are from as many sources and manufacturing processes as possible are available for analysis
The ECs and USP staff studied Maltol and Ethyl Maltol

- Maltol, *PF 46(2)*
  - Replace UV-based Assay procedure by a GC (gas chromatographic) method
  - The same GC method is used for Organic impurity analysis
  - Study results performed on multiple samples
    - a large range of samples needed to ensure that they are from as many sources and 3 manufacturers (US and Asian markets)
    - a statistical evaluation of the impurity levels for those samples
  - Specification proposed
    - assay limit is based on statistical analysis, 98.0% – 102.0%
    - no Individual impurity ≥ 0.10% is detected in any of the sample lots
The ECs and USP staff study on Maltol and Ethyl Maltol

- The limits for the minor components are set based on the process capability due to similarity of the toxicological data for the nominal and minor components.

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<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltol</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unidentified* impurity</td>
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<td>0.1</td>
</tr>
<tr>
<td>Total of all impurities</td>
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<td>1.0</td>
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</table>

* “unspecified” in PF 46(2) will be changed to “unidentified”
The ECs and USP staff studied Maltol and Ethyl Maltol. Ethyl Maltol, *PF 45*(4), similar studies conducted.

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</thead>
<tbody>
<tr>
<td>Maltol</td>
<td>0.83</td>
<td>0.3</td>
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<tr>
<td>Ethyl Maltol</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unidentified* impurity</td>
<td>—</td>
<td>0.1</td>
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*“unspecified” in *PF 45*(4) will be changed to “unidentified”*
Welcome public comments on PF 45(4) Ethyl Maltol and PF 46(2) Maltol. Up-to-now, USP hasn’t received any public comments, specifically on Impurity specifications.

The Excipient Program Unit Team continues to rely on support from external stakeholders specifically monograph (general chapter) sponsors as well as USP laboratories and input/comments from the Expert Committee and stakeholders including FDA to ensure that the excipient standards are current and up-to-date.
Thank You