USP Open Forum | Excipients

Historical and Current Overview of USP/NF Excipient Monograph Composition and Impurity Revision

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Description and Learning Objectives

- Overview of USP/NF Standard Setting Processes
- Overview of Monograph Development/Revisions from early 2000 – 2018
  - Update on Excipient Composition and Impurities work to date based on the general principles and approaches outlined in the 2018 *Stimuli* article

    2018 *Stimuli* Article: *PF* 44(3) [May – Jun 2018]: The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities
  - Examples of both Simple and Complex Excipients
- Current Status of Monograph Development/Revision
- Summary

Overview of USP/NF Standard-Setting Processes (1)

- Begin with using the *Request for Revision Guidelines* posted on USP website
- USP expert committees/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 better understanding of excipient composition
  - Introduce tests and limits for assays, impurities and appropriate concomitant 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

Overview of USP/NF Standard-Setting Processes (2)

- Working approaches of USP Excipient expert committees/staff
  - Introduce simple, specific, direct analytical methodologies which have a broad application into excipient standards
  - Propose limits based on supporting data/documents from sponsors as well as from the outcomes after toxicological, statistical and analytical studies of worldwide pharmaceutical grade excipients
  - Encourage all stakeholders to provide comments on an excipient standard proposal that has been published on the *Pharmacopeial Forum* (*PF*)
  - Equally value and process all comments from the public as well as feedback from monograph sponsors
  - DONOT apply ICH Q3A guidelines to any excipient, as documented in the 2018 *Stimuli* article

Overview of Monograph Development/Revision from Early 2000 – 2018 (1)

- USP/NF monograph development and update goals were to
  - Keep abreast of current industry practices, guidelines and capability
  - Introduce analytical methods and specifications for *Assay* and *Impurities* to simple organic excipients
    - Starting 2005, utilize a single chromatographic method to address *Assay* and *Impurities* for simple organic excipients if possible
  - Provide better analytical methodologies to evaluate complex excipients

- **2004**: The Excipient Monograph Content (EMC) expert committee in 2000-2005 proposed a new monograph, ***Sodium Caprylate***, in *PF* 30(3) page 990
  - **Assay**: NLT 99.0% and NMT 101.0% of sodium octanoate ($C_8H_{15}O_2Na$), calculated on the anhydrous basis
  - **Impurities**: Any impurity: NMT 0.3%
    Sum of all the impurities: NMT 0.5%

Overview of Monograph Development/Revision from Early 2000 – 2018 (2)

- **2005**: The 2000-2005 EMC proposed a new monograph, ***Isomalt***, in *PF* 31(1) page 88
  - **Assay:** NLT 98.0% and NMT 102.0% of a mixture … …
  - **Impurities:** Any individual impurity: NMT 0.5%
    Total impurities including mannitol and sorbitol: NMT 2.0%

  A single chromatographic method was proposed to address the *Assay* and *Impurities*.

- **2006:** Excipient Monographs 2 expert committee (EM205) in 2005-2010 proposed a revision to an official monograph, ***Hydroxypropyl Betadex***, in *PF* 32(5) page 1481
  - **Impurities**: Proposed addition of a test for *Limit of propylene oxide,* and the *Acceptance criteria* 0.0001%
    - Rationale: propylene oxide is a toxic and hazardous substance that is used as a starting material in the manufacture of Hydroxypropyl Betadex.

Overview of Monograph Development/Revision from Early 2000 – 2018 (3)

- **2007**: The Excipient monographs 1 expert committee (EM105) in 2005-2010 proposed a new monograph, ***Inositol***, in *PF* 33(4) page 711
  - **Assay:** NLT 97.0% and NMT 102.0% of $C_6H_{12}O_6$, calculated on the anhydrous basis
  - **Impurities:** Any impurity: NMT 0.3%
    Total impurities: NMT 1.0%
- **2012:** The Excipient expert committee in 2010-2015 (EXC2010) proposed a new monograph, ***Propanediol***, in *PF* 38(2) online
  - **Assay:** NLT 99.7% of 1,3-propanediol (C3H8O2)
  - **Impurities:** Each individual impurity: NMT 0.1%
    Total impurities: NMT 0.3%

Overview of Monograph Development/Revision from Early 2000 – 2018 (4)

- **2014**: The EXC2010 proposed an update to ***Butylated Hydroxytoluene***, in *PF* 40(2) to address the request from FDA Monograph Modernization Task Force group
  - One of the changes was to replace the thin-layer chromatographic method in the test for *Organic Impurities* with the HPLC method that is used in the *Assay*
    - Introducing new ***Acceptance criteria*** for the individual impurity at NMT 0.1% and for total impurities at NMT 0.7%

Name	Relative Retention Time	Relative Response Factor
p-Cresol or *m*-cresol[a]	0.12	1.9
3-*tert*-Butyl-4-hydroxyanisole (BHA)	0.19	1.1
3,5-Di-*tert*-butyl-4-hydroxybenzoic acid	0.20	3.6
2-*tert*-Butyl-4-methylphenol or 2-*tert*-butyl-5-methylphenol[b]	0.27	1.7
3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde	0.37	6.6
4,6-Di-*tert*-butyl-*m*-cresol	0.66	1.1
2,6-Di-*tert*-butyl-phenol	0.77	0.9
Any unspecified impurity	—	1.0

[a] The *p*-cresol and *m*-cresol peaks are not separated under the method conditions.
[b] The 2-*tert*-butyl-4-methylphenol and 2-*tert*-butyl-5-methylphenol peaks are not separated under the method conditions.

Overview of Monograph Development/Revision from Early 2000 – 2018 (5)

- **2018**: The Excipient monographs 1 expert committee (EXC12015) in 2015-2020 proposed an update to an official monograph, ***Hexylene Glycol***, in *PF* 44(4) online
  - **Assay:** NLT 98.0% and NMT 102.0% of 2-methylpentane-2,4-diol, calculated on the anhydrous basis
  - **Impurities:**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Acetone	0.42	0.9	0.1
2-Propanol	0.43	0.9	0.1
4-Methylpentan-2-one	0.77	1.3	0.1
4-Methylpentan-2-ol	0.81	1.4	0.1
Diacetone alcohol[a]	0.91	1.0	0.1
Hexylene glycol	1.0	—	—
Any other individual impurity	—	—	0.1
Total impurities	—	—	1.0

[a] 4-Hydroxy-4-methylpentan-2-one.

Summary: Overview of Monograph Development/Revision from Early 2000 – 2018 (6)

- All above simple organic excipient examples such as ***Isomalt***, ***Inositol***, ***Propanediol, Butylated Hydroxytoluene,*** and ***Hexylene Glycol*** confirm USP working approaches.
  - Monograph sponsors utilized specific chromatographic methodologies and submitted to USP Excipient expert committees (EXC ECs) compositional and impurity profiles.
  - The EXC ECs/Staff worked with the sponsors to propose the corresponding specifications for composition and impurities that includes content(s) of nominal component(s) and limits for all minor components.
  - Some simple organic excipients such as *Propanediol*, *Butylated Hydroxytoluene*, *Hexylene Glycol,* etc. are purified products with each individual impurity of NMT 0.1%.
- All revision examples presented above, demonstrate that the EXC ECs develop and update USP/NF monographs taking in consideration stakeholder input/support in setting specification for excipient composition and impurities

Overview of Monograph Development/Revision from Early 2000 – 2018 (7)

Complex and Polymeric Excipients: Multiple Test Methods are used to Determine Composition and Impurities

- **2013:** The EM205 published an article in *Pharmaceutical Technology*, 2013, pages 102-108, ***Fixed Oil Excipient Monographs, Development of USP Fixed Oil Reference Standards*** – Major work sets principles for working on ester-based excipients
  - Outlined a strategic analytical testing plan for fixed oil monographs
  - Included *Acid Value* spec. in ***Specific Tests***: determine the degree of an oil's hydrolysis – test for residual free fatty acids (impurities)
  - Included *Peroxide Value* spec. in ***Specific Tests***: determine the primary oxidation products (impurities)

Overview of Monograph Development/Revision from Early 2000 – 2018 (8)

- **2012:** EXC2010 published an update to an official monograph, ***Oleic Acid***, in *PF* 38(1) online
  - One of the changes was to add a test for *Content of Fatty Acids* under ***Specific Tests***.

Carbon-Chain Length	Number of Double Bonds	Percentage (%)
14	0	≤5.0
16	0	≤16.0
16	1	≤8.0
18	0	≤6.0
18	1	≥65.0
18	2	≤18.0
18	3	≤4.0
20, 22[a]	0	≤4.0

[a] The sum of these fatty acids should be NMT 4.0%.

  - Oleic Acid *NF* monograph represents two types (*mixture-type* and *purified-type)* of oleic acid that are used as pharmaceutical excipients.
  - USP has learned that if a *purified-type* oleic acid of NLT 98% is used, the other related fatty acids should be considered as impurities.

Overview of Monograph Development/Revision from Early 2000 – 2018 (9)

- **2014:** EXC2010 published an update to an official monograph, ***Oleyl Alcohol***, in *PF* 40(2) online
  - One of the changes was to add a test for *Content of Related Fatty Alcohols* under ***Impurities Section***

Component	Acceptance Criteria, NMT (%)
Cetyl alcohol	8.0
Stearyl alcohol	5.0
Linoleyl alcohol	3.0
Linolenyl alcohol	0.5
Arachidyl alcohol	0.3

  - Oleyl Alcohol *NF* monograph represents two types (*mixture-type* and *purified-type)* of oleic alcohol that are used as pharmaceutical excipients
  - USP has learned that if a *mixture-type* of oleyl alcohol of 78%-85% is used, the other related fatty alcohols should be considered necessary minor components.

Overview of Monograph Development/Revision from Early 2000 – 2018 (10)

- **2018**: *Stimuli article* in *PF* 44(3) outlines the following approaches
  - The current USP/NF monograph structure provides flexibility in listing impurities and components that are part of an excipient composition in different monograph sections:
    - ***Impurities*** versus
    - ***Specific Tests*** and/or
    - ***Other Components***
  - Encourage stakeholders to share USP EXC ECs relevant information in order to help properly classify components and avoid unnecessary reference to a specific component as an impurity
  - Stakeholder engagement in the standards setting process is critical

Current Status of Monograph Development/Revision

- Currently, USP has strong sponsorship engagement
  - Standard acquisition and sponsor engagement help develop and update excipient composition and impurities
    - Numerous sponsor meetings/communications among USP scientific liaisons, monograph sponsors, USP labs, and FDA for public standard development
  - A common set of principles and approaches as proposed by the *Stimuli* article in *PF* 44(3) are important for USP Excipient expert committees (EXC ECs) and stakeholders in order to accomplish a shared understanding and establish a path for next steps
  - According to 2020-2025 COE Rules and Procedures, the EXC ECs can post a call for expert advisors on the USP website to provide an opportunity to solicit additional expertise beyond the ECs. The EXC ECs plan is to engage expert advisors during USP standard-setting processes.

Summary

- From early 2000 to now, the Excipient expert committees have been working to develop and update excipient monographs by setting and establishing specifications for excipient composition and impurities.
- The Excipient expert committees truly welcome public comments on any *PF* proposals for excipient monographs and chapters, as many of *PF* publications are/will be providing excipient composition and impurity specifications.
- The Excipient Program Unit Team continues to rely on support from external global stakeholders, specifically monograph (general chapter) sponsors as well as USP laboratories, input/comments from the Expert Committee and stakeholders, including FDA to ensure that the excipient standards are current and up-to-date.

Thank You

Stay Connected

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