Stakeholder Forum Progress and Achievements

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Empowering a healthy tomorrow

Objectives

- **Overarching Purpose…**
  - To provide a forum for manufacturers, distributors, and users of excipients to discuss key issues/topics in an open forum setting.
  - To encourage excipient users to work openly and directly with USP as well as collaborate with fellow stakeholders.
- **Specifically** …
  - Extending opportunities for participation to a broad range of excipients stakeholders
    - Ensures industry-wide input to USP
    - Further understand excipient issues that will facilitate update and development of excipient monographs
  - Informing stakeholders on USP activities and initiatives that might affect excipients stakeholders
    - e.g., USP/NF standard setting process, harmonization, Global Education, and Verification programs.

Excipient Stakeholder Forum Meetings Prior to 2015

- **First Meeting – 07-Jun-2013** (all day in person and WebEx)
  - **Topics**:
    - Elemental Impurities
    - USP and FDA Excipient Activities including USP Excipients Standard-Setting Processes and FDA Perspective on Excipient Quality
    - Excipient Monograph Modernization and Related General Chapters
    - Pharmacopeial Education
- **Second Meeting – 18-Jun-2014** (all day in person and WebEx)
  - **Topics:**
    - USP and FDA Excipient Activities
    - Excipient Monograph Modernization including Updates from USP, EP, and FDA and Updates of Gelatin NF Identification Test
    - Standard Acquisition and Its Role in the Donor Recognition Program
    - USP Verification Program

  Both meetings had Stakeholder Roundtable Discussions

Excipient Stakeholder Forum Meetings After 2015

- **Third Meeting – 29-Sept-2016** (half day WebEx)
  - **Topics**:
    - Excipient Stakeholder Forum Updates including Stakeholder Forum Progress and Achievements and Excipient Monograph for Injection - Polysorbates
    - Dual Active Excipients
    - USP-NF Elemental Impurities including USP Overview and FDA Perspective on *Elemental Impurities in Drug Products Guidance for Industry*
- **Action Items from the Third Meeting – 29-Sept-2016**
  - Consider the route of administration when establishing excipient monograph specifications for intended use.
  - Further discussion needed with stakeholders to understand the challenges related to Atypical Actives.
  - Create the awareness among stakeholders to prepare for implementation of <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures* by January, 2018.

Standard Development/Modernization Strategies

- Traditional donor model ('externally sourced') – External Collaborations

  (Industry, Academia, FDA, Expert Panels, and Other Pharmacopeias)

  - Encourage sponsors to submit regulatory documents, information of manufacturing and processing, analytical procedures to control products, Certificates of Analysis (CoAs), and validation reports/data
  - Challenging to engage sponsors; and to acquire adequate procedures for Identification tests, Assay, and Impurities

- USP Laboratories ('Internally sourced') – Internal Laboratory Support

  (the US, India, China, and Brazil)

  - Support from USP laboratories: technical questions cannot be clarified by a monograph sponsor, data are incomplete or excipients are from multiple sources
  - Extensive testing facilities for procedure development
  - Collaborative testing sites in four different sites
  - **Challenging to set impurity specifications**

Stakeholder Collaboration

Significant Accomplishments include the following:

- Formation of USP expert panels for Glycerin, Povidones and Talc to revise these 5 high priority monographs
- Improved specificity of Identification tests and discriminatory power of assay methods for many excipients
- The following monographs have been modernized
  - Butylated Hydroxyanisole
  - Butylated hydroxytoluene
  - Calcium Stearate
  - Dextrose Excipient
  - Gelatin
  - Guar Gum
  - MCC
  - Shellac
  - Aspartame

Challenges and Opportunities in Developing Up-to-Date *USP-NF* Excipient Monographs, American Pharmaceutical Review, September/October 2015, Pages 48-53

Table 1. Excipient List of FDA Priority Monographs

FDA Letter	USP/NF Monographs
Nov. 16, 2010[6]	Talc, Povidone, Copovidone, and Crospovidone
July 2, 2012[7]	• Butylated Hydroxyanisole • Butylated Hydroxytoluene • Calcium Stearate • Crosslinked Sodium Carboxymethylcellulose • Sodium Carboxymethylcellulose • Dextrose Excipient • Gelatin • Guar Gum • Microcrystalline Cellulose (MCC) • Pregelatinized Starch • Shellac • Silicon Dioxide (Colloidal) • Titanium Dioxide
July 2012	Aspartame, Glycerin
Dec. 2013[8]	Gelatin

Case Studies: Castor Oil Updated for Intended Use

- Work with Castor Oil manufacturer and USP laboratory
  - Add an assay to determine the strength (content) to reflect its use as an active pharmaceutical ingredient (API)
  - Add "*Other Requirements*" for Castor Oil that is used in injectable dosage forms

BRIEFING

Castor Oil, *USP 40* page 3233 and *PF* 41(5) [Sept.–Oct. 2015]. A revised monograph proposal was presented in *PF* 41(5). The following revisions are retained from the previous proposal:

1. The CAS number and chemical structure were added.
2. The *Definition* was updated.
3. *Identification A, Identity by Fatty Acid Composition* was added. The procedure for *Identification A* is based on a GC method of analysis performed with the Agilent DB-225 or Restek Rtx-225 brand of column with phase G7.
4. The test for *Distinction from Most Other Fixed Oils* was moved from the *Specific Tests* section to the *Identification* section as *Identification B*.
5. The *Assay* procedure for *Triglyceride Composition* was added, and is based on analyses performed with the Phenomenex Prodigy ODS (3) or Phenomenex Ultremex C18 brand of column with 5-µm packing L1.
6. The specification in the test for *Fats and Fixed Oils (401) , Procedures, Free Fatty Acids* was replaced with a specification for *Acid Value*, and the test for *Hydroxyl Value* was modified, as determined from the specification for *Acid Value*. The specifications for *Peroxide Value* and *Unsaponifiable Matter* were added; and the specification for *Iodine Value* was deleted.
7. The test for *Water Determination* was also added.
8. The *Packaging and Storage* section was updated.
9. The sections for *Labeling* and *USP Reference Standards* were added.

On the basis of comments and data received, it is proposed to make the following revisions to the *PF* 41(5) proposal:

1. Delete the term "refined" from the *Definition*, as previously proposed.
2. Add *Identification C* which uses UV-Vis spectroscopy to provide an identity for Refined Castor Oil and Virgin Castor Oil.
3. In the test for *Fats and Fixed Oils (401) , Procedures, Peroxide Value*, change the previously proposed peroxide value from NMT 5.0 to NMT 10.0.
4. In the *Labeling* section, add the sentence "Where Castor Oil must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled."
5. Under the *Other Requirements*section, add the specification for *Peroxide Value*as NMT 5.0. Also add a test for *Ultraviolet Absorption*and the *Bacterial Endotoxins Test* for Castor Oil that is to be used in injectable dosage forms.

Case Studies: Castor Oil Updated for Intended Use

- Work with Castor Oil manufacturer and USP laboratory
  - Add an assay to determine the strength (content) to reflect its use as an active pharmaceutical ingredient (API)
  - Add "*Other Requirements*" for Castor Oil that is used in injectable dosage forms

■ • **OTHER REQUIREMENTS:** For Castor Oil intended for use in injectable dosage forms, which is specified in the *Labeling* section, the following specifications must be met:

A. Water Determination ⟨921⟩ **:** NMT 0.2%

B. Fats and Fixed Oils ⟨401⟩ **,** *Procedures, Acid Value* **:** NMT 0.8

C. Fats and Fixed Oils ⟨401⟩ **,** *Procedures, Peroxide Value* **:** NMT 5.0

D. Ultraviolet Absorption

Sample solution: Dissolve 1.0 g of Castor Oil in alcohol, and dilute with alcohol to 100 mL.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩ .)

Mode: UV-Vis

Analytical wavelength: 270 nm

Cell: 1 cm

Analysis: Determine the UV-Vis absorbance using the *Instrumental conditions* described above.

Acceptance criteria: The absorbance is within the range of 0.7–1.5.

E. Bacterial Endotoxins Test ⟨85⟩ **:** The level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Castor Oil is used can be met. Where the label states that Castor Oil must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Castor Oil is used can be met. ■2S (*USP41*)

Case Studies: Assays Added to Several Atypical Actives

- For each of the following atypical actives, USP Excipient Expert Committee works with material manufacturers and USP laboratories to add an assay to determine the strength (content) to reflect its use as an active pharmaceutical API
  - Polyethylene Glycol 3350 [*PF* (*Pharmacopeial Forum*) 39(6), *PF* 41(4)]
    - Main polymeric fraction by Size-exclusion chromatography with refractive index detection (RID)
  - Castor Oil [*PF* 43(4), *PF* 41(5)]
    - Triglyceride Composition by HPLC-Evaporative Light Scattering detection (ELSD)
  - Dextrose [*PF* 38(6), *PF* 34(6)]
    - Dextrose by HPLC-RID
  - Mannitol [*PF* 41(5), *PF* 34(6)]
    - Mannitol by HPLC-RID
  - Isopropyl Alcohol [*PF* 38(2)]
    - Content determined by GC
  - Deoxycholic Acid [*PF* 41(5)]
    - Content determined by HPLC-charged aerosol

New Project

Excipient Impurities

- Case Studies: Octyldodecanol is an excellent example (IRA, official 01-Jan-2017)
  - Different Organic Impurity Profiles
    - When different routes of synthesis yield different impurity profiles, different impurity test procedures may be needed. In this case, the additional applicable procedure should be included in the labeling (see section *B. 9.2 Labeling* below).

      ORGANIC IMPURITY TEST 1: LIMIT OF RELATED FATTY ALCOHOLS AND ALKANES
      ORGANIC IMPURITY TEST 2: LIMIT OF BRANCHED CHAIN FATTY ALCOHOLS AND BRANCHED CHAIN ALDEHYDE

      Labeling: If a test for Impurities other than *Organic Impurity Test 1* is used, the labeling states the test with which the article complies

New Project

Excipient Impurities

- Case Studies: Deoxycholic Acid is an excellent example (updated monograph officially adopted into *USP* 40-*NF* 35 *Supplement*: No. 1 Page 8256)
  - Different Organic Impurity Specifications are for Different Origins
    - **Organic Impurities**

Acceptance criteria

Deoxycholic Acid of animal origin

Cholic acid: NMT 1.0%

Total impurities: NMT 2.0%

Deoxycholic Acid of synthetic origin: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria NMT (%)
3α,12β-Dihydroxy-5β-cholan-24-oic acid	0.69	0.15
3α,12α-Dihydroxy-5β-chol-9(11)-en-24-oic acid	0.87	0.15
Ethyl 3α,12α-dihydroxy-5β-cholan-24-oate	1.61	0.15
Any individual unspecified impurity	—	0.10
Total impurities	—	2.0

■1S (*USP40*)

LABELING: Label it to indicate whether Deoxycholic Acid is derived from an animal or synthetic source. Deoxycholic Acid intended for use in preparing parenteral dosage forms is so labeled. ■1S (*USP40*)

Moving Forward

- Industry and regulatory agencies working together – utilizing and sharing each other's resources, experience and knowledge
  - **Need in-depth understanding and more studies on Excipient Impurities and Excipient Nomenclature**
- Communicate with and inform stakeholders on key issues relating to excipient monograph specifications so each can provide input into updating these standards.
- Collaborate with stakeholders in development and strengthening of compendial standards

Any questions?

Thank You

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