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U.S. Pharmacopeial Convention

The USP Excipients Stakeholder Forum
Meeting # 2
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USP Priority Excipient Monograph Modernization Updates

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USP Monograph Modernization

- Primary driver is maintaining up-to-date quality standards to support USP's commitment to public health
- Need for modernization
  - Monographs have been official for several years, decades in some cases
  - Content does not reflect current expectations for procedures and acceptance criteria
  - Complaints from the public
  - General lack of specificity
- Modernization is a subset of USP's ongoing revision work, started using the term "modernization" in 2009
- FDA Modernization Task Group (Nov. 2010)
  - FDA letters sent to USP with priority excipients for modernization - most recent, Dec. 2013. Total list of 19 to date.

USP Monograph Modernization

- Benefits
  - Strengthens the public standards
  - Moves from non-specific to specific procedures
  - Considers practical factors
    - removes unnecessary tests
    - Safety/environmental issues such as eliminating use of chlorinated solvents
    - hard to find equipment
  - Increases consistency across monographs

Monograph Updating Strategies

Monograph and Reference Material Procurement and Development

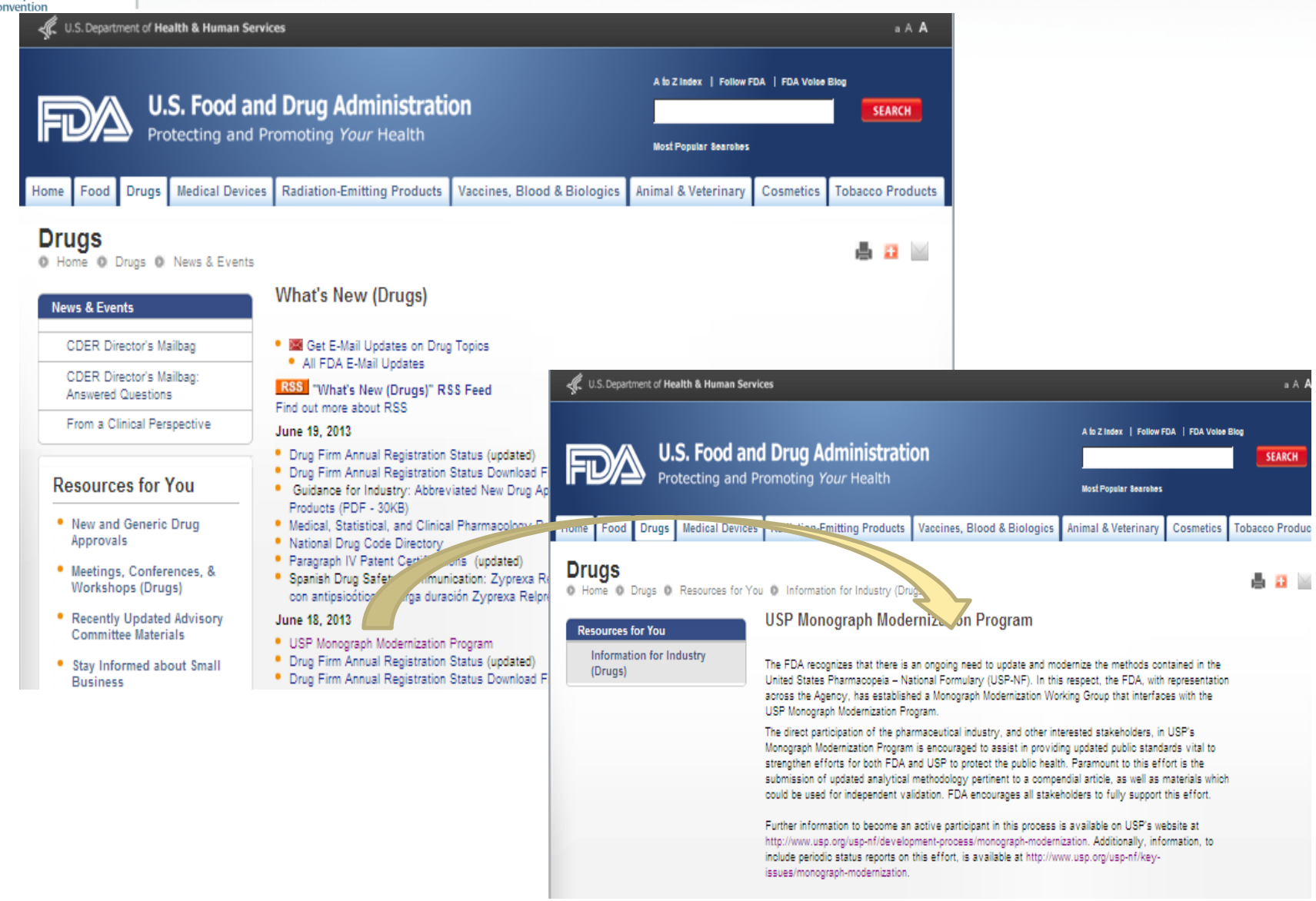
- Traditional donor model (‘externally sourced’)
  - Very difficult to engage sponsors
- USP laboratories (‘internally sourced’)
  - New technologies in Rockville labs
  - Extensive testing facilities in India, China and Brazil for method development
  - Collaborative testing sites in India, China and Brazil
  - MOU with China - excipient monograph development
- FDA (CRADA: ORA Labs)
- Adapt/Adopt (Other Pharmacopeias e.g. E.P., B.P., ChP)

Monograph Modernization Strategy and Approaches

Continued Collaboration with FDA and Industry

- Prioritization
- Timing considerations

FDA.gov Links to USP website on Monograph Modernization



Excipient Monograph Modernization: Prioritization of Categories

- No Identification or non-specific Identification procedures
- No Assay or non-specific Assay procedures
- Stainless steel/packed column GC procedures
- Titration to GC/HPLC where appropriate
- No impurity test, (e.g., Povidones and peroxides/aldehydes)
- Safety-related concerns (e.g., chlorinated solvents).
- Additional requirements
  - Labeling deficiencies , e.g., when used in parenteral/injectable applications
  - Missing specific tests to control quality (e.g., Microbial/BE)
- Nomenclature – Title and Definition issues reported to USP mainly by manufacturers

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Monographs in Need of Modernization (Last Updated 02-June-2014)

Yellow highlighting indicates a change in status since the last posting

Monograph Name	Date Added to List	Date of Last Status Change	Status	Publication	Monograph Type	Monograph Test	Procedure	Replace or Add Test	Replacement Procedures	Liaison	Comments
ALGINIC ACID	24-May 2010 (Initial posting)		Submission Needed		Excipient	Assay	Missing	Add		Hong Wang hw@usp.org	
ALKYL (C12-15) BENZOATE	24-May 2010 (Initial posting)		Submission Needed		Excipient	Assay	Missing	Add		Hong Wang hw@usp.org	
ALUMINUM MONOSTEARATE	24-May 2010 (Initial posting)		Submission Needed		Excipient	Identification	Wet Chemistry	Add	FTIR test	Galina Holloway gvh@usp.org	
AMMONIUM CARBONATE	24-May 2010 (Initial posting)		Submission Needed		Excipient	Identification	Wet Chemistry	Add	FTIR test or IC	Galina Holloway gvh@usp.org	
AMMONIUM PHOSPHATE	24-May 2010 (Initial posting)		Submission Needed		Excipient	Identification	Wet Chemistry	Add	FTIR test or IC	Galina Holloway gvh@usp.org	
AMMONIUM SULFATE	24-May 2010 (Initial posting)		Submission Needed		Excipient	Identification	Wet Chemistry	Add	FTIR test or IC	Galina Holloway gvh@usp.org	
ASPARTAME	17-06-2013 (Initial posting)		Submission Needed		Excipient	Assay	Titration	Replace	HPLC	Galina Holloway gvh@usp.org	ORA list
BENZALDEHYDE	24-May 2010 (Initial posting)	28-Nov-2012	Official	USP36-NF31	Excipient	Identification Assay Impurities	Missing Titration Missing	Add Replace Add	FTIR test Modern Procedure	Galina Holloway gvh@usp.org	Added IR for identification and chromatographic procedure for Assay.
BORIC ACID	24-May 2010 (Initial posting)		Submission Needed		Excipient	Identification	Wet Chemistry	Add	FTIR test	Galina Holloway gvh@usp.org	
BUTYL ALCOHOL	24-May 2010 (Initial posting)	8-Apr-2013	Official	USP36-NF31 S2	Excipient	Identification	Missing	Add	FTIR test or IC	Galina Holloway gvh@usp.org	Added IR for identification and GC procedure for Assay.
BUTYLATED HYDROXYANISOLE	27-Jul 2012 (Initial posting)		Submission Needed		Excipient	Identification	Wet Chemistry and Retention Time by HPLC	Add	More specific Instrumental Test	Galina Holloway gvh@usp.org	FDA priority
BUTYLATED HYDROXYTOLUENE	27-Jul 2012 (Initial posting)		Submission Needed		Excipient	Identification	Wet Chemistry and IR	Add	More specific Instrumental Test	Galina Holloway gvh@usp.org	FDA priority
CALCIUM SILICATE	24-May 2010		Submission		Excipient	Identification	Wet	Add	FTIR test	Galina Holloway	

CM Modernization | Excipients Modernization

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http://www.usp.org/usp-nf/development-process/monograph-modernization

MMTG list /ORA list of monographs for modernization - progress

MMTG list of monographs for modernization (combined with ORA list of 4)		
Excipient Monograph	**FDA letter/ORA list**	**Status**
1. Butylated Hydroxyanisole	Letter 2, July 2012	
2. Butylated Hydroxytoluene	Letter 2, July 2012	*PF* 40(2)
3. Dextrose Excipient	Letter 2, July 2012	
4. Silicon Dioxide (Colloidal)	Letter 2, July 2012	
5. Titanium Dioxide	Letter 2, July 2012	
6. Cross-linked Sodium Carboxymethylcellulose	Letter 2, July 2012	
7. Sodium Carboxymethylcellulose	Letter 2, July 2012	
8. Gelatin (H6)	Letter 2, July 2012	*RB USP* 36-*NF* 31
9. Guar Gum	Letter 2, July 2012	*PF* 39(5) *USP* 37-*NF* 32 2S
10. Microcrystalline Cellulose (MCC)	Letter 2, July 2012	
11. Pregelatinized Starch	Letter 2, July 2012	
12. Shellac	Letter 2, July 2012	*PF* 40(4)
13. Calcium Stearate	Letter 2, July 2012	*PF* 39 (3) *USP* 37-*NF* 32 1S
14. Talc	Letter 1, Nov. 2010	
15. Povidones (Povidone, Copovidone and Crospovidone)	Letter 1, Nov. 2010/Crospovidone ORA list	
16. Glycerin	ORA list	
17. Titanium Dioxide	Letter 2, July 2012/ ORA list	*PF* 40(1) – Stimulus article
18. Aspartame	ORA list	*PF* 40(2)
19. Gelatin	Letter 3, Dec. 2013	

http://www.usp.org/usp-nf/key-issues/monograph-modernization Update

Modernizations - China site

No	Monograph	Activities
1	Potassium Sorbate	Add ID by FTIR and HPLC Assay to replace titration Assay
2	Sorbic Acid	HPLC Assay to replace titration Assay can be done in conjunction with Potassium Sorbate
3	Adipic Acid	HPLC Assay to replace titration Assay
4	Galactose	Add assay
5	Monosodium Glutamate	Add specific ID and assay
6	Tributyl Citrate	Need GC Procedure without temperature-programmable injector
7	Acetyltriethyl Citrate	Need GC Procedure without temperature-programmable injector
8	Alginic Acid	Add specific ID and Assay.
9	Sodium alginate	Add specific ID and Assay
10	Potassium alginate	Add specific ID and Assay
11	Phenylmercuric Acetate	Add ID, FTIR Test
12	Phenylmercuric Nitrate	Add ID, FTIR Test
13	Titanium Dioxide	“Assay method is out of date: FDA recommendation: Use Ref: "A novel volumetric method for quantitation of titanium dioxide in cosmetics," (Journal of Cosmetic Science, Volume 57, Issue 5, Pages377-383, 2006).
14	Sodium Metabisulfite	Replace current Assay titration and modernize <191> ID and add impurities
15	Sodium Sulfite	Replace current Assay titration and modernize <191> ID and add impurities
16	Ammonium Carbonate	Replace current Assay titration and modernize ID and impurities
17	Ammonium Phosphate	Replace current Assay titration and modernize <191> ID and impurities with IC
18	Ammonium Sulfate	Replace current Assay titration and modernize <191> ID and impurities with IC
19	Magnesium Aluminometasilicate	Add ID, FTIR Test or other suitable test
20	Magnesium Aluminosilicate	Add ID, FTIR Test or other suitable test
21	Magnesium Aluminum Silicate	Add ID, FTIR Test or other suitable test
22	Magnesium Silicate	Add ID, FTIR Test or other suitable test
23	Potassium Metabisulfite	Add ID, FTIR Test or other suitable test
24	Calcium Sulfate	Add ID, FTIR Test or other suitable test
25	Calcium silicate	Add ID, FTIR Test or other suitable test
26	Potassium Hydroxide	Add ID, FTIR Test or other suitable test
27	Potassium metaphosphate	Add ID, FTIR Test or other suitable test
28	Potassium phosphate monobasic	Add ID, FTIR Test or other suitable test

USP Monograph Modernization Process

- Modernization of monographs achieved by
  - *Replacing* outdated technology and methodology with more current procedures
  - *Adding* critical tests to the monograph
  - *Deleting* non-value added tests, as needed (e.g., odor test, melting point)
- Follows the USP standards-setting process (i.e., with publication in PF for 90-day comment period)
- FDA to provide input to USP on prioritization (FDA MMTG and ORA lists)
- Other considerations
  - Use procedures from other pharmacopeias
  - May need RS materials
  - Revising the monograph “family”, as needed

FDA MMTG Nov.16, 2010 letter requested revisions:

- **USP Povidone, NF Crospovidone, NF Copovidone:**
  a) 3 Povidones not consistent w.r.t. impurity specifications. Should be harmonized within USP and to the EP monographs (Limit of Hydrazine; Limit of aldehydes; Peroxides; Heavy metals.
  b) Nitrogen assay test (<461> Nitrogen Determination (by Kjeldahl method)) is non specific. Prefer a more specific method due to concerns about economically motivated adulterants, eg., melamine.
- **USP Talc:**
  a. Labeling statement should be revised to match the statement from the FCC monograph's description thereby assuring that Talc is not sourced from mines that are known to contain asbestos.
  b. USP should consider revising the current test for *Absence of asbestos* to ensure adequate specificity.

FDA MMTG list of Monographs: Povidones status

- **Povidone:** PDG Stage 6 adoption includes the addition of tests for
    - Limit of hydrazine, Limit of aldehydes, Peroxides
- **Crospovidone:** PDG Stage 6 adoption includes the addition of tests for
    - Peroxides, Limit of monomers (vinylpyrrolidinone)
    - Both Stage 6 posted on harmonization website on Feb. 25, 2011
    - **Both Official Dec. 1, 2011 (Second Supplement to *USP* 34–*NF* 29)**
- **Copovidone:** PDG Stage 4 Official Inquiry
    - *PF* 37(4) [July – Aug. 2011]. Addition of Test for Lead. Revision of Limit of Monomers (change from titration,(0.1%) to HPLC (0.001%)
        - **Official *USP* 35-*NF* 30-2S publication**
- **Povidone:** PDG Stage 6 adoption
    - *PF* 38(2) [Mar. – Apr. 2012].
        - Revision of Identification test to include an FTIR spectroscopy test. EP monograph includes this test.
        - **Official *USP* 36-*NF* 31-1S publication**

USP Expert Panels (EP)

- The USP Excipient (Exc) Expert committee has created 3 Expert Panels to address FDA's request to modernize 3 excipient monographs for Glycerin (S3), Talc (S6) and Povidones (Povidone (S6), Crospovidone (S6) and Copovidone (S4)).
  - These Monographs are also part of the Pharmacopeial Discussion Group's workplan.
- Expert Panels allow for global participation of excipient users, makers, distributors, governmental and academics in method development and testing that provide recommendations to the Exc Expert Committee.
- Aim is to submit EP's/Exc EC proposed methods to PDG for consideration in the development of a harmonized S6 monograph.

Goal: Harmonized, modernized global quality standards for excipients in commerce

Expert Panel on Povidones

Povidones Expert Panel formed in 2011 for replacement of nonspecific Nitrogen assay test (<461> Nitrogen Determination (by Kjeldahl method)).

- Significant challenges exist to developing a replacement assay method for total nitrogen.
- Working with stakeholders including global experts from industry to look at other possible methodologies to detect potential intentional adulterants.
- Determine what level of detection can be established through existing USP compendial tests (s) or other procedures to be established.
  - –Monograph unable to detect all potential known and unknown intentional adulterants at levels as stated in the FDA Melamine guidance of 2.5ppm (0.00025%)
  - –Current compendial tests can control adulteration at levels greater than 5%, but are mostly inconclusive at levels below.
- NOT to focus specifically on individual adulterants such as melamine. Melamine is not the only intentional adulterant that may be introduced into pharmaceutical ingredients supply chain.
- Explore ways to control BOTH known and unknown intentional adulterants.

Povidones Expert Panel Challenges and Progress

- Consensus from Povidones EP is not to replace Kjeldahl Assay, but instead introduce a series of orthogonal ID and other tests to strengthen monograph.
- Recommendations of the EP on possible methods under consideration
  - Fast GPC for use as either an assay and/or impurities procedure
  - HPLC as a specific test to control organic impurities. Currently testing to see if conventional UV detector can be used.
  - Ash test as a specific test method to control for inorganic adulterants
  - Eliminate non-value added chemical identity methods where information is already provided in the newly added IR Identification.
- Submit to the EP/EXC EC and update on the progress at PDG June 2014 Rockville, MD meeting

Talc Expert Panel Challenges and Progress:

Pure Talc (hydrated magnesium silicate, $Mg_3Si_4O_{10}(OH)_2$)

- Request from FDA to revise Labeling statement and revise the current test for Absence of Asbestos to ensure adequate specificity.
- No one single method is sufficient to adequately control asbestos contamination as it depends on the type of asbestos and the combination of techniques used - a microscopy method is typical.
- Talc EP evaluated existing *Absence of Asbestos* test methods in USP and recommend alternative analytical methods and procedures. Currently,
  - **(XRD) has insufficient detection limit to be conditional (could lead to false negative).**
  - **(Light Microscopy) is not developed adequately (could lead to false positive).**
    - Strengthen the X-Ray Diffraction (XRD) methodology to include RS and eliminate IR test.
    - Development of orthogonal microscopy methods (Polarized Light Microscopy (PLM), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM)) depending on the type of asbestos .

Talc Expert Panel Challenges and Progress:

- Expert panel recommendations and key points published in a Stimuli article in *PF* 40(4)[July-Aug. 2014]
- Next steps
  - Submit the EP/EXC EC update to PDG on the development of a Stimuli Article to solicit stakeholder feedback to the appropriate methodologies and specifications for a compendial standard.
  - Educate users who are not familiar with the unique geological challenges of Talc.
- Labeling statement language to be addressed following finalization of methodology.

Glycerin Expert Panel

- Panel Formed in March 2013 with the goal to provide a global Stage 3 draft proposal to present to PDG.
- Provide a consensus on which methods should be included and which existing methods may not have value
- Three Subteams have been formed to work on different parts of the monograph
  - 1) Definition, Assay, ID, and Water
  - 2) Organic impurities, related compounds, aldehydes, chlorinated compounds, fatty acids, and esters
  - 3) ROI, Chloride, sulfate, heavy metals, Color
- EP Progress:
  - EP members conducting modification of the existing USP GC ID B/C procedure for suitability as an assay procedure
  - Evaluation of HPLC UV methods for aldehydes determination

Gelatin - FDA letter to USP, Dec. 2013

http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/2013-12-02_fda_mmtg_letter.pdf

- **FDA recommend s USP revise the ID section of Gelatin NF**

FDA has evaluated the melamine spiking study and other information submitted by GMIA and has conducted additional analytical studies to investigate further. The FDA studies include evaluations of several analytical methods to detect the presence of melamine spiked into samples of NF-grade gelatin. Two methods, powder x-ray diffraction (PXRD) and near-IR spectroscopy (NIRS), were found capable of producing accurate, quantitative measurement of melamine in gelatin in a reasonable timeframe, at levels greater than 1% w/w. More commonly-available methods found suitable of qualitative assessment of melamine in gelatin included Fourier transform infra-red (FT-IR) and Fourier transform Raman (FT-Raman) spectroscopy. This study data will be provided to you upon request.

We recommend that, as part of the general monograph modernization effort, USP consider adding a new analytical test or tests, as above, to the Gelatin, NF monograph. As noted in USP General Chapter <197>, IR and UV tests have general applicability to identification testing, and can be useful in detection of contaminants such as melamine. Additionally, we think that revision of the current *Identification* (Test B) might be useful so that it could qualitatively detect

the presence of certain adulterants, such as melamine, that can alter the physico-chemical characteristics of gelatin.

Conclusion

- Excipient monograph modernization is a major initiative in the 2010-2015 revision cycle
- Collaboration with FDA, industry and other stakeholders is key to advancing the work
- Long-term goal is to implement a regular monograph review process to monitor the needs for further modernization
- USP's Challenges
  - Obtaining procedures and acceptance criteria from sponsors
    - USP will continue to use its lab resources and engage stakeholders
    - Sourcing procedures from other compendia, literature, other
  - Prioritizing and requesting submissions - with FDA involvement , the hope is that industry is much more likely to submit a proposal

Thank You