Welcome
USP Monograph Modernization
Web Meeting
February 25, 2011
USP Monograph Modernization Initiative
FDA Monograph Modernization Task Group
CHPA Proposal
Priority Monograph Topics
- Acetaminophen
- Diphenhydramine
- Copovidone, Crospovidone, Povidone
- Talc
Stakeholder Participation/Getting Involved
Discussion
Wrap up
USP Monograph Modernization Initiative

Karen A. Russo, Ph.D.
Vice President, Small Molecules
April 24, 2010

Resolutions Supporting Public Health Adopted by Convention

Strengthen USP’s Relationship with the U.S. Food and Drug Administration. USP resolves to strengthen its relationship with the Food and Drug Administration (FDA), and work with FDA and other public and private stakeholders to explore mechanisms to enable USP to provide and maintain up-to-date national standards for legally marketed drugs and excipients in the United States.
Monograph Modernization

Revising monographs by

- *Replacing* outdated technology and methodology with more current procedures
- *Adding* critical tests to the monograph (e.g., impurities)
- *Deleting* non-value added tests, as needed (e.g., odor test, melting point)

Scope

- About 700 (possibly more?) Small Molecules and 96 Excipient monographs needing modernization

USP’s Challenges
- Obtaining procedures and acceptance criteria
- Timing
No impurity test

- Non-specific Identification procedures
- Non-specific Assay procedures
- Packed column GC procedures
- Safety-related concerns (e.g., chlorinated solvents).

- TLC (particularly <466> Ordinary Impurities), UV, or wet chemistry test for impurities
Monograph Modernization

Posted: February 8, 2011

As part of USP’s initiative to update and improve its monographs for drug substances and products in the United States Pharmacopeia and the National Formulary (USP-NF) compendia, USP is focusing on monographs identified recently as a priority by the U.S. Food and Drug Administration (FDA). **USP is seeking active input from industry in this monograph modernization initiative via a live Open Microphone Web Meeting on Friday, February 25, 2011, 1:00 to 3:00 p.m. ET. Register now for this event.**

A November 16, 2010 letter to FDA listed USP monographs for acetaminophen and diphenhydramine and for several related dosage forms as high priority for updating. Most of these monographs assist in controlling the quality of over-the-counter (OTC) medications. The letter also identified as high priority NF monographs for copovidone, crospovidone, povidone and talc for updating. The FDA letter, and USP’s December 20, 2010 response are available below.

**Correspondence between FDA and USP**
- November 16, 2010 Letter from FDA Task Group to USP (162KB)
- December 20, 2010 USP response to FDA Task Group (80KB)

**Priority Monographs**
- USP list of priority monographs (85KB)

**Background Information**
- About monograph modernization

**How to Comment**
USP seeks assistance and procedures from manufacturers of products and ingredients covered by the priority monographs, as well as from the practitioner community. To facilitate this and also to ensure adequate stakeholder input, USP will host an Open Microphone Web Meeting on Friday, February 25, 2011, from 1:00 p.m. to 3:00 p.m. ET. **Register now for this event.**

**Contacts**
- Small Molecules: Karen Russo (kar@usp.org or +1-301-816-8379)
- Media: Laura Provan (lpro@usp.org or +1-301-816-8268)
USP Monograph Modernization Web Page

- Launched in May 2010
- “Call for Submissions”
- Includes spreadsheet with top 200 small molecule monographs and 96 excipient monographs in need of modernization
- Monthly status updates (last Friday of the month, adjusted for holidays)
- Each month’s status changes are highlighted in yellow
USP Seeks Submission of Proposals for Monograph Modernization

May 28, 2010

The USP is actively engaged in efforts to modernize official USP-NF monographs for small molecules and excipients that utilize outdated technology (e.g., use of packed gas chromatography columns), have safety/environmental concerns (e.g., chlorinated solvents, etc.) or are missing procedures for key aspects such as impurities. For excipients, a major modernization goal is to replace relatively non-specific identification procedures with specific procedures (e.g., IR spectroscopy). To facilitate the modernization efforts, USP has identified and prioritized monographs in need of modernization and is seeking proposals to replace the current procedures or add procedures, as needed.

Monographs in need of modernization are presented in a downloadable spreadsheet that includes information on what procedure needs modernization and the current status of the modernization (separate tabs for small molecules and excipients). Some monographs have more than one procedure in need of modernization and each procedure is presented as a separate line item. In an effort to focus the modernization effort, the spreadsheet contains the top 200 small molecules monographs and 96 excipient monographs. There are more monographs in need of modernization and they will be added to the spreadsheet periodically as work progresses. Submissions for monograph modernizations that are not listed are also encouraged and can be submitted at anytime. The spreadsheet will be updated and posted on the USP Web site on a monthly basis on the last Friday of each month.

In order for USP to maintain consistency with FDA-approved control strategies, USP prefers to receive submissions from manufacturers of FDA-approved products (including drug substances and excipients that are known to be used in FDA-approved products) or manufacturers intending to seek FDA approval. The latter category of submissions will be initially considered for publication as a Pending standard (see USP Pending Monograph Guidelines). Submissions, especially new impurity procedures, from other sources (e.g., contract laboratories, academic institutions, analytical instrumentation/equipment manufacturers) can be accepted on a case-by-case basis and should follow ICH Q3 guidelines. All submissions should include data and other information recommended in the USP Guideline for Submission of Request for Revision to USP-NF. Please review the USP Submission Checklist for data and information that should be included in the submission.

Some modernized standards may generate new USP Reference Standards and USP invites the sponsor of the proposal to donate the necessary bulk reference materials. For more information, please review the USP Guideline for Suppliers of Reference Standard Materials.
Electronic submissions (e.g., pdf, access to ftp site) are preferred and can be submitted to Mr. Michael Goede for Small Molecules at myg@usp.org or to Mr. Jay Pearson for Excipients at wjp@usp.org. USP also accepts hard copies and they can be sent accordingly to the following address:

Mr. Michael Goede or Mr. Jay Pearson  
Manager, Standards Acquisition  
United States Pharmacopeia  
12601 Twinbrook Parkway  
Rockville, MD 20852

If your organization would like a list of company-specific modernization proposals needed, please contact Mr. Randy Kiser at rwk@usp.org.

For general information, please contact:

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Vice President, Small Molecules  
kar@usp.org 301-816-8379

Catherine Sheehan, M.S.  
Director, Excipients  
cxs@usp.org 301-816-8262

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**Small Molecules and Excipients Monographs Needing Modernization**

**Posting Date: February 25, 2011**

- Download the Monograph Modernization list (175KB) (updated February 23, 2011)

**Next Posting Date: March 25, 2011**
## Monographs in Need of Modernization

_Last Updated 23-February-2011_

<table>
<thead>
<tr>
<th>Monograph Name</th>
<th>Monograph Family</th>
<th>Date Added to List</th>
<th>Date of Last Status Change</th>
<th>Status</th>
<th>Publication</th>
<th>Monograph Type</th>
<th>Monograph Test</th>
<th>Procedure</th>
<th>Replace or Add Test</th>
<th>Replacement Procedures</th>
<th>Liaison</th>
<th>Comments</th>
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<tbody>
<tr>
<td>NAPROXEN SODIUM</td>
<td>NAPROXEN SODIUM</td>
<td>24-May 2010 (Initial posting)</td>
<td>18-Jun-2010</td>
<td>Submission Received</td>
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<td>Impurities</td>
<td>Missing</td>
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<td>Quantitative stability indicating procedure</td>
<td>Clydewyn Anthony <a href="mailto:cm@usp.org">cm@usp.org</a></td>
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<td></td>
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<td>Impurities</td>
<td>Missing</td>
<td>Add</td>
<td>Quantitative stability indicating procedure</td>
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<td>Replace</td>
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<td>Sujatha Ramakrishna <a href="mailto:srx@usp.org">srx@usp.org</a></td>
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<td>Replace</td>
<td>Modern Procedure</td>
<td>Sujatha Ramakrishna <a href="mailto:srx@usp.org">srx@usp.org</a></td>
<td>Added new item for monograph</td>
<td></td>
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</table>
Proposals Submitted for Publication in PF
- FY10 (July 1, 2009-June 30, 2010): 37
- FY 11 (since July 1, 2010): 23

In Development: 91 monographs/101 tests
- 45 USP-initiated/sponsored
- 46 Industry-sponsored

Activity on Web page listing since May 2010
- Commitments for 18 monographs/24 tests
- Received submissions for 7 monographs/9 tests
<table>
<thead>
<tr>
<th>Monograph</th>
<th>PF Citation</th>
<th>Modernization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alclometasone Dipropionate</td>
<td>PF 36(5) [Sep-Oct 2010]</td>
<td>Replace Ordinary Impurities by TLC with HPLC</td>
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<tr>
<td>Glycopyrrolate</td>
<td>PF 37(1) [Jan-Feb 2011]</td>
<td>Replace titration Assay with HPLC; replace Ordinary Impurities by TLC with HPLC; delete Melting Range or Temperature test; add test for Limit of Erythro Isomer by HPLC</td>
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<tr>
<td>Glycopyrrolate Tablets</td>
<td>PF 37(1) [Jan-Feb 2011]</td>
<td>Replace UV-based Assay and Dissolution procedure with HPLC; add impurities test</td>
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<tr>
<td>Spironolactone</td>
<td>PF 37(1) [Jan-Feb 2011]</td>
<td>Replace chloroform with alcohol in Specific Rotation test; replace &lt;197S&gt; using chloroform with &lt;197K</td>
</tr>
<tr>
<td>Temazepam</td>
<td>PF 36(6) [Nov-Dec 2010]</td>
<td>Replace TLC-based impurities procedure with HPLC procedures; removed use of Internal Standard from the Assay</td>
</tr>
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</table>
Continued Collaboration with FDA
- Prioritization
- Timing considerations

Sponsors/Sources of Data
- Manufacturers
- USP-generated data
- Other Compendia
- Others? (e.g. column manufacturers, CRADA, MOUs)

Revision Processes and Timing
- Routine In Process Revisions using *Pharmacopeial Forum*
- Accelerated revisions, as appropriate (e.g., Revision Bulletins and Interim Revision Announcements)
- Delayed-implementation of official date
Monograph Modernization Strategy and Approaches

Content

- Revision of individual monographs
- Revision to monograph “families”
- Drug-specific performance-based chapters, particularly for larger monograph families (e.g., impurities in acetaminophen-containing products)
- Consider tackling drug substance monographs first, then similar dosage forms (liquids, solid oral products, etc) and/or single active then combination products

USP Volunteers

- Continually engage Expert Committees
- Formation of Joint Sub-Committees and Expert Panels for topic-specific assignments
Communication and Outreach

- “Design phase” approach bringing together manufacturers, regulators, and stakeholders
  - Web meetings
  - Public forums, conferences and meetings
  - Work Shops
  - Stimuli Articles
- Use USP Web site for Hot Topics pages and initiative-specific content
- Pre-publication of high-impact revisions on Web site in advance of PF publication
What’s Next?

- Establish Expert Panel for Acetaminophen (and possibly Diphenhydramine) by May 1, 2011
  - Watch the Monograph Modernization Hot Topics page for the Call for Candidates—coming soon!

- OTC Workshop
  - September 8-9, 2011
  - USP Headquarters, Rockville, MD
FDA Monograph Modernization Task Group

Larry Ouderkirk
Consumer Safety Officer
Office of Compliance
FDA Monograph Modernization Task Group (MMTG)

A Task Group within the established FDA Pharmaceutical Quality Standards Working Group:

- Facilitate monograph modernization and monograph prioritization activities of FDA
- Develop a science- and risk-based approach for ongoing prioritization and oversight of USP monograph modernization efforts
- Work with USP to achieve improvements to compendial monographs in accordance with USP Resolutions adopted for the 2010-2015 cycle
- Focus ongoing efforts for USP monograph modernization on those monographs and general chapters whose improvement would most greatly benefit the public health by reducing potential risks
- Provide any evolved recommendations in writing to USP
USP Monograph Modernization

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Who is CHPA?

Committed to promoting the role of OTC and Dietary Supplement products through Science, Education and Advocacy

serving the self-medication industry since 1881
Who is CHPA?

78 Active Members
Who is CHPA?

118 Associate Members

Advertising Agencies
Cable, TV and Radio Networks
Consultants
Contract Manufacturers
Executive Search Firms
Ingredient Suppliers
Internet Services
Logistics Providers
Market Research Firms

Packaging Companies &
Graphics Developers
Print Media
Sales & Marketing Co’s
Retail Merchandising Co’s
Scientific/Regulatory
Consulting
Clinical Research Labs
Product Brokers
Mission

The MCC represents OTC interests on manufacturing and quality issues by participating in activities that will lead to clear and reasonable regulation/guidance and standards, based on risk analysis and science.
USP Monograph Modernization

Member Involvement

- BASF
- Bausch & Lomb
- Bayer Healthcare
- Boehringer Ingelheim Pharmaceuticals
- Carma Laboratories
- Chattem
- Colorcon
- Covidien
- GlaxoSmithKline
- IPEC-Americas
- Johnson & Johnson Consumer Companies
- McNeil Consumer Healthcare
- Merck Consumer Care
- Novartis Consumer Health
- Perrigo Company
- Pfizer Consumer Healthcare
- Pharmalytik
- Prestige Brands Holdings
- Purdue Pharma
- The Procter & Gamble Company
USP Monograph Modernization

Timeline:

May 2010: USP posts “Monographs in Need of Modernization” to their website (updated monthly)

August 2010: FDA/USP/CHPA Planning Committee is formed

October 2010: Scott Furness, Ph.D. (FDA) and Karen Russo, Ph.D. (USP) present at CHPA’s Manufacturing Controls Seminar

November 2010: FDA sends USP a letter containing FDA priority list

December 2010: USP responds to FDA’s letter

January 2011: CHPA sends commitment letter to FDA and USP
USP Monograph Modernization
CHPA’s commitment letter

Proposed FDA Role:

• Identify and prioritize OTC drug products in need of modernization
  – consumer exposure data (market volumes)
  – toxicity
• Transparency
• FDA’s involvement extends throughout the modernization process
Proposed USP Role:

- Utilize FDA’s priority list of products/ degradants
- Use existing or unique approaches to form teams (expert panels) comprised of subject matter experts (SMEs)
  - Involve FDA, USP and Industry experts
- Through full public review using current USP process
USP Monograph Modernization

CHPA’s commitment letter

CHPA Commitments

- Identify and provide industry experts to participate on each USP team (expert panel)
- Establish working groups of member companies
  - unprecedented effort at this scale - work as an industry to propose and submit revisions to USP
- Monograph revisions should be based on FDA’s “prioritization list”
- CHPA will work to provide limits
USP Monograph Modernization
CHPA’s commitment letter

CHPA’s Path Forward

• CHPA Acetaminophen Working Group
  – Begin with a focus on 4-aminophenol limits
  – Collecting and sharing company data
• CHPA Diphenhydramine Working Group
• CHPA member companies encouraged to work in parallel
USP Monograph Modernization

• FDA, USP, Industry
  – Partner in this effort (3-legged stool)
  – Continue to use FDA/ USP/ CHPA Planning Committee

• September 2011:
  Participate in Fall USP OTC workshop
Monograph Topics
Karen A. Russo, Ph.D.
Vice President, Small Molecules

Kevin Moore, Ph.D.
Senior Scientific Liaison
<table>
<thead>
<tr>
<th>Test</th>
<th>Limit/Endpoint</th>
<th>Procedure</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td></td>
<td>A: IR &lt;197K&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: UV &lt;197U&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: TLC &lt;201&gt;</td>
<td></td>
</tr>
<tr>
<td>Melting Range</td>
<td>Between 168 and 172</td>
<td>&lt;741&gt;</td>
<td>Needed?</td>
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<td>Water</td>
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<td>&lt;921&gt;, Method I</td>
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</tr>
<tr>
<td>Residue on Ignition</td>
<td>NMT 0.1%</td>
<td>&lt;281&gt;</td>
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</tr>
<tr>
<td>Chloride</td>
<td>Visual (0.014%)</td>
<td>&lt;221&gt;</td>
<td>Needed?</td>
</tr>
<tr>
<td>Sulfate</td>
<td>Visual (0.02%)</td>
<td>&lt;221&gt;</td>
<td>Needed?</td>
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<tr>
<td>Sulfide</td>
<td>Visual</td>
<td>Wet chemistry</td>
<td>Needed?</td>
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<tr>
<td>Heavy Metals</td>
<td>0.001%</td>
<td>&lt;231&gt;, Method II</td>
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<tr>
<td>Free p-aminophenol</td>
<td>0.005%</td>
<td>Spectrophotometric</td>
<td>Modernization</td>
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<tr>
<td></td>
<td></td>
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<td>needed. Limit?</td>
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<tr>
<td>Limit of p-chloroacetanilide</td>
<td>0.001%</td>
<td>TLC</td>
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<td></td>
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<tr>
<td>Readily Carbonizable</td>
<td>Visual</td>
<td>&lt;271&gt;</td>
<td>Needed?</td>
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<tr>
<td>Substances</td>
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<tr>
<td>Assay</td>
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<td>Spectrophotometric</td>
<td>Modernization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>needed</td>
</tr>
</tbody>
</table>
Add
- Add EP impurities procedure (HPLC)
  - Includes p-aminophenol with limit of 50 ppm and
    p-chloroacetanilide with a limit of 10 ppm

Replace
- Replace Assay with EP titration procedure (cerium sulfate titrant,
  1 hour reflux)??
  - EP limits are 99.0 to 101.0%

Delete
- Melting Range
- Chloride, Sulfate, and Sulfide
- Readily Carbonizable Substances
- Identification Test B and/or C
25+ dosage forms

Need to control p-aminophenol
  - Is a limit of 0.1% appropriate?

Oral liquids, solid oral dosage forms

Single and combination products

OTC and Rx

Revising individual monographs is possible but challenging

Potential General Chapter approach
  - For impurities
  - Default procedure(s) and sample preparation(s)??
  - Build in flexibility
Diphenhydramine Drug Substances

- **Diphenhydramine Hydrochloride**
  - Revision will appear in PF 37(3) [May-June 2011]
    - Comment period ends July 31, 2011
  - Added impurities procedure (EP procedure)
  - Replace Identification Organic Nitrogenous Bases <181> with IR by <197K>
  - Replace Assay (HPLC) with titration (EP procedure)?
  - Delete melting range

- **Diphenhydramine Citrate**
  - Needs impurity procedure—HPLC?
  - Assay is mercuric acetate titration—change to HPLC?
  - Will EP titration for DPh HCl work?
  - Other changes?
  - Submit proposals to USP by May 1, 2011
Diphenhydramine-containing Dosage Form Monographs
  - 4 Official monographs
  - Need impurity procedures
  - Other revisions?
Povidone
- Added tests for Peroxides, Formic Acid, and 2-Pyrrolidone

Crospovidone
- Added tests for Peroxides and Modernized test for Vinylpyrrolidone (replace titration with HPLC)

Copovidone
- Propose updating test for Monomers (replace titration with HPLC)

Talc
- Updated statement on Labeling to state “Talc is not derived from deposits that are known to contain associated asbestos” consistent with statements in Talc FCC monograph.
Povidone/Crospovidone/Copovidone
- Nitrogen assay test is nonspecific and it would be preferred to have a more specific assay due to concerns about EMA involving melamine.
- Significant challenges exist to developing replacement assay method other than total nitrogen.
- Working with experts at BASF and ISP to look at other possible methodologies (i.e. FTIR, NIR) to detect potential EMA adulterants.

Talc
- Current methods for absence of asbestos are not specific
- USP are currently seeking experts to assist in evaluating existing Asbestos methods in USP and offering potential alternatives.
Questions
Getting Involved

- Review PF proposals and submit comments
- Visit the USP Monograph Modernization Hot Topics page and Web site for updates
- Participate in Workshops, Stakeholder Forums, Web Meetings, etc.
- Consider applying for Expert Panels
- Submit modernization proposals
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Talc Monographs
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Thank You