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Welcome

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USP Monograph Modernization Web Meeting

February 25, 2011

Agenda

- 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

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USP Monograph Modernization Initiative

Karen A. Russo, Ph.D.
Vice President, Small Molecules

USP Commitment

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- *Replacing* outdated technology and methodology with more current procedures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

Monograph Modernization: Major Categories

- *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: Web Resources

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

ENGLISH ESPAÑOL 中文 PORTUGUÊS | Support

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Information For:


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Regulators


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HOT TOPICS

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 (162KB), letter to USP from 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 (60KB)

Priority Monographs

- USP list of priority monographs (59KB)

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 (lnp@usp.org or +1-301-816-8268)

Monograph Modernization: Web Resources

- 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
  - http://www.usp.org/USPNF/submitMonograph/improveMon.html

USP Monograph Modernization Web Page

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

USP Monograph Modernization Web Page

Search USP Careers

Attend a USP Event

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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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

Small Molecules Monograph Modernization List

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Monographs in Need of Modernization (Last Updated 23-February-2011)

Monograph Name	Monograph Family	Date Added to List	Date of Last Status Change	Status	Publication	Monograph Type	Monograph Test	Procedure	Replace or Add Test	Replacement Procedures	Liaison	Comments
NAPROXEN SODIUM TABLETS	NAPROXEN SODIUM	24-May 2010 (Initial posting)	18-Jun-2010	Submission Received		Drug Product	Impurities	Missing	Add	Quantitative stability indicating procedure	Clydewyn Anthony cma@usp.org	
NAPROXEN TABLETS	NAPROXEN	24-May 2010 (Initial posting)	18-Jun-2010	Submission Received		Drug Product	Impurities	Missing	Add	Quantitative stability indicating procedure	Clydewyn Anthony cma@usp.org	
OXAZEPAM	OXAZEPAM	24-May 2010 (Initial posting	23-Feb-2011	Submission Received		Drug Substance	Impurities	Missing	Add	Quantitative stability indicating procedure	Hariram Ramanathan hr@usp.org	
TIMOLOL MALEATE	TIMOLOL MALEATE	24-May 2010 (Initial posting)	22-Dec-2010	Submission Received		Drug Substance	Assay	Titration	Replace	Stability Indicating Assay	Sujatha Ramakrishna sxr@usp.org	
TIMOLOL MALEATE	TIMOLOL MALEATE	18-Jun-2010	22-Dec-2010	Submission Received		Drug Substance	Chromatographic Purity	TLC	Replace	Modern Procedure	Sujatha Ramakrishna sxr@usp.org	Added new li item for monograph

Monograph Modernization Progress

- 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

Monograph Modernization: Recent Examples

Monograph	PF Citation	Modernization
Alclometasone Dipropionate	PF 36(5) [Sep-Oct 2010]	Replace Ordinary Impurities by TLC with HPLC
Glycopyrrolate	PF 37(1) [Jan-Feb 2011]	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
Glycopyrrolate Tablets	PF 37(1) [Jan-Feb 2011]	Replace UV-based Assay and Dissolution procedure with HPLC; add impurities test
Spironolactone	PF 37(1) [Jan-Feb 2011]	Replace choloroform with alcohol in Specific Rotation test; replace <197S> using chloroform with <197K
Temazepam	PF 36(6) [Nov-Dec 2010]	Replace TLC-based impurities procedure with HPLC procedures; removed use of Internal Standard from the Assay

Monograph Modernization Strategy and Approaches

- 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

Monograph Modernization Strategy and Approaches

- 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

Consumer Healthcare Products Association

USP Monograph Modernization

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Who is CHPA?

CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

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

CHPA's Manufacturing Controls Committee

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

USP Monograph Modernization
CHPA's commitment letter

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

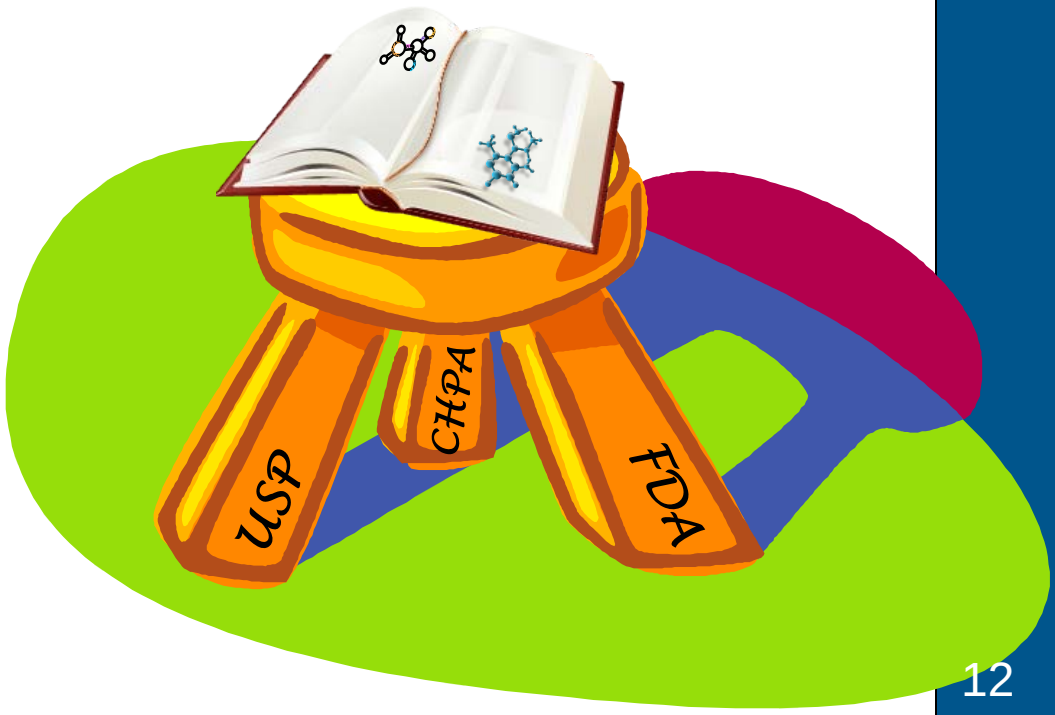
USP Monograph Modernization

- 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



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Monograph Topics

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Kevin Moore, Ph.D.
Senior Scientific Liaison

Acetaminophen Monograph

Test	Limit/Endpoint	Procedure	Comment
Identification		A: IR <197K> B: UV <197U> C: TLC <201>	
Melting Range	Between 168 and 172	<741>	Needed?
Water	NMT 0.5%	<921>, Method I	
Residue on Ignition	NMT 0.1%	<281>	
Chloride Sulfate Sulfide	Visual (0.014%) Visual (0.02%) Visual	<221> <221> Wet chemistry	Needed? Needed? Needed?
Heavy Metals	0.001%	<231>, Method II	
Free p-aminophenol	0.005%	Spectrophotometric	Modernization needed. Limit?
Limit of p-chloroacetanilide	0.001%	TLC	Modernization needed. Limit?
Readily Carbonizable Substances	Visual	<271>	Needed?
Assay	98.0 to 101.0%	Spectrophotometric	Modernization needed

Acetaminophen: Potential Revisions

- **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

Acetaminophen-containing Dosage Forms

- 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 Products

- Diphenhydramine-containing Dosage Form Monographs
  - 4 Official monographs
  - Need impurity procedures
  - Other revisions?

Monograph Modernization – Current 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.

Monograph Modernization – Future Projects

- 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.

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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

USP Contact Information

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Thank You