U.S. PHARMACOPEIA
The Standard of Quality℠

Isranalytica Conference

David InterContinental Hotel
Tel Aviv, Israel
8 February 2011

USP Monograph Initiatives

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

Quality Standards for Medicines | Dietary Supplements | Food Ingredients

Topics

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- **USP Overview**
- Monograph Modernization
- Flexible Monographs
- USP Pending Monographs

USP Convention Headquarters Rockville, MD USA

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

USP–An Overview

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Since 1820, nonprofit, private, independent, and self-funded
- Establishes public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods
- Expert volunteers are scientific decision-makers
- Headquartered in Rockville, MD; 600+ employees; facilities in India, China, Switzerland, Brazil

USP Sites

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

2010-2015 Expert Committee Structure

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

International Health Advisory Group

Council of Experts/ Executive Committee

Scientific Advisory Group

U.S. Pharmacopeia

A. Long	Small Molecules: K. Russo		Large Molecules: T. Morris		B. Jones
Nomenclature, Safety and Labeling	Small Molecules Monographs 1	Small Molecules Monographs 2	B&B Monographs 1	B&B Monographs 2	Reference Standards
	Small Molecules Monographs 3	Small Molecules Monographs 4			

General Chapters: A. DeStefano

Chemical Analysis	Physical Analysis	Biological Analysis	Dosage Forms	Microbiology	Packaging	Statistics	Toxicology

National Formulary	*Dietary Supplements Compendium*	*Food Chemicals Codex*	*Pharmacists' Pharmacopeia*
J. Griffiths	J. Griffiths	J. Griffiths	A. Long
Excipients	Dietary Supplements	Food Ingredients	Compounding

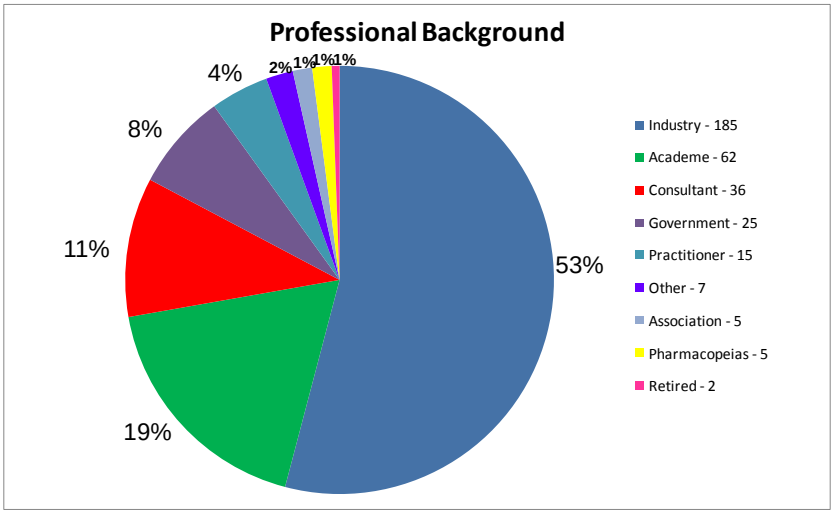
2010-2015 Council of Experts - Demographics

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- 332 expert volunteers serving on 20 Expert Committees
  - 75 international experts from 22 countries:
    - Argentina 1
    - Australia 2
    - Austria 1
    - Belgium 1
    - Brazil 3
    - Canada 15
    - China 8
    - Denmark 3
    - France 2
    - Germany 6
    - India 7
    - Israel 2
    - Jordan 1
    - Netherlands 2
    - Portugal 2
    - Saudi Arabia 1
    - South Korea 1
    - Spain 1
    - Sweden 1
    - Switzerland 2
    - Taiwan 1
    - United Kingdom 12

2010-2015 Council of Experts - Demographics

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



USP-NF

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

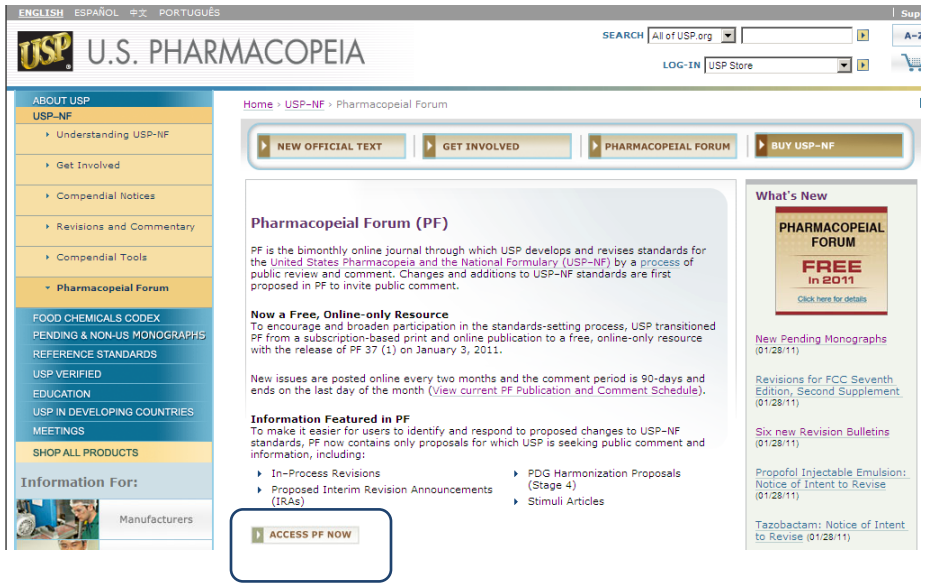
- Official authority—***FDA-enforceable standards***
- Time-tested, international resource
- More than 4,500 monographs
- Drug products and substances, excipients, dietary supplements, veterinary, biologics
- Continuously updated

Pharmacopeial Forum

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ***Free, online only as of 3 January 2011***
- To broaden participation in the public review process
- Beginning with PF 37(1) [Jan-Feb 2011]
- Includes an archive back to PF 28 (2002)
- Contains only proposals for which USP is seeking public comments
  - In process revisions (new and revised monographs and general chapters)
  - Stimuli Articles
  - PDG Harmonization Stage 4 proposals
  - Proposed Interim Revision Announcements (i.e., an accelerated revision)
- One-time registration is required

Pharmacopeial Forum



Topics

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- USP Overview
- **Monograph Modernization**
- Flexible Monographs
- USP Pending Monographs

Monograph Modernization

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- *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)
- Considerations
  - Use procedures from other pharmacopeias (e.g, EP, BP)
    - Will the same limits apply?
  - May need RS materials
  - Revising the monograph "family", as needed

Monograph Modernization Needs: Major Categories

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- *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: Recent Examples

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

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; added 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

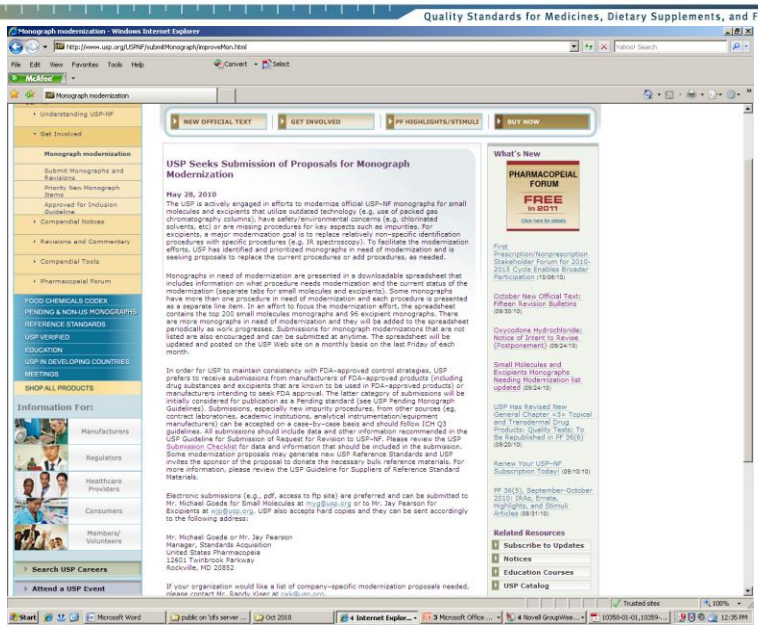
Monograph Modernization

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Significant focus for USP
- USP labs used to generate data to support revisions
- Submissions from manufacturers encouraged
  - *See USP Fact Sheet on Donor Recognition*
- USP Monograph Modernization Web Page
  - Launched in May 2010
  - 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

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

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:

Karen A. Russo, Ph.D.
Vice President, Small Molecules
kar@usp.org 301-816-8379

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

Small Molecules and Excipients Monographs Needing Modernization

Posting Date: October 29, 2010

- Download the Monograph Modernization list (151KB) (updated October 22, 2010)

Next Posting Date: November 29, 2010

Small Molecules Monograph Modernization List

Monographs in Need of Modernization (Last Updated 22-October-2010)

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
DEXBROMPHENIRAMINE MALEATE	DEXBROMPHENIRAMINE MALEATE	24-May 2010 (Initial posting)		Submission Needed		Drug Substance	Assay	Titration	Replace	Stability Indicating Assay	Domenick Vicchio dwv@usp.org	
DEXCHLORPHENIRAMINE MALEATE	DEXCHLORPHENIRAMINE MALEATE	24-May 2010 (Initial posting)	22-Oct-2010	Submission Committed		Drug Substance	Related Compounds	GC - Packed Column	Replace	Modern Procedure	Domenick Vicchio dwv@usp.org	
DEXCHLORPHENIRAMINE MALEATE	DEXCHLORPHENIRAMINE MALEATE	24-May 2010 (Initial posting)	22-Oct-2010	Submission Committed		Drug Substance	Assay	Titration	Replace	Stability Indicating Assay	Domenick Vicchio dwv@usp.org	
DIFLUNISAL	DIFLUNISAL	24-May 2010 (Initial posting)		Submission Needed		Drug Substance	Chromatographic Purity	TLC	Replace	Modern Procedure	Clydewyn Anthony cma@usp.org	
DIHYDROCODEINE BITARTRATE	DIHYDROCODEINE BITARTRATE	24-May 2010 (Initial posting)		Submission Needed		Drug Substance	Ordinary Impurities	TLC	Replace	Modern Procedure	Clydewyn Anthony cma@usp.org	
DIPHENHYDRAMINE CITRATE	DIPHENHYDRAMINE CITRATE	24-May 2010 (Initial posting)		Submission Needed		Drug Substance	Assay	Titration	Replace	Stability Indicating Assay	Domenick Vicchio dwv@usp.org	
DIPHENHYDRAMINE CITRATE	DIPHENHYDRAMINE CITRATE	24-May 2010 (Initial posting)		Submission Needed		Drug Substance	Impurities	Missing	Add	Quantitative stability indicating procedure	Domenick Vicchio dwv@usp.org	
DIPHENHYDRAMINE HYDROCHLORIDE	DIPHENHYDRAMINE HYDROCHLORIDE	24-May 2010 (Initial posting)		Submission Needed		Drug Substance	Impurities	Missing	Add	Quantitative stability indicating procedure	Domenick Vicchio dwv@usp.org	
DIPHENHYDRAMINE HYDROCHLORIDE CAPSULES	DIPHENHYDRAMINE HYDROCHLORIDE	24-May 2010 (Initial posting)		Submission Needed		Drug Product	Impurities	Missing	Add	Quantitative stability indicating procedure	Domenick Vicchio dwv@usp.org	
DIPHENHYDRAMINE HYDROCHLORIDE INJECTION	DIPHENHYDRAMINE HYDROCHLORIDE	24-May 2010 (Initial posting)		Submission Needed		Drug Product	Impurities	Missing	Add	Quantitative stability indicating procedure	Domenick Vicchio dwv@usp.org	
DIPHENHYDRAMINE HYDROCHLORIDE ORAL SOLUTION	DIPHENHYDRAMINE HYDROCHLORIDE	24-May 2010 (Initial posting)		Submission Needed		Drug Product	Impurities	Missing	Add	Quantitative stability indicating procedure	Domenick Vicchio dwv@usp.org	

Small Molecules | Small Molecules Archive | Excipients | Excipients Archive

Topics

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- Monograph Modernization
- **Flexible Monographs**
- USP Pending Monographs

Flexible Monograph Approach

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ***Need-based*** flexibility to account for different routes of synthesis, hydrates, solvates, polymorphs, or formulations
- Enables multiple procedures, preparations, and/or acceptance criteria within a single monograph
- Uses of the flexible approach
  - multiple formulation-specific dissolution procedures
  - multiple organic impurity procedures based on different impurity profiles
  - hydrate-specific water limits/ranges
  - polymorph-specific crystallinity requirement
- May need procedure-specific USP Reference Standards

Flexible Monographs: Examples

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Ethinyl Estradiol
- Loratadine
- Meloxicam
- Paclitaxel
- Paroxetine Hydrochloride
- Potassium Chloride Extended-Release Tablets
- Theophylline Extended-Release Capsules

Flexible Monograph Example: Paclitaxel

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Labeling—The labeling indicates the type of process used to produce the material and the Related compounds test with which the material complies.

Related compounds—

Test 1 (for material labeled as isolated from natural sources)—If the material complies with this test, the labeling indicates that it meets USP Related compounds Test 1.

Test 2 (for material labeled as produced by a semi-synthetic process)—If the material complies with this test, the labeling indicates that it meets USP Related compounds Test 2

Test 3 (for material labeled as produced by a plant cell fermentation process)—If the material complies with this test, the labeling indicates that it meets USP Related compounds Test 3.

Paroxetine Hydrochloride

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Water, Method I <921>: not more than 1.5% for the anhydrous form and between 2.2% and 2.8% for the hemihydrate form.

Chromatographic purity—[note—On the basis of the synthetic route, perform either Test 1 or Test 2. Test 2 is recommended if paroxetine related compound F or paroxetine related compound G is a potential related compound.]

Test 1— …

Test 2 — …

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USP Pending Monographs

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Initiated in February 2007
- Web-based publication of monographs
- Enables monograph development and publication before FDA approval has been granted to a generic manufacturer
- Ultimate purpose is to have an official *USP-NF* monograph ready as soon as possible after FDA approval of an application (i.e., ANDA)
- Not legally enforceable

USP Pending Monographs: Requirements

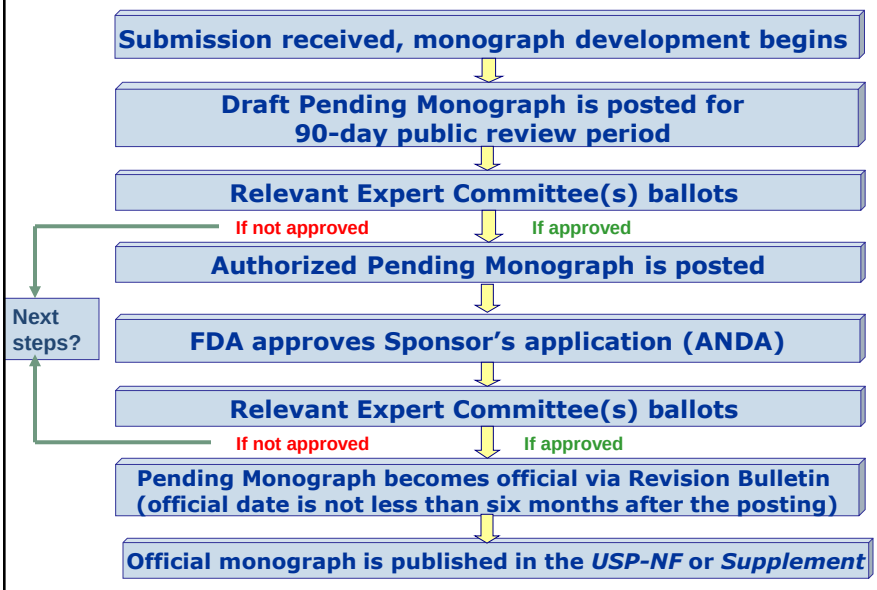
Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Sponsors

- Who have filed or intend to file with FDA an Abbreviated New Drug Application (ANDA) or Abbreviated New Animal Drug Application (ANADA) within six months; or
- Who have filed or intend to file with FDA a Biosimilar or Interchangeable Biologics License Application (a Public Health Service Act 351(k) BLA) within six months; or
- Who have submitted a Drug Master File (DMF) for an article to FDA; or
- Whose substance is or will be the subject of a Time and Extent Application or citizen petition to amend an FDA OTC drug monograph.

USP Pending Monographs Process

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



USP Pending Monographs: Current Status

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

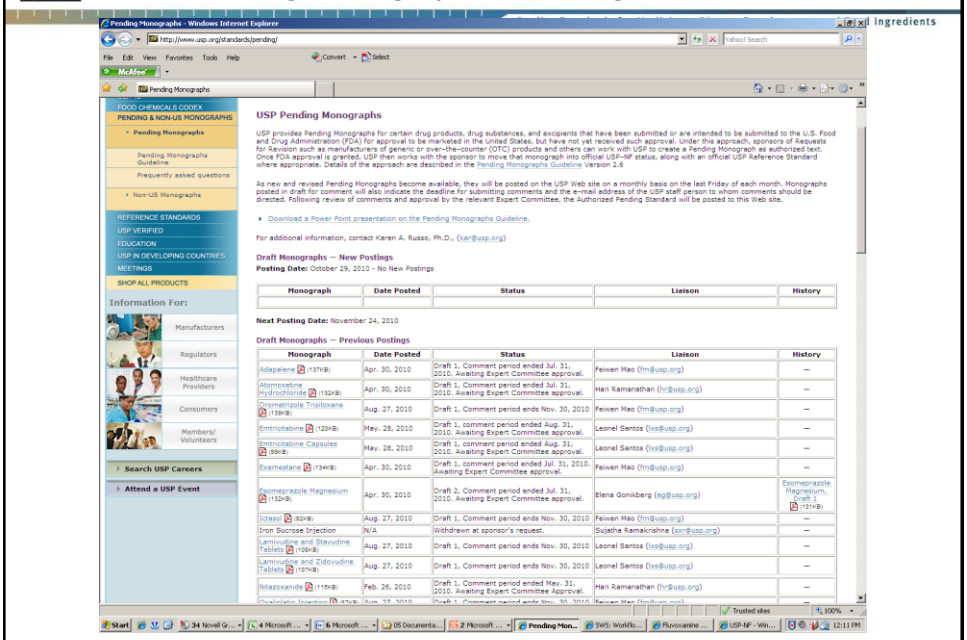
- Pending Monographs Advancing to USP–NF
  - –12 monographs have received full FDA approval and advanced to official USP text (in their entirety or specific sections)
- Authorized Pending Monographs
  - –48 Authorized monographs posted; sponsors waiting for full FDA approval
- Draft Pending Monographs
  - – 15 Draft monographs posted for public comment

USP Pending Monographs Web Page

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- USP Pending Monographs are posted on the USP web site at www.usp.org/standards/pending/
- Guideline is available on the web site
- Updated monthly (last Friday of the month, adjusted for holidays)

USP Pending Monographs Web Page



Parallel Submissions

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- May have Pending and USP submissions for the same monograph
- “First official” becomes Test/Procedure 1
- Not easy to predict outcome--depends on timing of submissions, FDA approval, etc

Comments and Commentary

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Interested parties may comment on any posted monograph at any time; deadlines observed for balloting purposes
- Regulatory status of commenter affects how the comments are handled
- Comments from Pending Manufacturer
  - Draft and Authorized Pending monographs may be revised, flexible approach possible
- Comments from FDA-approved manufacturer
  - Comments may be incorporated into the Pending monograph when it advances to official status
  - Commenter may opt to submit a parallel submission

Contact Information

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

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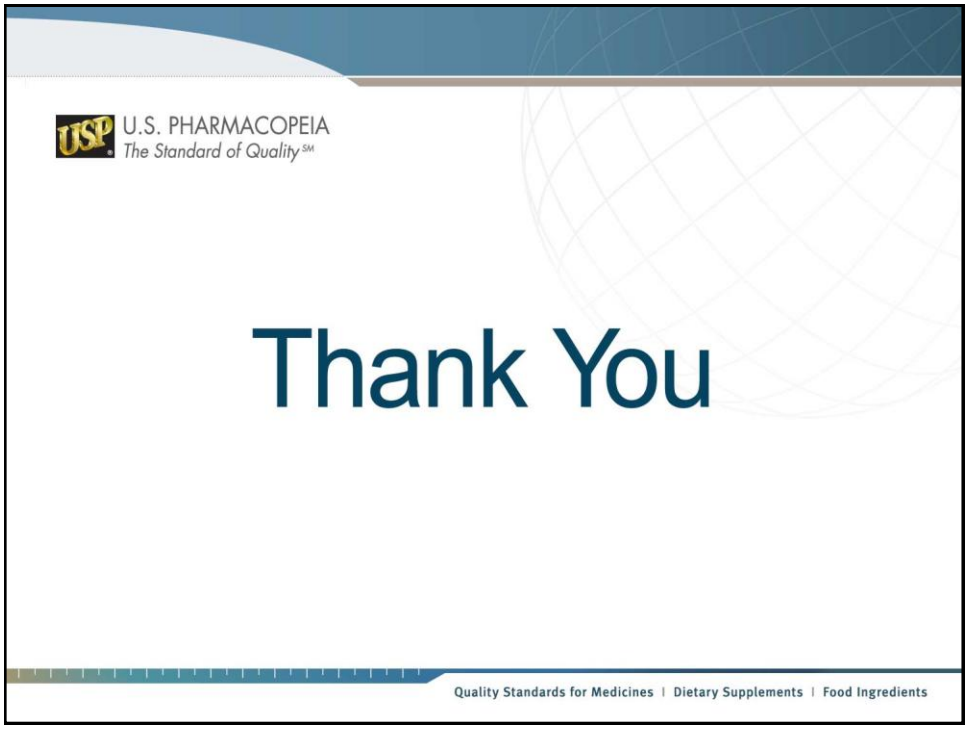
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Thank You
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