Welcome to the USP User Forum
Buenos Aires, Argentina
November 5, 2013
Today’s Agenda

- 8:30–9:00..... Welcome & Sign-In (Receive ticket for afternoon drawing)
- 9:00–10:30... USP Overview / Revision Process
  - USP Publications / Harmonization
- 10:30–10:45. Break
- 10:45–12:00. Reference Standards / Online Resources
  - Compendial Updates / USP Programs and Resources
- 12:00–1:00... Lunch and Discussion
- 1:00–2:15..... GC Updates: Validation and Verification, New Approaches
- 2:15–2:30..... Break
- 2:30–3:45..... GC Updates: Elemental Impurities
- 3:45–4:00..... Drawings (Winner must be present)
MISSION

To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.
Lyman Spalding surveyed physicians nationwide between 1817 and 1819.

Spalding and 10 fellow physicians met in the U.S. Capitol January 1–7, 1820 and the groundwork was laid for establishing the first *Pharmacopeia of the United States of America*.
How Did the U.S. Pharmacopeia Begin?
USP’s Global Locations

- USP Headquarters
  Maryland, USA

- Europe/Middle East/Africa
  Basel, Switzerland

- PQM Office
  Addis Ababa, Ethiopia

- USP–Brazil
  São Paulo, Brazil

- USP–China
  Shanghai, China

- USP–India Private Ltd.
  Hyderabad, India
USP is cited in law…

- **1848**: Drug Import Act
- **1906**: Pure Food and Drugs Act
- **1938**: Food, Drug and Cosmetic Act
  - USP and NF standards enforceable by FDA
    - Definition of a drug
    - Adulteration
    - Misbranding
    - Drug product name
- **1994**: Dietary Supplement Health Education Act
- **2003**: Medicare Modernization Act
  (Model Guidelines for Medicare Formularies)
USP’s Relationship to FDA

- **USP: Private Not-For-Profit Organization**
  - Compendial standards: development and revision
  - Public standards: identity, strength, quality, purity, packaging, and labeling

- **FDA: Government Agency**
  - Enforcement
  - Safety, efficacy; NDA, ANDA, BLA (private license) approvals for marketing, manufacturing processes, etc.

**USP is the only Non-Governmental Pharmacopeia in the World**
More than 1,000 volunteers

- USP Convention—Over 440 members
- Board of Trustees—13 elected voting members
- Council of Experts—25 elected Expert Committee chairs
- Expert Committees—394 elected Expert Committee members (some also serve on Expert Panels)
- Expert Panels—451 appointed experts (this number does not include Expert Committee members serving on Expert Panels)
- Government Liaisons—128 experts
USP Organizational Structure

**Convention Members**
- Policy Body
- Meets every five years
- Elects Board, COE Chairs and Adopts Resolutions

**Board of Trustees**
- Strategic, Fiduciary Body

**Council of Experts**
- Expert Committees
- Scientific Body
- Approve contents of the *USP–NF*, Food Chemicals Codex, other USP Compendia

**USP Staff 800+**
- Supports volunteers, Operations, Public Support
The USP Convention Composition

- Consumer and Other Organizations Representing the Public Interest: 46
- Non-Governmental Standards Setting and Conformity Assessment Bodies: 20
- Governmental Bodies, Divisions, or Associations Thereof: 50
- Manufacturer, Trade, and Affiliated Associations: 30
- Health Practitioner Professional and Scientific Associations: 125
- Academic Institutions and Associations Thereof: 200

Total: 446
2010–2015 Council of Experts - Demographics

- 394 Members serving on 25 Expert Committees
- 122 (32%) international experts from 29 countries:

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2010–2015 Council of Experts - Demographics

- 876 Expert Committee, Expert Panel and Advisory Group members; 259 (30%) intl. experts from 41 countries:

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USP Convention Observers

- U.S. (6)
- Canada (3)
- Mexico (3)
- Jamaica (1)
- Venezuela (1)
- Burkina Faso (1)
- Ghana (1)
- South Africa (3)
- Brazil (7)
- Peru (2)
- Urugua (1)
- Argentina (3)
- Brazil (7)
- United Arab Emirates (1)
- Saudi Arabia (2)
- Ethiopia (1)
- China (1)
- Thailand (1)
- Russia (4)
- Ukraine (2)
- Netherlands (1)
- Belgium (1)
- Italy (1)
- Turkey (3)
- Israel (1)
- Tunisia (1)
- Morocco (2)
- Egypt (2)
- Iran (1)
- India (2)
- Bangladesh (2)
- Indonesia (1)
USP is a self-supporting, private, non-profit organization.

Operating revenue is generated through sale of Reference Standards and publications.

Public, legally enforceable standards are established in an open system.

The standards are approved by elected volunteers (Expert Committee members).

Industry and FDA collaborate with USP on Reference Standard characterization and other compendial issues.
Questions
USP Revision Process
<table>
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<th>Type of Article</th>
<th>Inclusion Criteria</th>
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| Therapeutics (drug      | **USP:** Approved by US FDA  
| substances, drug         | **Pending:** Submitted/intend to submit for FDA approval  
| products, biologics)     | **Non-U.S.:** Approved by stringent regulatory authority for treatment of neglected, infectious disease; Prequalified by WHO                                                                                      |
|                         |                                                                                                              |
| Excipients              | **NF:** Listed on FDA’s Inactive Ingredients Database; FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations (OB)                                                                                       |
|                         |                                                                                                              |
| Dietary Supplements     | **DSC:** Listed by FDA as an ODI or NDI (Old or New Dietary Ingredient); Marketed in the USA                                                                                                                        |
|                         |                                                                                                              |
| Food Ingredients        | **FCC:** Flavors: FEMA GRAS status  
|                         | Non-Flavors: direct food additives on FDA’s EAFUS or GRAS notices lists  
|                         | Non-US: permitted for use in food by any regulatory authority where *FCC* is recognized                                                                               |
USP–NF Revision Process

1. Submission is received/development initiated

2. Scientific Liaison performs technical review and drafts the monograph

3. Proposal is published for 90-day public review and comment period

4. Scientific Liaison reviews and submits comments to Expert Committee

   - Significant comments

5. Expert Committee ballots

   - Not Approved
   - Approved

   Monograph is published in compendium (USP–NF, FCC) or on Web site (Pending, Non-U.S.); commentary generated
For admission into USP–NF, the industry sponsor verifies that its substance/product is approved by FDA.

Monograph submission ideally includes

- Proposed tests, limits, and validation (according to <1225>)
  - Identification test(s)
  - Impurity test(s)
  - Potency/assay test (preferably stability-indicating)
  - Performance test(s) for dosage form monograph submissions
- Packaging, storage, and labeling requirements
- Reference Standard commitments
  - Statement on suitability for use of any existing USP Reference Standards
  - Commitment to provide candidate materials for new USP standards
Submission to USP Must Include

- Reasonable justification
- Adequate supporting methods, specifications, and data
- Details found at www.usp.org/USPNF/submitMonograph/
Many USP monographs need to be updated to modern analytical methodologies.

- Organoleptic tests, TLC impurity tests, etc.

See website for details
www.usp.org/USPNF/submitMonograph/improveMon.html
Companies seeking FDA approval can also submit test method packages to USP for posting to the Pending Monograph section of the website. After 90-day comment period, and upon FDA approval, monographs can be made official via expedited process (Revision Bulletin). Applies to cases when no USP monograph exists, or to cases when process or product specific acceptance criteria are proposed. Allows quick compendial acceptance of applicant’s procedures.
Impact by

- Review/evaluation of public comments
- Obtaining additional information
- Publishing responses
- Testing in USP’s Applied Compendial Research Laboratories
Initiated in February 2007

Web-based publication of monographs

Enables monograph development and publication before FDA approval has been granted

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
Pending Monographs

USP provides Pending Monographs for certain drug products, drug substances, and excipients that have been submitted or are intended to be submitted to the U.S. Food and Drug Administration (FDA) for approval to be marketed in the United States, but have not yet received such approval. Under this approach, sponsors of Requests for Revision such as manufacturers of generic or over-the-counter (OTC) products and others can work with USP to create a Pending Monograph as authorized text. Once FDA approval is granted, USP then works with the sponsor to move that text to the USP/NF.
Benefits of Participating in Standards-Setting Process

- Contribution to global public health, quality of foods & medicines
- Regulatory authorities enforce the standards (drugs & excipients)—the standards you help to establish
- U.S. tax law provides tax benefit to US-based donors
- USP’s Donor Recognition Program
  - Certificate of Appreciation
  - Public recognition (website, science meetings)
  - Complimentary registration to USP Workshops and/or Science Meetings
  - Complimentary subscriptions to the USP publications
  - Complimentary Reference Standards
  - Donor-specific progress reports
  - USP’s summary data package and a traceability statement after lot release
- Less expensive to follow the standard you create than one set by your competitors
Questions
USP Publications
USP–NF Formats

Hardcover Print
- Published Annually
- Facilitates tracking of revisions and additions
- Thumb tabs for easy access to sections

Electronic
- Online (internet-based)
- Single User USB Flash Drive
The *USP 36–NF 31* contains 50 new Monographs, 3 new General Chapters, 56 revised Monographs, and 7 revised General Chapters.

- **USP 36–NF 31 Main Edition**
  - Publication Date: November 1, 2012
  - Official Date: May 1, 2013

- **USP 36–NF 31 First Supplement**
  - Publication Date: February 1, 2013
  - Official Date: August 1, 2013

- **USP 36–NF 31 Second Supplement**
  - Publication Date: June 1, 2013
  - Official Date: December 1, 2013
The USP 37–NF 32 contains 104 new and revised Monographs and 8 new and revised General Chapters

- NEW! - 4 Volume Set
- Publishes on November 1, 2013
- Official May 1, 2014
Zinc Sulfate

\[
\text{ZnSO}_4 \cdot x\text{H}_2\text{O}
\]
Sulfuric acid, zinc salt (1:1), hydrate;
Zinc sulfate (1:1) monohydrate
Zinc sulfate (1:1) heptahydrate
Anhydrous

179.46
287.56
[7446-20-0]
[7733-02-0]

DEFINITION
Zinc Sulfate contains one or seven molecules of water of hydration. The monohydrate contains NLT 89.0% and NMT 90.4% of \text{ZnSO}_4, corresponding to NLT 99.0% and NMT 100.5% of \text{ZnSO}_4 \cdot \text{H}_2\text{O}, and the heptahydrate contains NLT 55.6% and NMT 61.0% of \text{ZnSO}_4, corresponding to NLT 99.0% and NMT 108.7% of \text{ZnSO}_4 \cdot 7\text{H}_2\text{O}.

IDENTIFICATION
• A. IDENTIFICATION TESTS—GENERAL, Zinc (191): Meets the requirements
• B. IDENTIFICATION TESTS—GENERAL, Sulfate (191): Meets the requirements

ASSAY
• PROCEDURE
Sample solution: Equivalent to 1.70 mg/mL of \text{ZnSO}_4 in water
Analyzed: To 100 mL of the Sample solution add 5 mL of ammonia-ammonium chloride buffer TS and 0.1 mL of eriochrome black TS, and titrate with 0.05 M edetate disodium VS until the solution is deep blue in color. Each mL of 0.05 M edetate disodium is equivalent to 8.072 mg of \text{ZnSO}_4.
Acceptance criteria
Monohydrate: 89.0%-90.4% of \text{ZnSO}_4, corresponding to 99.0%-100.5% of \text{ZnSO}_4 \cdot \text{H}_2\text{O}
Heptahydrate: 55.6%-61.0% of \text{ZnSO}_4, corresponding to 99.0%-108.7% of \text{ZnSO}_4 \cdot 7\text{H}_2\text{O}

IMPURITIES
• LIMIT OF ARSENIC, Method I (211)
Test preparation: Dissolve a portion equivalent to 215 mg of \text{ZnSO}_4 in 35 mL of water.

SPECIFIC TESTS
• ACIDITY
Sample solution: 28 mg/mL of \text{ZnSO}_4
Acceptance criteria: The Sample solution is not colored pink by methyl orange TS.

ADDITIONAL REQUIREMENTS
• PACKAGING AND STORAGE: Preserve in tight containers.
• LABELING: The label indicates whether it is the monohydrate or the heptahydrate. Label any oral or parenteral preparations containing Zinc Sulfate to state the content of elemental zinc.

Zinc Sulfate Injection

Zinc Sulfate Injection is a sterile solution of Zinc Sulfate in Water for Injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of zinc (Zn).

Packaging and storage—Preserve in single-dose or multidose containers.

Labeling—Label the injection in terms of its content of anhydrous zinc sulfate (\text{ZnSO}_4) and in terms of its content of elemental zinc. Label it to state that it is not intended for direct injection but is to be added to other intravenous solutions.

USP Reference standards (11)—
USP Endotoxin RS
Identification—it responds to the tests for Zinc (191) and for Sulfate (191).
Bacterial endotoxins (85)—It contains not more than 25.0 USP Endotoxin Units per mg of zinc.
PřH (791): between 2.0 and 4.0.
Particulate matter (788): meets the requirements for small-volume injections.
Other requirements—it meets the requirements under injections (1).
Assay—[Note—The Standard preparations and the Assay preparation may be diluted quantitatively with water, if necessary, to...]

Global Expert | Improved Standards | Improved Health  Copyright 2019. All Rights Reserved.
FDA-recognized source for established drug names in the U.S. and around the world

- Includes
  - U.S. Adopted Names (USANs), International Non-proprietary Names (INNs), Brand Names and manufacturers, BANs, JANs
  - Unique Ingredient Identifier (UNII) codes established by the FDA/USP Substance Registration System for substance tracking
- Chemical names and structures, formula weights, pharmacologic and therapeutic categories
- Published annually in April
- Print and online formats
Food Chemicals Codex

The comprehensive reference for purity and quality standards for food-grade substances: preservatives, flavorings, colorings, and nutrients

- Monographs provide essential data: formulas, description, identification, function, assay, physiochemical characteristics, residual solvents, packaging and storage
- Internationally recognized
- Published every two years, with two annual Supplements between editions
- Print and online formats, English only
- Updated via the free online FCC Forum, open twice a year for 90-day comment periods
Combines *USP–NF* dietary supplement standards with information from the *FCC*, regulatory documents, and other industry resources.

- Approximately 400 *USP–NF* monographs for dietary supplement manufacturing
- More than 150 *FCC* monographs
- Approximately 150 *NF* excipient monographs
- Step-by-step tests, assays, and procedures
- Full color illustrations
- Reference tables, charts, and federal and regulatory guidance from FDA, industry, and more
- 2012 DSC is currently for sale (Two Volume Set)
  - 64 new monographs
  - Excipients section
  - More illustrations (Over 230 pages)
Now a **Free** online-only resource!

- Provides brand names of columns used in validating all proposed and official gas- and liquid-chromatographic procedures in *PF* and *USP–NF*
- Includes an index of manufacturers
- Increases accuracy and consistency of results in official tests and assay
- Go to [www.uspchromcolumns.com](http://www.uspchromcolumns.com) to access this resource (a one time registration is required)
The *PF* is the bimonthly online journal through which USP develops and revises standards for the *USP–NF* by a process of public review and comment.

- The *PF* includes the following:
  - Standards Development
  - How to Use *PF*
  - In–Process Revision
  - Proposed Interim Revision Announcements (IRAs)
  - PDG Harmonization Proposals (Stage 4)
  - Stimuli Articles
- Go to [www.usppf.com](http://www.usppf.com) to access the *PF* (a one time registration is required)
The following items that were formerly located in the PF print subscription have been relocated to appropriate locations on the USP website:

- Policies and Announcements
- Final IRAs
- IRA Reference Standard Information
- Errata
- Previous PF Proposals Still Pending
- Canceled Proposals
- PDG Harmonization Process and Harmonized Standards (Stage 6)

Links to these items will be maintained on USP website at http://www.usp.org/USPNF/pf/
Questions
Overview of Pharmacopeial Harmonization
Pharmacopeial Discussion Group (PDG)

- Began as an informal group in 1989; participants include USP, EP, and JP (WHO joined as an observer in 2001)
- Focuses on selected official, broad-impact general chapters and excipient monographs
- Eliminates/minimizes need to perform multiple tests and procedures and to comply with multiple acceptance criteria for the same article
- Detailed process, with specific stages and terminology
- Meets twice a year
- PDG linked to ICH (until 2011)
Pharmacopeial and Regulatory Approaches

JP (PMDA)  Governmental

Ph. Eur. (EDQM)  Governmental

USP  Independent of Government
**Harmonized:** A pharmacopeial general chapter or other pharmacopeial document is harmonized when a pharmaceutical substance or product tested by the document’s harmonized procedure as published in EP, JP and USP yields the same results, and the same accept/reject decision is reached.

- Text does NOT have to be identical.

- Each Pharmacopeia can adapt the text to local style, and take into consideration local reference standards and reagents.
Stages of PDG Harmonization

Stage 1: Identification

Stage 2: Investigation

Stage 3: Proposal for Expert Committee Review

Stage 4: Official Inquiry

Stage 5A: Provisional Consensus
Stage 5B: Sign-off

Stage 6A: Regional Adoption
Stage 6B: Implementation (in each Pharmacopoeia)
Stage 6C: Indication of Harmonization

Stage 7: Inter-Regional Acceptance
### Carboxymethylcellulose Calcium (Case study)

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<td>Loss on Drying</td>
<td>Loss on Drying</td>
<td>Loss on Drying</td>
</tr>
<tr>
<td>Residue on Ignition</td>
<td>Residue on Ignition</td>
<td>Sulphated Ash</td>
<td>Residue on Ignition</td>
</tr>
<tr>
<td>Organic Volatile Impurities</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Global marketing test requirements = 37 without harmonization; 10 with harmonization.
Harmonization by Attribute

- Applied retrospectively when agreement was unable to be reached on specific tests in a monograph or parts of a General Chapter.

- Instituted as a means to move items forward where there was agreement on the main attributes (i.e. assay, identification) as opposed to delaying entire monograph or chapter.

- Attributes may have been determined to be non-harmonized by PDG for the following reasons
  - (1) Differing regulatory or legal requirements
  - (2) Non-harmonized methodology for procedures
  - (3) Differences in scientific expert opinions

- PDG have committed to work transparently in clearly identifying which specific attributes in a monograph or chapter are harmonized.

- PDG have committed to working on eliminating non-harmonized attributes where possible.
Revisions to Harmonized Items

- No pharmacopeia can unilaterally change harmonized text once Stage 6 is reached

- Revisions are initiated through a formal request to PDG (at least 2 months prior to a meeting)

- PDG approves or rejects the revision
  - If approved, a Coordinating Pharmacopeia (CP) is nominated (does not have to be the original CP for the item)

- The new CP prepares the revised draft
  - Major revisions are introduced at Stage 3
  - Minor revisions can be introduced by rapid revision at Stage 5A
  - Decision on major or minor status must be agreed upon by PDG
Information can be found at: http://www.usp.org/usp-nf/official-text/stage-6
USP General Information Chapter

- Pharmacopeial Harmonization <1196>
  - Outlines the PDG working procedures
Why Global Harmonization?

- Benefits to stakeholders
  - Elimination of redundant testing
  - Multi-compendial compliance

- Benefits to the pharmacopeias
  - Stronger monographs with a global set of experts setting and reviewing standards
  - Specifications (and test methods) are representative of the global supply chain
Prospective Harmonization

- Initiated in July 2008 in response to proposals from manufacturers.

- Pilot study between the European Pharmacopoeia and USP to develop early harmonized monographs and reference standards for four drug substances.

- Monographs
  - Celecoxib
  - Montelukast Sodium
  - Rizatriptan Benzoate
  - Sildenafil Citrate

- Reference Standards
  - Eleven materials to support the four monographs.

- See *Stimuli* articles in PF 36(6).
Prospective Harmonization

- All four monographs now official in both EP and USP
- All eleven reference materials available for use
- Some corresponding drug product monographs are being simultaneously developed by the British Pharmacopoeia (BP)/USP
- Additional projects are underway with one company
USP resolves to strengthen and expand its efforts to work with pharmacopeias, industry, academia, regulators, international organizations and other stakeholders around the world to develop harmonized global standards.
Questions