INTERNATIONAL MEETING OF WORLD PHARMACOPOEIA
29 February to 2 March 2012

The United States Pharmacopeia

Angela G. Long, M.S.
Senior Vice President, Global Alliances and Organizational Affairs

Roger L. Williams, M.D.
CEO and Chair, Council of Experts
1. Name of the Pharmacopoeia

- The *United States Pharmacopeia* and the *National Formulary*

*and others…*
USP’s Compendial Activities

- The *United States Pharmacopeia* and the *National Formulary* (USP–NF)
- *Food Chemicals Codex*
- *USP Dietary Supplements Compendium*
- *USP Medicines Compendium (MC)*
- Reference Standards
- Other Resources
  - *Pharmacopeial Forum*
  - *FCC Forum*
  - *USP Dictionary*
  - *Chromatographic Columns*
2. Recognition in National/Regional Legislation

- United States Pharmacopeia
- National Formulary
- Homeopathic Pharmacopeia

**USP in the 1938 Food, Drug and Cosmetic Act**
- Definition of a drug
- Adulteration
- Misbranding
- Drug product name
3. National/Regional Legislation Includes Reference to Other

- National pharmacopoeia(s)  
  No
- Regional pharmacopoeia(s)  
  No
- International pharmacopoeia(s)  
  No

Note: FDA MAPP 5310.7 notes the use of the British, Japanese, and European Pharmacopoeias during CMC review for INDs and NDAs. The MAPP states, however, that these compendia are not intended to be in place of or addition to the official USP-NF.
4. Publication of Latest Edition

- **United States Pharmacopeia 35 - National Formulary 30**
  - Published November 2011; official May 1, 2012

- **Supplement 1 to the United States Pharmacopeia 35 - National Formulary 30**
  - Published February 2012; official August 1, 2012
5. Update Frequency

- The *United States Pharmacopeia* and *National Formulary* are updated annually, plus two supplements are published each year.
- Accelerated revisions are published monthly on the USP website.
  - IRAs are published every-other-month and include a comment period
  - Revision Bulletins are published every month and do not have a comment period.
6. Covered Products

- Drug Substances/APIs
- Drug Products
- Biologics
- Excipients
- Dietary Supplements/Herbal Products
7. Number of Monographs

In the *USP-NF*

- Total Monographs: About 4,500
- Monographs for APIs: 1402
- Monographs for Finished Dosage Forms: 2454 in *USP*, 446 Excipients in *NF*
- Monographs for Biologicals: 153
- General Chapters: About 300
- Supplementary Texts: *General Notices*, Reagents, Indicators, and Solutions, Description and Solubility
8. Collaboration with National/Regional Pharmacopoeias

- USP is a member of the Pharmacopoeial Discussion Group (PDG)
- USP has adopt-adapt agreements with many pharmacopoeias in the world
- USP has participated in a “Prospective Harmonization” pilot with EDQM
USP incorporates PDG harmonized text in the *USP-NF*:

- 41 of 61 Excipient Monographs, 28 of 35 General Chapters harmonized so far*

- Note General Chapter <1196> *Harmonization* will be omitted because PDG working procedures are now posted on USP’s website

*This number varies due to changes in the PDG Work Programme*
10. Interactions with Stakeholders, Including Regulators

- **US Food and Drug Administration**
  - FDA enforces USP standards
  - Government Liaison program to USP standards Expert Committees
  - FDA comments on USP’s proposed standards
  - USP comments on FDA proposed Guidances, etc.
  - FDA requests actions on USP standards
  - FDA and USP staff share development information
  - FDA participates in collaborative testing through a CRADA
  - USP assists with substance registration project
  - Participation in USP Workshops and Annual Science and Standards Symposium

- **Stakeholders**
  - Worldwide Stakeholder Forums
  - Project Teams
  - Workshops
  - Annual Science and Standards Symposium
2010–2015 USP Council of Experts

United States Pharmacopeia

- Chemicals: K. Russo
- Small Molecules Monographs 1
  - G. Van Buskirk
- Small Molecules Monographs 2
  - E. Parente
- Small Molecules Monographs 3
  - E. Olsen
- Small Molecules Monographs 4
  - M. Cutrera

Council of Experts/Executive Committee
R. Williams

USP Medicines Compendium

- V. Srinivasan
- S. Asia (India)
  - A.R. Gomas
- E. Asia (China)
  - J. Tu
- E. Europe
- Latin America/Caribbean
- MENA
- Sub-Saharan Africa
- W. Europe
- North America

National Formulary

- C. Sheehan
- Excipients
  - L. Block

Dietary Supplements Compendium

- G. Giancaspro
- Dietary Supplements
  - D. Gorecki
- Food Ingredients
  - A. Ebert

Food Chemicals Codex

- M. Lipp
- Compounding
  - G. Davidson

Pharmacists' Pharmacopeia

- S. Becker

Biologics: T. Morris

- B&B Monographs 1
  - M. Mulkerrin
- B&B Monographs 2
  - J. Huxsoll

General Chapters and Cross-Cutting Expert Committees

- General Chapters: A. DeStefano

  - Chemical Analysis
    - T. Wozniak
  - Biological Analysis
    - W. Workman
  - Microbiology
    - J. Akers
  - Statistics
    - R. Singer
  - Physical Analysis
    - G. Amidon
  - Dosage Forms
    - J. DeMuth
  - Packaging
    - M. Foster
  - Toxicology
    - R. Osterberg

- B. Jones

  - Reference Standards
    - M. Borer
2010-2015 Council of Experts - Demographics

- 729 Expert Committee and Expert Panel members
  - 193 international experts from 33 countries:

<table>
<thead>
<tr>
<th>Country</th>
<th>Members</th>
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<td>Argentina</td>
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<td>Venezuela</td>
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• 343 Expert Committee members serving on 22 Expert Committees
• 386 Expert Panel members* serving on 57 Expert Panels
• 103 Government Liaisons
  – 99 FDA Liaisons
    – CDER: 69
    – CFSAN: 12
    – CBER: 10
    – CVM: 5
    – ORA: 3
  – 2 Health Canada Liaisons
  – 1 NIST Liaison
  – 1 European Food Safety Authority Liaison

* This number does not include Expert Committee members serving on Expert Panels.
11. Strategy for the Future
### Current Status for US Compendia

#### In Compendia

<table>
<thead>
<tr>
<th>Compendium</th>
<th>Expert Committee</th>
<th>In Compendia</th>
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#### Modernization

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<td>Total</td>
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<td><strong>3090</strong></td>
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Public standards are critically important, especially where regulatory and compendial resources are constrained or absent. The USP Medicines Compendium (MC) represents a novel approach to bring good public standards—monographs with reference materials—into the public domain as early as possible after access in a national market. Reliance on these standards can occur at the time of approval through regulatory decision-making and allows marketplace surveillance by manufacturers, purchasers, and the regulatory authority itself. Without the public monograph, some regulatory agencies may need to conduct the same kind of review that is accomplished independently by the USP Council of Experts. The MC thus reinforces the use of good quality standards by ethical manufacturers and can conserve scarce regulatory resources. The MC can become one of a series of safety nets that help combat counterfeit and substandard medicines. Read more.

The MC is offered online only and is freely available for use by any interested party.
2010–2015 USP Council of Experts

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Compounding:
G. Davidson

General Chapters and Cross-Cutting Expert Committees
General Chapters: A. DeStefano

Nomenclature, Safety, and Labeling: T. Reinders

Chemical Analysis: T. Wozniak

Biological Analysis: W. Workman

Microbiology: J. Akers

Statistics: R. Singer

Reference Standards: M. Borer

Physical Analysis: G. Amidon

Dosage Forms: J. DeMuth

Packaging: M. Foster

Toxicology: R. Osterberg
History: Science


- USP Council of Experts, USP Reference Standards Committee, Hauck WW, Primary and Secondary Reference Materials to Test the Quality of Medicines and Foods, Pharm Res., accepted. (chemicals)
USP independently can create a monograph with reference materials.

A PBM *For Development* monograph followed by a *For Comment* monograph with Reference Procedure (source independent).

Donor-submitted procedures may be optimized for a particular manufacturer, resulting in an “Acceptable Procedure (flexible monograph).”

USP can strengthen its ability to gain reference materials independently through synthetic capabilities.

Donations remain important!

Certified Reference Materials (CRMs) for Assay allow comparisons across procedures (additional flexibility).

No separate labeling for reference materials in catalog, instead study any reference materials for one or more new uses.
More Learnings for the Future

- **The Drug Product**
  - General Chapter <12> *Assessing Drug Product Performance* supports optimally bioavailable drug products
  - Leads to global Reference Listed Drug (Global Comparator Pharmaceutical Product)
  - Global RLD supports global system of interchangeable products, with BA/BE for some based on in vitro dissolution studies alone
  - Might be used for about 70% of chemically-based drugs.

- **Biologic Medicines**
  - USP can build monographs and RMs for batch release, in support to WHO IU
  - May protect private processes, specifications and reference materials.

- **Spectral Libraries**
  - Spectral images can supplement primary testing monograph with reference materials
  - Useful for field screening
  - Supplements ‘suitcase’ (wet chemistry) approaches
  - Adds to public confidence
EFAVIRENZ

C<sub>14</sub>H<sub>3</sub>ClF<sub>3</sub>N<sub>2</sub> 315.67

(S)-2H-3,1-Benzoxazin-2-one, 6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-
(S)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one
[154568-62-4].

Efavirenz is a white needle-shaped crystalline powder. It is freely soluble in methanol, ethanol, and
isopropanol; practically insoluble in water.

Performance-Based Monograph
(Contains tests, procedures, and acceptance criteria for the material under test. It also includes
the criteria-based procedures to demonstrate that an Acceptable Procedure is equivalent to the Reference
Procedure.)

DEFINITION
Efavirenz contains NLT 98.0% and NMT 102.0% of efavirenz (C<sub>14</sub>H<sub>3</sub>ClF<sub>3</sub>N<sub>2</sub>), calculated on the anhydrous basis.

IDENTIFICATION
• A. INFRARED ABSORPTION <197K>

ASSAY
• PROCEDURE
  Standard solution: USP Efavirenz CRM in an appropriate diluent
  Sample solution: Efavirenz in an appropriate diluent
  Analytical system: Use a procedure validated as described in MC general chapter Assessing

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of Efavirenz in the Sample solution:

\[ \text{Result} = \left( \frac{r_u}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 \]

\( r_u \) = peak response from the Sample solution
\( r_S \) = peak response from the Standard solution
\( C_S \) = concentration of USP Efavirenz CRM in the Standard solution
\( C_U \) = concentration of Efavirenz in the Sample solution

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES
• RESIDUE ON IGNITION <281>: NMT 0.1%
• ELEMENTAL IMPURITIES <232>: Proceed as directed in the chapter.
• RESIDUAL SOLVENTS <467>: Proceed as directed in the chapter.

ORGANIC IMPURITIES
Standard solution: USP Efavirenz CRM and all appropriate USP Impurity RSs, at concentrations corresponding to the Acceptance criteria of the impurity, in an appropriate diluent
Sample solution: Efavirenz in an appropriate diluent

Analytical system: Use a procedure validated as described in MC general chapter Assessing Validation Parameters for Reference and Acceptable Procedures <10>.

System performance requirements
  Precision: Meets the requirements
  Accuracy: Meets the requirements
  Ruggedness: Meets the requirements
  Specificity: Meets the requirements

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the Sample solution:

\[ \text{Result} = \left( \frac{r_u}{r_S} \right) \times \left( \frac{C_d}{C_U} \right) \times 100 \]

\( r_u \) = peak response of each impurity from the Sample solution
\( r_S \) = peak response of each impurity RS from the Standard solution. [NOTE—If no
(R)-Efavirenz: NMT 0.2%
Any other individual impurity: NMT 0.1%
Total impurities: NMT 2.0%

SPECIFIC TESTS
• WATER DETERMINATION, Method I <921>: NMT 0.5%

ADDITIONAL REQUIREMENTS
• MC REFERENCE STANDARDS <11>
  USP Efavirenz CRM
  USP Efavirenz Impurity A RS
(S)-5-Chloro-o-cyclopropylethynyl)-2-amino-o-(trifluoromethyl)-benzene methanol.
  USP Efavirenz Impurity B RS
(S)-5-Chloro-o-cyclopropylethynyl)-2-[4′-methoxybenzoylamino]-o-(trifluoromethyl)-benzene methanol. (Use USP Efavirenz Related Compound B RS)
  USP Efavirenz Impurity C RS
  6-Chloro-2-cyclopropyl-4-(trifluoromethyl) quinoline.
  USP Efavirenz Racemic RS
(+/-)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

REFERENCE PROCEDURES
(This section provides detailed descriptions of procedures that may be used for the evaluation of the material under test. These procedures have been fully validated, and the data is available on the MC website.)

ASSAY
• PROCEDURE
Solution A: Water, methanol, and trifluoroacetic acid (900:100:0.5)
Solution B: Water, methanol, and trifluoroacetic acid (100:900:0.5)
Diluent: Water and acetonitrile (1:1)
Mobile phases: See Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
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<td>16</td>
</tr>
<tr>
<td>23</td>
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<tr>
<td>28</td>
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</tbody>
</table>

System suitability solution: 0.25 µg/mL each of USP Efavirenz CRM and USP Efavirenz Impurity B RS
Standard solution: 0.1 mg/mL of USP Efavirenz CRM in Diluent
Sample solution: 0.1 mg/mL of Efavirenz in Diluent
Chromatographic system
(See Chromatography <821>, System Suitability.)
Mode: LC
Detector: PDA (scan 200–700 nm). [NOTE—Calculations should be based on the chromatograms collected at 250 nm.] [NOTE—To confirm the absence of co-eluting known and unknown impurity peaks, substitute the detector used in the test for Organic Impurities.]
Column: 4.6-mm × 15-cm, 3.5-µm packing (similar to Zorbax SB-CN).
Flow rate: 1.5 mL/min
Column oven temperature (°C): 40
Injection volume: 35 µL
System suitability
Sample: System suitability solution
Suitability requirements
Resolution: NLT 1.5 between efavirenz impurity B and efavirenz
Relative standard deviation: NMT 1.0% for the efavirenz peak
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of efavirenz:

\[ \text{Result} = \left( \frac{r_s}{r_U} \right) \times \left( \frac{C_s}{C_U} \right) \times 100 \]

- \( r_U \) = peak response of efavirenz from the Sample solution
- \( r_s \) = peak response of efavirenz from the Standard solution
- \( C_s \) = concentration of USP Efavirenz CRM in the Standard solution [NOTE—The potency of the Reference Material is included in this term.]
- \( C_U \) = concentration of Efavirenz in the Sample solution

IMPURITIES
• Organic Impurities
System suitability solution: 0.25 µg/mL each of USP Efavirenz CRM, USP Impurity A RS, USP Impurity B RS, and USP Impurity C RS in Diluent

Sample solution: 0.25 mg/mL of Efavirenz in Diluent

Detector: PDA and MS in series
PDA wavelengths: 200–700 nm
MS source: ES scan (+ and –)
MS conditions
- Capillary (kv): 3.00
- Cone (v): 20.0
- Extractor (v): 2.0
- RF lens (v): 0.1
Temperatures
- Source: 80°
- Desolvation: 400°

System suitability
Sample: System suitability solution
Suitability requirements
- Resolution: NLT 1.5 between efavirenz and efavirenz impurities peaks
- Relative standard deviation: NMT 1.0% for the efavirenz peak

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Efavirenz taken: [NOTE—Where an impurity other than those included in the Standard solution is found in the Sample solution, the peak response and concentration of efavirenz in the Standard solution is used for the calculation.]

Result = \( \frac{r_U}{r_S} \times \frac{(C_U/C_S)}{100} \)

\( r_U \) = peak response of each impurity from the Sample solution
\( r_S \) = peak response of each impurity from the Standard solution
\( C_S \) = concentration of each impurity in the Standard solution. [NOTE—The potency of the Reference Material is included in this term.]
\( C_U \) = concentration of Efavirenz in the Sample solution

Detector: PDA (scan 200–700 nm). [NOTE—Calculations should be based on the chromatograms collected at 250 nm.]
Column: 4.6-mm × 25-cm; 5-µm packing,
Chiralcel OD-H
Flow rate: 1 mL/min
Column oven temperature: 35°
Injection volume: 20 µL

System suitability
Sample: System suitability solution
Suitability requirements
- Resolution: NLT 3.0 between (R)-efavirenz enantiomer and (S)-efavirenz enantiomer
- Relative standard deviation: NMT 1.0% for (R)-efavirenz enantiomer

Analysis
Samples: System suitability solution and Sample solution
Calculate the percentage of (R)-efavirenz:

Result = \( \frac{r_R(r_R + r_S)}{100} \)

\( r_R \) = peak response of (R)-efavirenz enantiomer from the Sample solution
\( r_S \) = peak response of (S)-efavirenz enantiomer from the Sample solution
Reference Procedure can support any pharmacopeia including that of *USP-NF*

Valuable for OMCLs, which may have to scrutinize multiple products with similar ingredients

Acceptable Procedures still ok but should be in monograph (no alternative tests)

CRM with statements of traceability and uncertainty part of SI yardsticks

WHO IU yardstick for biologics
Responsibilities of a Pharmacopeia

- Comprehensive
- Modern
- Reference Materials
Thank You