Meeting Compendial Requirements

Todd Cecil, Ph.D.
Vice-president, Standards Development
Overview

- Introduction
- The USP System
- Worldwide compendial Requirements
- Harmonization
- PAT and the Pharmacopeias
- Protein A Example
- Summary
General Principles

- Definitions
  - Standard
  - Specification
  - Compliance
  - Pharmacopeial / Compendial
  - Requirements
  - Validation/Verification/Concentrations/Water/Alcohol/Syrup/Ointment/Temperature/Odor/About/ ...
What is a standard?

How are standards created?

Who creates a standard?

Why do we need standards?

Where do we find the standard?

When do standards apply?
What is “The” Specification?

Who defines the specification?

Where does a specification come from?

When do specifications matter?

Why do we need specifications?

How does a specification become a standard?
Compliance

- What is compliance?
- Who measures compliance?
- Where is compliance important?
- When do we have to show compliance?
- Why is compliance required?
- How do we comply?
The United States Pharmacopeia
The Founding of USP, 1820
The USP – What is it?

- Legally binding document governing the quality, strength and purity of medical items of commerce in the United States.
What is the USP (cont.)?

- Subject to multiple interpretations
What is the USP (cont.)?

- Standard (not cutting edge) technologies and procedures capable of being performed by any manufacturing company or testing laboratory
Recognized requirements through expiration
USP/NF Background Information

- Independent Standard Setting Organization
- Established in 1820 by Medical Community
- Recipes for Pharmacist
- Permanent Legal Recognition in late 1800’s
  - via State Laws
- Permanent National Recognition in 1906
  - via Pure Food and Drugs Act
- Food, Drug and Cosmetic Act in 1938
  - Created FDA & Mandated Enforcement of USP
USP’s Legal Recognition (1)

- 1820 – United States Pharmacopeia Founded: USP standards for 217 drugs
- 1848 - Drug Import Act: USP legislatively mandated
- 1906 - Federal Pure Food & Drugs Act: USP and NF standards recognized
- 1938 - Federal Food, Drug & Cosmetic Act: USP and NF standards enforceable by FDA
- 1975 USP purchased NF from APhA
- 1994 - DSHEA “official compendium” conformity for dietary supplements (voluntary)
USP's Legal Recognition (2)

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

- **FDA**: Government Agency
  - Enforcement
  - Safety, Efficacy, NDA (private license) approvals for marketing, manufacturing processes, etc.
Federal Law

- 1938 - Federal Food, Drug & Cosmetic Act: USP and NF standards enforceable by FDA

- **SEC. 501. [351]** A drug or device shall be deemed to be adulterated - If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium
SEC. 201. [321] For the purposes of this chapter -

- (g)(1) The term "drug" means articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them.

- (j) The term "official compendium" means the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them.
If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice. The suitability of all testing methods used shall be verified under actual conditions of use.
1) Industry or other interested parties (including Ad Hoc Advisory Panels) work with USP scientific staff expert to draft proposal.

2) Scientific staff approves item for publication *Pharmacopeial Forum* for public review and comment.

3) Public comments received.

4) USP Scientific Liaison review and submits comments to the USP Expert Committee.

5) If no further revisions are needed, Expert Committee ballots for official adoption.

6) Board of Trustees approves.

7) Revised Standard Appears in the USP, NF, Supplement, or other official publication.
Published Bi-monthly
- Jan/Feb, Mar/Apr, May/Jun, Jul/Aug, Sep/Oct, Nov/Dec
Established 1975
Publishes Excerpts from JPF & PHARMEUROPA
Contents
- Policies and Announcements
- Pharmacopeial Previews
- In-process Revision
- Stimuli to the Revision Process
- Nomenclature
- Interim Revision Announcements
- Reference Standards Catalog
- Harmonization
Worldwide Compendial Requirements
About 42 Globally
Most are branches of the Government
2 are designed with international scope (EP & Int. Pharm.)
Others are accepted internationally (USP)
All are independent of the compliance sections
2 supply certification (EP & USP)
All but USP are constrained to include only membership and standards for materials on their market
<table>
<thead>
<tr>
<th>Pharmacopeias of the World (source: WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America (1)</strong></td>
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<tr>
<td>The United States (USP-NF)</td>
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<td><strong>Latin America (3)</strong></td>
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<tr>
<td>Argentina</td>
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<tr>
<td>Brazil (Farmacopéia Brasileira)</td>
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<td>Mexico (FEUM)</td>
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<td><strong>Asia-Oceana (8)</strong></td>
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<tr>
<td>China (Pharmacopoeia of the PRC)</td>
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<td>India (Indian Pharmacopoeia)</td>
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<td>Indonesia (Farmakope Indonesia)</td>
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<td>Japan Japanese Pharmacopoeia</td>
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<td>Korea (Korean Pharmacopoeia)</td>
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<td>Pakistan</td>
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<td>Thailand (Thai Pharmacopoeia)</td>
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<td>Vietnam (Pharmacopoeia Vietnemica)</td>
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<td><strong>Africa-Middle East (3)</strong></td>
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<td>Africa (African Pharmacopoeia)</td>
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<td>Egypt (Egyptian Pharmacopoeia)</td>
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<td>Iran (Iranian Pharmacopoeia)</td>
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<td><strong>Europe (26)</strong></td>
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<tr>
<td>Europe (European Pharmacopoeia)</td>
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<tr>
<td>Austria (Österreichisches Arzneibuch)</td>
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<td>Croatia</td>
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<td>Czech Republic</td>
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<td>Denmark</td>
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<td><strong>Finland</strong></td>
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<td>France (Pharmacopée française)</td>
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<td>Germany (Deutsches Arzneibuch)</td>
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<td>Greece (Greek Pharmacopoeia, Elliniki Pharmacopoiia)</td>
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<td>Hungary (Pharmacopoea Hungarica)</td>
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<td>Italy (Farmacopea Ufficiale della Repubblica Italiana)</td>
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<td>Yugoslavia (Pharmacopoea Jugoslavica)</td>
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<td><strong>Other (1)</strong></td>
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<td>World Health Organization (The International Pharmacopoeia)</td>
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</table>
Pharmacopeias of the World

USP Reference Standards and standards information are used to assure the quality of medicines in over 130 countries.
Compliance to a Compendium

- Compliance to the local Pharmacopeia is a common requirement.
- Some countries allow optional compliance (e.g., Canada).
- Even when tests are the same, reference to the local Pharmacopeia is required for market approval.
- Each Pharmacopeia therefore reflects their marketplace and users.
- Differences in style, marketplace expectations, language, scope, and intent lead to different standards.
Harmonization

PDG, PWG, and ICH
Harmonization efforts

- **Pharmacopeial Discussion Group (PDG)**
  - USP
  - EP
  - JP
  - Began in 1989

- **Pharmacopeial Working Group (PWG)**
  - Affiliated with PAHNDRA of PAHO
  - USP
  - Argentine Pharmacopeia
  - Brazilian Pharmacopeia (Farmacopéia Brasileira)
  - Mexican Pharmacopeia (FEUM)
  - Began 2000

- **International Conference on Harmonization**
  - Began 1990
  - European Regulators and Industry
  - US Regulators and Industry
  - Japanese Regulators and Industry
  - Pharmacopeias are Not members of ICH
Stage 6A Monographs (Yokohama, June 06)

- Alcohol
- Alcohol Dehydrated
- Benzyl Alcohol
- Calcium Disodium Edetate
- Calcium Phosphate Dibasic
- Calcium Phosphate Dibasic (Anhydrous)
- Carboxymethylcellulose Calcium
- Croscarmellose Sodium
- Cellulose, Microcrystalline
- Cellulose, Powdered
- Cellulose Acetate
- Cellulose Acetate Phthalate
- Citric Acid, Anhydrous
- Citric Acid, Monohydrate
- Ethyl cellulose
- Hypromellose
- Hypromellose Phthalate
- Lactose, Anhydrous
- Lactose Monohydrate
- Methylcellulose
- Butyl, Ethyl, Methyl, Propyl Paraben
- Saccharin
- Saccharin Calcium
- Saccharin Sodium
- Sodium Chloride
- Sodium Starch Glycolate
- Starch, Corn
- Starch, Potato
- Starch, Wheat
- Talc
Current Stage of Q6A General Chapters

- Extractable Volume *  Stage 6
- Residue on Ignition – Rev. 2*  Stage 6
- Particulate Matter – Rev. 1*  Stage 6
- Sterility *  Stage 6
- Dissolution *  Stage 6
- * Submitted to Q4B EWG
- Disintegration  Stage 6
- Uniformity of Mass/Content  Stage 6
- Microbial Contamination  Stage 6

- Bacterial Endotoxins (Rev.1)  Stage 3
- Color(instrumental measurement)  Stage 3
## Q6A Chapters and Interaction with Q4B

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Package submitted to Q4B</th>
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<tr>
<td>Dissolution</td>
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<td>Uniformity of Content/Mass</td>
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<td>Microbial Enumeration chapters**</td>
<td>2Q 07</td>
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<td>Enumeration test methods &lt;61&gt;</td>
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<td>Tests for specified micro-organisms &lt;62&gt;</td>
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<tr>
<td>Acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use &lt;1111&gt;</td>
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<tr>
<td>Bacterial Endotoxins</td>
<td>Stage 3</td>
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<tr>
<td>Color (instrumental liquid)</td>
<td>Stage 3</td>
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<tr>
<td>Extractable volume</td>
<td><strong>Acceptable</strong></td>
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<tr>
<td>Test for particulate contamination</td>
<td>Submitted</td>
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<tr>
<td>Residue on Ignition/Sulfated Ash</td>
<td><strong>Acceptable</strong></td>
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<tr>
<td>Sterility</td>
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*PDG is working to eliminate residual differences with stakeholder support

** Official Aug. 1, 2007
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<th>Chapter</th>
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<th>Stage / Publication</th>
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<tr>
<td>Analytical sieving</td>
<td>USP</td>
<td>6A USP 28 2S</td>
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<td>Bulk density/Tapped density</td>
<td>EP</td>
<td>4 PF 31(3)</td>
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<tr>
<td>Density of solids</td>
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<td>Laser diffraction measurement</td>
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<td>Powder fineness</td>
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<td>Optical Microscopy</td>
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<tr>
<td>Specific surface area</td>
<td>EP</td>
<td>6A USP 28 1S</td>
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PAT, QbD, and the Pharmacopeias
How does USP Support the PAT Framework?

- The pharmacopoeias establish marketplace legal standards which help to assure practitioners and patients that products meet their quality requirements.
- The marketplace standard must be met regardless of how products are produced (from compounding to PAT-based manufacturing process).
- The pharmacopoeias, correctly, do not dictate or define how to achieve the established marketplace standards.

Source: Ajaz S. Hussain, Ph.D. Deputy Director Office of Pharmaceutical Science CDER, FDA The Process Analytical Technology Initiative: PAT and the pharmacopeias EDQM Spring Conference, Cannes, 3-4 May 2004
“The USP standards reflect the standards of the industry. If the industrial standard shifts to PAT, the USP standards must change to reflect that.”

Dr. Roger L. Williams, CEO, USP
Pharmaceutical Technology
AUGUST 2004
IN-PRESS PROCESS TESTING AND MANUFACTURING

**Active Ingredients:**
- Acetaminophen

**Inactive Ingredients:**
- Starch,
- Hydroxyethyl Cellulose,
- Magnesium Stearate,
- Microcrystalline Cellulose,
- Titanium Dioxide

**USP Monograph Acetaminophen Tablets**
- Acetaminophen Tablets must contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of acetaminophen (C8H9NO2).

**Raman Spectrophotometry**
- 1120

**Near Infrared Spectrophotometry**
- 1119

**Effusivity**
- 1073

**Through Manufacturing...**

- **BLENDING**
  - <1005> Acoustics
  - <1073> Effusivity
  - <1119> Near Infrared Spectrophotometry

- **GRANULATION**
  - FBD / Granulation
  - <1119> Near Infrared Spectrophotometry

- **MILLING**
  - Commuting Mill
  - <1119> Near Infrared Spectrophotometry

- **COMPRESSION**
  - Tablet Compression
  - <1119> Near Infrared Spectrophotometry

**IN COMMITTEE UNDER DEVELOPMENT:**

- Rapid Microbiological Methods
- Chemometrics: Multivariate Analysis*
- Chemical Imaging*
Requirements for Chemometric-based PAT

- STANDARDIZED ALGORITHM CODES FOR CALIBRATION
- STANDARD SAMPLES FOR INSTRUMENT MONITORING AND CALIBRATION TRANSFER
- STANDARD ‘OUTLIER’ DETECTION METHODS
- STANDARD ANALYZER FUNCTIONALITY TESTS
- STANDARD CALIBRATION AND VALIDATION PROTOCOLS (BASED ON SOUND PRINCIPLES OF EXPERIMENTAL DESIGN)
Biologics and Biotech

- Biotech and large-molecule manufacture
  - Analogous to QbD and PAT approaches
  - Require increased testing loads
  - Require higher technology approaches
  - Standards needed to accelerate
    - Protein A
    - Fetal Bovine Serum
    - Others
Objective is to develop the Monographs and the associated Reference Standards for the Protein A molecules that are used in the purification of Monoclonal Antibodies

Intended for two uses
- Standard for demonstration of monograph compliance
- Standard for the Protein A impurity ELISA

Monograph for each Protein A
Protein A: Background

What is Protein A?

- 42kDa protein in its natural form
  - Located on the outer membrane surface of S. aureus
  - Linked to the cell surface through its C-terminal region

- Single polypeptide chain
  - N-terminal region contains 5 homologous domains, each binding human IgG
  - Two active binding sites per domain
  - Association constant (Ka) ~ $10^8 \text{M}^{-1}$
## Workshop Consensus

<table>
<thead>
<tr>
<th>Tests</th>
<th>Current Tests Used by Sponsors</th>
<th>Monograph Test: Workshop Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identity</strong></td>
<td>Coomassie SDS-PAGE SEC-HPLC Mass Spec</td>
<td>SDS-PAGE (resolution?) Back-up: HPLC assays</td>
</tr>
<tr>
<td><strong>Strength (Protein concentration)</strong></td>
<td>OD$_{275}$ Radial immunodiffusion SEC-HPLC</td>
<td>OD$_{275}$</td>
</tr>
</tbody>
</table>
## Workshop Consensus

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<th>Tests</th>
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</thead>
</table>
| **Purity**             | SEC-HPLC  
Mass Spec  
N-terminal and C-terminal sequencing  
IEF gel  
RP-HPLC  
UV spectral analysis | SEC-HPLC and SDS-PAGE (semi-quantitative)                                                   |
| **Potency (Functional Test)** | BIAcore analysis  
Binding to IgG columns | Binding to IgG column (issues: vendors)                                                   |
| **Impurities**         | Bioburden, Endotoxin, Protease, Enterotoxins, Residual Triton | Bioburden & Endotoxin – yes  
Protease & Enterotoxins – nPA only  
Triton – rPA only |
Protein A Reference Standard

- **Formulation**
  - concentration and excipients
- **Final vial form**
  - Configuration
  - lyophilized, frozen, liquid, temperature
- **From the manufacturers**
  - What stability data is available
- **Candidate materials**
  - Who will make them
  - How much – depends on the design of the collaborative study Elisa study Market
- **Vialing**
  - Facility
  - Labeling
Beyond the Workshop...

- Submit monographs for inclusion in Pharmacopeial Forum
- Procure bulk materials
- Reference standard (RS) fill and testing

- Manage collaborative studies
  - Protein A RS testing for monograph compliance
  - Protein A RS as used in residual ELISA testing

- Review collaborator test results Committee approval
- RS packaging
- QA review and release of RS
The Road Map

Protein A Ad Hoc Advisory Panel

Monographs: consensus

Monographs in dev

Monographs in PF

Official Monographs

Stage 1 Study

Manage Stage 1 Study

Collate data & Submit to RSC

RSC approval

Stage 2 Study

Manage Stage 2 Study

Collate data & Submit to RSC

Finalize study protocol

Bulk procurement initiated

Bulk procured

Official RS

Stage 1 Study

Manage Stage 1 Study

Collate data & Submit to RSC

RSC approval

Bulk procurement initiated

Official RS

RS: consensus
draft study protocol

Official RS
Goals of the studies:

- **Stage 1** – to establish USP protein A reference standard(s) (3-6 laboratories)

- **Stage 2** – to demonstrate the intended use for the Protein A ELISA (15-20 laboratories, based on a 0.9 confidence level)
Specific Goals of Stage 2

- ELISA kits: cross-platform variability
- Inter-laboratory variability
- Plate effect
- Appropriateness of USP Protein A reference standard configuration
- Harmonized protocol!
- Others
Content of the Monograph:

- What types of testing?
  - Identity
  - Purity
  - Strength
  - Potency
  - (Impurities)

- Testing protocols
  - SOPs provided by the sponsors
  - Assay development required?
  - Access to instrument (BIAcore)
Summary
Standard in the Pharmacopeia

- What is a standard?
  - A recognized common practice
- How are standards created?
  - In collaboration with interested parties
- Who creates a standard?
  - The users of the standard
- Why do we need standards?
  - To simplify and streamline work and expectations
- Where do we find the standard?
  - USP
- When do standards apply?
  - From manufacture to expiry
What is “The” Specification?
- Tests, Procedures and Acceptance criteria for shelf-life of a drug

Who defines the specification?
- The manufacturer

Where does a specification come from?
- The manufacturer

When do specifications matter?
- always

Why do we need specifications?
- To evaluate consistency and acceptability

How does a specification become a standard?
- Through common usage and the USP process
Compliance to a Pharmacopeia

- What is compliance?
  - A measure of the degree to which a drug matches the standard

- Who measures compliance?
  - The FDA, the manufacturer, the user, the USP?

- Where is compliance important?
  - Locally

- When do we have to show compliance?
  - If tested

- Why is compliance required?
  - Food Drug and Cosmetic act* and your need

- How do we comply?
  - Meet all the tests in a monograph
Thank You