U.S. PHARMACOPEIA
The Standard of Quality℠

USP Overview and Some Current Activities

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USP's Mission

To improve the health of people around the world through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.

USP Facts

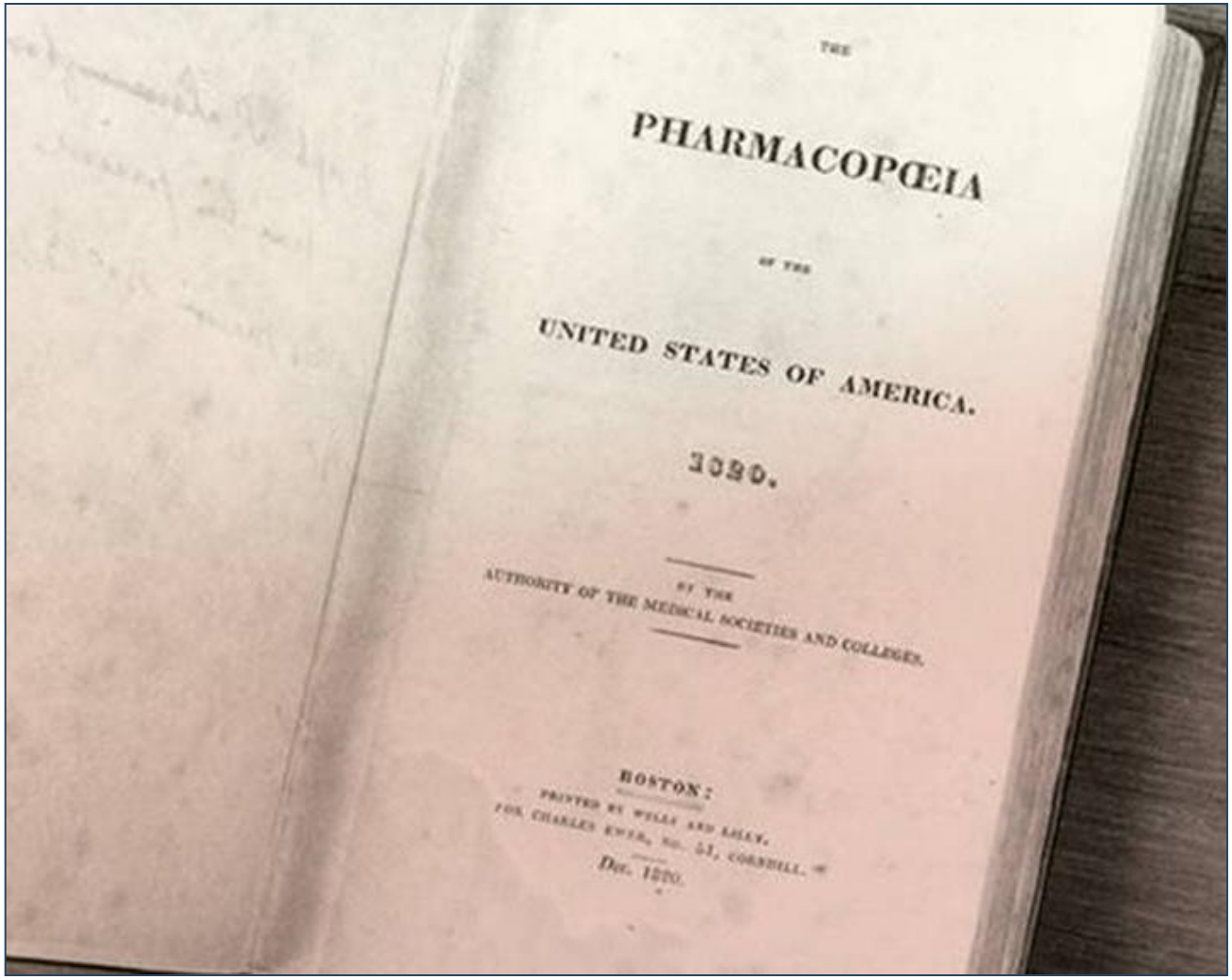
- Since 1820, nonprofit, private, independent, and self-funded
- Headquartered in Rockville, MD; 600+ employees; facilities in India, China, Switzerland, Brazil
- Establishes public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods
- Expert volunteers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

USP and *NF* Are Official Compendia

USP Is Cited in Law…

- **1848:** Drug Import Act
- **1906:** Pure Food and Drug Act
- **1938:** Federal Food, Drug and Cosmetic Act
  - Definition of a drug
  - Adulteration
  - Misbranding
  - Drug product name
- **1994:** Dietary Supplement Health and Education Act
- **2003:** Model Guidelines for Medicare Formularies

The First Pharmacopoeia, 1820


THE

PHARMACOPŒIA

OF THE

UNITED STATES OF AMERICA.

1820.

BY THE

AUTHORITY OF THE MEDICAL SOCIETIES AND COLLEGES.

BOSTON:

PRINTED BY WELLS AND LILLY,

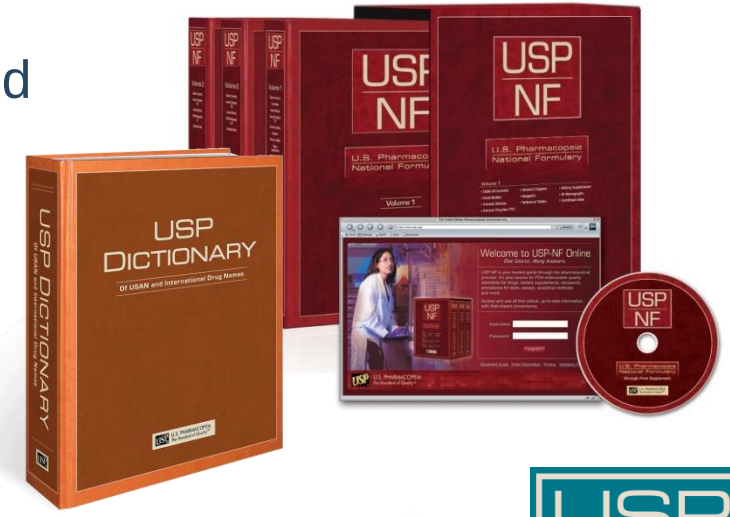
FOR CHARLES EWER, NO. 51, CORNHILL.

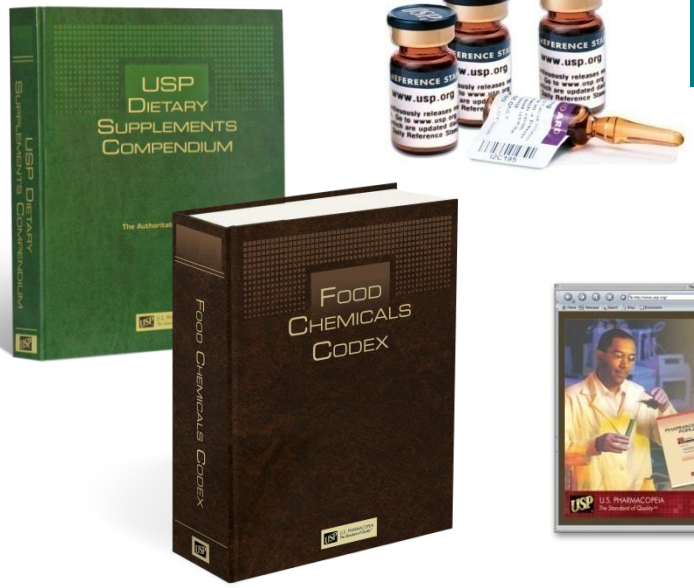
DEC. 1820.

The first *Pharmacopoeia of the United States* contained 217 of the “most fully established and best understood” medicines in the U.S. It was published “by the authority of the medical societies and colleges.”

Core Compendial Programs

- 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*





Pharmacopeial Forum and *FCC Forum*

- USP's vehicles for public notice and comment
- *PF* a complimentary online-only service
- *FCC Forum* Web only
- Contents
  - Interim Revision Announcements (*PF* Only)
  - In-process Revision
  - Stimuli to the Revision Process
  - Nomenclature
  - Harmonization

USP Reference Standards

- More than 2,800 Reference Standards are now available.
- Support FDA-enforceable standards and tests in the *USP–NF*
- 100% pure (unless label states a specific potency or content)
- Collaborative testing in multiple labs: USP, industry, and regulatory labs
- Extensive testing beyond the compendial tests

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.

Role of USP in Law

- Both USP and NF = "**official compendia**"
- Drug with name recognized in USP must comply with **identity** standards, or be deemed adulterated, misbranded, or both
- Must comply with standards for **strength, quality & purity**, or be deemed adulterated, unless labeled otherwise
- Also **packaging and labeling** standards
- **Dietary supplements** – if labeled as USP, deemed misbranded food if fails to so conform

USP's Legal Recognition

- 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.

Testing & Testing Frequency– 'Will Pass If Tested'

- USP standards (monograph, general chapters and general notices) apply at any time in life of article.
  - Repeats, replicates, whether to batch test or not, are neither specified nor proscribed.
- *Frequency* of testing and sampling are left to the preferences of those performing compliance testing, and other users of USP-NF (manufacturers, buyers, regulatory authorities).
- Standards apply *at all times.*
- Any official article is expected to meet USP standards *if* tested, and any article *actually* tested must meet USP standards to demonstrate compliance.
- USP is silent on testing. USP develops standards – FDA enforces them

FDA-USP Compendial Interactions

Drugs	Foods	Veterinary
FDA: CDER, CBER	FDA: CFSAN	FDA: CVM
USP: USP, NF, P2	USP: DSC, FCC	USP: USP, NF, P2

FDA Liaisons to Expert Committees and Expert Panels
Comments on Revision Proposals

Small Molecules/OTCs	Dietary Supplements	Veterinary Drugs
Excipients	Food Ingredients	
Biologics/Biosimilars		
General Chapters		
Compounding		

FDA-USP Interactions

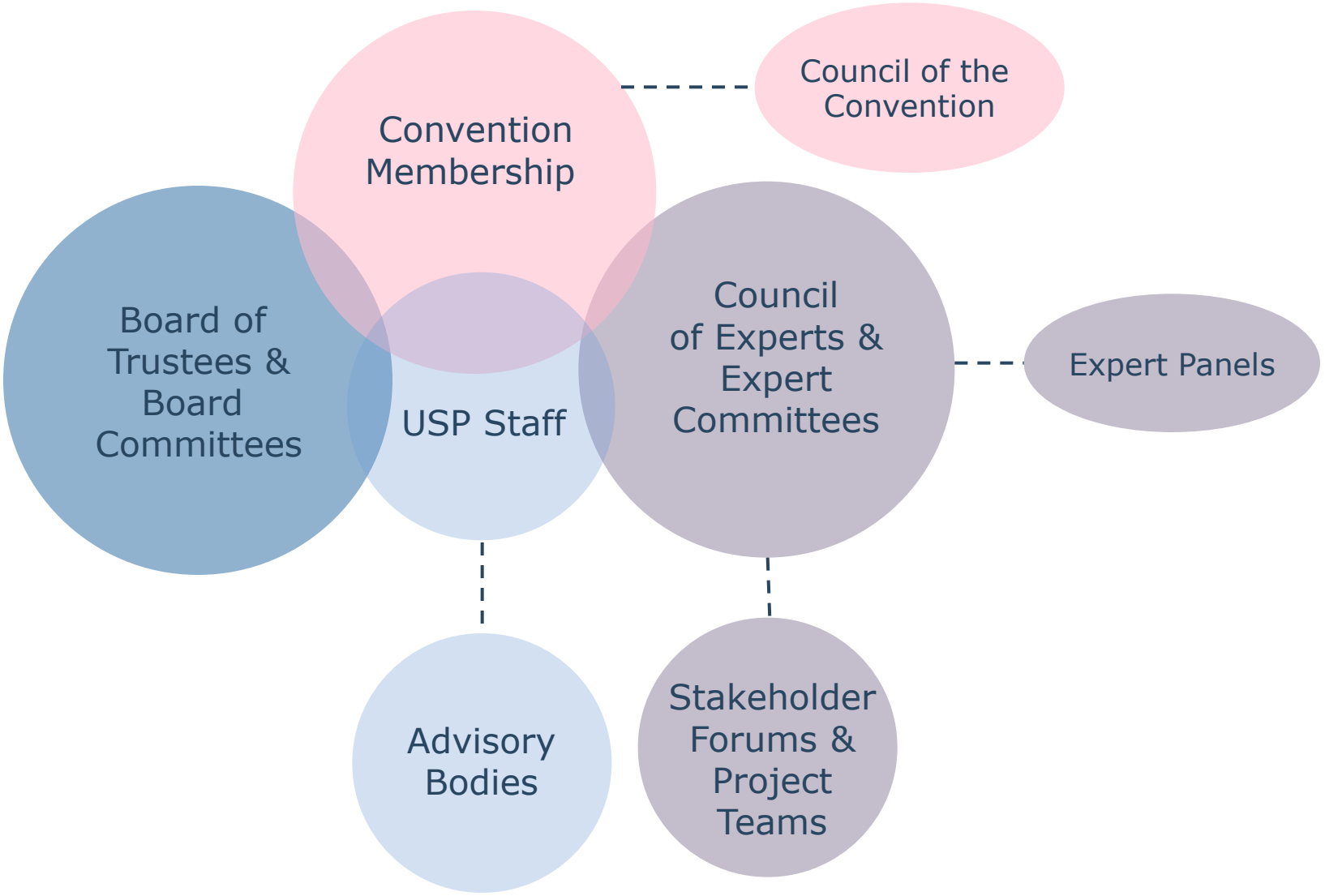
- Convention participation
  - Delegates from each Center and the Office of the Commissioner
  - Resolutions
  - Convention committees, task forces
- CRADAS
  - Office of the Commissioner: Substance Registration System Project
  - ORA/FDA: collaborative testing, monograph modernization, screening methods and technology
- International
  - Office of International Programs
  - USP sites in India, China, Brazil and other global activities
- Compendial interactions

How USP and FDA Work Together

- As part of USP Expert Committee process, FDA liaisons communicate regularly with USP
- FDA staff review and comment on *USP–NF* and *FCC* proposals
- FDA participates in USP workshops and meetings—including internationally
- FDA standards-setting committees have links with USP
- USP works with each FDA center
- FDA and USP have worked on increasing and improving communications

USP Governing and Advisory Bodies

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



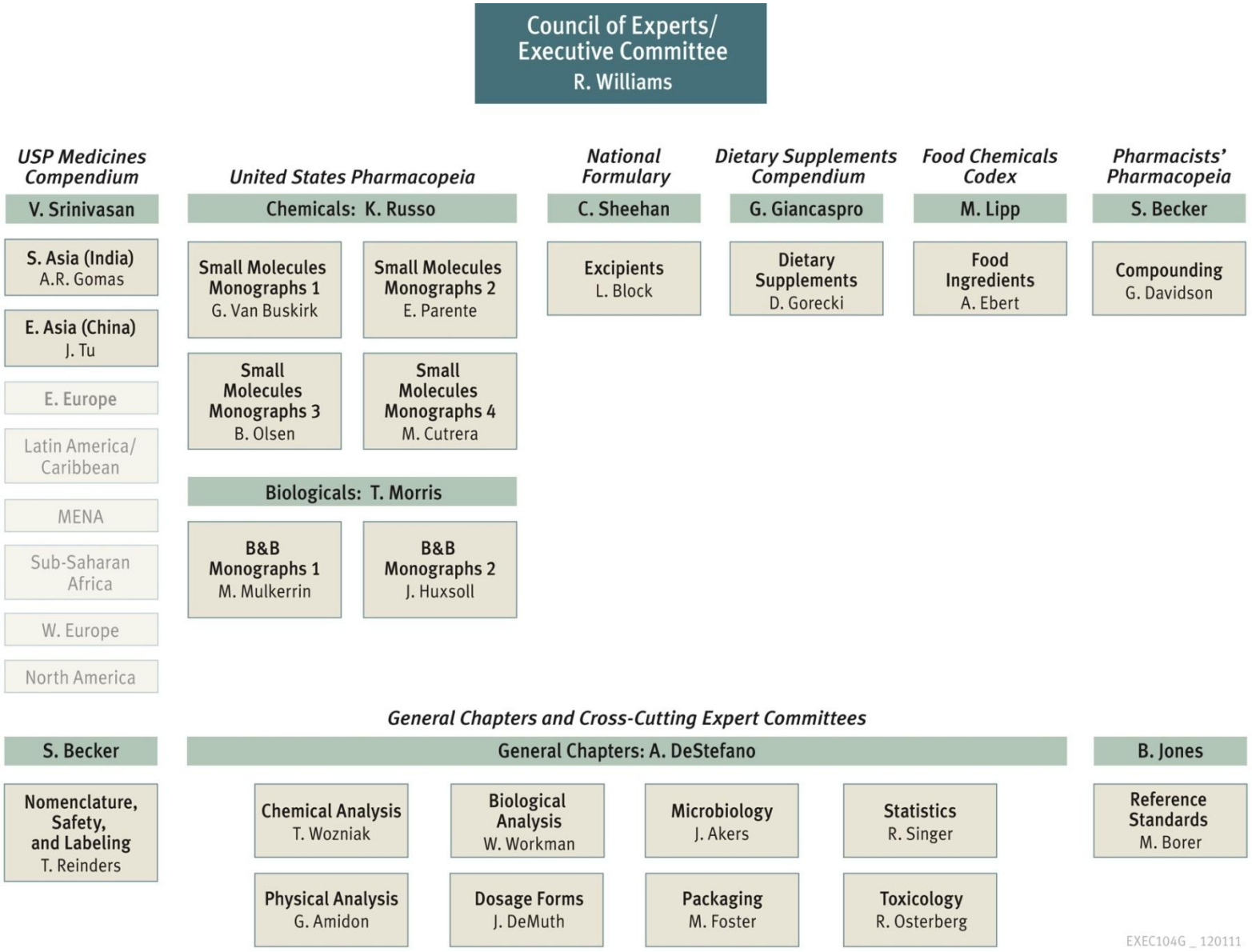
2010–2015 USP Convention Membership

Total of 600 Organizations

- Academic Institutions
- Health Practitioner Professional and Scientific Associations
- Manufacturer, Trade, and Affiliated Associations
- Governmental Bodies or Divisions or Associations Thereof
- Consumer and Public Interest Organizations
- Non-governmental Standards-setting and Conformity Assessment Bodies
- Observers

2010-2015 USP Council of Experts

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



2010-2015 Council of Experts - Demographics

- 832 expert volunteers serving on 22 Expert Committees and 57 Expert Panels.
  - 343 Expert Committee members
  - 386 Expert Panel members*
- 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.

Current Expert Panels

1. <1> Injections
2. <671> Containers - Performance Testing
3. <761> Nuclear Magnetic Resonance (NMR)
4. <771> Ophthalmic Preparations
5. <787> Particulate Matter in Biopharmaceutical Injections
6. <1050> Viral Clearance
7. <1059> Excipient Performance
8. <1102-1105> Immunological Test Methods
9. <1118> Monitoring Devices - Time, Temperature, and Humidity
10. <1197> Good Distribution Practices for Bulk Pharmaceutical Excipients
11. <1207> Sterile Product Packaging
12. <1240> Viral Testing for Human Plasma Designated for Further Manufacturing
13. <1664> Leachables Threshold and Best Practices
14. Acetaminophen
15. Beta-alanine Review
16. Bioassays General Chapters
17. Compounding with Hazardous Drugs
18. Cryopreservation
19. Drugs for Positron Emission Tomography PET-Compounding
20. Elemental Impurities
21. Food Ingredients Intentional Adulterants
22. Glucagon

Current Expert Panels - continued

23. Glycoconjugate Vaccines
24. Glycoprotein and Glycan Analysis
25. Immunogenicity
26. Impurities in Drug Products
27. Insulin
28. Liquid Filled Capsules
29. Low Molecular Weight Heparins
30. Mass Spectrometry
31. Modernization of Microbial Assays
32. Pharmaceutical Enzymatic Preparations
33. Plasma Protein Analytical
34. Plasma-Derived and Recombinant Coagulations Factors
35. Povidone Methods
36. Prescription Container Labeling
37. Recombinant Therapeutic Monoclonal Antibodies
38. Residual DNA Measurement
39. Scanning Electron Microscopy
40. Solubility Criteria for Veterinary Drugs
41. Spanish Translation
42. Sterile Packaged Water Attributes
43. Talc
44. Therapeutic Proteins

Current Expert Panels - continued

45. Tissue and Tissue-based products
46. Total Protein Measurement of Biotechnology-Derived Products
47. Unfractionated Heparin
48. Use of Enzymes in the Dissolution Testing of Gelatin Capsules
49. USP Evidence-Based Reviews
50. Vaccines
51. Vaccines for Human Use - Viral Vaccines
52. Validation and Verification
53. Visual Inspection of Parenterals
54. Water for Analytical Purposes
55. Water for Pharmaceutical Purposes
56. Weight and Balances
57. X-Ray Fluorescence (XRF) Spectrometry

Expert Panels in Formation/Call for Candidates Process:

58. Biological Reference Standards
59. Chinese Translation
60. Erythropoietin Bioassays
61. Extended–Release Dietary Supplement Formulations
62. Modernization of Identification Tests
63. Russian Translation

What are the Expert Committees doing?

Expert Committee (EC) Work Plans

- http://www.usp.org/aboutUSP/governance/councilOfExperts/expertCommittees.html -
- Focus areas for the EC (e.g., therapeutic areas for monograph EC, scientific/technical areas for general chapter ECs)
- Lists EC members
- Provides information on work in progress and planned work
- To be updated three times a year

Standard Setting Process

Topics

- **General Chapters Updates**
  - Dosage Form General Chapters
  - <231> Heavy Metals
  - <1086> Impurities
  - <851> Spectroscopy and Light Scattering
  - <621> Chromatography
  - Packaging, Storage and Distribution EC Activities

Types of USP Standards

- Monographs (Vertical Standards)
  - Specifications for pharmaceutical articles in commerce
  - Specifications – Tests, assays and acceptance criteria needed to demonstrate the article meets required quality standards
- General Chapters (Horizontal Standards)
  - Required (numbered <1000)
  - Informational (numbered >1000)
  - Support monographs by centralizing methods and procedures
- Physical Reference Materials
  - Provide traceable standards to demonstrate broad-based acceptability of procedures

Required General Chapters (<1000)

- Methods and procedures referenced in monographs
- Avoid repeating the tests in many monographs
- Centralize and standardize tests found in multiple monographs
  - Residual solvents <467> or pH<791>
- Can be updated without changing monographs in which they appear
- Can contain criteria needed for demonstration of equivalence of alternative methods or procedures.
- Monographs can reference a core procedure with sample preparation requirements or acceptance criteria residing in the monograph (e.g., pH)

Informational Chapters (>1000)

- Not required, no acceptance criteria
- Companions for required chapters with
  - Background
  - Theory
  - Future directions
  - Applications
  - Not-yet-mature technology
- Background, guideline or “best practice” chapters for good pharmaceutical practices
  - Background: <1086> Impurities
  - Best practices: <1225> Validation

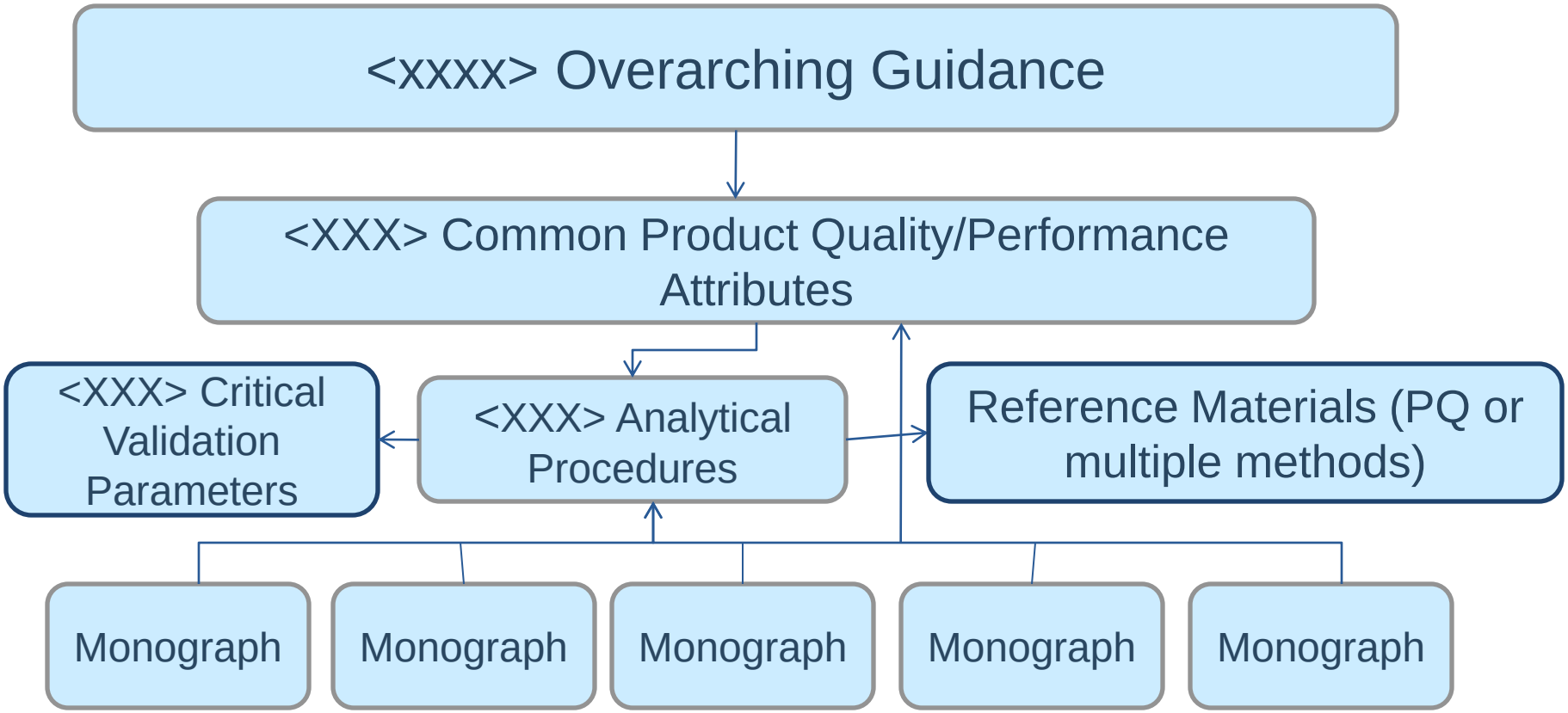
USP Dosage Form Taxonomy

- Taxonomy based on three tiers
  - Tier 1 – Route of administration
  - Tier 2 – Physical form
  - Tier 3 – Release pattern
- <1151> - Pharmaceutical Dosage Forms
  - Information for each dose form
  - Basic preparation and manufacturing information
  - Typical tests
  - Glossary of terms
    - All currently used terms

Routes of Administration

- Oral
- Aerosols
- Injectable – Parenteral
- Mucosal
- Skin – Topical and Transdermal

Structure - Product Quality/Performance Chapters



Product Quality Chapter – Scope and Purpose

- Define quality attributes common to a route of administration or product class
- Establish a “pick list” of procedures suitable and necessary to establish quality, strength and purity across the product class
- Define methods, procedures and acceptance criteria for product-related impurities or degradants
- Establish accepted assay approach
- Link to validated and public compendial procedures that apply broadly to the entire product class
- Follow to the extent possible Q6A guideline for testing requirements

Product Performance Chapters

- Per USP convention, refers to procedures that determine or our surrogates for determining the rate and extent of in-vitro drug release.
- Examples:
  - <711> Dissolution
  - <724> Drug Release
  - <1724> Semi-Solid Drug Products – Performance Tests
  - <601> Product Performance Tests – Nasal, Inhalation, Aerosols, Sprays and Powders

Product Quality/Performance Chapters by Route of Administration

- Oral
  - <2> Default conditions for oral solid dosage forms
  - <701> Disintegration
  - <711> Dissolution
- Skin – Topical and Transdermal
  - <3> Topical and Transdermal – Product Quality Tests
  - <724> or <1724> Semi-Solid Drug Products - Performance Tests
- Aerosol Drug Products
  - <5> Inhalation and Nasal Drug Products – Product Quality Tests
  - <601> Inhalation and Nasal Drug Products – Product Performance Tests
- Injectable - Parenteral
  - <1> Injections – Product Quality Tests
  - <xxx> Injections – Product Performance Tests
- Mucosal
  - <4> Mucosal - Product Quality Tests
  - <xxx> Mucosal - Product Performance Tests

Route of Administration Example – Topical/Dermal

- <3> Topical and Transdermal Drug Products
  - Introduction
  - Glossary
  - Product Quality Tests
    - For topical drug products
    - For transdermal drug products
  - Product Performance Test/Performance Verification Test Referenced (<1724> Topical and Transdermal Drug Products)
- Will be official in *USP 35-NF30* May 1, 2012.

Chapters Addressing Product Performance Tests

<1151> Pharmaceutical Dosage Forms

<1> Injections	<2> Oral	<3> Topical	<4> Mucosal	<5> Inhalation

<1724> Semi-solid Drug Products - Performance Tests

Topics

- **General Chapters Updates**
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  - Packaging, Storage and Distribution EC Activities

<231> Heavy Metals

- Introduced in USP VIII (1905)
- Consists of three procedures, all involving
  - Sulfide precipitation of metals
  - Visual comparison to lead standards
- Difficulties in reproducibility
- Difficulties with reagents – safety issues
  - All procedures generate H_2S (USP via thioacetamide reaction with base). H_2S more toxic than cyanide
- Nondiscriminatory screening test
- Visual comparison test

Publications

New *General Chapters*:

<232> Elemental Impurities – Limits

PF 36(1) [Jan-Feb 2010], revised in PF 37(3) [May-June 2011]

<233> Elemental Impurities – Procedures

PF 36(1) [Jan-Feb 2010], revised in PF 37(3) [May-June 2011]

<2232> Elemental Contaminants in Dietary Supplements <2232>

PF 36(1) [Jan-Feb 2010]

Stimuli articles presented in PF 36(1) [Jan-Feb 2010]:

Elemental Impurities—Information

Elemental Impurities—Comments and Responses

<232> Elements

- Elements in the environment – Lead, Arsenic, Mercury and Cadmium
- EMEA Guideline on the Specification Limits for Residues of Metal Catalysts (CPMP/SWP/4446/00) lists 14 catalysts used in pharmaceutical synthesis
  - Exclude zinc and iron, which are not toxic at levels relevant in pharmaceuticals
- Need to control in drug products if presence is possible
  - Deliberately added (catalyst)
  - Possible supply-chain contaminant or adulterant
  - Process issue (equipment)
- Applies to Drug Products but levels in excipients must be known and reported

<233> Basics

- Proposes ICP-OES and ICP-MS and procedures of choice
  - Screening tools
  - Highly specific and sensitive
- All procedures need to be validated
- Provides validation parameters (what is sufficient to demonstrate that the procedure is accepable for its intended purpose)

<2232> Basics

- Applies to Dietary Supplements
  - Dietary Ingredients
- Does **not** apply to drug products
- Procedures in *Elemental Impurities – Procedures* <233> are specified
- Speciation is critical for Dietary Supplements
  - Arsenic and Mercury procedures addressed in this Chapter
- Only As, Hg, Cd, and Pb considered

Next Steps

- <232> and <233> have been finalized by the Expert Panel and are being balloted on by the Chemical Analysis Expert Committee
- If approved, the chapters will be official in USP 35, Supplement 2.
- As with residual solvents, references to the chapters will come from the General Notices and not be in each individual monograph
- There will be a delayed implementation date that will be triggered by the General Notices statement

Topics

- **General Chapters Updates**
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Definition (ICH Q3A)

- Classification of Impurities
  - **Organic**
  - Inorganic
    - Elemental Impurities, to be discussed later
    - Nonspecific tests (residue on ignition)
    - Specific tests for functional groups (chloride, sulfate, phosphate)
  - Residual solvents
    - Covered by USP General Chapter <467>

What Does USP Say About Impurities?

- USP primarily accepts limits established by FDA for innovator and generic pharmaceutical products
- Primary general chapter addressing these issues is <1086> - Impurities in Drug Substances and Drug Products.
- The chapter contains
  - Classification of drug substance impurities
  - High-level discussion of specification setting for drug products
  - Definitions

Current USP Directions

- USP is beginning to make its expectations clearer – providing minimum standards and elaborating <1225> and <1226> as they pertain to a particular chapter
  - Elemental Impurities – Procedures <233>
  - Spectroscopy chapters (e.g., NMR, UV, AA)
- Necessary but not necessarily sufficient criteria for what is acceptable
- A more detailed description of expectations for impurities would be helpful and is consistent with USP's current approaches

USP <1086> Expert Panel

- USP has established an Expert Panel to work on updating <1086>
- Charter - The purpose of this Expert Panel will be to revisit <1086> in the new context of current regulatory thinking with regard to over–the-counter and generic product testing.

Starting Points

- ICH Q3A (R2) – Impurities in New Drug Substances
- ICH Q3B (R2) – Impurities in New Drug Products
- Guidance For Industry: ANDAs – Impurities in Drug Products
- Some Potential Outcomes -
  - High-level guidance chapter
  - Requirements, for example ICH, in a below 1000 chapter
  - Deletion of <466> Ordinary Impurities
  - General Notices statements

Topics

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Spectroscopy and Light-Scattering <851>

- In USP 25 (2002)
  - –Described all spectroscopic techniques
  - –Very little detail
- Will be replaced in part by a family of chapters pertaining to atomic absorption, UV-Vis, infrared, and fluorescence spectroscopy.
- Each of these chapters will be presented in pairs (one numbered sub-1000 and one numbered greater than 1000).

A change in stages

First stage: Published in PF 37(5). Deadline for comments was November 30th

<852> Atomic absorption
<854> Mid-infrared spectroscopy.
<857> Ultraviolet-visible spectroscopy
<1857> Ultraviolet-visible spectroscopy – Theory and Practice
<1854> Mid-infrared spectroscopy. – Theory and Practice
<1852> Atomic absorption – Theory and Practice

Second stage: Future PF

<853> Fluorescence spectroscopy
<xxx> NIR
<xxx> Raman
<1853> Fluorescence spectroscopy – Theory and Practice
<1119> Near Infrared – Theory and Practice
<1120> Raman spectroscopy Theory and Practice

Content

- Mandatory Chapters (<1000): Focus is on the performance of the test for compendial purposes.
  - Introduction
  - Instrument qualification
  - Procedure
  - Procedure Validation / Verification

- Informational chapters (>1000): Work in concert with mandatory chapters by describing theory and instrumentation in some detail, include analytical considerations that could help in method development.

Content Examples: Atomic Absorption <852>

- **Accuracy**—For Category I assays or Category II tests, accuracy can be determined by conducting recovery studies with the appropriate matrix spiked with known concentrations of elements. It is also an acceptable practice to compare assay results obtained using the AA procedure under validation to those of an established, analytical procedure.

  Validation Criteria: 98%-102% recovery for drug substances and drug product assay and 70%-150% recovery for impurity analysis. These criteria should be met throughout the intended range.

Content Examples: Atomic Absorption <1852>

<1852> Atomic Absorption Spectroscopy-Theory and Practice

Chapter Sections:

- Theory
- Instrumentation
- Sample Cell Design
- Line Sources
- Wavelength Selectors
- Detection Systems
- Background Correction
- Analytical Considerations
- Other Sources of Information
- Appendix: Acronyms

Topics

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<621> Chromatography

Major revision to <621> Chromatography, official in *USP 34-NF 29* (May 1, 2011)

- Deleted from <621>: descriptive or noncritical information (e.g., theory of chromatography).
- Retained in <621>: all required critical information needed in order to perform a monograph procedure
  - definitions
  - calculations
  - interpretation of chromatograms

<621> Chromatography

- The revision is also harmonized, to the extent possible, with the equivalent chapter in the European Pharmacopoeia (Eur. Ph.), 2.2.46, Chromatographic Separation Techniques
- Goal is to harmonize with European and Japanese Pharmacopeias through the Pharmacopeial Discussion Group – Stage 3 document under discussion
- New proposal to allow an HPLC column with different dimensions to those prescribed in the official procedure (different length, internal diameter, and/or particle size) though verification rather than validation is under discussion

Topics

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Packaging Materials/Components

- *New* <659>*Packaging and Storage Requirements*
  - Official: May 1, 2012 (USP35-NF30 1S)
- <660> *Containers – Glass*
  - *PF 37 (2) IPR Official: Aug.1 2012* (USP35-NF30 1S)
    - *Powder Glass Test updated*
    - *Water Attack at 121° deleted*
- <661> *Containers – Plastics*
  - <661> *Materials of Construction, PF 2013*
  - *<661.1> Containers for Pharmaceutical Use, PF 2013*
- <662> Containers—Metal (Planned)
  - PDS EC seeking experts and planning to form Expert Panel to start discussions on chapter development (2013)

Packaging Materials/Components

- <1660> Evaluation of Inner Surface Durability of Glass Containers
  - Factors that affect durability of inner surface of glass containers
    - Forming
    - Formulations
  - Visualization of glass particles and lamellae
  - Tests to predict durability of inner surface
  - PF 38 (3) May-June

Packaging Materials/Components

- <1663> Extractables Testing for Pharmaceutical Packaging Systems
  - Chapter will describes a framework for considering the issues associated with the proper design and justification of the extraction process used to assess the potential impact of contact between a packaging material and a drug product.
  - *Target Publication:Q1 2013*
- <1664> *Best Practices: Leachables Testing and Thresholds*
  - Chapter will describes the development of scientifically supported testing and safety evaluation threshold for leachables; based on the PQRI OINDP and PODP recommendations
  - *Target Publication:Q1 2013*

Storage and Distribution

- <1079> *Good Storage and Shipping Practices*
  - *IPR, PF 37 (4) Official: Dec. 1 2012* (USP35-NF30 2S)
- *New* <1083> Good Distribution Practices—Supply Chain Integrity
  - *IPR, PF 38 (3)*
    - 1) Importation; 2) Counterfeit Drugs and Medical Devices; 3) Best Practices to Combat Counterfeit Drugs and Medical Devices; and 4) Diversion and Theft
  - *Supply Integrity Workshop May 22-23, 2012*
- <1118> *Monitoring Devices – Time, Temperature and Humidity*
  - *IPR, PF 38 (2)*

Upcoming USP Workshops

Probiotics	May 9-10, 2012
Supply-Chain Integrity	May 22-23, 2012
Challenges in Dissolution	June 11-12, 2012
Microbiology	July 23-24, 2012
Heparin Characterization	Aug 14-15, 2012
Vet Drugs – Solubility	Nov 7-8, 2012
Bioassay	Dec 4-5, 2012
Storage and Distribution	May 20-23, 2013
Ophthalmic Ointments	Oct 21-24, 2013
Extractables/Leachables	Dec 9-12, 2013

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Thank You