November 29, 2006

Demystifying The Standards-Setting Process of the *USP-NF*

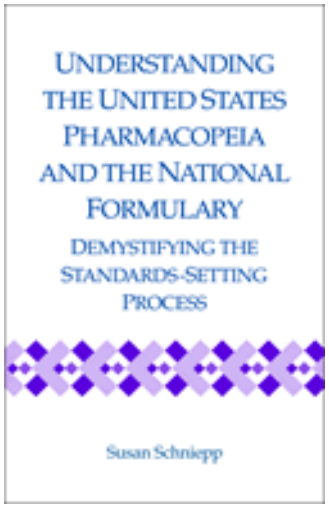
Presented to: PDA Midwest Chapter

Susan Schniepp
Quality Manager
Hospira, Inc.

Hospira

Book Contents

- Table of Contents
- Forward (By Mark Ehlert, Hospira)
- Preface (By Roger Williams, USP)
- References
- Charts
- Tables
- Flow Diagrams
- Case Studies
- Pictures



Hospira

Table of Contents

Hospira

Chapter 1
Glossary of Terms: Learning the Language

- *Pharmacopeia:* Legally binding document governing the quality, strength and purity of medical items of commerce in a specific geographical region. *USP-NF* applies to products marketed in the United States of America as well as many other countries around the world that have voluntarily adopted it; the *European Pharmacopoeia* (*Ph. Eur.*) applies to products marketed in the European Union and the *Japanese Pharmacopoeia* (*JP*) applies to products marketed in Japan.

Hospira

The USP is…

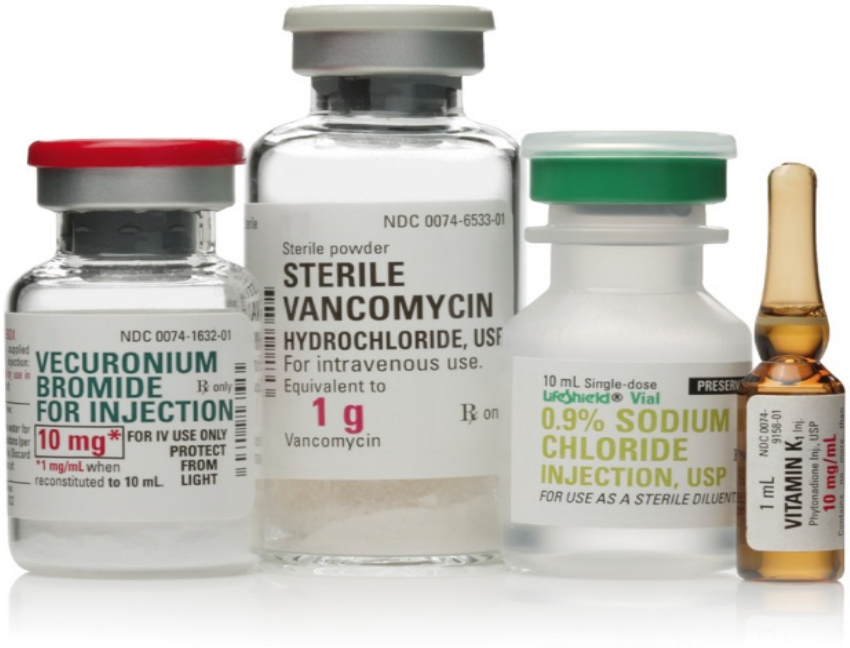
- Subject to multiple interpretations

The USP is…

- Standard (not cutting edge) technologies and procedures capable of being performed by any manufacturing company or testing laboratory

The USP is…

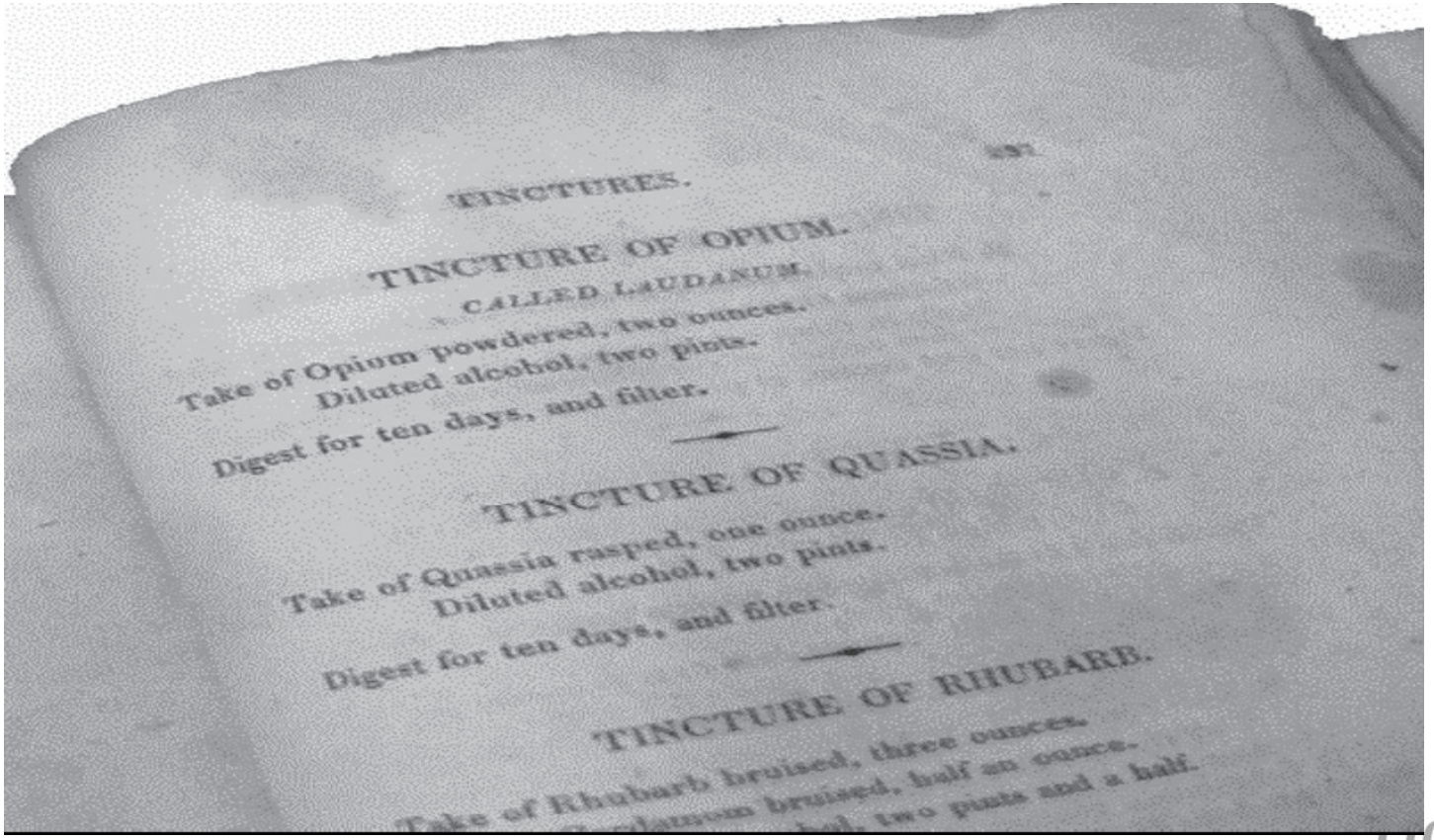
- Recognized requirements through expiration



Hospira

The USP is…

- The oldest continuously revised compendial standard in the world.



TINCTURES.

TINCTURE OF OPIUM.

CALLED LAUDANUM.

Take of Opium powdered, two ounces.
Diluted alcohol, two pints.
Digest for ten days, and filter.

TINCTURE OF QUASSIA.

Take of Quassia rasped, one ounce.
Diluted alcohol, two pints.
Digest for ten days, and filter.

TINCTURE OF RHUBARB.

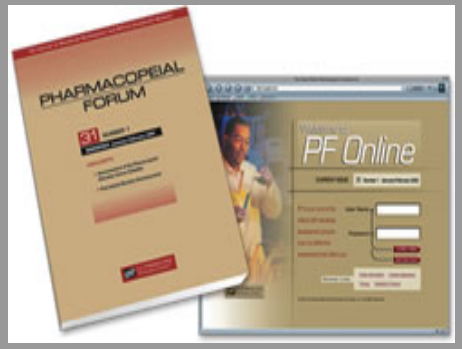
Take of Rhubarb bruised, three ounces.

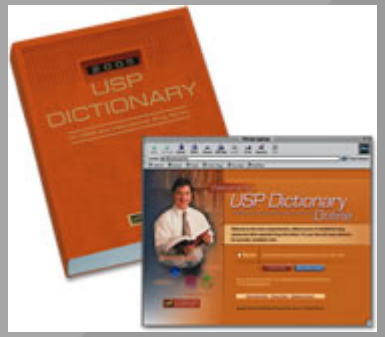
Chapter 2
Brief History of the *USP-NF*

- 1820: USP Established
- 1848: Recognized in the Federal Drug Import Act
- 1880-1900: Recognized by state laws and statutes
- 1906: Recognized in the Pure Food and Drug Act
- 1938: USP & NF Standards recognized in FD&C Act
- 1941: Congress states insulin must comply to USP
- 1965: Social Security Act recognizes USP standards
- 1975: USP and NF merge; 1st PF is published
- 2005: USP provides Medicare Model Guidelines
- 2020: USP to Celebrate 200th Anniversary

Hospira

Chapter 3
USP Publications: Up-to-Date Information





Hospira

Publication and Comment Schedule for 2007 and Beyond

Publication and Comment Schedule for USP 30-NF 25

	Comment Deadline	Published	Official
Main Edition	May 15, 2006	November 2006	May 1, 2007
1st Supplement	August 15, 2006	February 2007	August 1, 2007
2nd Supplement	December 15, 2006	June 2007	December 1, 2007

Hospira

Chapter 4
The USP Convention Process

Defining the Five-Year Revision Cycle

Hospira

USP/NF Policies and Procedures

- Policies and Procedures are voted on by the United States Pharmacopeial Convention

Hospira

The United States Pharmacopeial Convention

- Meets Every 5 years
- Last Convention: March 9-13, 2005
- Next Convention: March 2010

Convention Membership

- U.S. Colleges and Schools of Medicine
- State Medical Societies
- U.S. Colleges and Schools of Pharmacy
- State Pharmacy Associations
- National and State Professional and Scientific Organizations
- Governmental Bodies
- Health Science and Other Foreign Organizations and Pharmacopeias
- Consumer Organizations and Individuals Representing Public Interests
- Domestic, Foreign, and International Manufacturers, Trade, and Affiliated Associations
- Members at Large

Hospira

Convention Responsibilities

- Member Organizations Elect/Appoint Delegates to Attend Convention
  - Vote on Bylaws and Constitution
  - Vote on Council of Experts Chairs
  - Conduct Business Meetings
  - Debate and Vote on Resolutions

Hospira

Chapter 5
The Standards-Setting Process: From Idea to Standard

Hospira

USP Standards Adoption Process

Note: Industry can participate at any point during the process

- Process Step 1 – Resolution Adopted at QM
  - Resolutions may be submitted by any interested party through USP Headquarters

- *Case Study:*
- *Resolution 10 - QM 1995:*
  - *USP is encouraged to identify compendial items for which storage and shipment in the distribution system are of special concern, so proper storage and shipment instructions can be included with the compendial item, such that the integrity of the item is maintained until received by the patient*

Hospira

Standards Adoption (cont.)

- Process Step 2 – Stimuli to the Revision Process
  - Committee of Experts publish position paper in Pharmacopeial Forum introducing concept for change and areas targeted for change (typically General Chapters).

- *Case Study:*
- *USP Committee of Experts published a series of articles starting in 1996:*
  - *Survey to Provide Data for Proper Shipment and Distribution Conditions*
  - *A Review of Storage Conditions for Compendial Dosage Forms*
  - *Temperature Fluctuations During Mail Order Shipment of Pharmaceutical Articles using Mean Kinetic Temperature*
  - *Drug Products Distribution Chain (May-June 2003)*

Hospira

Standards Adoption (cont.)

- Process Step 3 – Open Discussion (optional)
  - Committee of Experts can chose to hold an open discussion to obtain industry input.
  - Open Discussions can deal with more than one resolution

- *Case Study:*
  - *Open Discussions (Open Conferences) were held in June 1998, August 1999 and October 2003*

- Note – Open Conferences have been replaced by the Annual Scientific Meeting and Semi-annual Stakeholders Forum Meetings.

Hospira

Standards Adoption (cont.)

- Process Step 4 – Pharmacopeial Forum Publication
- Committee of Experts publishes actual changes to affected monographs based on:
  - Resolution Objective
  - Open Discussion Comments
- Proposal is assigned a targeted supplement date

- *Case Study:*
  - *Proposals began appearing in PF in late 1997*
  - *Initial Proposals were to General Notice, <1191> stability Considerations in Dispensing Practice, <661> Containers and <671> Containers-Permeation*
  - *New General Chapter proposed <386> Environmentally Sensitive Preparations*
  - *Proposals targeted for 6, 7 and 8 Supplement to USP 23*
  - *<386> targeted for 1S USP 27*

Hospira

Standards Adoption (cont.)

- Process Step 5 – Interim Revision Announcement
  - Reserved for items requiring immediate change
  - Items in IRA are official and carry the same weight as items in the USP/NF and Supplements

- *Case Study:*
  - *All affected proposals were actually adopted in the 8th Supplement but due to industry objection they were rescinded via an IRA (Mar/Apr 1999, 28th IRA)*

Hospira

Standards Adoption (cont.)

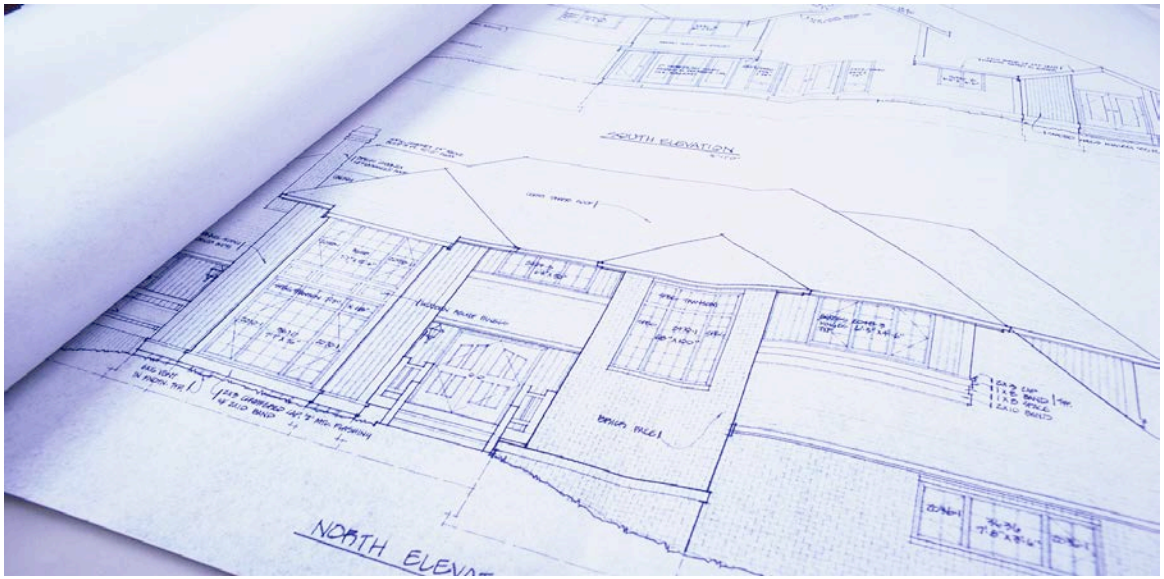
- Process Step 6 – Official Supplements
  - Adoption mechanism of approved PF proposals

- *Case Study:*
  - *Proposals were adjusted after 1999 Open Discussion*
  - *Reproposed in Jan/Feb 2000 PF*
  - *Further modified after October 2003 Discussion*
  - *Labile Preparations was changed to Environmentally Sensitive Preparations*

Hospira

Resolutions from the 2005 Convention

- 13 Resolutions adopted
- Define USP's strategic plan through 2010
- Define Expert Committee Focus
- Determines USP priorities and resources



Resolutions 2005

- **New Science and Technology**
  USP resolves to work with appropriate stakeholders to track emerging sciences and technologies, and when appropriate, to develop information, best practices, and standards that have direct applications to the public health and patient care.

Hospira

Resolutions 2005 (continued)

- **USP International Presence**
  USP resolves to continue working with international governmental and nongovernmental bodies to increase the impact of its public health programs internationally. Furthermore, USP resolves to provide assistance in improving regulatory mechanisms and in building capacity to monitor drug quality for countries that lack appropriate resources.

Hospira

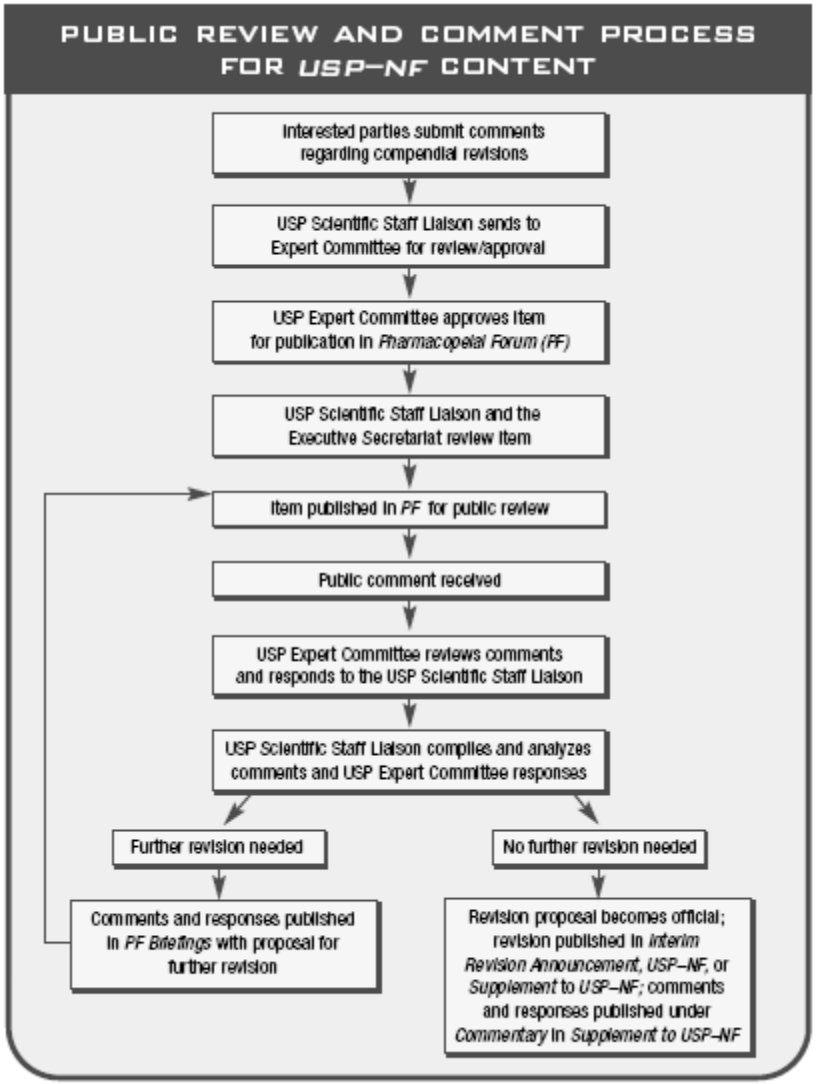
Resolutions 2005 (continued)

- **International Harmonization**
  USP resolves to continue its efforts to harmonize compendial standards with the Pharmacopeial Discussion Group (PDG) and other pharmacopeias

Hospira

Chapter 6
The Monograph Adoption Process: The Backbone of USP-NF

Hospira


PUBLIC REVIEW AND COMMENT PROCESS FOR USP–NF CONTENT
Interested parties submit comments regarding compendial revisions
USP Scientific Staff Liaison sends to Expert Committee for review/approval
USP Expert Committee approves item for publication in Pharmacopeial Forum (PF)
USP Scientific Staff Liaison and the Executive Secretariat review item
Item published in PF for public review
Public comment received
USP Expert Committee reviews comments and responds to the USP Scientific Staff Liaison
USP Scientific Staff Liaison compiles and analyzes comments and USP Expert Committee responses
Further revision needed
No further revision needed
Comments and responses published in PF Briefings with proposal for further revision
Revision proposal becomes official; revision published in Interim Revision Announcement, USP–NF, or Supplement to USP–NF; comments and responses published under Commentary in Supplement to USP–NF

The Old Monograph Look

» Acebutolol Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{28}N_2O_4 \cdot HCl$, calculated on the dried basis.

Assay— *Mobile phase*—Prepare a filtered and degassed mixture of methanol, a 0.3% aqueous solution of sodium dodecyl sulfate, and glacial acetic acid (675:325:20). Make adjustments if necessary to achieve a retention time for acebutolol of between 4 minutes and 7 minutes (see *System Suitability* under *Chromatography* 621).

Standard preparation—Quantitatively dissolve an accurately weighed quantity of *USP Acebutolol Hydrochloride RS* in water to obtain a solution having a known concentration of about 0.14 mg per mL.

Assay preparation—Transfer about 35 mg of Acebutolol Hydrochloride, accurately weighed, to a 250-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* 621)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of C18H28N2O4 · HCl in the portion of Acebutolol Hydrochloride taken by the formula:

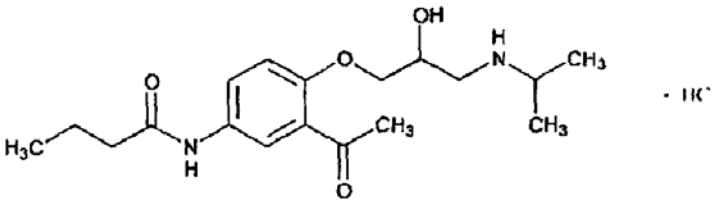
$$250C(rU / rS)$$

in which *C* is the concentration, in mg per mL, of *USP Acebutolol Hydrochloride RS* in the *Standard preparation;* and *rU* and *rS* are the acebutolol peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Hospira

The New Monograph Look

Acebutolol Hydrochloride



DESCRIPTION

$C_{18}H_{28}N_2O_4 \cdot HCl$ 372.89

Butanamide, *N*-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl) amino]propoxy]phenyl]-, monohydrochloride, (±)-.

(±)-3′-Acetyl-4′-[2-hydroxy-3-(isopropylamino)propoxy]-butyranilide monohydrochloride [*34381-68-5*].

Melting range ⟨741⟩: between 140° and 144°.

pH ⟨791⟩: between 4.5 and 7.0, in a solution (1 in 100).

Loss on drying ⟨731⟩— Dry it at 105° for 3 hours: it loses not more than 1.0% of its weight.

IDENTIFICATION

Identification

A: *Infrared Absorption* ⟨197K⟩

B: The retention time of the major peak in the chromatogram of a mixture of *Assay preparation* and Standard Preparation (1:1) corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

C: It responds to the tests for *Chloride* ⟨191⟩, when tested as directed for alkaloidal hydrochlorides.

ASSAY

Mobile phase—Methanol, 0.3% aqueous solution of sodium dodecyl sulfate, and glacial acetic acid (675:325:20).

Standard solution—0.14 mg /mL of *USP Acebutolol Hydrochloride RS*

Test solution—0.14 mg/mL

Chromatographic system—liquid chromatography
- Detector—254-nm
- Column—3.9-mm × 30-cm, L1 packing
- Flow Rate—about 2 mL per minute
- Injection Size about 10 µL

System Suitability—
- SAMPLE—*System Suitability Solution [or] Standard Solution*
- *Suitability Acceptance Criteria*
  - column efficiency—NLT 1500 theoretical plates
  - tailing factor—NMT 2.5
  - relative standard deviation NMT 2.0%.

Assay Acceptance Criteria—*NLT* 98.0% and NMT 102.0% of $C_{18}H_{28}N_2O_4 \cdot HCl$, calculated on the dried basis

Hospira

Chapter 7
Dissecting the Information: Interpreting the contents of the book

Hospira

USP Monograph Hierarchy

- Monograph Instructions take precedence over General Test Chapter Instructions
- General Test Chapter Instructions take precedence over General Notices
- General Notices are the basic concepts governing the information in the General Test Chapters and Monographs
  - Defines temperature scale
  - Defines rounding rules
  - Other

Hospira

Misinterpretation: “about = ± 10%”

- *Misinterpretation:*
- The use of the word “about” in the USP means ± 10% of the original value/parameter

- *Clarification:*
- Yes – for weights, volumes, dimensions
- No – for temperatures, times, acceptance criteria

- *Location in USP:*
  - General Notices and Requirements
  - Section: Tests and Assays
  - Subsection: Procedures

Hospira

Actual Phrase

- “In stating appropriate quantities to be taken for assays and tests, the use of the word “about” indicates a quantity within 10% of the specified weight or volume. However, the weight or volume is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions”

Hospira

Misinterpretation: Sample Size

- *Misinterpretation:*
- I have 10 results when I perform content uniformity testing because I use 10 units per USP test

- *Clarification:*
- No, No, No – you have one result

- *Location in USP:*
  - General Notices and Requirements
  - Section: Tests and Assays
  - Subsection: Test Results, Statistics and Standards

Hospira

Actual Phrase

- “Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for Dissolution and Uniformity of dosage units, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen”

Hospira

Interpretation: Establishing Incubation Times

- *Question:* The USP specifies an incubation time of 48 hours and my procedure specifies an incubation time of 2 days. Am I in compliance?

- *Answer:* Maybe, it depends on how you are recording your incubation start/stop points

- Typically, USP indicates incubation times in terms of hours for tests completed in three days or less and in terms of days for tests requiring 5 days or more incubation time

Hospira

Supporting Evidence

- Review of the following General Test Chapters allows you to establish USP's incubation time pattern
  - <51>, Antimicrobial – Effectiveness Testing
  - <55>, Biological Indicators – Resistance Performance Tests
  - <61>, Microbial Limits Tests
  - <71>, Sterility Tests

Hospira

Recommendations

- For Misinterpretations:
  - Read USP General Notices in their entirety!
  - Read other pertinent USP sections in their entirety!

- For Interpretations
  - Read the Pharmacopeial Forum briefings
  - Read related USP Chapters
  - Justify, in writing, the interpretation your company has agreed to
  - Update as USP changes

Hospira

Chapter 8
Method Validation/Verification Concepts: Ensuring Compliance to the Standard

Hospira

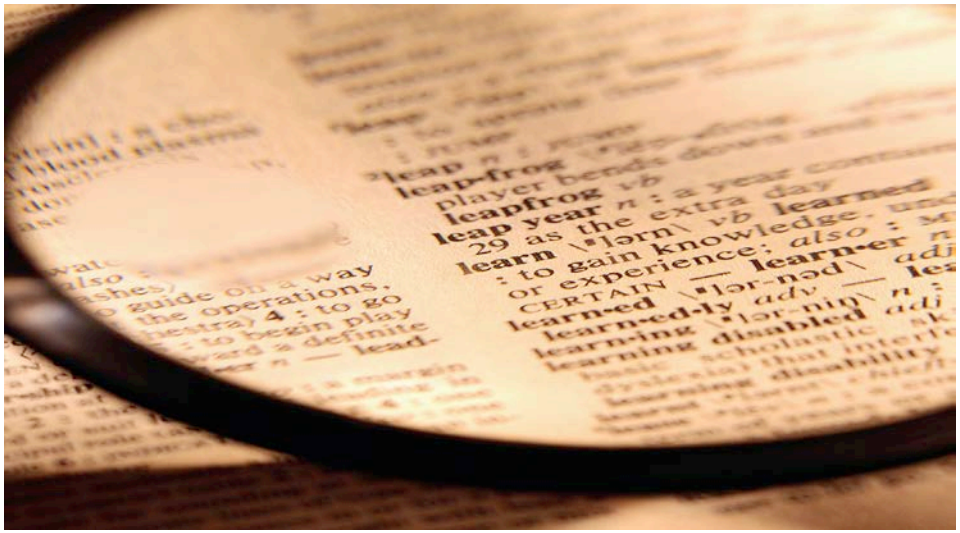
Federal Food, Drug and Cosmetic Act - Section 501.[351](b)

- Synopsis: Assays and specifications in monographs of the United States Pharmacopeia and the National Formulary constitute legal standards.

Hospira

CFR 211.194(a)

- a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays…..



CFR 211.194(a)(2) - Laboratory Records

- If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods,\1\ 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.

Hospira

USP Validation Requirements

Defined in USP General Information Chapters:

- <1225> Validation of Compendial Methods
  - Used for Chemistry and Physical Test Methodology
- <1227> Validation of Microbial Recovery from Pharmacopeial Articles
- Text Harmonized with ICH documents
  - Validation of Analytical Procedures
- Guideline for Submitting Requests for Revision – PF 31(1)
  - Incorporates ICH Q3A, Q3B, Q3C, Q6A and Q6B

Hospira

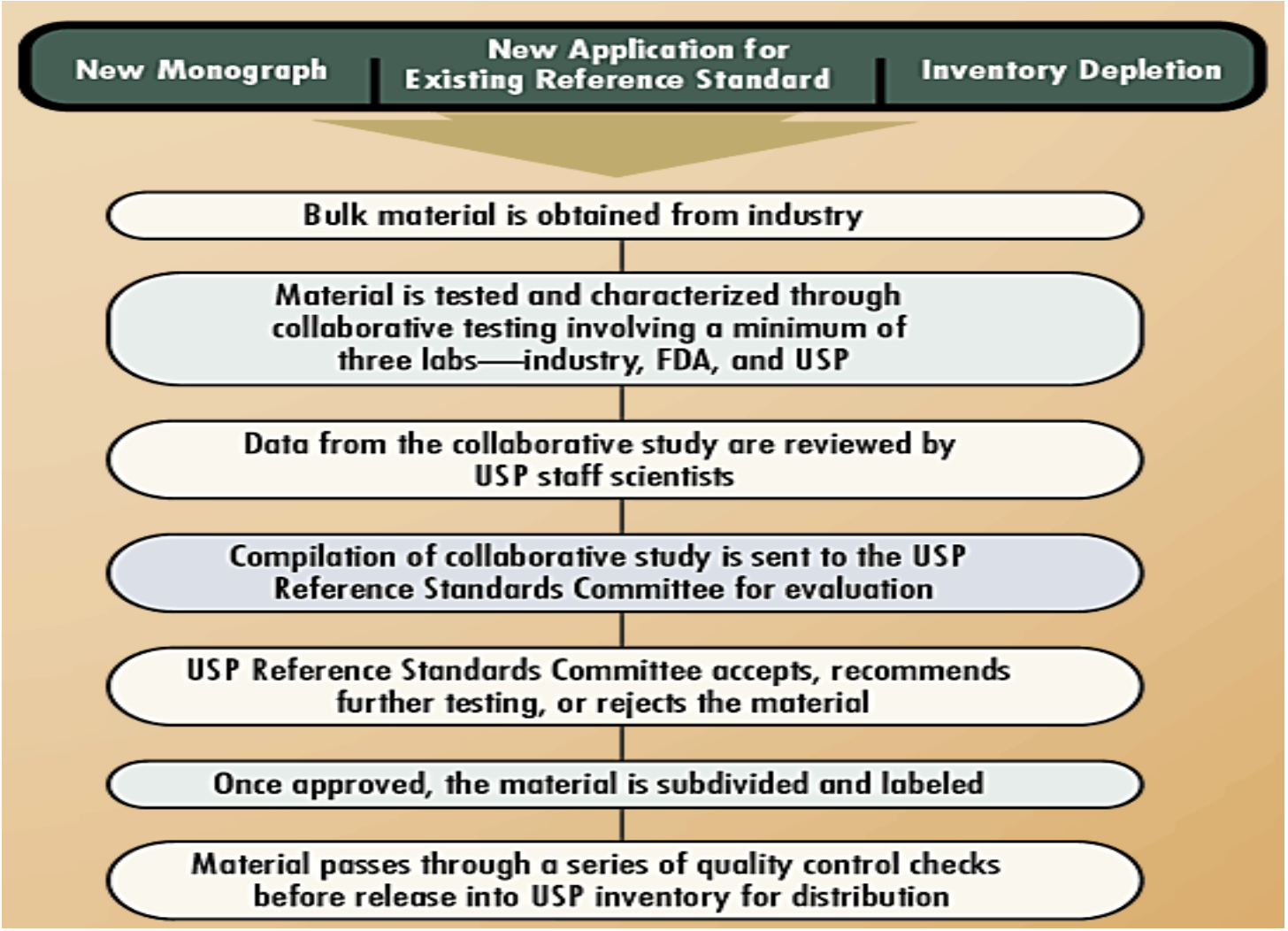
Chapter 9
Reference Standards: The Basis for Determining Quality

Hospira

Reference Standards

- Over 1800 USP Reference Standards
- Assumed 100% pure (Unless label states otherwise)
- Support FDA-enforceable standards and tests in *USP-NF*

Reference Standards Process



Hospira

Reference Standards Process (cont.)

- Testing
  - Collaborative testing in multiple labs: USP, Industry, and FDA
  - Extensive testing beyond the Compendial tests
- Approval
  - Reference Standards Committee
  - Unanimous approval required on voting
  - Single NO vote sends material back for additional testing and/or clarification

Hospira

The Use of Reference Standards

- Approved as suitable for use in comparison testing
  USP General Notices and Requirements, USP Reference Standards, p5
- Where reference standards are called for in monograph testing the nomenclature is *"USP xxx RS"*
  USP General Notices and Requirements, USP Reference Standards, p5
- Labeling instructions on the vial take precedence over those printed in USP 28/NF 23 and Pharmacopeial Forum
- Other sources/grades of substances* may be acceptable when the designation RS is not present in the monograph
  USP General Notices and Requirements, USP Reference Standards, p5
- Potency is assumed 100.0% (unless otherwise labeled)
  USP General Test Chapter <11> USP Reference Standards
- Suitability for non-compendial application is "left up to the user"
  USP General Test Chapter <11> USP Reference Standards
- Recognizes American Chemical Society (ACS) Reagents as suitable
  USP General Notices and Requirements, Reagent Standards, p5

*Requirements defined in Reagents, Indicators, and Solutions

Hospira

Chapter 10
The Future of the USP

Hospira

USP-NF Programs

- Harmonization with Ph. Eur. and JP
- SAPFA (Standards for Articles Pending FDA Approval)
  - Submit at time of filing
  - Maintained confidentially at USP
  - Immediately Official upon FDA approval
- Flexible Monographs
  - Allows more than 1 test procedure for monograph attribute
- Monograph Redesign
  - Monographs to read like laboratory procedures (2008)

Hospira

Questions?

Thank You

Hospira