Understanding the USP Compendial Process: Monograph Development

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Outline

- USP Standard Setting Process
  - Roles of USP's Standards
  - Expert Committees
  - Monograph Development
- Monograph Modernization and Up-to-Date
  - What is monograph modernization and up-to-date
  - USP's strategy
  - Examples
- Summary

USP's Relationship to US FDA

- USP: Private Not-For-Profit Organization
  - Engaged in the development and revision of compendial standards for drugs (and other products)
  - Public standards related to identity, strength, purity, quality, packaging, labeling
- US FDA: Government Agency
  - Engaged in the promulgation and enforcement of drug (and other product) regulatory requirements
  - Safety, Efficacy, NDA/ANDA (private license) approvals for marketing, manufacturing processes, etc.

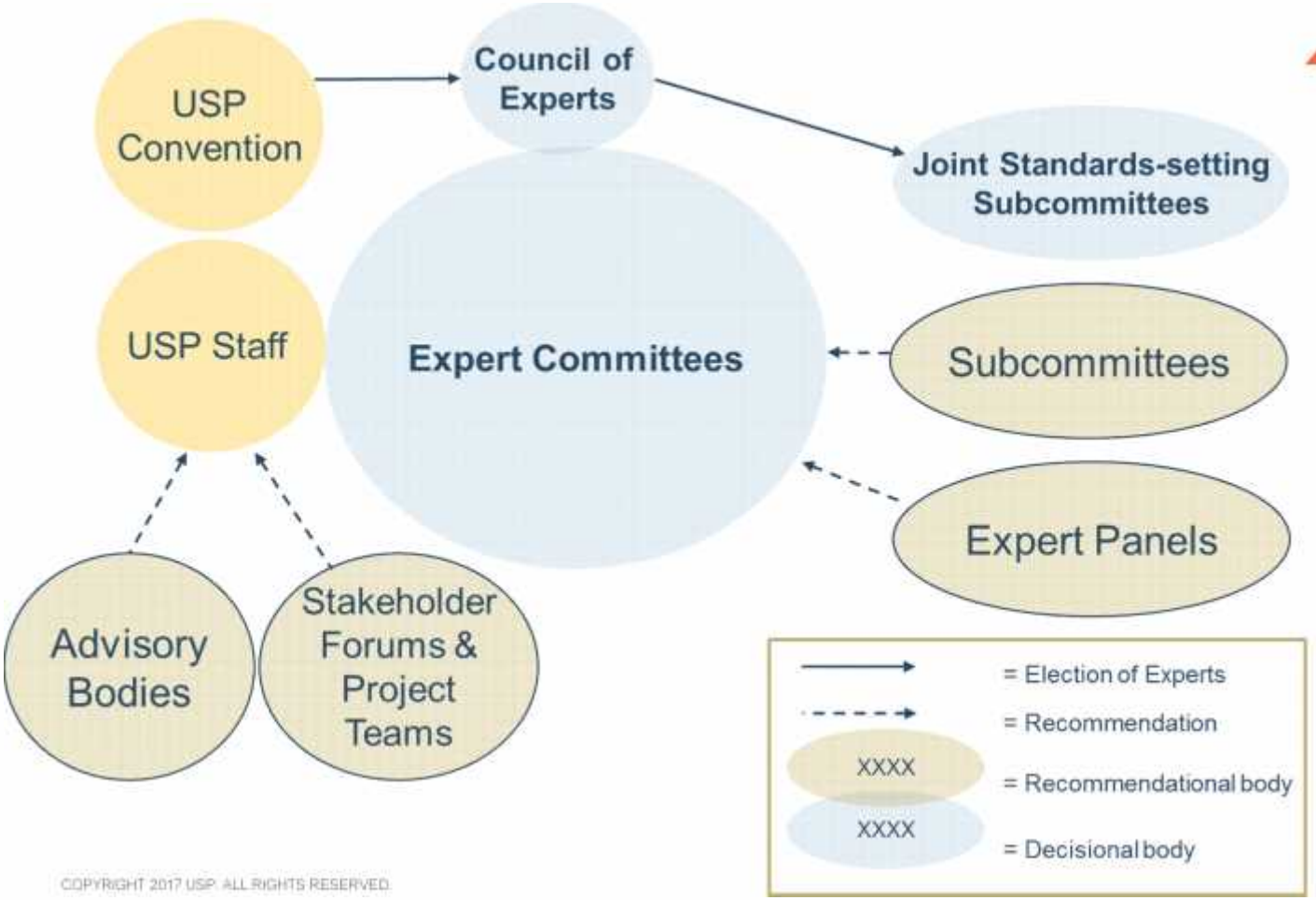
USP is the only major Non-Governmental Pharmacopeia in the World!

What is USP's Role in U.S. Law?

- **Adulteration –** Drug/biologic "shall" generally be deemed 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 standards set forth in such compendium." FDCA 501(b)
  - "Official compendium" means the current version of USP or NF deemed official by USP, including any supplements. FDCA 201(j)

- **Tests –** "Such determination as to strength, quality or purity shall be made in accordance with the tests or methods of assay set forth in such compendium, ..." FDCA 501(b)
- **Misbranding –** Drug/biologic "shall" be deemed misbranded "if it purports to be a drug the name of which is recognized in [*USP-NF*]," unless "packaged and labeled as prescribed therein." FDCA 502(g)
- **Enforcement –** USP has no role in enforcement of USP standards; responsibility of FDA and other authorities in U.S. and elsewhere.

USP Standards-Setting Structure



Collaborative Groups

Biologics

Biologics Monographs 1 - Peptides & Oligonucleotides
Michael De Felippis

Biologics Monographs 2 - Proteins
Wendy Saffell-Clemmer

Biologics Monographs 3 - Complex Biologics & Vaccines
Earl Zablackis

Biologics Monographs 4 - Antibiotics
Matthew Borer

Biologics Monographs 5 - Advanced Therapies
Mehrshid Afai

Small Molecules

Small Molecules 1
Mary Seibel

Small Molecules 2
Justin Pennington

Small Molecules 3
Eric Kesslen

Small Molecules 4
Kim Huynh-Ba

Small Molecules 5
Amy Karren

Over-the-Counter (OTC) Methods & Approaches
Raphael Ornaf

Excipients

Simple Excipients
Eric Munson

Complex Excipients
Otilia Koo

Excipients Test Methods
Chris Moreton

General Chapters

General Chapters-Dosage Forms
Martin Coffey

General Chapters - Chemical Analysis
Nancy Lewen

General Chapters-Microbiology
Donald Singer

General Chapters-Packaging & Distribution
Renaud Janssen

General Chapters - Measurement & Data Quality
Jane Weitzel

General Chapters-Statistics
Charles Tan

General Chapters - Physical Analysis
Xiaorong He

Healthcare Quality & Safety

Nomenclature & Labeling
Stephanie Crawford

Healthcare Safety & Quality
Melody Ryan

Compounding
Brenda Jensen

Healthcare Information & Technology
Jeanne Tuttle

Dietary Supplements & Herbal Medicines, Food Ingredients

Botanical Dietary Supplements & Herbal Medicines
Robin Marles

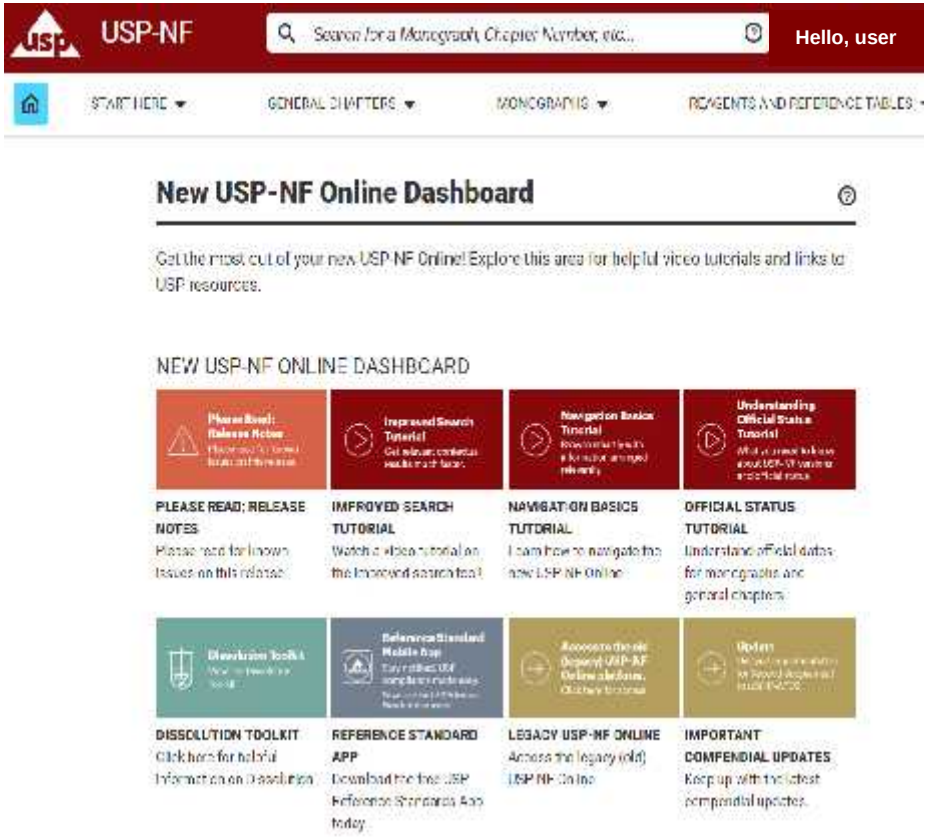
Non-botanical Dietary Supplements
Guido F Pauli

Dietary Supplements Admission Evaluation & Labeling
Tieraona Low Dog

Food Ingredients
Jon DeVries

USP – Public standards

USP standards used in over 140 countries



Go to www.usppf.com to access the *PF*

Drug Monographs in *USP–NF*

- *General Notices* contain requirements applicable throughout *USP–NF* unless superseded by a chapter or monograph
- *General Chapters*
  - Required when monograph cites them or through General Notices
  - Support monographs by centralizing methods and procedures
  - Informational (numbered >1000)
  - General Chapter requirements supersede General Notice requirements in case of conflict
- *Monographs*
  - Specifications for pharmaceutical articles in commerce (from release through product shelf life)
  - Specifications – Tests, assays and acceptance criteria needed to demonstrate the article meets required quality standards
  - Monograph requirements supersede General Notices and general chapter requirements in case of conflict
- *Reference Standards (RSs): Physical Reference Materials*
  - Provide traceable standards to demonstrate broad-based acceptability of procedures

Monograph Revision Categories

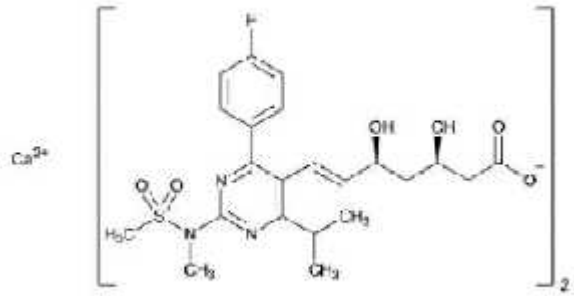
- **New Monograph** – introduce new monograph for an article legally marketed in US
- **Regular Revision** – revise the text in an existing official monograph or chapter
- **Major revision** – (for chapters) revision of a chapter impacting more than 100 monographs or affecting ≥50% of the text of a chapter
- **Accelerated Revisions:**
  - *Errata*
  - *Interim Revision Announcement (IRA)*
  - *Revision Bulletin (RB)*
- Monograph Omission
- Pending Monograph (Monograph for articles pending FDA Approval)

Sources of Requests for Revision

- Manufacturers with or without US-FDA approval
- US-FDA
- Expert Committee Members
- Expert Panels
- Harmonization with other pharmacopeias
- Trade and other organizations

How do we develop a monograph?

Rosuvastatin Calcium



$Ca(C_{22}H_{27}FN_3O_6S)_2$ 1001.14

6-Heptenoic acid, 7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-, calcium salt (2:1), (3*R*,5*S*,6*E*); [*S*-(*R**,*S**-(*E*))]-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, calcium salt (2:1); Calcium (3*R*,5*S*,*E*)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoate salt (1:2) [147098-20-2]

DEFINITION

Rosuvastatin Calcium contains NLT 97.0% and NMT 103.0% of rosuvastatin calcium [$Ca(C_{22}H_{27}FN_3O_6S)_2$], calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A.** Infrared Absorption ⟨197K⟩ or ⟨197A⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the test for *Enantiomeric Purity*.
- **C.** Identification Tests—General ⟨191⟩, Chemical Identification Tests, Calcium

Sample solution: 8 mg/mL of Rosuvastatin Calcium in a mixture of methanol and water (1:1)

Acceptance criteria: Meets the requirements

ASSAY

- **Procedure**

Protect all solutions containing rosuvastatin calcium and its related compounds from light.

Solution A: Acetonitrile, 1% (v/v) aqueous trifluoroacetic acid, and water (200:100:700)

Solution B: Acetonitrile, 1% (v/v) aqueous trifluoroacetic acid, and water (750:100:240)

Mobile phase: See Table 1.

Supported by:

- Validation package(s)
- SOPs
- Letter of approval
- Additional supporting data (such as CoAs, stability data)

Submission Guidelines

- https://www.usp.org/get-involved/donate/submission-guidelines
  - General Information for Submitting for Revision to *USP-NF*
  - USP recognizes that some manufacturers may not wish to sponsor a standard until an article approaches multi-source status. Although there may be circumstances meriting the development of a standard by USP without a sole-source sponsor, it is USP's policy to first seek to work exclusively with an FDA-approved manufacturer (typically the relevant patent holder) until approximately five years prior to potential generic entry. If at that time the manufacturer remains unwilling or unable to provide the necessary information or material, USP may work with another manufacturer willing to sponsor a submission or begin development internally.
- Submission Guidelines for Small Molecules (Chemical Medicines)
  - https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/chemical_medicines_rfr_guideline_-28apr16.pdf

Monograph Modernization (Up to Date)

- Documentary standards for drugs must undergo continuous revision, or modernization in order to reflect “state-of-the-industry” practices at any given time.

USP Convention Resolution 2:

USP will work to:

- **eliminate the existing backlog of monographs in need of modernization, and**
- **proactively evaluate and update monographs to maintain their relevance given scientific advances and evolving manufacturing and regulatory approaches.**

USP will work with industry and FDA to explore new strategies for sharing analytical methods and specifications needed to modernize monographs.

USP-NF Up to Date

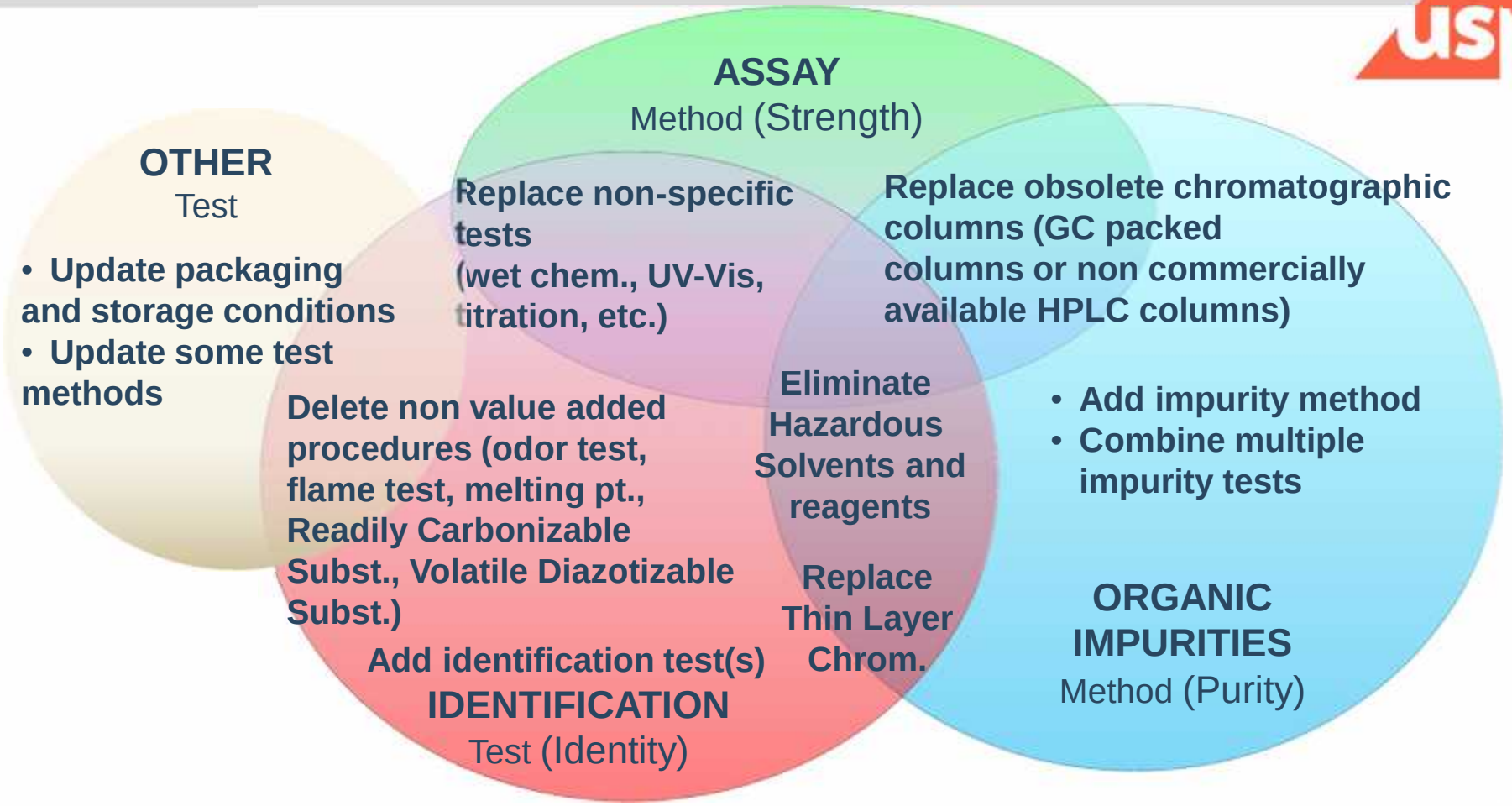
What does "*USP-NF* Up to Date" mean?

Current:
Add new monographs & general chapters in timely manner.
Omit monographs / general chapters that are no longer needed

Relevant:
Modernize and/or revise monographs & general chapters to reflect "state of the industry" practices.
Ensure availability of Reference Standards

Suitable for their intended use:
All components clear, complete and correct.
Remove unnecessary tests.
Appropriate selection of reference standards

USP-NF Up to Date



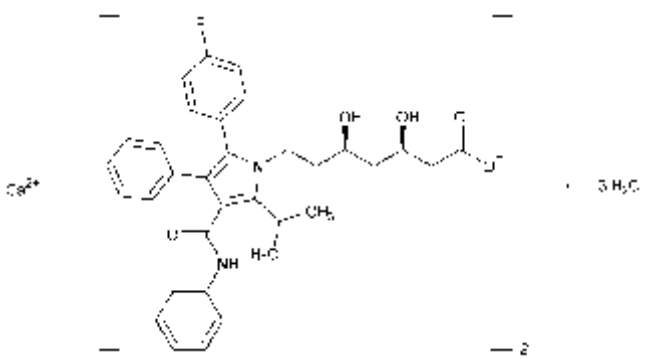
Flexible Monograph Approach

- **Enables multiple procedures, preparations, and/or acceptance criteria within a single monograph**
- **Address differences** in drug substance, ingredient, or product attributes
  - Polymorphic forms
  - Impurity profiles
  - Product-specific dissolution tests
- Labeling
- Different tests or acceptance criteria as approved by the **US FDA**
- Flexible approach is not used for **Assay**

Different polymorphic forms

Example- Atorvastatin Calcium

Anhydrous [134523-03-8]; UNII: C0GEJ5QCSO.
$C_{66}H_{68}CaF_2N_4O_{10} \cdot 3H_2O$ 1209.41
Trihydrate [344423-98-9]; UNII: 48A5M73Z4Q.
$C_{66}H_{68}CaF_2N_4O_{10} \cdot C_3H_8O_2$
Propylene glycol solvate 1231.46



SPECIFIC TESTS

•**WATER DETERMINATION,** *METHOD IA* ⟨921⟩**:**

Acceptance criteria: *3.5%–5.5% for the trihydrate form. If labeled as amorphous or as semicrystalline, NMT 6.0%. If labeled as a propylene glycol solvate, NMT 1.0%.*

LABELING:

Where it is an amorphous form, the label so indicates. Where it is a semicrystalline form, the label so indicates. Where it is a propylene glycol solvate form, the label so indicates.

Multiple Organic Impurities Procedures

Atorvastatin Calcium - Example

[Note—On the basis of the synthetic route or of the solid state nature of the drug substance, perform either Procedure 1 or Procedure 2. Procedure 2 may be suitable when atorvastatin lactone, atorvastatin epoxy tetrahydrofuran analog, and atorvastatin acetonide are possible related compounds, and it may be suitable for an amorphous form of the drug substance.]

- **Organic Impurities, Procedure 1**

Table 3

Name	Relative Retention Time	Acceptance Criteria NMT (%)
[illegible]	[illegible]	[illegible]
[illegible]	0.3	0.3
Atorvastatin	1.0	
[illegible]	1.2	0.2
[illegible]	2.1	0.2
Any other individual impurity	–	0.1
[illegible]		1.1

LABELING: *If a test for Organic Impurities other than Procedure 1 is used, the labeling states the test with which the article complies.*

- **Organic Impurities, Procedure 2**

Table 5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Atorvastatin diamine[a]	0.58	0.74	0.15
Atorvastatin related compound A[b]	0.69	1.0	0.3
Atorvastatin related compound B[c]	0.94	1.0	0.3
Atorvastatin	1.0	–	–
Atorvastatin related compound C[d] (if present)	1.1	1.0	0.3
Atorvastatin 3-deoxyhept-3-enoic acid[e]	1.45	1.0	0.10
Atorvastatin related compound H[f]	1.60	1.0	0.15
Atorvastatin epoxy tetrahydrofuran analog[g]	2.00	0.71	0.15
Atorvastatin ethyl ester[h]	2.08	1.0	0.15
Atorvastatin related compound D[i]	2.18	1.3	0.15
Atorvastatin related compound F[j]	2.75	1.0	0.15
Any other individual impurity	–	1.0	0.10
Total impurities[k]	–	–	1.0

Product-specific Dissolution Tests

Example-Metformin Hydrochloride Tablets

Dissolution ⟨711⟩: Differences in any of the dissolution conditions and/or in the tolerances constitutes a new test

Test 1:
- *Medium: pH 6.8 phosphate buffer; 1000 mL*
- *Apparatus 1: 100 rpm*
- *Time: **45 min***
- *Tolerances: NLT 70% (Q) of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.*

Test 2:

If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*
- *Medium: pH 6.8 phosphate buffer; 1000 mL*
- ***Apparatus 2: 50 rpm***
- *Time: **30 min***
- *Tolerances: **NLT 75% (Q)** of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.*

Test 3:

If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.

Medium: pH 6.8 phosphate buffer; 1000 mL
Apparatus 1:100 rpm
*Time: **60 min***
Tolerances: NLT 70% (Q) of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.

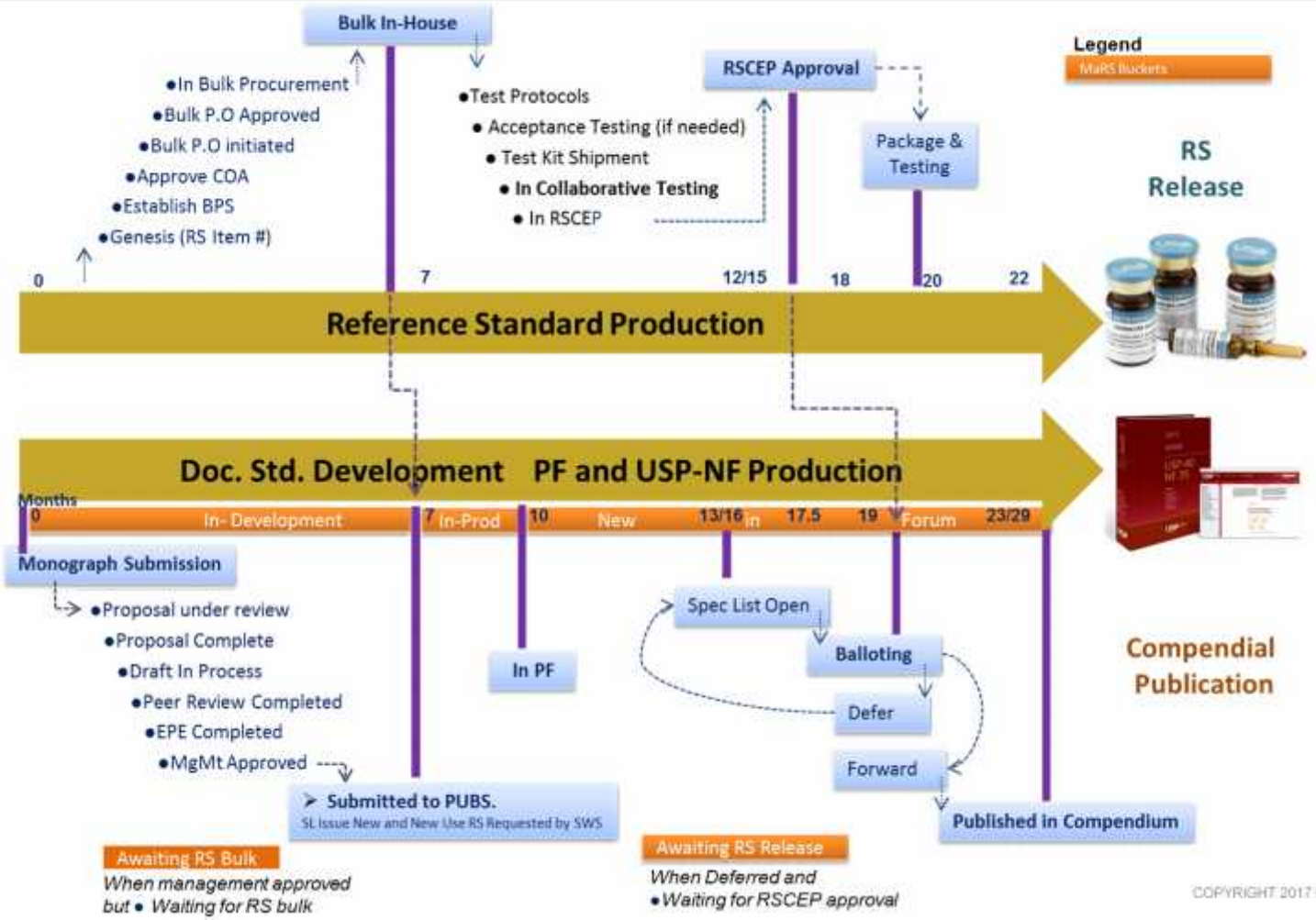
•**LABELING:** *When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.*

Potential Timelines and Expectations

Submission to Official Date 24-36 months

- Submission complete through Donor Portal
- 2-3 Months Internal USP Development and Review
- 1-2 Months Donor Review
- 1-2 Months Editorial/QC Review
- Published in Pharmacopeial Forum
- 90 day (3 Months) comment Period
- Comments Addressed
- 2-4 Months for EC Review and Ballot
- 3-4 months for publishing
- 6 months delayed implementation
- Official Date

Monograph and Reference Standard Development



Summary

- USP works with stakeholders in the development of new and revised standards
- Public, legally enforceable standards are established in an open system
  - Any proposal will go through a public review and comment period in the Pharmacopeial Forum (PF)
  - The USP Expert Committee ballots and votes on the inclusion of a new or revised standard to the USP-NF
  - When published in the USP-NF, industry will have 6 months implementation of a new or revised standards
- Monograph modernization (up-to-date) effort is to
  - Add new monographs to support generic manufacturers
  - Update monographs to maintain their relevance given scientific advances and evolving manufacturing and regulatory approaches
  - Omit the monographs for the products have been discontinued in US

Resources

https://www.usp.org/resources

Thank You