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U.S. Pharmacopeial Convention

USP Stakeholder Forum,
Meeting #1
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USP Excipients Standards Setting Process

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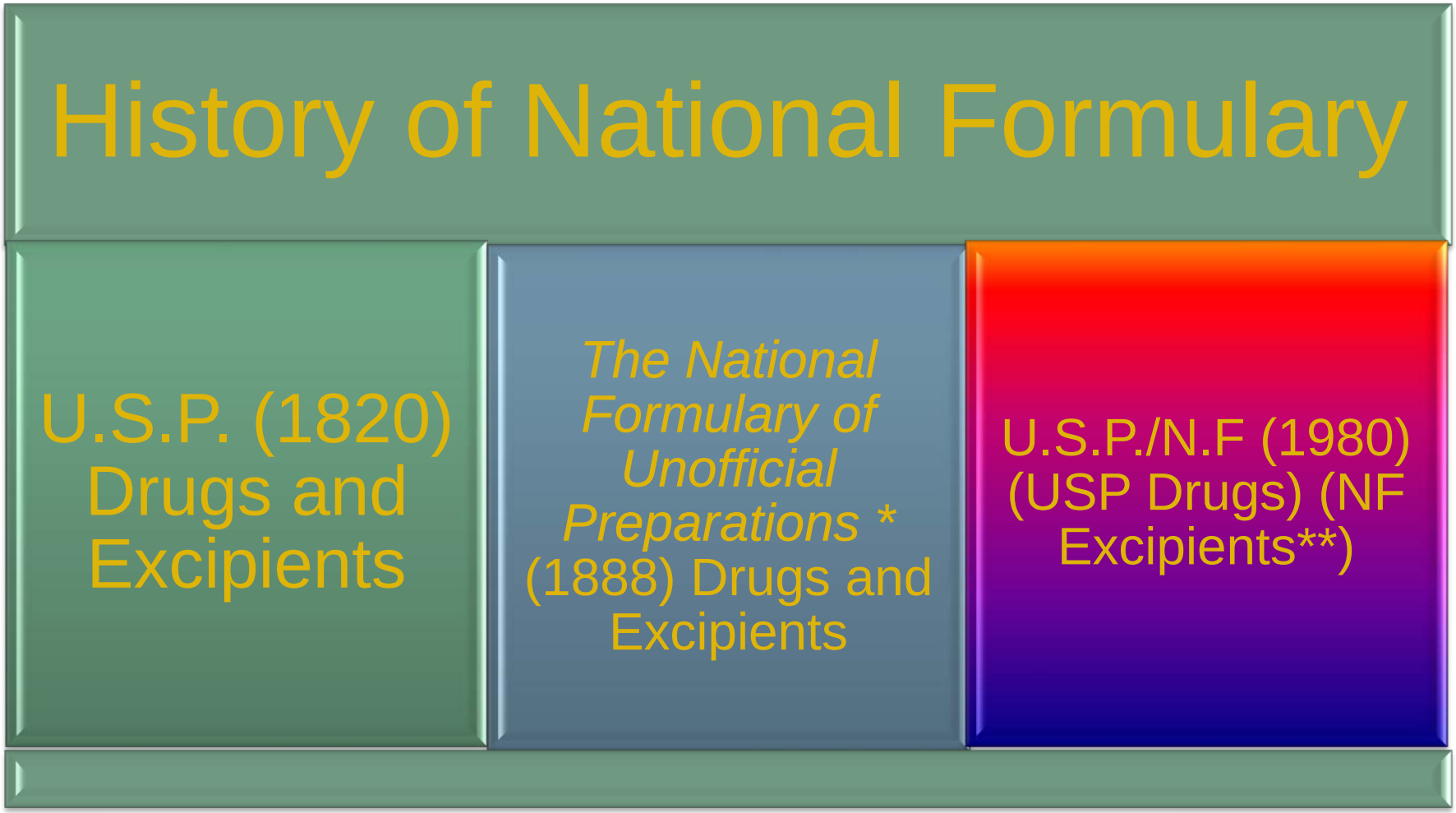
Historical Background on the *National Formulary*

- The first edition of the National Formulary (*NF*) originally named "*The National Formulary of Unofficial Preparations*" was first published in 1888 by the American Pharmaceutical Association.
- USP was founded in 1820. However, instead of working in competition with the USP, the NF served as a complement to it.
- While the USP served to set standards for base drugs, the NF served to standardize the higher-level or compound drugs which made use of more than just one base drug. These included formulations and unofficial preparations for widely sold products.
- In 1975, USP purchased the NF, combining the two publications under one cover to create the United States Pharmacopeia–National Formulary (USP–NF).
- NF contains excipients standards with references to allied reference materials.

Historical Background on the *National Formulary*



**First published in 1888 by the American Pharmaceutical Association

*Shangraw, Ralph Ph.D., Drug Development and Industrial Pharmacy, 13(13), 2421-2439 (1987), Compendial Standards for Excipients

1888 *National Formulary* Monograph

81. ELIXIR PEPSINI.

Elixir of Pepsin.

Pepsin (N. F.)	128 grains.
Hydrochloric Acid	30 minims.
Glycerin	2 fluidounces.
Compound Elixir of Taraxacum	1 fluidounce.
Alcohol	3 fluidounces.
Purified Talcum	120 grains.
Sugar	4 troy ounces.
Water	enough to make 16 fluidounces.

Mix the Pepsin with *six* (6) *fluidounces* of Water, add the Glycerin and Acid, and agitate until solution has been effected. Then add the Compound Elixir of Taraxacum, Alcohol, and the Purified Talcum, and mix thoroughly. Set the mixture aside for a few hours, occasionally agitating. Then filter it through a wetted filter, dissolve the Sugar in the filtrate, and pass enough Water through the filter to make the whole product measure *sixteen* (16) *fluidounces*.

Each fluidrachm represents 1 grain of Pepsin (N. F.)

82. ELIXIR PEPSINI, BISMUTHI ET STRYCHNINÆ.

Elixir of Pepsin, Bismuth and Strychnine.

Sulphate of Strychnine	1¼ grains.
Elixir of Pepsin and Bismuth	16 fluidounces.

Dissolve the Sulphate of Strychnine in the Elixir.

Each fluidrachm represents $\frac{1}{100}$ grain of Sulphate of Strychnine, 1 grain of Pepsin (N. F.), and 2 grains of Citrate of Bismuth and Ammonium.

83. ELIXIR PEPSINI ET BISMUTHI.

Elixir of Pepsin and Bismuth.

Pepsin (N. F.)	128 grains.
Citrate of Bismuth and Ammonium	256 "
Water of Ammonia	a sufficient quantity.
Glycerin	2 fluidounces.
Alcohol	3 "
Syrup	4 "
Compound Elixir of Taraxacum	1 fluidounce.
Purified Talcum	120 grains.
Water	enough to make 16 fluidounces.

Dissolve the Pepsin in *four* (4) *fluidounces* of Water. Dissolve the Citrate of Bismuth and Ammonium in *one* (1) *fluidounce* of warm Water, allow the solution to stand until clear, if necessary; then decant the clear liquid, and add to the residue just enough Water of Ammonia, to dissolve it, carefully avoiding an excess. Then

Pharmaceutical Excipients – DEFINITION*

Pharmaceutical Excipients—Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients can do the following:

- aid in the processing of the drug delivery system during its manufacture,
- protect, support, or enhance stability, bioavailability, or patient acceptability,
- assist in product identification, and
- enhance any attribute of the overall safety
- assist in the effectiveness and/or delivery of the drug in use
- assist in maintaining the integrity of the drug product during storage

** Modified from* **USP General Information Chapter, <1078> Good Manufacturing Processes for Bulk Pharmaceutical Excipients**

USP's Legal Recognition

- In the United States under the Federal Food, Drug, and Cosmetic Act (FD&C Act), both *United States Pharmacopeia* (*USP*) and the *National Formulary* (*NF*) are recognized as official compendia for drugs marketed in the United States.
- **US Federal Law**
    - 1938 - **Food Drug and Cosmetic Act (FD&CA) .** *USP* and *NF* standards are enforceable by FDA
- USP sets federally recognized standards for the identity, strength, quality and purity of prescription and over-the-counter medications, which are enforced by the FDA.
- **USP does not enforce its standards**

Role of USP Quality Standards in Law

- **Under FD&CA**
  - **Section 501 - Adulterated Drugs and Devices**
    - A drug with a name recognized in *USP-NF* must comply with compendial identity or be deemed adulterated, misbranded , or both (501(b) & 502(e)(3)(b)). …..***Cannot label away from identity*!**
    - Must also comply with compendial standards for strength, quality, and purity, unless labeled to show all differences (501(b) & 21 CFR 299.5).
    - Removing the *USP-NF* designation from labeling does not obviate the requirement to conform to compendial requirements.

Role of USP Quality Standards in Law

- **FD&C Act**
  - **[21 U.S.C. 321] Section 201(g)(1)**
    - The term “drug” means:
    - recognized in an official US compendium: United States Pharmacopeia, Homoeopathic Pharmacopoeia, or National Formulary
    - intended to provide diagnosis, cure, mitigation, treatment, or prevention of disease
    - intended to affect the structure or any function of the body
    - **intended for use as a COMPONENT of any article meeting the above criteria**

Code of Federal Regulations (CFR): Definitions and Requirements

- **21 CFR § 210.3 Definitions (under cGMP for Drugs; General)**
  - a(4) Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain active ingredient, but is intended to be used as a placebo.
  - a(3) Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such a drug product.
  - a(8) Inactive ingredient means any component other than an active ingredient
- **21 CFR § 211.84(d)(l) Control of Components…** (Subpart E)
  - *"At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used."*

Types of Public Standards in the USP

- 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

General Notices, General Chapters, and Monographs

- General Notices contain requirements applicable throughout *USP–NF* unless superseded by a chapter or monograph

- General Chapters contain requirements applicable to monographs to which they apply
  - General Chapter requirements supersede General Notice requirements in case of conflict

- Monograph requirements are specific to the monograph in which they appear
  - Monograph requirements supersede General Notice and General Chapter requirements in case of conflict

Public Standards in the US 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
- Applicability of Standards - General Notices 3.10.10.
  - *Applicability of Standards to Drug Products, Drug Substances, and Excipients. The applicable USP or NF standard applies to any article marketed in the United States that (1) is recognized in the compendium and (2) is intended or labeled for use as a drug or as an ingredient in a drug. The applicable standard applies to such articles whether or not the added designation "USP" or "NF" is used.*

General Notices 3.20. Indicating Conformance

A drug product, drug substance, or excipient may use the designation "USP" or "NF" in conjunction with its official title or elsewhere on the label only when (1) a monograph is provided in the specified compendium and (2) the article complies with the identity prescribed in the specified compendium.

When a drug product, drug substance, or excipient differs from the relevant USP or NF standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.

When a drug product, drug substance, or excipient fails to comply with the identity prescribed in USP or NF or contains an added substance that interferes with the prescribed tests and procedures, the article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in USP or NF.

Specification in the US Pharmacopeia

- What is “The” Specification?
  - Tests, Procedures and Acceptance criteria for shelf-life of an official article*.
- Who defines the specification?
  - The manufacturer working with FDA
- Where does a specification come from?
  - The manufacturer
- Why do we need specifications?
  - To evaluate consistency and acceptability
- How does a specification become a standard?
  - Through common usage and the USP process

*Official articles include both official substances and official products. An official substance is a drug substance, excipient, dietary ingredient, other ingredient, or component of a finished device for which the monograph title includes no indication of the nature of the finished form. An official product is a drug product, dietary supplement, compounded preparation, or finished device for which a monograph is provided. General Notices 2.30

Summary

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

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

USP Standards Established through a Public Process

USP creates and continuously revises USP–NF standards through a unique public–private collaborative process, which involves pharmaceutical scientists in industry, academia, and government as well as other interested parties from anywhere in the world.

Public input and interaction are vital to the development of these standards. The standards generally originate from sponsors who provide draft standards and supporting data to either create new or revise (*modernization*) existing monographs and general chapters.

USP Standards Established through a Public Process

USP's scientific staff and volunteer experts review this input, conduct laboratory tests (if necessary), and forward the new or revised monograph or general chapter to *Pharmacopeial Forum* (PF) for public review and comment. *PF* is free, online only resource.

The public process helps to refine USP standards for publication as official text in the *USP–NF*.

Prior to publication as official text, all monograph and general chapter proposals must be approved by a USP Expert Committee, which comprise volunteer scientists, academicians, practitioners, and other professionals elected on the basis of their knowledge and expertise.

http://www.usp.org/usp-nf/pharmacopeial-forum

Monographs – Excipient Expert Committee (EXC EC) 2010-2015 Cycle

Monographs – Excipient Expert Committee (EXC)

Total of 12 Subcommittees

EXC A (158 monographs)	EXC B (121 monographs)	EXC C (117 monographs)	EXC Pharmacopeial Discussion Group (PDG) D – K (62 monographs)	EXC Cross Cutting General Chapters (GC) (22 chapters)

Area of Focus

Small Molecules	Polymer, Proteins, Clay	Oils, Fats, Waxes, Plants	**EXC D** (Cellulosics)	**EXC E** (inorganic mineral/salts)	**EXC F** (organic alcohols/glycols)	**EXC G** (Povidones)	**EXC H** (starches	**EXC I** (sweetners)	**EXC J** (water)	**EXC K** (waxes, organic polymers, stearates)	Excipient-related General chapters

PDG consists of 8 Subcommittees D –K

EXC D Subcommittee PDG Cellulosics :

- Carmellose Calcium (E07)
- Carmellose Sodium (E08)
- Croscarmellose Sodium (E09)
- Microcrystalline Cellulose (E10)
- Powdered Cellulose (E11)
- Cellulose Acetate (E12)
- Cellulose Acetate Phthalate (E13)
- Ethylcellulose (E17)
- Hydroxyethylcellulose (E18)
- Hydroxypropylcellulose (E19)
- Hydroxypropylcellulose, LS (E20)
- Hydroxypropylmethylcellulose (E21)
- Hypromellose Phthalate (E22)
- Methylcellulose (E26)
- Carmellose (E52)

EXC E Subcommittee PDG Inorganic Minerals (Inorganic Minerals/Salts):

- Calcium Disodium Edetate (E04)
- Calcium Phosphate Dibasic (E05)
- Calcium Phosphate Dibasic Anhydrous (E06)
- Silicon Dioxide (E36)
- Silicon Dioxide Colloidal (E37)
- Sodium Chloride (E38)
- Talc (E46)
- Titanium Dioxide (E47)
- Calcium Carbonate (E53)

Talc Expert panel

EXC F Subcommittee PDG Organic Small Molecules (Organic Small Molecules/ Alcohols/Glycols):

- Alcohol (E01)
- Dehydrated Alcohol (E02)
- Benzyl Alcohol (E03)
- Glycerin (E51)
- Propylene Glycol (E59)
- Citric Acid, Anhydrous(E14)
- Citric Acid, Monohydrate (E15)
- Methylparaben (E27)
- Ethylparaben (E48)
- Propylparaben (E49)
- Butylparaben (E50)

Glycerin Expert panel

EXC G Subcommittee PDG Povidones :

- Crospovidone (E16)
- Povidone (E32)
- Copovidone (E54)

Povidones Expert panel

EXC H Subcommittee PDG Starches:

- Sodium Starch Glycolate (E39)
- Corn Starch (E40)
- Potato Starch (E41)
- Rice Starch (E42)
- Wheat Starch (E43)
- Pregelatinized Starch (E61)

EXC I Subcommittee PDG Sweeteners:

- Lactose, Anhydrous (E23)
- Lactose Monohydrate (E24)
- Saccharin (E33)
- Saccharin Sodium (E34)
- Saccharin Calcium (E35)
- Sucrose (E45)
- Glucose (E56)
- Mannitol (E58)
- Lactose for Inhalation (E63)
- Isomalt (E64)

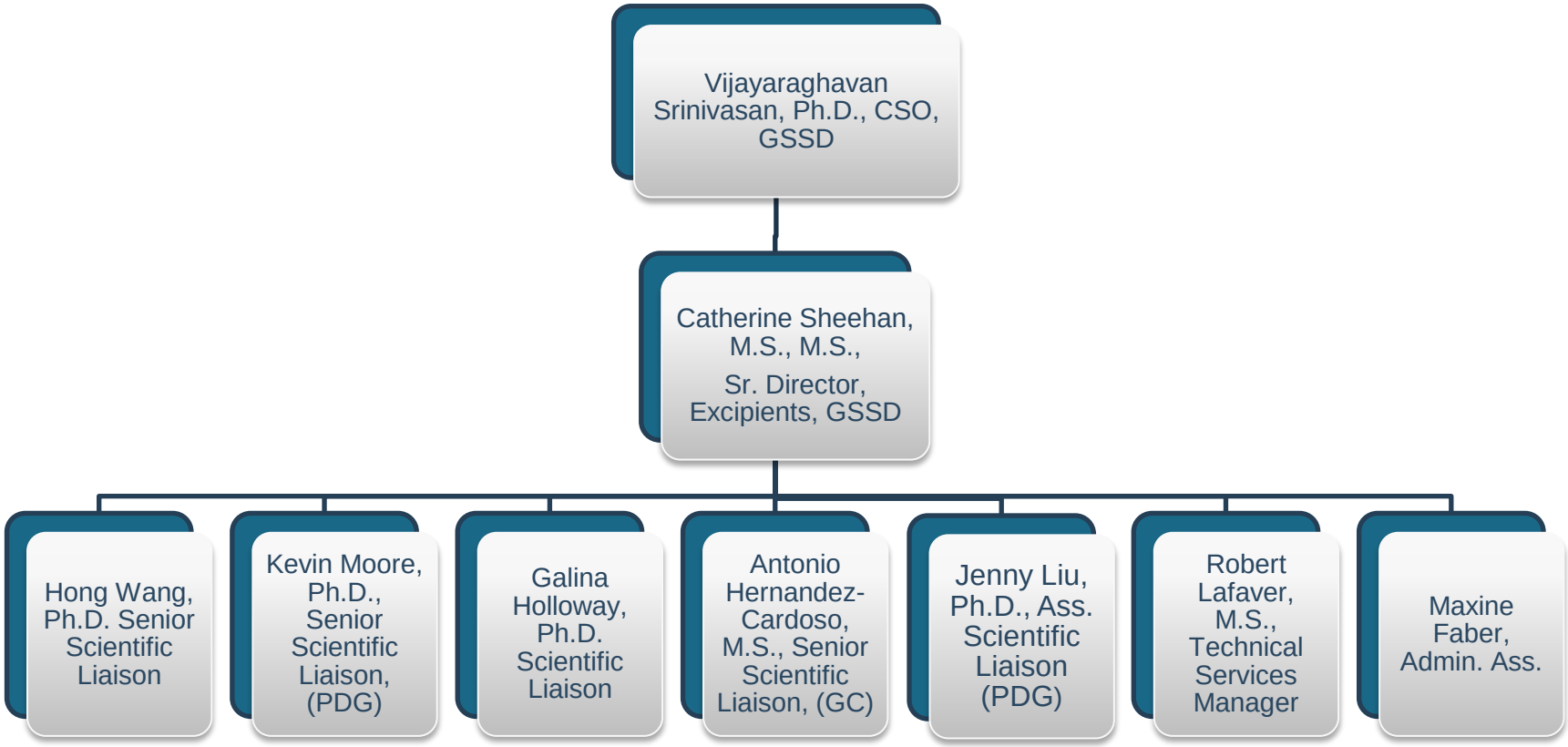
EXC J Subcommittee PDG Water:

- Sterile Water for Injection in Containers (E62)

EXC K Subcommittee PDG Waxes/OrganicPolymers/Stearates:

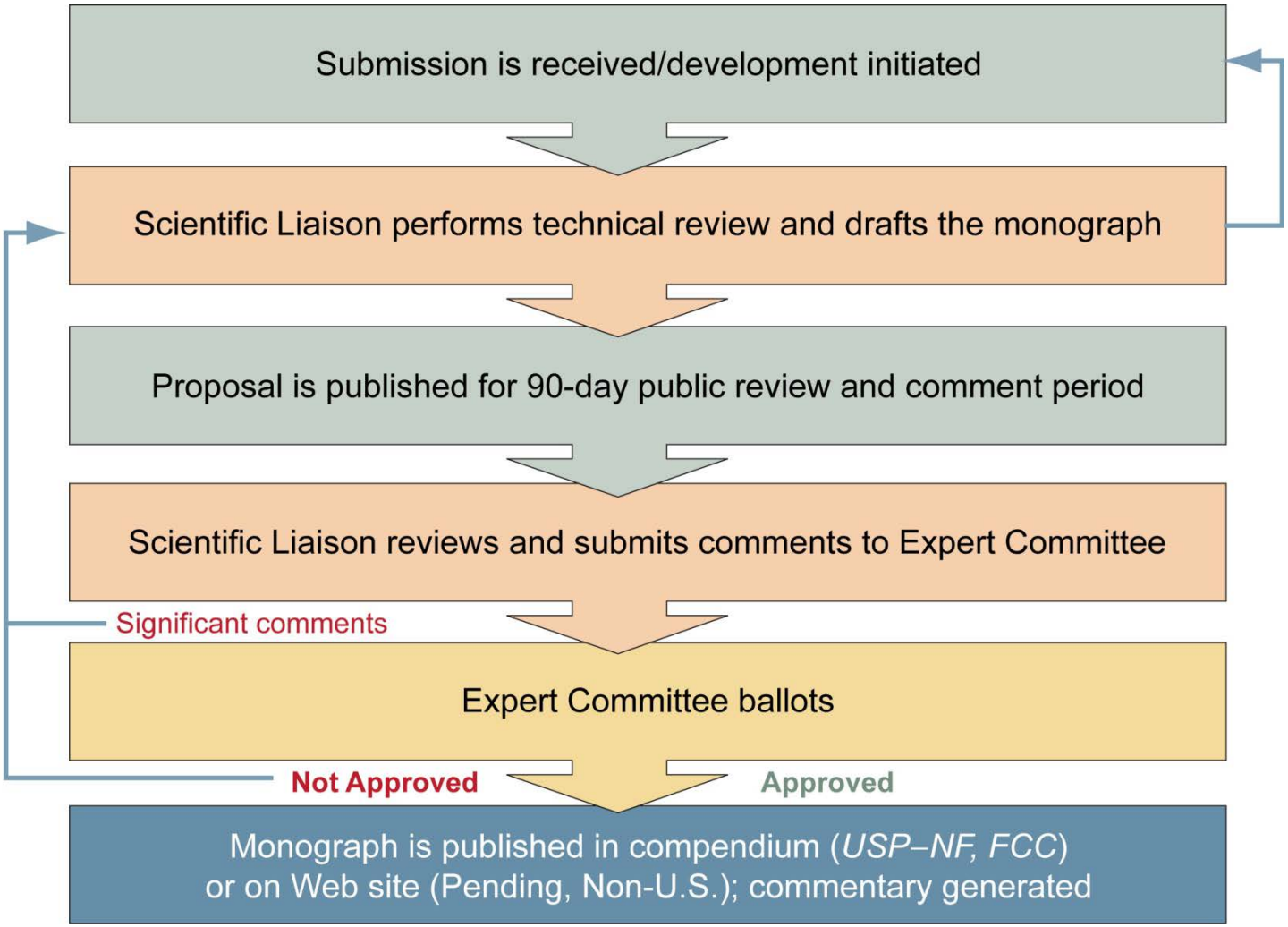
- Petrolatum (E28)
- White Petrolatum (E29)
- Polyethylene Glycol (E30)
- Gelatin (E55)
- Polysorbate 80 (E31)
- Sodium Lauryl Sulfate (E60)
- Magnesium Stearate (E25)
- Stearic Acid (E44)
- Glyceryl Monostearate (E57)

Excipients Group Staff



USP–NF Revision Process

http://www.usp.org/app/education/pe/courses/moreInfo.html?courseID=284



USP–NF New Monograph Submission Requirements

- Regulatory status (e.g, permitted for use in an FDA regulated drug product)
- Rationale (for revisions)
- Proposed tests, procedures and acceptance criteria
  - Identification test(s)
  - Impurity test(s)
  - Assay test (preferably stability-indicating)
- Validation data (according to <1225>)
- Packaging, storage, and labeling requirements
- Reference Standard commitments
  - Statement on suitability for use of any existing USP Reference Standards
  - Commitment to provide candidate materials for new USP standards

Monograph Development

Typical time line: 18 to 24 months from submission to official adoptions but it can take longer

Impacted by-

- Review/evaluation of public comments
- Obtaining additional information
- Publishing/republishing responses
- Testing in USP's Laboratory
- Availability of reference materials

Resource-

- Monograph Submission Guideline
- USP Guideline for Submitting Requests for Revision to *USP-NF*…. Excipients - Chapter 3

http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/chapter3.pdf

Key Areas for Excipients

- Developing new monographs
  - Pending monographs- *http://www.usp.org/usp-nf/pending-monographs*
- Updating/modernizing existing monographs
- Harmonization of Excipient Monographs
- Reformatting ('monograph redesign')
  - Completed for *USP 36-NF 31*

U.S. Pharmacopeial Convention

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Calendar | Suppo

About USP | USP–NF | Dietary Supplements | Food Ingredients | Reference Standards | Around the World

Overview | Calendar | Symposia | Stakeholder Forums | W

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Past Symposia

10th Annual Science & Standards Symposium—Partnering Globally for 21st Century Medicines

September 18, 2013 - September 19, 2013

REGISTER

Overview | Agenda | Registration Information

2013 Baltimore Marriott Waterfront, Baltimore, Maryland

Excipient track

Track Session 1: Modernization of NF Excipient monographs.
Track Session 2: Developing / harmonizing excipient monograph standards.
Track Session 3: Defining Excipient Quality

USP Pharmacopeial Education course on <1059>Excipient Performance

September 17, 2013, Baltimore Marriott Waterfront, Baltimore, MD

Thank You