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Trusted Standards
Improved Health

The USP Excipients Stakeholder Forum
Meeting # 2
June 18, 2014

USP - Excipients Standards Setting Process

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Standards Established through a Public Process

- ▶ USP creates and continuously revises USP–NF standards through a unique public–private collaborative process
- ▶ This 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.

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- ▶ General Notices contain requirements applicable throughout *USP–NF* unless superseded by a chapter or monograph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

- ▶ Two types of monographs:
 - Official Substances
 - Including bulk drugs and excipients
 - Official Products
- ▶ The USP contains monographs for Official Products and Official Substances that are mainly classified as bulk drugs
- ▶ The NF contains monographs for Official Substances that are mainly classified as excipients.
- ▶ Some grey areas, e.g:
 - Atypical actives (dual actives)

▶ Safety

- We do not want to harm the patient

▶ Identity

- We want to make sure we are using the correct material and grade.
 - Using the wrong grade or even the wrong excipient may cause harm to the patient, e.g. dose dumping of an extended release product.
 - Absence of e.g. adulterants and contaminants.

▶ ‘Purity’

- For Excipients this means the absence of harmful and/or other undesirable components.

There are three types of General Chapters in the USP-NF:

- ▶ General Chapters <1000
 - These are mandatory when applicable.

- ▶ General Information Chapter 1000 – 1999
 - These are not mandatory unless they are specifically referenced in a monograph in which case they become mandatory for that monograph.

- ▶ Dietary Supplement General Chapters \geq 2000
 - Only applicable to dietary supplements.

Standards Established through a Public Process

USP's scientific staff and volunteer experts review a request for revision to the *USP-NF*, 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. <http://www.usp.org/usp-nf/pharmacopeial-forum>

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*.

Comprised of volunteer scientists, academicians, practitioners, and other professionals elected on the basis of their knowledge and expertise.



2010–2015 Council of Experts

Healthcare Quality

**Nomenclature,
Safety,
and Labeling**
T. Reinders

**Therapeutic
Information
and Formulary
Support**
J. Braden

Compounding
G. Davidson

General Chapters

Chemical Analysis
T. Wozniak

**Biological
Analysis**
W. Workman

Microbiology
J. Akers

Statistics
R. Singer

Physical Analysis
G. Amidon

Dosage Forms
J. DeMuth

Packaging
M. Foster

Toxicology
R. Osterberg

Reference Standards

**Reference
Standards**
M. Borer

USP Chemicals

**Small Molecules
Monographs 1**
G. Van Buskirk

**Small Molecules
Monographs 2**
E. Parente

**Small
Molecules
Monographs 3**
B. Olsen

**Small
Molecules
Monographs 4**
E. McGonigle

USP Biologicals

**B&B
Monographs 1**
M. Mulkerrin

**B&B
Monographs 2**
J. Huxsoll

NF Excipients

Excipients
L. Block

Dietary Supplements and Foods

**Dietary
Supplements**
D. Gorecki

**Food
Ingredients**
A. Ebert

MC Chemicals

Chemicals (S. Asia)
A.R. Gomas

Chemicals (L. America)
I. Santoro

Chemicals (NIS)
A. Mikhaylova

MC Biologicals

Biologics
D. Patankar

MC Excipients

Excipients (E. Asia)
J. Tu

Herbal Medicines Compendium

S. Asia (India)
S.S. Handa

E. Asia (China)
Z.Qian

Expert Panels and Stakeholder Forums

- ▶ Expert Panels— The Chair of the Council of Experts may appoint Expert Panels to assist the Council of Experts by providing advisory recommendations to particular Expert Committees in response to a specific charge consistent with the Expert Committee's Work Plan. Expert Panels are continuously formed.
- ▶ Stakeholder Forums and Project Teams— USP has formed several domestic and international Stakeholder Forums and Project Teams to exchange information on the use and implementation of USP's standards. Stakeholder Forums may form Project Teams to work on selected topics.
 - North American Stakeholder Forums (United States and Canada) Prescription/Nonprescription
 - Dietary Supplements
 - Excipients
 - Food Ingredients
 - Veterinary Drugs
 - International Stakeholder Forums India
 - Mexico
 - Brazil
 - Others
 - USP also conducts Science and Standards Symposia in the United States, India, China, Latin America, Middle East/North Africa, and in other regions of the world.

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 D - K**

**EXC Cross Cutting
General Chapters**

Area of Focus

Small Molecules

Polymer, Proteins, Clay

Oils, Fats, Waxes, Plants

EXC D
(Celluloses)

EXC E
(inorganic mineral/salts)

EXC F
(organic alcohols/glycols)

EXC G
(Povidones)

EXC H
(starches)

EXC I
(sweeteners)

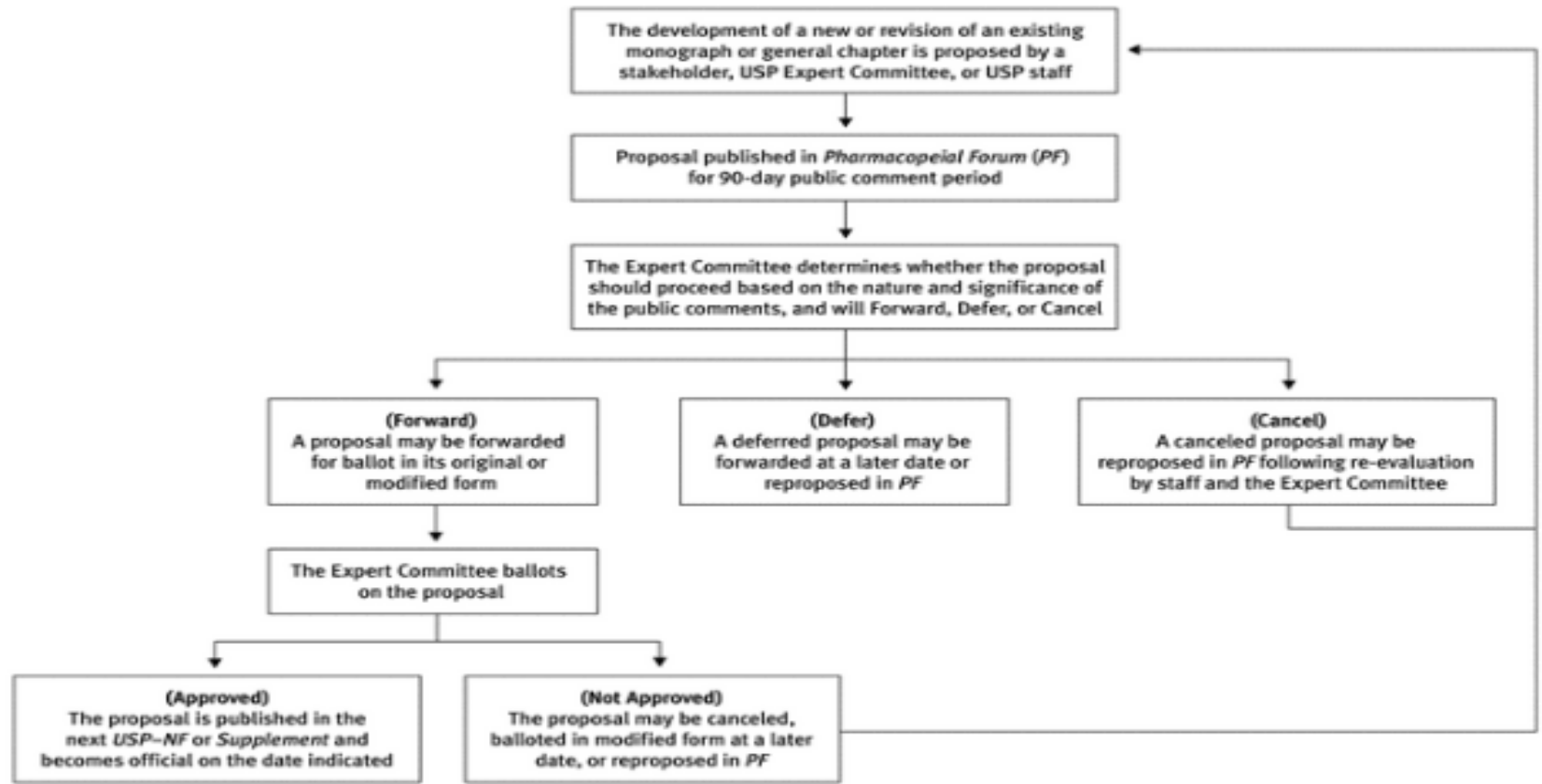
EXC J
(water)

EXC K
(waxes, organic polymers, stearates)

Excipient-related General chapters

- ▶ **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 Practices for Bulk Pharmaceutical Excipients



▶ Commentary

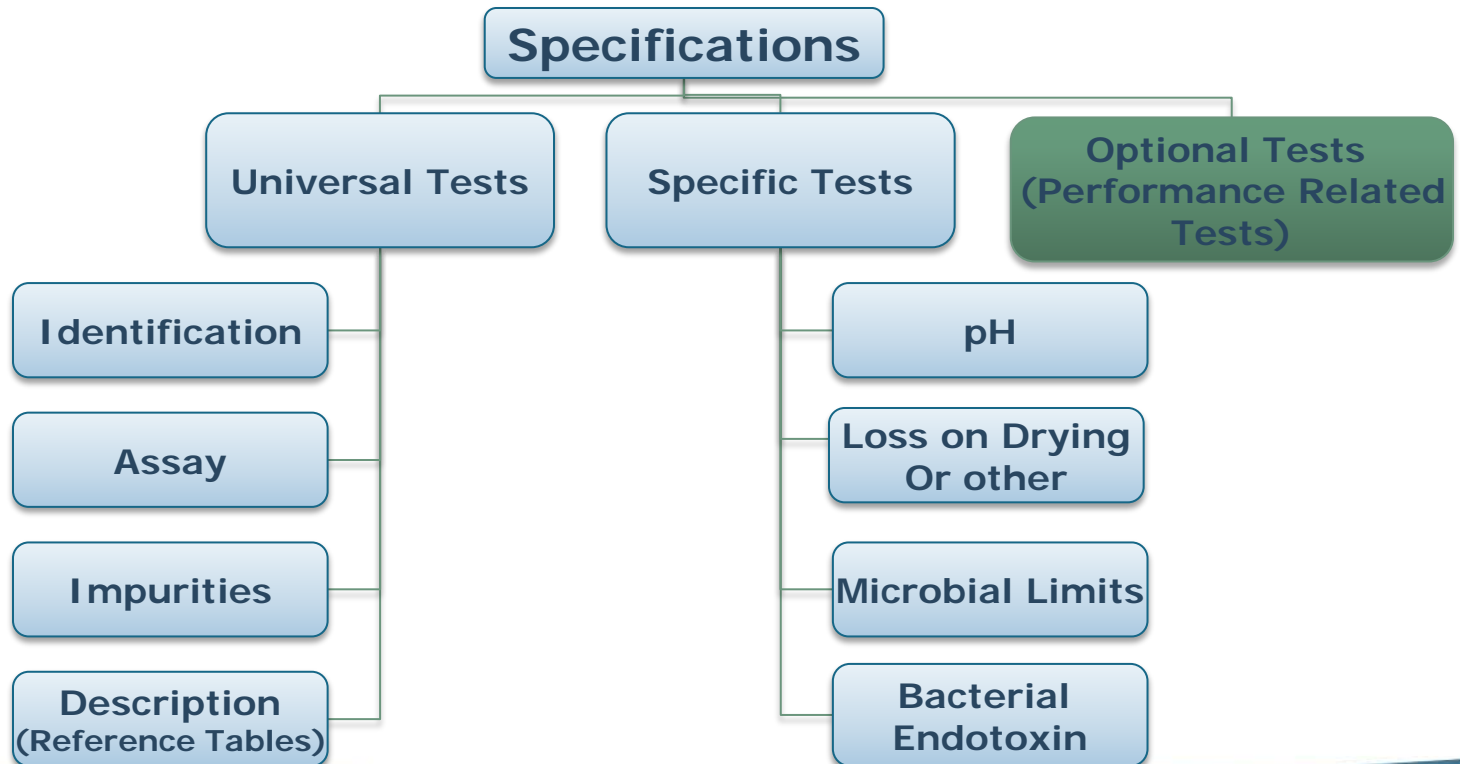
- In cases where proposals advance to official status without republication in PF, a summary of comments received and the appropriate Expert Committee's responses are published in the Commentary section of the USP website at the time the revision is published.
- The Commentary is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of the Expert Committee's response to public comments.

Excipient Compendial Testing and Excipient Performance

The emphasis of compendial tests for an excipient relate to Specifications for Identity, Quality and Purity

ICH Guidelines Q6A and Q6B – Specifications (Tests, Procedures and Acceptance Criteria)

Tests for some (but not all) physical and chemical properties of the material





Change to read:

4. MONOGRAPHS AND GENERAL CHAPTERS

4.10. Monographs

Monographs set forth the article's name, definition, specification, and other requirements related to packaging, storage, and labeling. The specification consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality, and purity of the article. For general requirements relating to specific monograph sections, see section 5, *Monograph Components*.

Because monographs may not provide standards for all relevant characteristics, some official substances may conform to the *USP* or *NF* standard but differ with regard to nonstandardized properties that are relevant to their use in specific preparations. To assure interchangeability in such instances, users may wish to ascertain functional equivalence or determine such characteristics before use.

- ▶ Title
- ▶ Definition
 - Contains a chemical definition with content limits, or describes the substance and the source(s) from which it is obtained. It may also refer to the method of manufacture.
 - Any permitted additives will also be indicated.
- ▶ Identification
- ▶ Assay
- ▶ Other Components
- ▶ Impurities
- ▶ Specific Tests
- ▶ Additional Requirements
 - Packaging and Storage
 - Labeling
 - USP Reference Standards
- ▶ Note: Not every excipient monograph will contain every section

▶ Dibasic Calcium Phosphate Dihydrate USP

- Dibasic Calcium Phosphate Dihydrate contains two molecules of water of hydration. It contains NLT 98.0% and NMT 105.0% of dibasic calcium phosphate dihydrate ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$)

▶ Olive Oil NF

- Olive Oil is the refined fixed oil obtained from the ripe fruit of *Olea europaea* Linné (Fam. Oleaceae). It may contain suitable antioxidants

▶ Microcrystalline Cellulose NF

- Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

- ▶ Traditionally these have been ‘wet’ chemistry tests relating to color changes, solubility, or precipitation.
- ▶ Not all ID tests are specific for the particular molecule
- ▶ NF monographs include instrumental methods such as:
 - Infra Red spectroscopy
 - Chromatographic peak retention time
- ▶ NF monographs can have physical tests
 - Degree of substitution (based on intrinsic viscosity)
- ▶ Where possible, USP is moving to more reliable instrumental methods.
- ▶ Where necessary USP will be including compound-specific tests in monograph (to help combat intentional adulteration).

- ▶ Not all NF excipient monographs have assays.
 - e.g. Microcrystalline Cellulose, Polyethylene Oxide.
- ▶ Not all assays are specific for the nominal component.
 - e.g. <461> Kjeldahl Nitrogen Determination for nitrogen-containing excipients,
 - e.g. Povidone
- ▶ USP is looking to develop/obtain more specific assays for those excipients that do not have them.

- ▶ In general, most excipients are not ‘pure’ due to presence of “other components” (sometimes referred to as Concomitant Components) that can be classified as:
 - Desirable (Functional)
 - They contribute to excipient performance and do not present a safety concern (e.g. additives/processing aids with a limit (*Gen. Notices* 5.20. Added Substances)
 - Acceptable
 - They do not present a safety concern.

- ▶ However, both the *USP-NF* and FDA categorize Impurities as
 - Inorganic (<281> Residue on Ignition)
 - Organic (<466> Ordinary Impurities)
 - Residual solvents (<467> Residual Solvents)

▶ Packaging and Storage

- More specific instructions will be introduced for some excipients.

▶ Labeling

- Specific details required to be included on the label or labeling.

▶ USP Reference Standards

- A list of USP Reference Standards required to complete all the tests included in the monograph.

What a USP-NF Excipient Monograph does not contain

- ▶ Appearance
- ▶ Solubility
- ▶ Performance tests, except where they are required for e.g. grade differentiation
 - However, the intent is to differentiate between different grades of the same excipients, not to assess performance per se.
 - Performance requirements are application-specific, and there is no way a pharmacopeia monograph can cover all applications.
 - Performance assessment is for the excipient user, and perhaps the excipient manufacturer.

In the context of the Pharmacopeias we have two options:

- ▶ In the monograph
 - In a Labeling Section
 - In a ‘non-mandatory’ Section
- ▶ In a General Information Chapter
 - Detailing tests that might be appropriate when excipients are used for a particular purpose.
 - Listing the appropriate tests for each material.

- ▶ There is a range of opinion regarding the benefit of including additional performance based testing of excipients into pharmacopeias.
- ▶ A major concern revolves around unnecessary testing that may be “required” by:
 - Uninformed excipient users requesting unnecessary testing from suppliers
 - Regulatory agencies requiring unnecessary testing because it is in the monograph

<1059> Excipient Performance, how can the Pharmacopeia help?

- ▶ By providing guidance as to which properties might be important for a particular material in a particular application.
- ▶ By providing standard methods that can be used by both manufacturers and users:
 - Makes communication more straightforward
 - Avoids an unnecessary plethora of test variations for a particular parameter.
- ▶ By keeping the tests non-mandatory.
- ▶ By avoiding confusion with mandatory tests and labeling tests.
- ▶ By not imposing limits/specifications.
- ▶ Provides a framework for applying Quality by Design concept to excipient quality control.
 - As an important component of drug products, variation in excipient performance characteristics may affect critical quality attributes and process parameters of drug products, and the robustness of manufacturing process

- ▶ Regulatory status (e.g, permitted for use in an FDA regulated drug product marketed in the US)
- ▶ Rationale (for revisions)
- ▶ Proposed tests, procedures and acceptance criteria
 - Identification test(s)
 - Impurity test(s)
 - Assay test (preferably stability-indicating)
- ▶ Validation data
- ▶ 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

- ▶ 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
 - Monograph Submission Guideline
 - ▶ <http://www.usp.org/usp-nf/development-process/submit-new-monographs/submission-guidelines>
 - 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



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Thank You