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U.S. Pharmacopeial Convention

The USP Excipients Stakeholder Forum
Meeting #1
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Excipient Related General Chapters

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General Chapters Overview

General Chapters can be

- Required (numbered below <1000>)
- Informational (numbered <1xxx>)
- Specific for dietary supplements (numbered <2XXX>)

Required Chapters (Below <1000>)

- When referenced in monographs, are procedures used by the FDA to demonstrate compliance to a specification
- Typically are procedures referenced in multiple monographs
  - Chapter status avoids duplication and simplifies updating
- Typically consist of method and procedure
  - Acceptance criteria – in the General Chapter or the monograph
- Can apply to monographs even if not specifically called out in the monograph
- Tests need to be verified by users for their applications

Informational Chapters (<1xxx>)

- Provide information or guidelines
- Are not intended to be enforced by regulatory agencies
  - –Some countries enforce the entire *USP–NF*
  - –FDA reserves the right to enforce if appropriate
- Should be devoid of acceptance criteria to minimize misunderstandings
- May become enforceable if referenced without disclaimer in a monograph or General Chapter numbered below <1000>

General Chapters – Our Starting Point this Cycle

- Chapters have been
  - Written and updated over many years
  - Under the auspices of many Expert Committees
  - Updated without vision for style and content

- Styles, formats, and information content depend on
  - Committee and USP norms at the time
  - Maturity of technology at time of updating

USP Chapters grouping	
Chemical analysis	Packaging Storage and Distribution
Physical analysis	Dosage forms
Biological analysis	Healthcare quality standards
Microbiology	Toxicology and statistics

Objective for the 2010-2015 Cycle

- Review the approximately 240 current chapters for content and format
- Prioritize the updating of those that need it using the appropriate committee, subcommittee or panel
- Develop and write new chapters as determined by each committee
- Collect broad-based stakeholder input for high-impact chapters

General Chapter Development

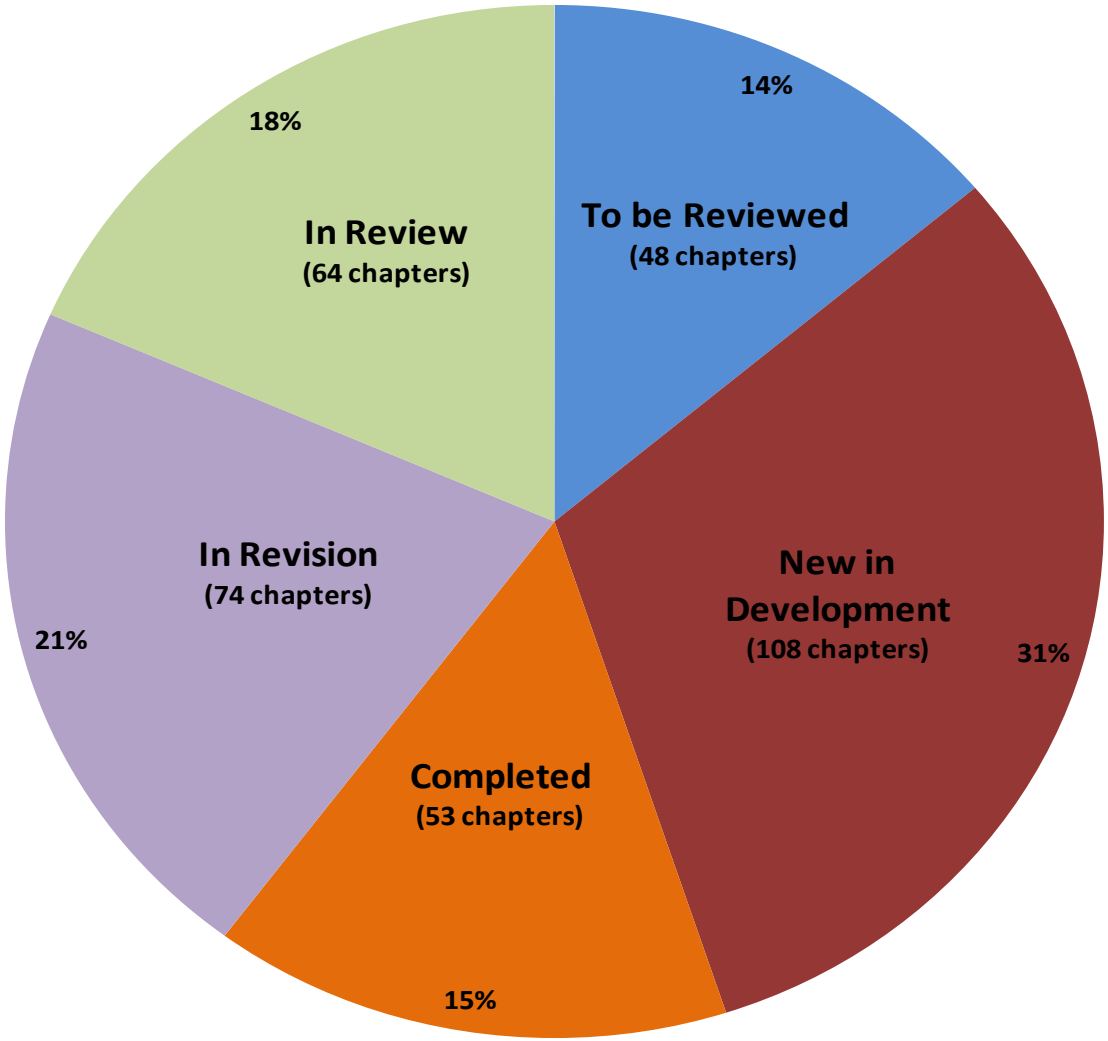
New Chapters or Major Revisions

- Proposal for new General Chapter or major revision comes from staff, committee member, or external source
- Committee, sub-committee, or panel evaluates idea and develops a *Pharmacopeia Forum (PF)* proposal
- Public comment solicited
  - Stimuli Article (common for new General Chapter) or draft chapter published in *PF*
  - "Design phase" of workshop or other public meeting scheduled for "high-impact" chapters (required chapters with broad industry impact)
- Comments collected from public forums and shared with committee/panel

Vision for General Chapters

- Required chapters
  - Current technology
  - Easy to read, understand, execute
  - Clear acceptance criteria
- Informative chapters
  - Current guidance, no acceptance criteria
  - Context for enforceable chapters
  - Forward looking
  - Relevant to real-world pharmaceutical issues
- All look and read as if edited by one person
- Summarized in *PF* 35(5) Sept/Oct 2009 Stimuli Article

New & Official General Chapters, 2010-2015 CoE Cycle



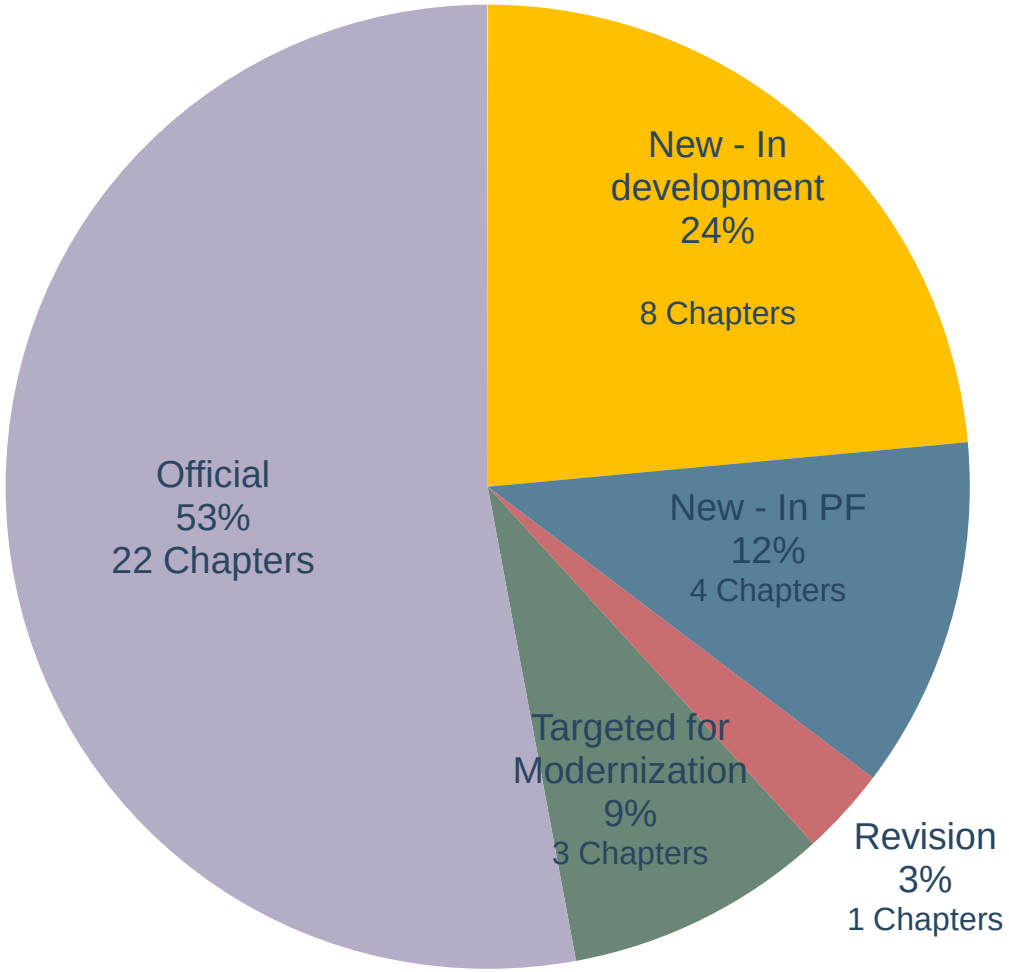
Excipient Related General Chapters - Chemical

Official Status	General Chapter	Title
New in PF	<202>	Identification of Fixed Oils by Thin-Layer Chromatography
Official	<228>	Ethylene Oxide and Dioxane
New in Development	<264>	Nickel in Hydrogenated Oils and Saturated Esters
Official	<311>	Alginates Assay
Official	<401>	Fats and Fixed Oils
New in Development	<402>	Fatty acid assay
New in Development	<403>	Fatty alcohol assay
Official	<431>	Methoxy Determination
New in PF	<469>	Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Ethoxylated Substances
Official	<525>	Sulfur Dioxide
Official	<651>	Congealing Temperature

Excipient GC – Physical

Official Status	General Chapter	Title
Official	<267>	Porosimetry by Mercury Intrusion
New in PF	<268>	Porosimetry by Nitrogen Adsorption–Desorption
Official	<616>	Bulk Density and Tapped Density
Official	<699>	Density of Solids
Official	<786>	Particle Size Distribution Estimation by Analytical Sieving
Official	<811>	Powder Fineness
Official	<911>	Viscosity - Capillary Viscometer Methods
Official	<912>	Rotational Rheometer Methods
Official	<913>	Rolling Ball Rheometer Method
New in Development	<1028>	Particle Size Measurement
Official	<1059>	Excipient Performance
New in Development	<1062>	Compactability Test
Stim Article – New in Dev	<1063>	Shear Cell Methodology for Powder Flow Testing
Official	**<1078>**	**Good Manufacturing Practices for Bulk Pharmaceutical Excipients**
Official	**<1080>**	**Bulk Pharmaceutical Excipients–Certificate of Analysis**
Official	<1081>	Gel Strength of Gelatin
Official	<1174>	Powder Flow
Official	**<1195>**	**Significant Change Guide for Bulk Pharmaceutical Excipients**
Official	<1196>	Pharmacopeial Harmonization
Official	<1197>	Good Distribution Practices for Pharmaceutical Grade Excipients
New in PF	<1911>	Rheometry
New in Development	<XXXX>	Good Importation Practices
New in Development	<XXXX>	Excipient Stability

Excipients – New and Official GC, 2010-2015 CoE Cycle (34 Chapters)



Excipient Related General Chapters Update: <1059> *Excipient Performance*

- **USP General Notices 4.10 .** Because of the vast diversity of the application of excipients in product development, it is impossible to include all performance test methods/procedures in the compendial monograph.
- Therefore, not all the critical physical properties **may be identified in excipient monographs with compendial test methods and specifications.**

> *"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."*

Rational for General Chapter <1059> *Excipient Performance*

- Provides guidelines as to which non standard properties might be important for a particular excipient in a particular drug application
- 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.
- Keeping the tests non-mandatory (not in a monograph)
- Avoiding confusion with mandatory tests and labeling tests.
- Not imposing limits/specifications.
- Providing a framework for applying Quality by Design (QbD) concept to excipient quality control
  - Variation in excipient performance characteristics may affect critical quality attributes and process parameters of drug products, and the robustness of manufacturing process.

Microcrystalline Cellulose

Cellulose [9004-34-6].

- **Labeling:** The labeling indicates the nominal loss on drying, bulk density, and degree of polymerization values. Degree of polymerization compliance is determined using *Identification* test *B*. Where the particle size distribution is stated in the labeling, proceed as directed in the test for *Particle Size Distribution*. The labeling indicates with which technique the particle size distribution was determined if a technique other than analytical sieving was used; and the labeling indicates the d_{10}, d_{50}, and d_{90} values and the range for each.

- **Particle Size Distribution**

  [Note—In cases where there are no functionality-related concerns regarding the particle size distribution of the article, this test may be omitted.]

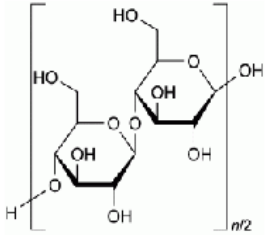
  Where the labeling states the particle size distribution, determine the particle size distribution as directed in *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, or by a suitable validated procedure.

1. USP Monograph: all tests mandatory
2. USP: Integration of Test methods in monograph (*Where Appropriate and without Specifications*)
3. A separate non-mandatory General Information Chapter <1059> Excipient Performance.

01/2009:0316

CELLULOSE, MICROCRYSTALLINE

Cellulosum microcristallinum



$C_{6n}H_{10n+2}O_{5n+1}$

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient ▶ (see chapter 5.15) ◀. This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for microcrystalline cellulose used as binder, diluent or disintegrant.

Particle-size distribution (2.9.31 or 2.9.38).

Powder flow (2.9.36).

1. EP Monograph: contains non-mandatory section
2. EP: Functionality Related Characteristics (FRC): non-mandatory section of monograph

Rationale for <1197> General Information Chapter

- USP General Information chapter , <1197> Good Distribution Practices for Bulk Pharmaceutical Excipients
- Outlines key strategies needed for
  - Qualification of starting materials of good quality
  - Maintenance of quality throughout the distribution chain
  - Confirmation of the quality by the users of starting materials
- Potential issues and misunderstandings can arise as to whether the sourced material can qualify as suitable for its intended use
  - Substandard ingredients can infiltrate the pharmaceutical supply chain if not properly qualified for intended use
- Provides key information to help assure excipient quality and help prevent intentional adulteration

Additional Excipient Related Chapters update

- **<268> Porosity by Nitrogen Adsorption–Desorption**: alternative to GC *Porosimetry by Mercury Intrusion* <267>. Use to access critical material attributes (CMAs) for pore volume or porosity. Useful GC that will be utilized in GC <1059> Excipient Performance.
- **<1911> Rheometry: C**ontains theories and practices of rheology and applications of viscometers and rheometers. Three chapters <911>, <912> and <913> contain key elements of viscosity testing associated with the chapter <1911>.
- **<202> Identification of Fixed Oils by Thin-layer Chromatography**: Used as an orthogonal method to the current test for *Fatty Acid Composition* identification test. The procedure is harmonized with *European Pharmacopoeia* general chapter 2.3.2. *Identification of Fatty Oils by Thin-Layer Chromatography.* The procedure is suitable for 11 fixed oil excipient and 3 fixed oil dietary supplement monographs.
- **<469> Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Ethoxylated Substances**: Chapter determines the concentration of residual ethylene glycol, diethylene glycol, and triethylene glycol in ethoxylated products. Ethoxylated products may contain residual ethylene glycol, diethylene glycol, and triethylene glycol as a result of the manufacturing process. The procedure is suitable for 17 excipients.

Some Key General Chapter Updates

- *<191> - Identification Tests – General*: Modernization of wet chemistry tests (e.g. remove flame) and introduction of alternative instrumental procedures (e.g. AAS-ICP, ICP-MS, IC, RAMAN, XRF)
- *<232> and <233> Elemental Impurities Limits and Procedures*: USP decided to delay implementation. An Advisory Group will be convened to develop an implementation strategy/plan
- *<621> Chromatography*: Harmonization of terminology and expectations with Europe and Japan. Stage 3 draft document in process
- *<1086> Impurities in DS and DP*: Modernization of organic impurities chapter (replacement of *<466>* with new chapter *<476>*), revision of *<1086>* and *General Notices 5.60.*

Some Key General Chapter Updates

- *<1083> Supply Chain Management*: Publication in PF 40(1) of four new chapters for GDP: *Quality Management System*, *Environmental Conditions Management*, *Importation & Exportation Management*, *Supply Chain Integrity & Security*. Specific chapters would be developed
- *<1225> Validation of Compendial Procedures*: There is an Expert Panel working in the revision of *<1224>*, *<1225>* and *<1226>*. A stimuli article will be published in PF 39(5)

New Excipient-Related Chapters targeted for Development for FY14

No	Chapters	Target PF
1	<1062> Compactability Test	TBD
3	<XXXX> Good Importation Practices	TBD
3	<XXXX> Excipient Stability	TBD

Excipient-Related Chapters targeted for Modernization for FY14

No	Chapters	Target PF
1	<1078> Good Manufacturing Practices For Bulk Pharmaceutical Excipients	TBD
2	<1080> Bulk Pharmaceutical Excipients—Certificate Of Analysis	TBD
3	<1195> Significant Change Guide For Bulk Pharmaceutical Excipients	TBD