Society for Nuclear Medicine  Winter Meeting
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USP Monograph Submission Requirements

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Topics

- Standards for PET Drugs in USP-NF
- Monograph Development Process
- Monograph Submission Contents
- Expert Committee Participation
- Challenges in the Monograph Development Process
Legally binding document governing the quality, strength and purity of medical items of commerce in the United States

Federal Food, Drug, and Cosmetic Act (FDCA) § 201(j)

“The term ‘official compendium’ means the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them.”
FDCA 501(b) – Adulteration

“A drug or device shall be deemed to be 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.”

(Section 501(b) of the Federal Food, Drug, and Cosmetic Act).

If you use the monograph title for your drug, and you don’t meet the monograph requirements, your drug is adulterated
# USP's Relationship to FDA

<table>
<thead>
<tr>
<th>USP</th>
<th>FDA</th>
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<tbody>
<tr>
<td>Private Not-For-Profit Organization</td>
<td>Government Agency</td>
</tr>
<tr>
<td>Development and Revision of Public (Compendial) Standards</td>
<td>Enforcement of Public Standards</td>
</tr>
<tr>
<td>Strength, Purity, Quality, Packaging, Labeling and Nomenclature</td>
<td>Safety, efficacy, NDA / ANDA (private license) approvals for marketing, manufacturing processes, etc</td>
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USP General Chapters for PET Drug Standards

- <821> RADIOACTIVITY
- <823> RADIOPHARMACEUTICALS FOR POSITRON EMISSION TOMOGRAPHY—COMPOUNDING
- <1015> AUTOMATED RADIOCHEMICAL SYNTHESIS APPARATUS

Assigned to General Chapters Physical Analysis Expert Committee
PET Drug Standards in USP-NF

**Carbon-11**
- Sodium Acetate C 11 Injection
- Methionine C 11 Injection
- Raclopride C 11 Injection
- Flumazenil C 11 Injection
- Mespiperone C 11 Injection
- Carbon Monoxide C 11 Injection

**Fluorine-18**
- Fludeoxyglucose F 18 Injection
- Sodium Fluoride F 18 Injection
- Fluorodopa F 18 Injection

**Oxygen-15**
- Water O 15 Injection

**Nitrogen-13**
- Ammonia N 13 Injection

**Rubidium-82**
- Rubidium Chloride Rb 82 Injection

Assigned to Monographs- Small Molecules 4 Expert Committee
Topics

- Standards for PET Drugs in USP-NF
- **Monograph Development Process**
- Monograph Submission Contents
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### Documentary Standards Setting Process

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Manufacturer submits proposal</td>
</tr>
<tr>
<td>2</td>
<td>Monograph development is initiated</td>
</tr>
<tr>
<td>3</td>
<td>Scientific Liaison performs technical review and drafts monograph, USP evaluates procedures requiring RS prior to publication and RS collaborative testing (optional)</td>
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<tr>
<td>4</td>
<td>Proposal is published for 90-day public comment period</td>
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<tr>
<td>5</td>
<td>Scientific Liaison and Expert Committee reviews comments</td>
</tr>
<tr>
<td>6</td>
<td>Expert Committee ballots to adopt proposal</td>
</tr>
<tr>
<td>7</td>
<td>Monograph is published in compendium (USP-NF, FCC) or on web site (Pending Monograph). USP-NF text becomes official six months after publication unless otherwise indicated. Commentary generated.</td>
</tr>
</tbody>
</table>

**Next steps?**

- Not Approved
- Approved
Documentary Standards Setting Process

Development begins

- Pharmaceutical companies are the primary source of monograph submissions (i.e., data to support the monograph)
- USP may initiate development for a revision or a new monograph (<823> revision initiated by USP)
- Each monograph is assigned to a Scientific Liaison and to an Expert Committee
  - PET monograph liaison: Ravi Ravichandran
  - Expert Committee: Monographs- Small Molecules 4
Documentary Standards Setting Process

Scientific review
- Scientific Liaison reviews the submission and works with the monograph sponsor to resolve issues; prepares draft monograph
- May need input from other Scientific Liaisons/Expert Committees, FDA, or lab support

Review of the draft monograph
- Prior to publication in a forum
- At least one other Scientific Liaison and other USP staff (such as Reference Standard Scientists) as needed; this process is called “peer review”
- USP management, as needed
- Expert Committee
  - Supporting data and information are available to Expert Committees electronically
  - Monograph sponsor
Documentary Standards Setting Process

Procedure evaluation

- Recent addition to the standards-setting process, implemented in March 2011
- USP evaluates the procedures and materials in a USP lab
- Primarily for
  - procedures introducing new USP RS or possibly new uses of existing USP RS
  - Chromatographic procedures (e.g., assay, impurities, etc) but could also apply to other technologies
  - Anticipated use for new monographs (especially drug substances), revision proposals introducing new USP RS or newer technology (e.g., UHPLC)
Draft monographs are published in the *Pharmacopeial Forum* (PF) or on the USP web site for Pending Monographs for a 90-day comment period

- PF is published six times per year (Jan, Mar, May, July, Sep, Nov)
- Primary vehicle for public comments on proposals for the *USP-NF*
- Freely available, online only beginning in January 2011

Scientific Liaison collects and evaluates all comments received, and shares them with the Expert Committee

Depending on the comments, the monograph may

- Advance to the ballot with no changes
- Advance to the ballot with minor changes
- Undergo revision and republication in PF
Documentary Standards Setting Process

6. Expert Committee votes to approve the monograph
   - Voting is done electronically
   - Each USP-NF Book and Supplement has its own ballot
   - A majority of “Yes” votes are needed for the monograph to be approved
   - Members with a conflict of interest are not allowed to vote

7. Approved monograph text is published in the annual USP-NF book or Supplement
   - USP-NF is published annually (Nov) with two Supplements (February and June)
   - The newly approved text becomes official six months after the book or Supplement is published (e.g., USP 34-NF 29 was published in November 2010 and will be official on May 1, 2011)
Commentary is generated for each USP Book and Supplement

- Created by the Scientific Liaisons for each compendial publication
- Summarizes comments received
- Indicates Expert Committee decisions
- Explains changes to previously published text (i.e., text incorporated or removed without republishing the proposal)
- Posted on the USP Web site to coincide with the publication of the final text

USP35NF30Commentary.pdf
Monograph Development Time Line

- Depends on several factors such as the level of sponsor participation, complexity of the information, etc.
- Typically three to six months for preparation of draft (Steps 1-2); some monographs may take much longer
- It can take 18 to 24 months for a monograph to become official (Steps 1 through Step 7)
- If a revision needs to become official quickly, the Accelerated Revision process may be used.
Topics

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Monograph Submission Content

- Contents vary depending on the nature of the submission (new monograph, revision to existing monograph, substance, dosage form, etc.).

- Exceptions may apply on an individual basis

- Tests, procedures, and acceptance criteria to support the monograph

- Regulatory status (i.e., FDA approval) is important and determines if the draft will be published in PF or on the Pending web site
  - Pending Monographs are for sponsors in the process of obtaining FDA approval

- Rationale for a revision to an existing monograph (including flexible approach)
Validation data
– For tests and procedures developed by the sponsor (e.g., chromatographic procedures, etc.)
– Not generally needed for tests that follow USP General Chapters without deviation (e.g., pH, Loss on drying, Residue on ignition, etc.)

Chromatographic column information (brand name, packing, particle size, etc.)

Representative chromatograms, spectra

Structures and chemical names of impurities, degradation products

Certificate of Analysis for three production lots (if available)
Monograph Submission Content

- Related information (as applicable)
  - Packaging and storage information and/or package insert
  - Labeling requirements, particularly safety-related requirements
  - NF category (for excipients)

- Sponsors may submit a draft monograph and/or their test methods (both very helpful), but these are not mandatory

- Other necessary data or information may be identified on an individual basis.

Useful links:


Submission Guidelines.htm

All first-time USP Reference Standard candidates required in a proposed new/revised monograph or General Chapter need to be received by USP prior to publication for public review and comment.

New monographs/chapters and revisions that introduce new USP Reference Standards will not become official until the required USP Reference Standard(s) are available for sale.

Exceptions to one or both of these practices may be made on an individual basis with the approval of USP management.
Topics

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2010-2015 Small Molecules Expert Committees

- Four Expert Committees for Small Molecule monographs in the 2010-2015 cycle
- Every Expert Committee has a Work Plan outlining goals for the five years and tracking progress
- Each Small Molecule Expert Committee has 800-1000 assigned monographs
- Responsible for all monograph content except the monograph name
  - Monograph name is approved by the Nomenclature, Safety and Labeling Expert Committee before publication of proposal
- Responsible for developing new monographs and revising existing monographs
- Approve uses of USP Reference Standards in monographs
Expert Committee Participation

Communications with USP staff
- Daily or weekly interactions for routine work
- At least one official (face-to-face) meeting at USP each year
- Telecons with USP staff at regular intervals or when needed

Responsibilities
- Advise Scientific Liaisons about technical, compendial and regulatory matters
- Evaluate monograph/chapter content and associated information
- Evaluate comments
- Decide if a monograph/chapter is ready to advance to a ballot
- Approve monograph/chapter text
Topics

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Monograph Development Challenges

- Some sponsors do not want to share their data with USP
- Submissions and/or comments from multiple sponsors
- Receiving comments after the public review and comment deadline
- Procurement of reference standard materials
- Political implications, high-profile standards
- Insufficient data to support request for revision
- Long lead times for publication
Monograph development process applies to new monographs and revisions to monographs.

Manufacturers are the primary source of monograph information.

Typically takes up to 24 months for a monograph to become official.

Expert Committees are the decision-making body.

Several challenges encountered throughout the process.
Thank You