FDA's Participation in USP-NF Revision Process- Challenges and Solutions

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December 11, 2025

Outline

- Overview of FDA- USP interactions
- Importance of public standards
- Government liaison program
- FDA review process for USP Pharmacopeial Forum
- Role of industry
- Questions and Answers

FDA-USP Interactions

- Compendial Operations and Standards Staff (COSS)
- Active role in the review and comment of USP standards proposals including nomenclature
- Email inquiries- Pre and post PF
- Government liaison program
- Meetings on broad impact policy issues
- FDA-USP quarterly meetings
- Meetings between leadership of the two organizations
- USP Convention
  - USP Convention delegate/s and submit resolution proposals
  - Member of Council of the Convention
  - Member of Nominating Committee
- Pharmacopeial Harmonization through PDG

Why Are Standards Important?

Consistency + Predictability + Credibility

= Science-Based Decisions

USP-NF: Legal Status

FD&C Act Chapter II - Definitions:

- Sec. 201. [321] For the purposes of this chapter –
  - **(j)** The term "official compendium" means the official **United States Pharmacopoeia**, official **Homeopathic Pharmacopoeia of the United States**, official **National Formulary**, or any supplement to any of them.

USP-NF: Legal Status (1/3)

The USP and NF official standards for strength, quality, purity, identity, packaging, and labeling can be used by FDA (via the FD&C Act) to support charges of:

- Adulteration [FD&C Act, Sec. 501(b)]
- Misbranding [FD&C Act - Section 502(g); 502(e)]

USP-NF: Legal Status (2/3)

Adulteration Charge

- **FD&C Act CHAPTER V - DRUGS AND DEVICES**
  - **SEC. 501.** A drug or device shall be deemed to be **adulterated** –

    (b) "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 standard set forth in such compendium…[unless] its difference in strength, quality, or purity from such standards is *plainly stated on its label.*"

USP-NF: Legal Status (3/3)

Misbranding Charge

- **FD&C Act - Section 502:** a drug or device shall be deemed to be **misbranded**—
  - **(e)** unless it is labeled with the "established name," [the title as established by FDA, if any, or used in USP monograph, if any, or the "common or usual name"].
  - **(g)** If it purports to be a drug the name of which is recognized in an official compendium, unless it is *packaged* and *labeled* as prescribed therein.

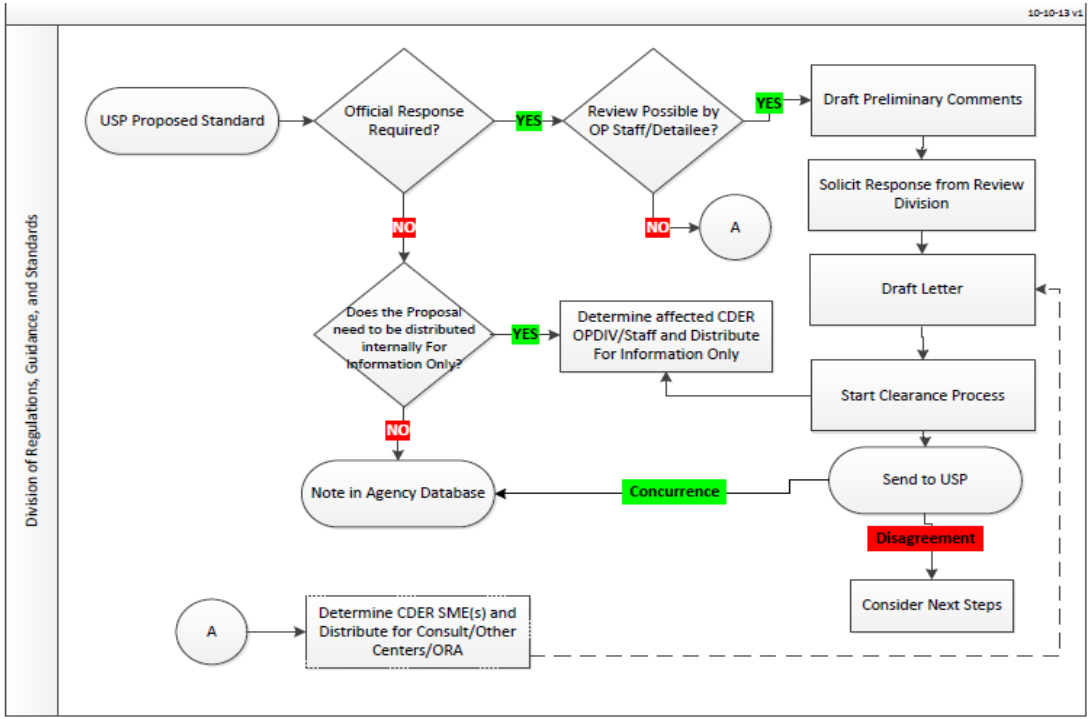
Government Liaison Program

Government Liaison (GL) Program

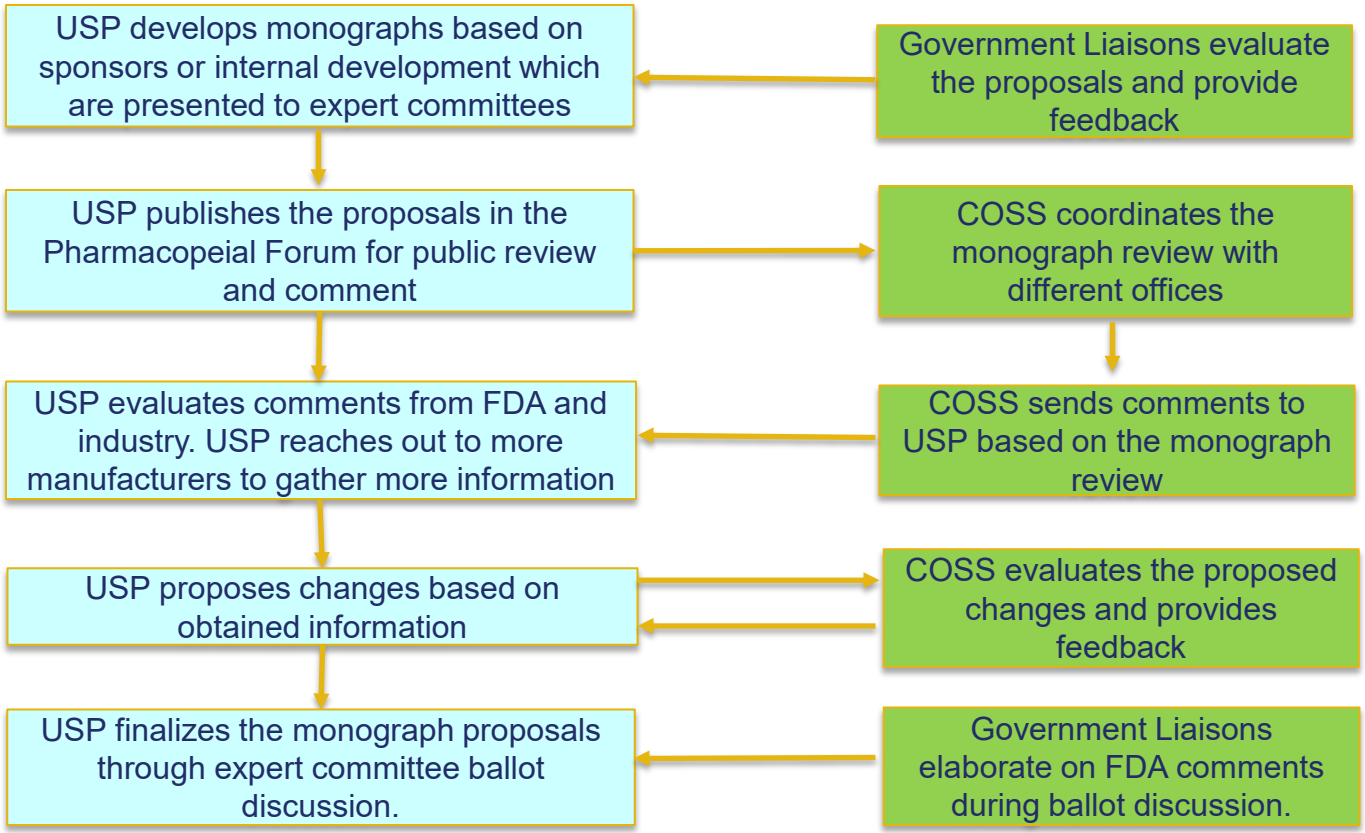
- FDA representatives on USP Expert Committees, Panels
- Participation by all FDA Centers, OII, Commissioner's Office
- 130+ CDER staff served in the GL role in the USP 2020-2025 cycle
- Provide input on behalf of FDA
  - Enable alignment between FDA regulatory thinking and USP standards
  - Provide clarity for stakeholders
- Information shared within FDA as needed to develop feedback on proposals
- Coordinated by COSS

FDA Review and Comment of Pharmacopeial Forum

FDA Review: Revision Proposals in PF



FDA Participation during USP Monograph Development



Challenges for FDA Review and Comment

- FDA is unable to disclose specific information necessary to revise monographs; the information must come from the applicant/DMF holder/manufacturer.
- Not practical for FDA to review information in each application/DMF while performing review of a monograph proposal
- Process employs sampling of applications.
- Impurity information and acceptance criteria are considered company confidential information unless already in the public domain.
- FDA comments indicate the problem with specific monograph section/s and recommend USP to contact manufacturers.

Importance of USP Monograph Standards to FDA and Industry

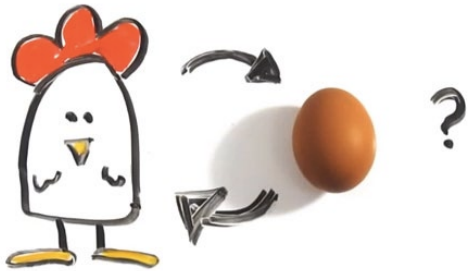
- USP monograph standards are not only applicable to approved applications, but also significantly impact pending applications' review.
  - ➢ Can improve efficiency
    - Provides information for product development (e.g., impurity profile, analytical procedure, acceptance criteria)
    - When firms follow USP method and acceptance criteria method verification/demonstration of suitability of use is generally acceptable
  - ➢ Outdated monographs impede efficiency
    - Can be misleading to firms during product development.
    - If an applicant is following an outdated monograph, can lead to more review cycles.

Solutions- Role of Industry

- Applicants/DMF holders/manufacturers should have a robust process for reviewing and commenting on USP/PF monograph proposals.
- Consider your data while commenting- If data indicates your product can meet proposed criteria, there is no need to petition USP for wider acceptance criteria.
- Contributing improved analytical procedures to USP enables keeping USP monographs up-to-date, so they are beneficial to public health.

Pending Monograph Process

Chicken or the egg?



FDA

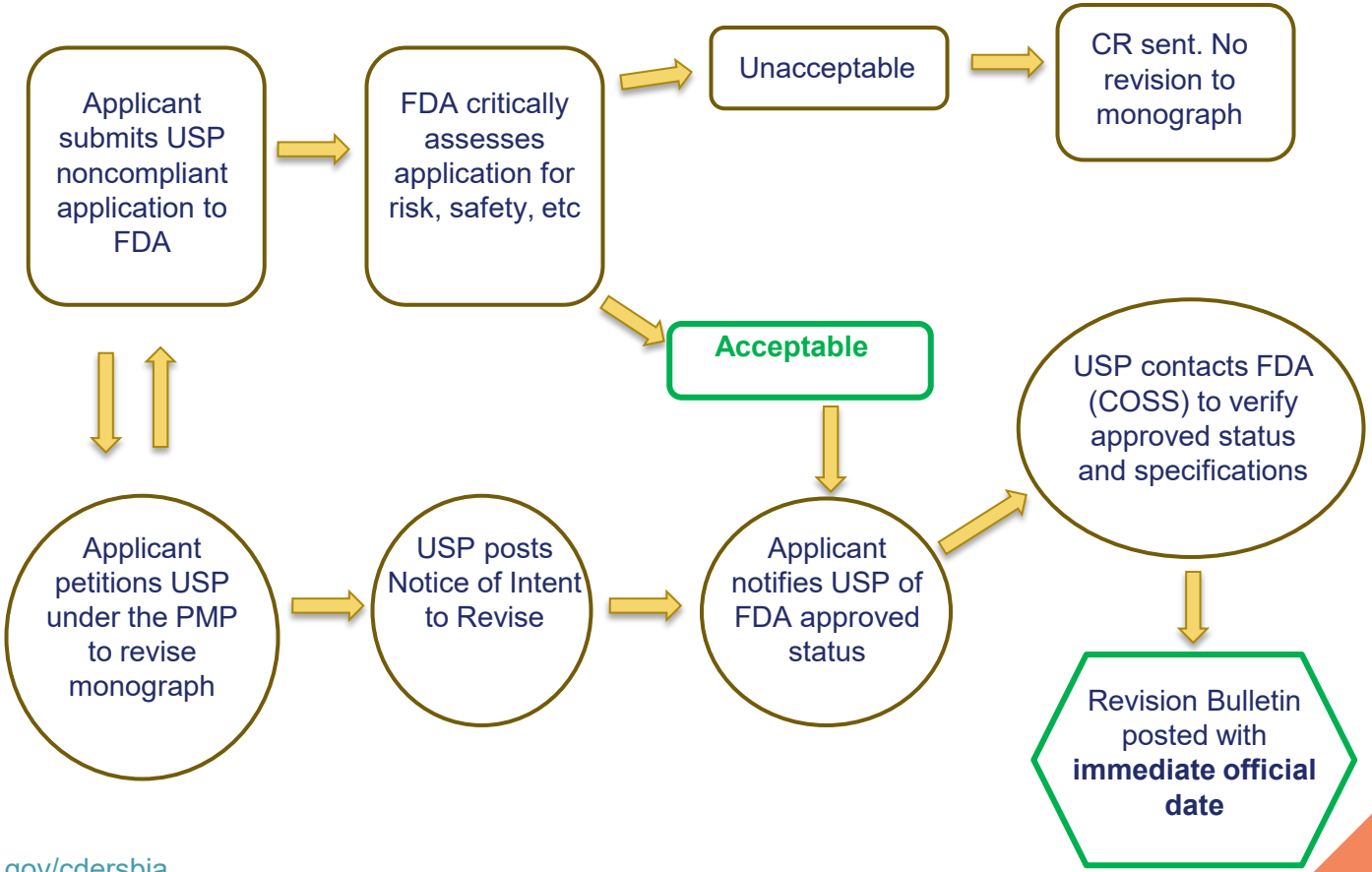
cannot approve application that does not comply with USP monograph

USP

cannot revise monograph because application is not FDA approved

Results in delayed approvals for 505b(2) and ANDAs!

Pending Monograph Process



Advantages of Up-to-date USP Standards

Modern USP Monograph Standards Can Potentially Provide:

- A public standard developed through a process that is open and provides for broad stakeholder input.
- A minimum legal standard for a Drug Substance, Drug Product and Excipient.
- Standardized quality and purity requirements for drug products across manufacturers.
- Equalized, standardized quality and purity requirements between OTC drug products and Rx drug products.
- Effective tools that can be used in FDA review and enforcement activities

Closing Thoughts

- Manufacturers are responsible for compliance with applicable USP requirements throughout product lifecycle.
  - Engaging with USP in the review and comment on USP proposals is an essential step.
- Approval letter templates for NDAs and ANDAs and quality supplements now include language regarding USP compliance.
- Information sharing challenges- FDA cannot share specific information needed to develop/update monographs.
- Pending Monograph Process is a specific process to address USP-NF non-compliance of an application under FDA review. ***USP making the change official is contingent upon FDA approval of the original application/supplement proposing the change.***

Resources

- Access USP-NF at www.uspnf.com , no username and password is required
- Access PF at www.usppf.com , free access, individuals must set up account
- Pending monograph
  - FDA Guidance https://www.fda.gov/regulatory-information/search-fda-guidance-documents/harmonizing-compendial-standards-drug-application-approval-using-usp-pending-monograph-process
  - USP guideline http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/pendingStandards/2015-06-01-pending-monograph-guideline.pdf
- Acceptability of Standards from Alternative Compendia (BP/EP/JP) https://www.fda.gov/media/72412/download
- Nomenclature guideline
  http://www.usp.org/sites/default/files/usp_pdf/EN/2014-12-01_nom_guidelines.pdf
- CDER's Application of the USP Salt Policy
  http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM360816.pdf

Questions?

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