Pending Monograph Process Overview

The webinar will begin at 10:30am ET

- Download the **course material** for the presentation from your account in the USP Education site (https://education.usp.org). Instructions can be found in your reminder email.
- You can connect to the **audio** by selecting the tab ‘Audio→ Audio Conference’ on the top of your screen
- You will remain **muted** throughout the presentation
- **Questions** can be sent through the Q&A panel to the right of your screen during the presentation & they will be addressed during the Q&A session.

*Technical Difficulties: Contact WebEx Technical Support at 1-866-229-3239

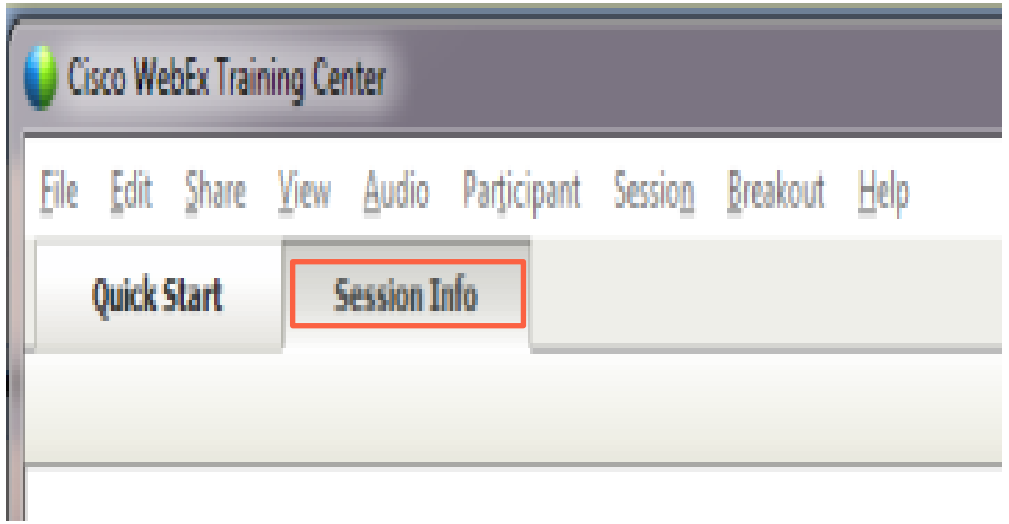
If you cannot hear the speaker at this time

Click:

- Audio
- Audio Conference

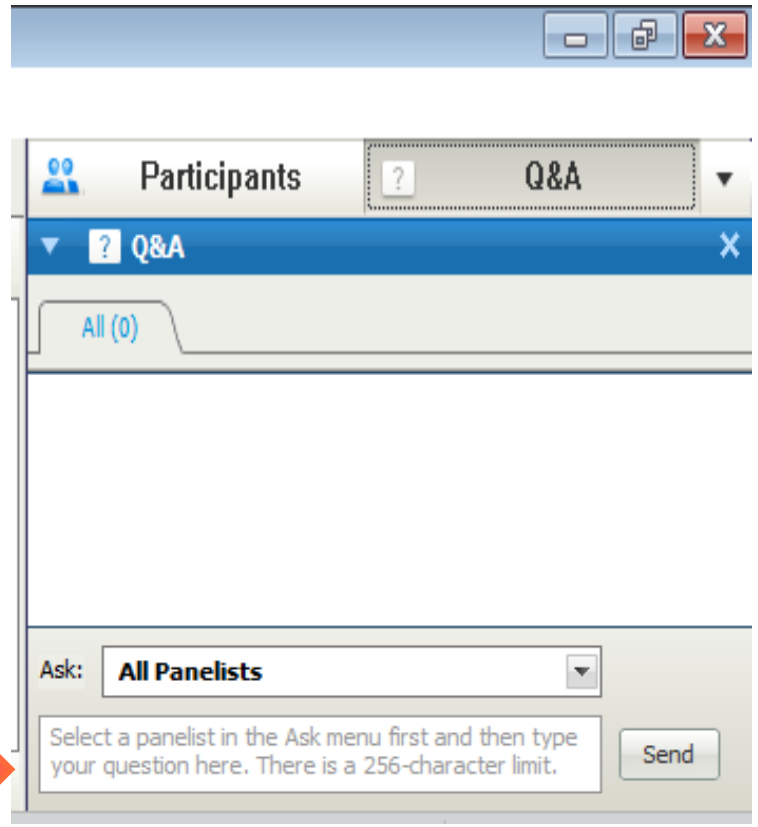
OR, Click:

- Session Info
- Use your telephone to dial in using the audio connection information shown



Question and Answer Session

You may type in questions at anytime during the webinar by using the Q&A feature to the right of your screen



1. Select the Q&A tab

2. Make sure 'All Panelists is selected

3. Type in your question and click send

Questions will be addressed at the conclusion of the course.


EVALUATION
Outstanding
Very Good
Satisfactory
Marginal
Unsatis

USP Education

Pending Monograph Process Overview

Amber Day

Program Manager, Standards Operations

Last Update: July 31, 2020

USP Course Owner Amber Day

Course ID: USPNF-03

Webinar Viewing Permissions

Each registration is unique and grants the right for the individual registrant only to view this webinar. Sharing this webinar with unregistered viewers either during or after its performance violates USP's copyright and is prohibited.

Disclaimer

Because USP text and publications may have legal implications in the U.S. and elsewhere, their language must stand on its own. USP shall not provide an official ex post facto interpretation to one party, thereby placing other parties without that interpretation at a possible disadvantage. The requirements shall be uniformly and equally available to all parties.

In addition, USP shall not provide an official opinion on whether a particular article does or does not comply with compendial requirements, except as part of an established USP verification or other conformity assessment program that is conducted separately from and independent of USPs standards-setting activities.

Certain commercial equipment, instruments or materials may be identified in this presentation to specify adequately the experimental procedure. Such identification does not imply approval, endorsement or certification by USP of a particular brand or product, nor does it imply that the equipment, instrument or material is necessarily the best available for the purpose or that any other brand or product was judged to be unsatisfactory or inadequate.

USP has tried to ensure the proper use and attribution of outside material included in these slides. If, inadvertently, an error or omission has occurred, please bring it to our attention. We will in good faith correct any error or omission that is brought to our attention. You may email us at: legal@usp.org.

Amber Day

USP Affiliation: USP Employee

Title: Program Manager, Standards Operations
Company: USP
Education: BS - Biological Sciences

Amber Day is Program Manager for Standards Operations in USP's Volunteer and Compendial Operations Department. With over 10 years of experience within the Pharmaceutical Industry, Amber collaborates with USP and FDA staff to manage the Pending Monograph Process. Before joining USP, she managed compendial updates, assisted with change control process improvements, and was an analyst in several Quality Control Laboratory. Amber has also been involved with various joint industry Groups and USP Initiatives. Her previous memberships include the New Jersey Pharmaceutical Quality Control Association, USP Customer Advisory Board for the *USP–NF*, General Notices Project Team, and co-chairing the Midwest Compendial Discussion Group.

Lana Bruney, Ph.D., MHA

USP Affiliation: Invited Guest Presenter

Title: Pharmacologist
Company: US Food and Drug Administration
Education: PhD - Pharmacology
MHA – Masters of Health Administration

Dr. Lana Bruney is a pharmacologist on the Compendial Operations and Standards Staff, in the Office of Policy for Pharmaceutical Quality, in the Center for Drug Evaluation and Research (CDER) at FDA. Currently, Lana serves as the policy lead for the Pending Monograph Process, where she is responsible for the development of CDER's policies and procedures regarding applicant utilization of the process, and for the training of CDER assessors on these policies. Previously, Lana was named a national 2015 STEM Presidential Management Fellow, where she began her policy review work. During her doctoral studies, Lana received multiple National Institute of Health research awards, including the exclusive National Institute of Health Ruth L. Kirschstein National Research Service F31 Award and a Life Sciences Fellowship.

Overview

- Introduction & Background
- USP Process
- FDA Process and Recommendations
- FAQs
- Resources
- Q&A

Development of the Pending Monograph Process

- Issue Identified
  - Traditional USP revision process can take 18-24 months depending on the revision.
  - Could create compliance gaps for applications that receive approval from the FDA.
- Solution
  - Can start the revision process sooner – process coincides with the FDA approval timeline
  - Minimize the compliance gap after approval
- Developed in close collaboration with the FDA and utilizing feedback from industry
- Originally developed in 2007; evolved into its current form in 2015

Who is the PMP for?

- Any company that has filed any of the following with the FDA:
  - Abbreviated New Drug Application (ANDA)
  - Abbreviated New Animal Drug Application (ANADA)
  - Submitted a Drug Master File (DMF) that is referenced in an ANDA, ANADA, or BLA
  - Whose substance is or will be the subject of a Time and Extent Application or citizen petition to amend an FDA OTC Drug Monograph
  - 505(b)(2) NDA – New use application
- Submissions from other sponsors may also be accepted on a case-by-case basis.

Request for Revisions Basics

- Stakeholders can submit a request for revision to:
  - Publish a new monograph
  - Make revisions to a current monograph, including:
    - Modernizing a test method
    - Adding impurities
    - Adding a test method
- Traditional Requests for Revision are published in the *Pharmacopeial Forum* (PF)
  - Open for public comment for 60 days, unless otherwise noted
- Voted on by the Expert Committees to be included in the *USP–NF*

Common Terms

- Pharmacopeial Forum (PF)
  - Free bimonthly online journal in which USP publishes proposed revision to the *USP–NF* for public review and comment
- Notice of Intent to Revise (NITR)
  - Alerts to notify stakeholders that there is a potential revision to a monograph
  - Published on www.uspnf.com
  - Not every NITR posted will become an official revision
- Revision Bulletin (RB)
  - One type of accelerated revisions that the USP uses to update monographs
  - Monograph revisions posted by RB become official the business day after posting

Common Terms

- Reference Standard (RS)
  - Are authentic specimens that have been approved as suitable for use as comparison standards in *USP* or *NF* tests and assays.
  - See section 5.80 of the General Notices in the *USP–NF* for more information on USP Reference Standards

Initiating the Revision Process

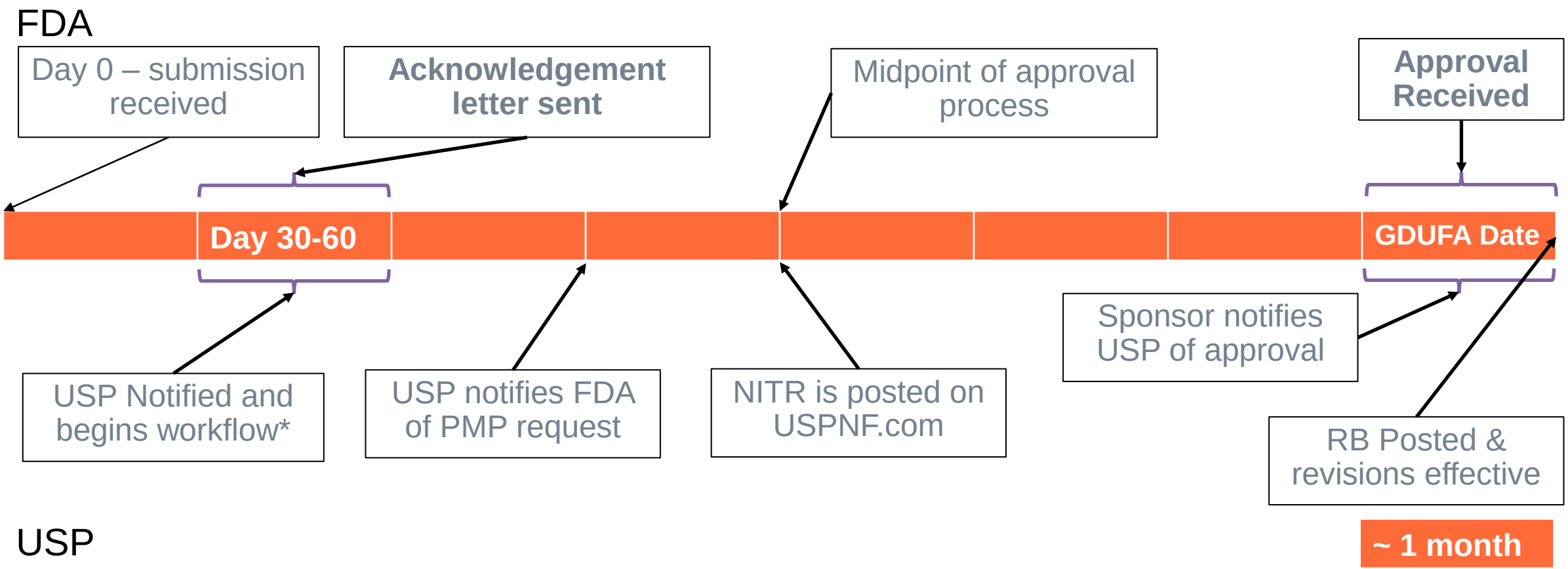
- When
  - Contact USP as soon as possible after filing the application with the FDA and receiving an Acknowledgement Letter
  - Early PMP submissions can help support the Sponsor's application process
  - Sponsors can reach out to USP independent of their FDA application
- How
  - Email pendingrevisions@usp.org

Timeline Comparison

- Traditional Timeline
  - Typically takes 18-24 months from Request For Revision to Official
  - Required to go through PF for public comment
  - Requires approval by the appropriate Expert Committee
- PMP Timeline
  - Average time is 10 months from Request For Revision to Official
  - Not all requests need to go through PF for public comment
    - Only go to PF if there is an impact to compliance for other manufacturers

USP Process

Timeline – Best case scenario



* Sponsor must have received acknowledgement letter from FDA before contacting USP to initiate PMP

USP Education

Application Requirements

- Must have submitted an application to the FDA and received Acknowledgement Letter
  - ANDA and Supplements
  - ANADA and Supplements
  - 505(b)(2) NDA – New use application
  - DMF Holder
  - Other application types on case-by-case basis – contact USP for more information
- Sponsor must agree to provide necessary reference materials, if required
  - USP is unable to start working on the Request for Revision until the reference materials are received.
- Sponsor must provide USP with information on changes to their FDA application

Application Process

- Notify USP by emailing pendingrevisions@usp.org
- Supply required documentation, as appropriate
  - Copies of FDA correspondence
  - Supporting Data and Documentation – See the Guideline for Submitting Requests for Revision to the USP-NF
- Communicate with USP with changes to their approval status
  - Changes to specifications
  - Application status
- Supply any necessary Reference Standard Materials

USP Process

Revision Process

- Scientific Liaisons integrate revisions into the monograph
- Approvals received from management and the Expert Committee
- Notice of Intent to Revise Posted on USPNF.com & FDA Notified
  - Mid-point of the ANDA application process
- Notification from Sponsor of approval
  - Confirm approved specifications with the FDA
  - Revision Bulletin posted on USPNF.com
  - USP committed to posting within 10 business days

Sitagliptin Phosphate

Type of Posting	Notice of Intent to Revise
Posting Date	28–Aug–2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 3

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 3 Expert Committee intends to revise the Sitagliptin Phosphate monograph. This Notice of Intent to Revise replaces a revision that was previously posted with a tighter water content limit of NMT 0.5%.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the following sections to accommodate the anhydrous form of the drug substance:

1. Chemical information: include the chemical name and molecular weight for the anhydrous form.
2. *Water Determination*: include the water limit of NMT 1.0% for the anhydrous form.
3. *Labeling*: Add a *Labeling Section* to accommodate the addition of the anhydrous form.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Andrea Carney, Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8155 or afc@usp.org).

NITR Disclaimer

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Types of PMP Requests

- Requests for Revision of Existing Monograph
  - No Comments Required
  - Comments Required
- Request for Revision to add a New Monograph
- Sponsors do not need to know what type of request they have at submission – USP will determine

Requests for Revision on Existing Monograph: No Comments Required

- For revisions that are not compliance-related revisions
- Proposed revisions will **NOT** be published in the PF for public comment
  - Only go to PF if there is an impact to compliance for other manufacturers
- Typical revisions
  - Widening limits (pH, assay, etc.)
  - Adding a dissolution test
- Currently the most common revision type

Requests for Revision of Existing Monograph: Comments Required

- Used for revision requests that may impact other manufacturers
- Published in PF for Public Comment and voted on by the Expert Committee
  - Can be found under “Pending” section of the USP-PF
- Includes note that they are “…contingent on the FDA approval of a product that meets the proposed monograph.”
- Potential compliance gap with the currently official monograph
- Typical revisions:
  - Adding impurities
  - Adding a new method
  - Updating a method

New Monographs – Comments Required

- New monograph for submission into the *USP–NF*
- Published in PF for public comment and voted on by the Expert Committee
  - Can be found under “Pending” section of the USP-PF
- Includes note that they are “…contingent on the FDA approval of a product that meets the proposed monograph.”
- Associated RS developed using sponsor provided material
  - RS may be available in the USP Store before the monograph is official
- Will be included on the deferrals list until associated FDA application is approved
  - Must be republished in PF after 2 years

Communication with the FDA

- USP will share sponsor name and title of the monograph being revised with the FDA
  - When request to use the Pending Monograph Process is received
  - When a revision is posted in the USP-PF for comment
  - When the Notice of Intent to Revise is published – 4-5 months prior to the GDUFA date
  - When the Revision Bulletin is published
  - Changes in status to the revision request (cancellation, change in revision type)
    - Cancellation of application
    - If a different revision type needs to be used
  - Confirmation that the proposed revisions included in the application were approved by the FDA

FDA Perspective and Recommendations for PMP

Lana Bruney, PhD
Pharmacologist, Policy Lead
Center for Drug Evaluation and Research
Office of Policy for Pharmaceutical Quality

How FDA Works with USP

- FDA and USP work closely to ensure appropriate public standards are available
  - Per Federal Food, Drug, and Cosmetic Act (FD&C Act), USP Compendial identity standards and standards for strength, quality, purity, packaging and labeling may support FDA enforcement actions

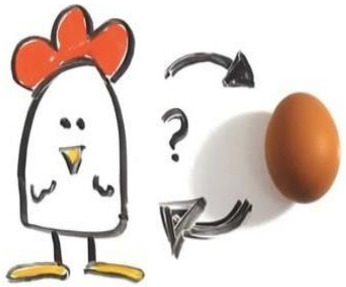
- Drugs that do not meet minimum standards can be considered:
  - **Adulterated** [FD&C Act, Sec 501(b)]
    - A drug or device shall be deemed adulterated "if it purports to be or is represented as a drug the name of which is *recognized in an official compendium,* and its *strength* differs from, or its *quality* or *purity* falls below, the standard set forth in such compendium…[unless] its difference in strength, quality, or purity from such standards is plainly stated on its label."
  - **Misbranded** [FD&C Act, Sec. 502(e); 502(g)
    - 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 the 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."

Traditional Revisions May Cause Approval Delays

- Approval of an application may be delayed while the applicant is asked to petition USP, leading to a chicken-or-egg situation

FDA

*cannot approve adulterated drug product (application which does not comply with USP monograph)**



USP

cannot revise monograph to include specifications because application is not FDA approved

- Often, product would have to be labeled to indicate difference from USP while petition processed

*Application could be approved as meeting the official monograph for identity but must include labeling statement with all differences plainly stated

Advantages of PMP

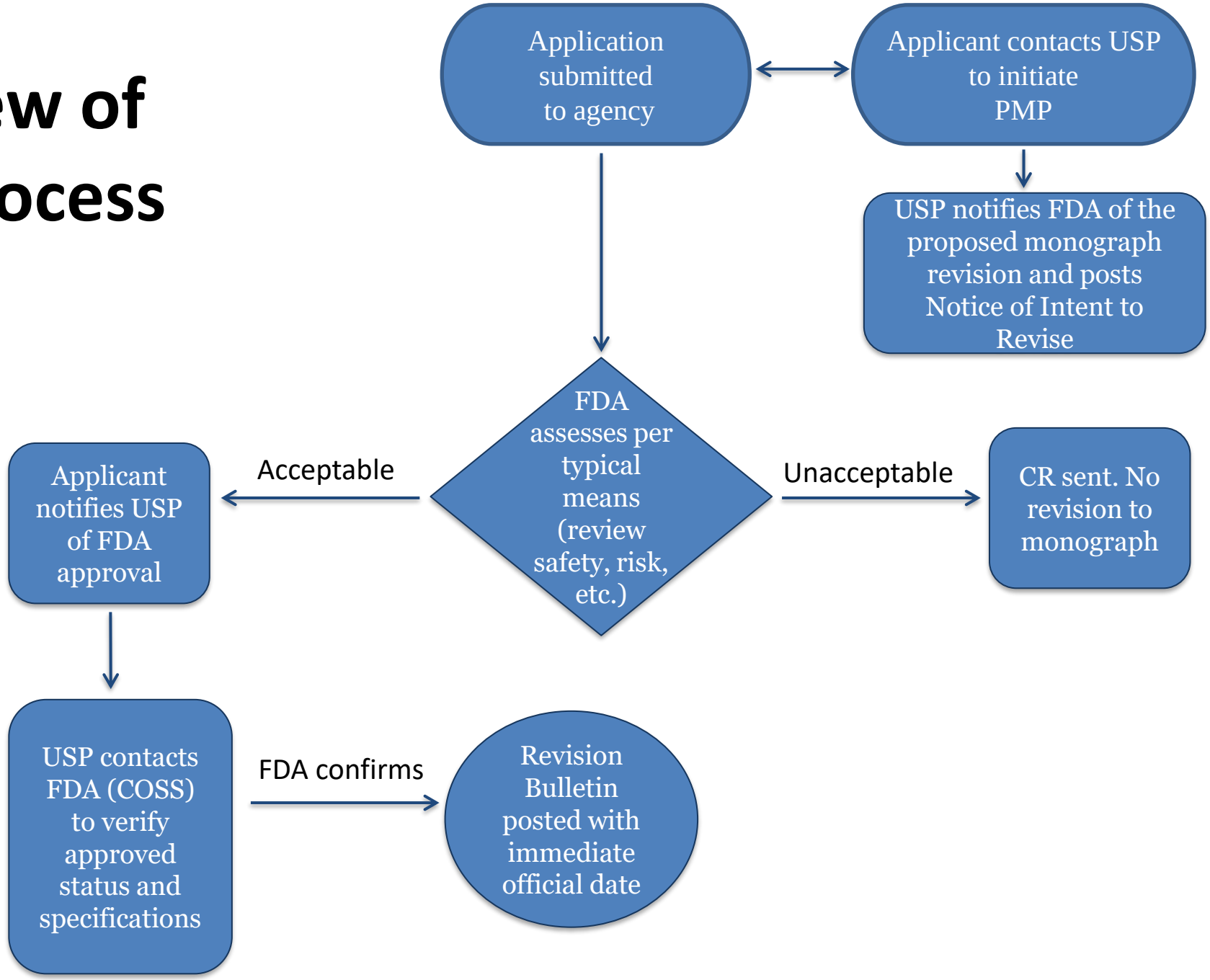
Traditional Approach	USP-PMP
Monograph revision requires FDA approval of application	Monograph revision can be proposed before FDA's approval
Revised monograph would not become official for 6 months or more (slow)	Immediately following FDA approval, USP makes a revised monograph available (fast)
Approval may be delayed as applicant is asked to label product with differences from USP (and begins revision process after)	Decreased changes of approval delays due to monograph compliance

Path to PMP

- FDA is committed to ensuring availability of safe and effective drugs
  - Avoid approval delays
  - Retain public confidence in approved drugs

- Collaborated closely with USP on PMP
- Draft Guidance published (July 2019)
  - Commenting period closed

Overview of FDA's Process



PMP Process – Notes

- Initiation does not infer specification acceptability
- PMP is not a shortcut to approval – all applications are fully assessed
- Applicants are responsible for ensuring that the compendial standards in the proposal reflect the standards in the application at the time of approval
- Monograph will be revised only after USP receives FDA confirmation of application status (approval) and approved specification(s)

Recommendations for Applicants

- Key suggestions in the draft Guidance include:
  - Those who intend to initiate the PMP should begin working on a proposal concurrent with the application's filing at FDA. (Please refer to USP Process slides)
  - Indication of PMP initiation should be placed in the cover letter and prominently displayed in all applicable section(s) (i.e., for DS -> 3.2.S.4.1; for DP ->3.2.P.5.1)
  - PMP initiator should keep USP apprised of their application's status

Key Points

- Initiation of the PMP is not required for approval. However, applicants who do not initiate the PMP when recommended may risk delay in the approval. (Alternatively, an application could be approved as meeting the official monograph for identity but then must have all other differences from the monograph plainly stated on the product label, as per current regulations.)

- It is not necessary to initiate the PMP for an analytical method that is different from USP (method equivalency should be shown)

- PMP was developed as a practical way to expedite necessary monograph revisions; the Agency typically does not require monograph development when no monograph exists

FAQs

1. What happens if my product isn't approved?
   a. The request for revision to the monograph associated with the FDA application will not be made official.
2. What happens if the specifications approved by the FDA differ from what is posted in the NITR?
   a. Sponsor needs to advise USP of any changes to the filing so the appropriate edits can be made. USP verifies that the revision complies with the specifications approved for the sponsor.
3. What happens if I don't want to donate Reference Materials and/or Reference Standard?
   a. Not every PMP revision request requires reference materials. If materials are required, the request for revision will be "on hold" until they can be supplied. We prefer monograph sponsors to donate reference materials.

FAQs

4. How do I know if I qualify for the PMP if I don't have a letter from the FDA?
   a) Sponsors should have evaluated conformity to the USP-NF standards during the drug development process. If you have questions, please contact pendingrevisions@usp.org for more information.
5. Will Novel Excipients qualify for PMP?
   a) Possibly. Please contact pendingrevisions@usp.org to determine eligibility.

Letter Samples

FDA Acknowledgement Letter

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

- Note: PMP will be referenced in all ANDA applications, regardless of if it needed or not. Applicant should review USP monograph to determine if revision to monograph is needed

FDA Information Request

- Example of Reference to PMP in Information Request

2. We acknowledge that the recommended dissolution acceptance criteria for your product, [redacted] differ from the USP. Please initiate a revision to an official monograph for [redacted] to the USP under the USP Pending Monograph Process. Until your product is in alignment with the dissolution specifications (method and acceptance criteria) in the USP monograph, include the following statement in the description section on Labeling: *FDA approved dissolution specifications differ from the USP dissolution specifications.*

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

FDA Information

- Example of Reference to PMP in Complete Response Letter

FDA Comment:

"Please note that a drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labelled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). Because the proposed specifications for your product do not conform to the USP monograph for [redacted] *with regard to the specified impurity* [redacted] *acceptance criterion, you are advised to contact USP upon receipt of this communication to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application."*

Resources

- USP Guideline
- FDA Draft Guidance
- Guideline for Submitting Requests for Revision to the USP-NF
- www.uspnf.com
  - Access the *Pharmacopeial Forum* and *USP–NF*
  - Browse current Notices of Intent to Revise and Revision Bulletins
- pendingrevisions@usp.org

USP Education

Formally created in 2000, we assist in our Capability Building activities by:

- Easing adoption of standards for manufacturers and practitioners
- Helping ensure standards have the intended impact on quality through correct implementation

Instructor-led classroom & lab training

Live online programs

Self-paced video and eLearning courses

Permanent Training Facilities
Additional off-site Course Locations

> 80,000 since 2000
> 10,000 students per year

Discussion

Empowering a healthy tomorrow

USP Education

Thank You

Empowering a healthy tomorrow

USP Education

Stay Connected

https://education.usp.org | Education@usp.org

Empowering a healthy tomorrow

USP Education