SBIA-DMF Drug substance workshop

March 3 & 4, 2021 (Virtual)

USP Pending Monograph Process and USP Compliance for Industry

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Virtual

PURPOSE

The USP Pending Monograph Process (PMP) enables the development of monographs or monograph revisions for articles prior to FDA's approval. FDA has published a draft guidance titled "Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process" in July 2019.

In addition, it is the responsibility of DMF holders to ensure that a drug substance complies with applicable standards in the USP-NF.

OBJECTIVE(S)

This poster provides information on FDA's current thinking on the USP-PMP and recommendations for drug master file (DMF) holders.

This poster also describes the allowable variations in chromatographic methods to be considered as the USP methods without full validation, the differences in data elements required for method verification versus method validation and common deficiencies regarding USP compliance

METHOD(S)

USP-PMP:

- Introduction and Background for USP-PMP
- Overview of USP pending monograph process
- Recommendations for DMF holders

USP COMPLIANCE:

- Allowable variations in chromatographic methods considered to be USP compliant (compliance with USP <621>)
- Common deficiencies regarding USP compliance
- Differences in data elements required for method verification vs. method validation (compliance with USP <1225> and USP <1226>)

RESULT(S)

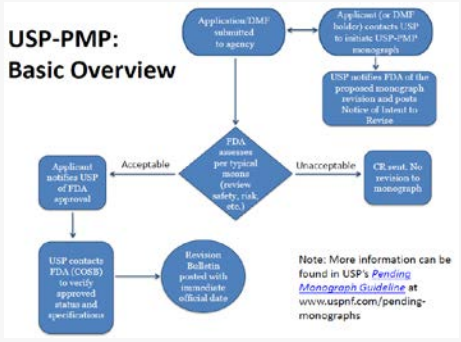
USP PENDING MONOGRAPH PROCESS:

Why the USP-PMP was developed?

- US Pharmacopeia (USP) sets compendial identity standards and **minimum** legal standards for strength, quality, and purity for drugs.
  - ✓ Under the FD&C Act [Sec. 501 and 502], drugs can be considered **adulterated, misbranded**, or both if not complying with compendial identity standards.
  - ✓ Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show difference.
- Applicants and MF holders can petition USP to revise standards in official monographs.
  - ✓ USP only accepts revision proposals (or a new monograph proposal) from applicants with **FDA-approved** drugs and other legally marketed products
  - ✓ **Approval** of the application was **delayed** in some cases if the proposed specifications do not comply with the current monograph. Often, the drug product would have to be **labeled to indicate the difference** from USP. Revised monograph would not become official for 6 months or more.
  - ✓ The USP-PMP was developed to address these issues and allow for **rapid revision** of official monographs to align with FDA approved specifications.

How does the USP-PMP Work?

The USP-PMP details procedures for monograph revisions (and/or monograph development) for applications that are being assessed by FDA.



Recommendations to DMF holders:

- Those who intend to initiate the USP-PMP should begin working on a proposal concurrent with the application's submission at FDA
- Indication of USP-PMP initiation should be stated in the cover letter and prominently displayed in all applicable section(s) (i.e., for DS: 3.2.S.4.1)
- USP-PMP initiator should
  - ✓ follow USP's guideline and submit the appropriate information directly to USP
  - ✓ keep USP apprised of the application's status
  - ✓ work with USP to ensure that the compendial standards in the proposal reflect the standards in the application at the time of approval

USP COMPLIANCE:

Allowable variations in the chromatographic methods considered to be USP compliant with verification, but not full validation

Notes:
1. Changes in the chemical characteristics ("L" designation) of the stationary phase will require full validation.
2. Adjustments to the composition of the mobile phase in gradient elution may cause changes in selectivity and are not recommended.
3. For gradient separations, changes in length, column inner diameter and particle size are not allowed.

Common deficiencies regarding USP compliance

- Because the USP monograph for your drug substance has already become official since May 2020, please update your drug substance specification to comply with that in the current USP monograph. Also please update your stability specification accordingly.
- The USP monograph for your drug substance will become official in May 2021. Please be aware that your drug substance specification needs to comply with the USP monograph once it becomes official. Please also keep in mind that method equivalency between in-house and USP methods need to be demonstrated in the event you decide to keep your in-house methods. If you decide to adopt the USP methods, please verify the compendial methods under actual conditions of use according to USP <1226> and demonstrate the method equivalency between in-house and USP methods as appropriate to bridge the methods used for formal stability testing.
- We acknowledge that you have adopted the USP organic impurities method and verified the method under actual conditions of use. However, we note there are three specified impurities that are not listed in the USP monograph. Please provide the full validation data to show the USP organic impurities method is suitable for analyses of these additional impurities.

Differences in data elements required for method verification vs. method validation

Analytical performance characteristics	Method Validation		Method Verification	
	Assay method	Organic Impurities and Residual Solvents methods	Assay method	Organic Impurities and Residual Solvents methods
System suitability	Yes	Yes	Yes	Yes
Accuracy	Yes	Yes	No	No
Precision	Yes	Yes	Yes	Yes
Specificity	Yes	Yes	Yes	Yes
Quantitation limit	No	Yes	No	Yes
linearity	Yes	Yes	No	No
Range	Yes	Yes	No	No
Robustness	Yes	Yes	No	No
Solution Stability	Yes	Yes	Yes	Yes

CONCLUSION(S)

- The USP-PMP allows the new or revised monograph to become official much faster than would be possible if monograph development or revision started only after final FDA approval of the drug product.
- A drug substance with a name recognized in USP-NF should comply with applicable standards in the USP-NF, such as tests and the acceptance criterion of each test, regardless of whether "USP" is used with the established name.
- The USP methods can be adopted with method verification as per USP <1226> or the in-house methods can be used with full method validation as per USP <1225> and method equivalency data to show the in-house method is equivalent or superior to the USP method of the same test.

WHERE TO GET MORE INFORMATION & LINKS.

FDA's Draft Guidance "Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process"
https://www.fda.gov/media/128689/download

USP Pending Monograph Guideline

USP <1225> : VALIDATION OF COMPENDIAL PROCEDURES

USP <1226> : VERIFICATION OF COMPENDIAL PROCEDURES

USP <621> : CHROMATOGRAPHY

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– Chemist

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Purpose and Objectives

The USP Pending Monograph Process (PMP) enables the development of monographs or monograph revisions for articles prior to FDA's approval.

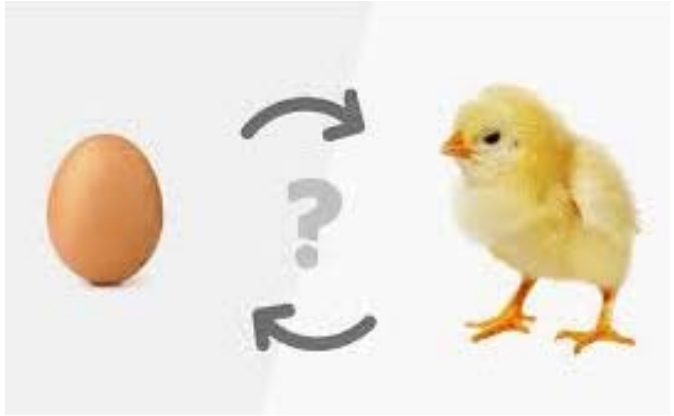
- ✓ Why USP-PMP was developed
- ✓ How does USP PMP work
- ✓ Recommendations for DMF holders

It is the responsibility of DMF holders to ensure that a drug substance complies with applicable standards in the USP-NF.

- ✓ Allowable variations in chromatographic methods considered to be USP compliant (compliance with USP <621>)
- ✓ Differences in data elements required for method verification vs. method validation (compliance with USP <1225> and USP <1226>)
- ✓ Common deficiencies regarding USP compliance

Why was USP-PMP developed?

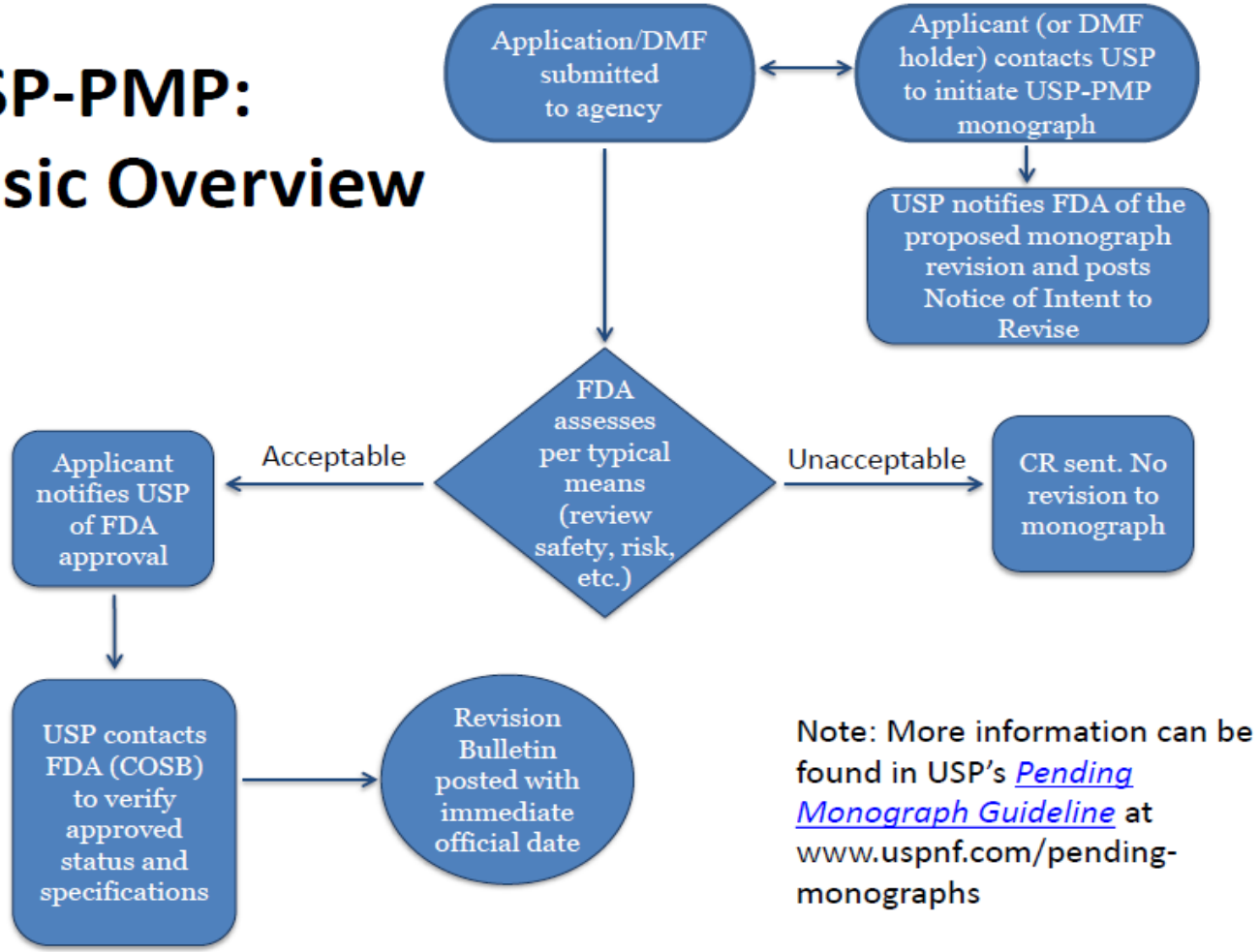
FDA **cannot approve** adulterated drug product that does not comply with USP.



USP only accepts revision proposals (or a new monograph proposal) from applicants with **FDA-approved drugs.**

- USP sets **minimum** legal standards for strength, quality, purity, packaging, and labeling for drug products.
- Under the FD&C Act [Sec. 501 and 502], drug products can be considered **adulterated, misbranded**, or both if not complying with compendial standards.
- If the proposed specifications of an application do not comply with the current official monograph, approval of the application was sometimes **delayed**.
  - ✓ Because the applicant is asked to petition USP.
  - ✓ The drug product would have to be **labeled to indicate the difference** from USP while petition processed (Undesirable).
  - ✓ Revised monograph would not become official for 6 months or more.
- The USP-PMP was developed to address these issues and allow for **rapid revision** of official monographs.

USP-PMP: Basic Overview



Note: More information can be found in USP's *Pending Monograph Guideline* at www.uspnf.com/pending-monographs

- Participation in the USP-PMP does not confer FDA acceptability of proposed standards of the product.
- Pending monographs will not advance to an official status until after FDA approval of the application and confirmation of the compendial specifications.

Recommendations to DMF holders

- Those who intend to initiate the USP-PMP should begin working on a proposal concurrent with the application's submission to FDA.
- Indication of USP-PMP initiation should be stated in the cover letter and prominently displayed in all applicable section(s) (i.e., for DS: 3.2.S.4.1)
- USP-PMP initiator should
  - ✓ follow USP's guideline and submit the appropriate information directly to USP
  - ✓ keep USP apprised of the application's status
  - ✓ work with USP to ensure that the compendial standards in the proposal reflect the standards in the application at the time of approval

Commonly asked questions?

- Q: My product is not expected to meet the USP-NF monograph, but I will not use the "USP" designation in the established name. Does this exempt my product from complying with the USP NF monograph (and thus negate the need for a USP-PMP proposal)?

  A: No. A drug with a name recognized in an official compendium is subject to the monograph standards found within.

- Q: I'm an MF holder. There's no monograph for my drug substance, but my client has submitted an application to FDA. Can I use the USP-PMP to develop a monograph for my drug substance?

  A: Yes. Only the specifications found in the approved application can be confirmed to USP.

- Q: We have submitted our MF to FDA with analytical methods for the drug substance that are not compliant with the official USP-NF monograph. We have demonstrated, through method equivalency studies, that our in-house methods are either equivalent or superior to the USP methods. Do we need to initiate the USP-PMP process to have our methods added to the drug substance USP-NF monograph?

  A: No. It is not necessary to initiate the USP-PMP for analytical method equivalency.

Allowable Variations in Chromatographic Methods Considered to be USP Compliant

	HPLC	GC
Column length	±70%	
Column internal diameter	Can be adjusted to keep constant linear velocity	±50%
Particle size	Reduction of 50%, no increase	Changes allowed SST must pass
Film Thickness	N/A	-50 to +100%
Flow rate	±50%	±50%
Column temperature	±10°C	N/A
Oven Temperature	N/A	±10%
Injection volume	May be decreased if precision, linearity and detection limit are ok	May be adjusted if detection limit and repeatability are ok
pH	±0.2 units	N/A
UV wavelength	No deviation permitted	N/A
Conc. of salts in buffer	±10%	N/A
Ratio of components in mobile phase	Minor components (≤50%) ±30% relative, but not exceeding ±10% absolute	N/A

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Differences in Data Elements Required for Method Verification vs. Method Validation

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Common Deficiencies Regarding USP Compliance

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Resources

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Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@FDA.HHS.GOV by 2/15/2021 for inclusion in the poster Q&A session on March 4th
- Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.