USP Monograph Modernization

Procedure Review and Development

Donald Min

Todays topics

- USP basic
- USP publications
- USP monograph modernization
- Assay and organic impurities procedures
- Analytical method validations and guidelines

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USP basic

Since USP's founding in 1820, our operations have grown exponentially: from 11 volunteers collaborating from their respective places of practice and research in the U.S. to more than 850 volunteers and more than 750 staff working together from five international locations.

US Pharmacopeia

USP – United States Pharmacopeia, a private, non-profit and non-governmental organization.

USP is recognized as the official compendium for drugs in the U.S. according to the FD&C Act (21CFR211.194(a)(2)).

USP sets the standards for drug identity, strength and purity.

FDA enforces the standards set by USP.

USP History

- USP published *United States Pharmacopeia (USP)* since 1820.
- In 1975, USP acquired the *National Formulary (NF),* which contains excipients standards
- USP acquired the *Food Chemicals Codex* (*FCC) in 2006.*
- Provides quality standards (*USP, NF, FCC*)

- Expert volunteers (Expert Committees) are scientific decision-makers

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USP/NF Publication

General Notices

Applies to all articles in USP/NF, such as

- 5.30 Solubility and Description
- 6.50 Preparation of Solutions

General Chapters

- <621> Chromatography – compendial compliance
- <1225> Validation of Compendial Procedures – general information

Monographs

- Identification
- Assay
- Impurities

Pharmacopeial Forum's (PF) Public Review and Comment Process

- PF is published on bimonthly basis to provide an opportunity to review and comment on new or revised standards.
- Posted in USP website: http://www.usppf.com/pf/login
- Free of charge

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USP Monograph Modernization

Monograph Modernization message in USP website

USP Seeks Submission of Proposals for Monograph Modernization

March 28, 2014

USP has embarked on a global initiative to modernize many of our existing monographs across all compendia. Having current monographs is tantamount to our mission of providing high-quality public standards. Towards that end, we are seeking industry collaborators to assist us in the development of these monographs. Please review the attached list. It contains the names of the top 500 high priority monographs requiring modernization.

USP intends to modernize these monographs as soon as possible utilizing one of two primary ways: traditional submission from a stakeholder (e.g. manufacturer of article) or USP's internal laboratory efforts. Monographs for which USP fails to receive submissions by December 26, 2014 will be directed to our laboratory.

There are two ways in which you can help:

- Submit your current analytical methods
- Provide sample amounts of the article for USP's internal lab development

Monograph Modernization List

Monographs in Need of Modernization (Last Updated

Yellow highlighting indicates a change in status since the last posting

Monograph Name	Monograph Family	Monograph Test	Development Step	Commen
Acyclovir	Acyclovir	Impurities	Submission Committed	
Acyclovir Capsules	Acyclovir	Identification	Submission Committed	
Acyclovir for Injection	Acyclovir	Identification	Submission Committed	
Acyclovir Ointment	Acyclovir	Identification	Submission Committed	
Acyclovir Oral Suspension	Acyclovir	Identification	Submission Committed	
Acyclovir Tablets	Acyclovir	Identification	Submission Committed	
Alprostadil	Alprostadil	Impurities	Modernization Not Needed	
Alprostadil Injection	Alprostadil	Impurities	Sourcing	

Family product profiles (different dosage forms)

Same API is formulated different ways based on delivery route…
Same analytical procedure may be developed...

Current USP monograph for Doxorubicin HCl Injection

Doxorubicin Hydrochloride Injection

» Doxorubicin Hydrochloride Injection is a sterile solution of Doxorubicin Hydrochloride in Sterile Water for Injection made isoosmotic with Sodium Chloride, Dextrose, or other suitable added substances. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{27}H_{29}NO_{11}\cdot HCl$.

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type I glass, protected from light. Store in a refrigerator. Injection may be packaged in multiple-dose containers not exceeding 100 mL in volume.

USP Reference standards 11 —

USP Doxorubicin Hydrochloride RS

USP Endotoxin RS

Identification—When chromatographed as directed in the *Assay*, the *Assay preparation* exhibits a major peak for doxorubicin, the retention time of which corresponds to that exhibited by the *Standard preparation*. …

No organic impurities procedure in the monograph.
Product stability, impurity monitoring,
Purity of the standard

USP monograph to be modernized and why

- A *USP–NF* monograph for an official substance or preparation includes the article's definition; packaging, storage, and other requirements; and a specification (including one or few tests and acceptance criteria).
- The monograph is likely submitted by the pharmaceutical product/substance manufacturer years ago with out dated analytical techniques.
- The analytical procedures in the monograph are based on product development and manufacturing process and may not be in the submitted documents at that time.
- The detailed information for the tests in the monograph are not always available.

Monograph Modernization Tasks and Milestones*

- Monograph identified for Modernization: 2600+
- Actively in Development: 330+
- Currently under revision (in PF): 110+

*as of 2014-6

Challenges: resources, sample procurements and acceptance limit for impurities

Monographs required for modernization

- USP monograph contains one of the following tests:
  - Identification by non-specific and outdated method, e.g. titration, wet chemistry.
  - Assay by non-specific or outdated techniques, e.g. GC with packed column, TLC, titration, wet chemistry and spectrophotometer.
  - Drug substance or drug product monograph without organic impurities test.
  - Non-value added test, e.g. melting point, clarity and color
  - Safety or environmental concerns, e.g. odor or chlorinated solvents used in the test

Benefits from USP monograph modernization

- Regulatory: consistent with ICH guidelines; harmonized with EP/BP specified impurities
- Public: Quality of medicine (with quality standards)
- Manufacturing: Efficient operation with assay and organic impurities using the same (similar) test procedures. Product compliance with global quality standard
- USP: Increase the quality of standard and global reach.

Procedure review and approval for USP monograph revision proposal

- USP lab method development and validation
- USP Scientific Liaison collaborates with lab and EC for monograph revision proposal
- Expert Committee (EC) review and approve the proposal and publish in PF
- Public review and comment
- Regulatory review and approval

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USP Monograph Modernization Objectives

- Establish orthogonal (second) identifications
- Develop stability indicating Assay and Organic Impurities by HPLC
- Modern technology use consideration
- (UHPLC, LC/MS) and alternate detections (CAD, ELSD...)
- Procedures are developed by USP Laboratories

Analytical procedure development

- Sample procurement:
  - API's and Drug Products
    - Global supply of pharmaceutical products
    - Sourced from different suppliers
  - Difference in the manufacturing process
    - Synthetic or process impurities or starting materials
  - Product quality, Impurity control and detection
    - Supplier CoA, package insert or ICH limit

More on Analytical Procedure Development

- Multi sourced samples
- Literature search and compendial collaborations from EP/BP
  - Organic impurity procedures and specified impurities
- Test method development and method validation
  - USP <621> " Chromatography", USP <1225> "Validation of Compendial Procedures"
- Monograph specification review
  - USP acceptance criteria not changed if available
  - FDA approved limits
  - Donor submissions
  - ICH limit Q3A/B

HPLC method development

- HPLC parameter considerations
  - Mobile phase compatible with mass spec. (e.g water, methanol, acetonitrile, acetic acid or ammonium acetate etc.)
  - HPLC column dimensions, column temperature, and pressure
  - Multistep gradient and flow rate
  - Reverse-phase and other surface modification of the stationary phases
- USP <621> Chromatography
  - System suitability requirements
  - HPLC parameters adjustments
  - Method robustness

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USP <621> Chromatography

- System suitability
  - Relative Standard Deviation Requirements, e.g. 0.73% for 5 replicate injection for drug substance assay
  - Tailing factor consideration, e.g. NMT 2.0 for assay
  - Resolution requirement, e.g. NLT 1.5, for organic impurities
  - Sensitivity solution, signal/noise ratio…for organic impurities
- HPLC parameters adjustments
  - pH of mobile phase, concentration of salts in buffer , binary mixtures
  - Wavelength of UV-Visible detector , column length, inner diameter, column temperature
  - Flow rate, Injection volume

HPLC Validation

- USP new general chapter <1200> proposal*:
  - Changes to criteria must be justified through data
  - Proposal review in PF39(6)
  - Method Accuracy, Precision and Transferability are emphasized
  - Statistical analysis and quality experimental design
- Forced Degradation:
  - Degraded samples will be used to evaluate method specificity in the validation.
  - Identification of degradants, wherever possible

* Published in PF39(6) – Requirements for Compendial Validation

Other related USP chapters for method development, validation and transfer

- USP <1224> " Transfer Analytical Procedures "
- USP <1226> " Verification of Compendial Procedures "
- USP <1010> " Analytical Data – Interpretation and Treatment "
- USP < 41> " Balances "
- USP <11> " USP Reference Standards "

Doxorubicin Hydrochloride Injection in PF40 (3)

BRIEFING

Doxorubicin Hydrochloride Injection, *USP 37* page 2715. As part of USP monograph modernization efforts, it is proposed to revise the monograph as follows:
1. The current *Assay* by HPLC is replaced with an UHPLC procedure that uses mass spectrometry-compatible mobile phase and an advanced analytical column. The procedure uses the Acquity BEH-C18 brand of L1 column manufactured by Waters, in which doxorubicin elutes at about 6 min.
2. Add a UHPLC test for *Organic Impurities*. The procedure uses the same chromatographic parameters as proposed in the *Assay*.
3. Add *Identification* test *B* based on the UV spectrum of the main peak in the *Assay*.
4. Add USP Reference Standards for impurities in the *USP Reference Standards* section to ensure the impurity separations and quantitation in the test for *Organic Impurities*.
Additionally, minor editorial changes have been made to update the monograph to current *USP* style.
(SM1: D. Min.)
Correspondence Number—C133150
Comment deadline: July 31, 2014
Doxorubicin Hydrochloride Injection

Organic impurities procedure by stability indicating UHPLC developed and validated

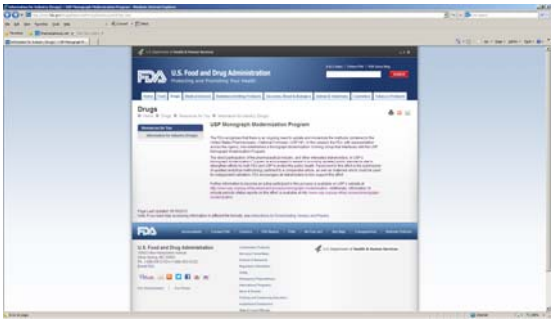
Further benefits from the modernized monograph

- Procedures developed by USP lab from multi-sourced samples
  - With orthogonal Identifications
  - Uses mass spec compatible mobile phase
  - Assay and Organic Impurities in a single procedure
  - Specified impurities, predicted impurities (through literature degradation pathway, patent search, EP/BP) are selected with acceptable criteria for the analysis.
  - USP provides impurity reference standards to better control the impurity profile and quality of the product.

Challenges and comments from the modernized monographs

- Challenges/comments
  - Lack of synthetic routes and related process impurities for drug substance procedure
  - Lack of formulation information and related degradation products for drug product procedure
  - Lack of specified and unspecified regulatory limit setting
  - Impurity availability for method development
  - Organic impurity profile vs. stability study profile

FDA support



FDA has established a Monograph Modernization Working Group that interfaces with the USP Monograph Modernization Program……FDA encourages all stakeholders to fully support this effort.

USP Modernized Monograph

- Proposal reviewed and approved by expert committee, regulatory agency and pharmaceutical manufacturers
- Feedbacks from public reviews
- Continuous improvements

USP Mission Statement:

To improve globe health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods

Questions

Thank You

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