Commentary

Interim Revision Announcements

November 18, 2022

In accordance with USP's *Rules and Procedures of the Council of Experts ("Rules")*, and except as provided in Section 9.02 *Accelerated Revision Processes*, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary* (*USP–NF*) for public review and comment in the *Pharmacopeial Forum (PF),* USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status*,* a summary of comments received and the appropriate Expert Committee's responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section of *USPNF*.com at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference or conflict between the contents of the *Commentary* and the official text, the official text prevails.

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Comments were received for the following when they were proposed in *Pharmacopeial Forum*:
Acetaminophen
Enoxaparin Sodium

No comments were received from the following proposals:
Ammonium Sulfate

Monograph Section(s): Acetaminophen/Multiple Sections

Expert Committee(s): Small Molecules 2
No. of Commenters: 5
Comment Summary #1: The commenter requested changing the Relative Standard Deviation from NMT 0.73% to 0.8% in the Assay procedure.
Response: Comment not incorporated. General Chapter <621> discusses the application of the permitted % Relative standard deviation for an n=5, with a B (%) of 2.0 valuation as a value of 0.73%.
Comment Summary #2: The commenter requested rationale for an injection volume change from 5 µL to 25 µL in the Assay procedure and requested a more incremental change of 10 µL.
Response: Comment not incorporated. The higher volume change was initiated in concert with a complementary reduction in the standard and sample concentrations. A stock solution in methanol is introduced to allow for complete solubilization of the acetaminophen active, and then is proportionally diluted (1:5 ratio) using 100% aqueous buffer (Solution A) for the standard and sample solutions. The procedure thus maintains the column loading as per the current monograph, while addressing the root cause of reproducibility issues - peak splitting due to high methanol content in the current standard/sample solvent as compared to the low methanol concentration in the initial mobile phase gradient composition.
Comment Summary #3: The commenter suggested adding a reproducibility requirement in the Organic Impurities procedure for the Acetaminophen related compound J.
Response: Comment not incorporated. The reproducibility requirement of Acetaminophen related compound D supports the System suitability requirements of the analytical system.
Comment Summary #4: The commenter questioned whether the proposed increase in injection volume would resolve an observed baseline disturbance in the Assay procedure and suggested application of the EP titration method as a more harmonized resolution to the issue.
Response: Comment not incorporated. The Expert Committee's decision was to retain the more specific HPLC procedure.
Comment Summary #5: The commenter recommended retention of "anhydrous" wording for the dibasic sodium phosphate reagent in the Assay procedure.
Response: Comment incorporated.

Monograph/Sections: Enoxaparin Sodium/Identification D
Expert Committee(s): Biologics Monographs 3 – Complex Biologics and Vaccines
No. of Commenters: 2

Comment Summary #1: The commenter suggested keeping the original method for Identification D test and making it an alternative method of the proposed method.
Response: Comment not incorporated. However, the official date for the proposed revision is extended from November 1, 2022 to December 1, 2023, providing additional time to prepare for compliance.

Comment Summary #2: The commenter suggested deleting the statement “It contains NMT 0.01 USP Endotoxin Unit/IU of Anti-Factor Xa activity” and adding “Where the label states that Enoxaparin Sodium is sterile or must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Enoxaparin Sodium is used can be met.” in the *Bacterial Endotoxins Test.*

Response: Comment not incorporated. The comment is outside the scope of the proposed revisions. The EC will consider future revisions to the monograph.

Comment Summary #3: The commenter suggested adding the statement of “Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable forms to ensure acceptable levels of bacterial endotoxins.” to the *Labeling* section.

Response: Comment not incorporated. The comment is outside the scope of the proposed revisions. The EC will consider future revisions to the monograph.