



**Commentary – *Pharmacopeial Forum* 35(5) Sept.-Oct. 2009
Interim Revision Announcements to USP 33-NF 28 Reissue**

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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. If there is a difference between the contents of the *Commentary* and the official text, the official text prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the *Commentary*, shall prevail.

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Monograph/Section(s): Budesonide/Limit of 11-ketobudesonide
Expert Committee(s): Monograph Development-Pulmonary and Steroids
No. of Commenter(s): 1
Content Summary #1: The commenter noted that it was unnecessary to add a requirement that the mobile phase be preheated to stabilize the retention times.
Response: Comment not incorporated.
Reason for Revision #1: The resolution requirements under the test for *Limit of 11-ketobudesonide* were removed as part of the system suitability requirements based on comments received indicating that the resolution cannot be established due to the absence of signal for 14,15-dehydrobudesonide and 21-dehydrobudesonide.
Reason for Revision #2: The requirement that the *Mobile phase* be pre-heated in order to stabilize the retention times was added.

Monograph/Section(s): Heparin Sodium/Multiple Sections
Expert Committee: Biologics and Biotechnology–Blood and Blood Products
No. of Commenters: 19
Comment Summary #1: The commenters suggested that the *¹H Nuclear Magnetic Resonance (NMR) spectrum identification* test be written more prescriptively to include detailed acquisition and analysis parameters.

Response: Comment not incorporated because the current method describes operating parameters in sufficient detail.

Comment Summary #2: The commenters suggested revising the ^1H NMR preparation of *System suitability solution* to reflect 1% (w/w) Oversulfated Chondroitin Sulfate (OSCS) in 20 mg/mL of heparin.

Response: Comment incorporated.

Comment Summary #3: The commenters suggested revising the ^1H NMR spectrum identification by allowing the use of an NMR spectrometer operating at “NLT 300 or 400 MHz.”

Response: Comment not incorporated because 500 MHz is the minimal requirement set by the Food and Drug Administration (FDA).

Comment Summary #4: The commenter suggested revising the ^1H NMR spectrum identification by replacing the parts per million (ppm) range for residual solvents with the following statement: “Residual solvent signals may be observed. Heparin Sodium must meet the requirements stated in *Residual Solvents <467>*.”

Response: Comment not incorporated because no supporting data was provided.

Comment Summary #5: The commenters suggested modifying ^1H NMR identification acceptance criteria ranges based on the data submitted.

Response: Comment not incorporated because the *Acceptance criteria* are based on the validation data generated using numerous heparin batches.

Comment Summary #6: The commenter suggested defining the ^1H NMR spectrum identification sample solution pH interval because the pH value can vary signal chemical shifts, which is particularly significant for nuclei near protonation sites (i.e., H5 of iduronic acid).

Response: The comment was not incorporated because the pH of heparin is typically between 5 and 7, and water has little buffering capacity.

Comment Summary #7: The commenter suggested revising the *Chromatographic identity* by specifying a high capacity (HC) column, which gives better resolution and peak shape. The commenter also indicated a temperature control may generally provide a more reproducible result.

Response: Comment was not incorporated but has been deferred to a future monograph revision.

Comment Summary #8: The commenter suggested revising the *Chromatographic identity* to not use perchlorate in the eluant, if possible, for safety and environmental reasons.

Response: Comment not incorporated because the method validation was carried out using the perchlorate in the eluant.

Comment Summary #9: The commenters suggested removing Dermatan Sulfate (DS) from the *Chromatographic identity system suitability solution* as its presence and the concomitant criterion for resolution are not necessary to demonstrate the suitability of the system for the intended purpose.

Response: Comment not incorporated because the intent of the *System suitability solution* is to demonstrate the method’s ability to separate various chondroitins (i.e., Dermatan Sulfate and Oversulfated Chondroitin Sulfate) from Heparin.

Comment Summary #10: The commenter indicated the *Chromatographic identity* should list separate specifications and USP Reference Standards should be developed for bovine heparin sodium because the monograph does not specifically address the heparin sodium source.

Response: Comment not incorporated because all licensed heparin products in the United States are porcine-derived.

Comment Summary #11: The commenter suggested specifying a column temperature for the *Chromatographic identity* analysis.

Response: Comment incorporated to include a column temperature parameter of 40°C.

Comment Summary #12: The commenter suggested performing an evaluation of the *Anti-factor Xa* and *Anti-factor IIa* assays, with their associated variation, to show that they support the *Anti-factor Xa to Anti-factor IIa ratio* of 0.9-1.1.

Response: Comment not incorporated because both historical data and recent extensive collaborative study results fully support the proposed specification.

Comment Summary #13: The commenters indicated that it is not possible to estimate the impact of the proposed specification change of the *Anti-factor Xa activity* at this time due to simultaneous changes of the *Anti-factor IIa potency* method, the lot of USP Heparin Sodium for Assays Reference Standard (RS), and the method used to establish the declaration value of the USP Heparin Sodium for Assays Reference Standard.

Response: Comment not incorporated because the Expert Committee determined that the USP Heparin Sodium for Assays Reference Standard will become available in time for industry to prepare before the monographs become official.

Comment Summary #14: The commenter suggested that the allowances made in the *Anti-factor IIa* method for the use of an automated instrument are incorporated into the *Anti-factor Xa* method in order to standardize the two methods.

Response: Comment incorporated.

Comment Summary #15: The commenters indicated that USP must ensure the USP Heparin Sodium for Assays Reference Standard (qualified by the proposed *Anti-factor IIa potency*) will become available with enough time for industry to evaluate the *Anti-factor IIa potency* assay method and the 180 Units per mg specification for commercially available raw materials and finished products.

Response: Comment incorporated.

Comment Summary #16: The commenters suggested an *Anti-factor IIa potency* specification of Not Less Than (NLT) 160 Units per mg or lower.

Response: Comment not incorporated the specification would detract from the goal of improving the quality of unfractionated heparin (UFH).

Comment Summary #17: The commenter suggested that the *Anti-factor IIa potency* section describes appropriate characterization of the substrate by (1) determining the dilution values and defining in chromogenic activity units, and/or (2) specifying the purity of thrombin in terms of alpha, beta, and gamma content.

Response: Comment was not incorporated but has been deferred to a future monograph revision.

Comment Summary #18: The commenter suggested revising the *Anti-factor Xa activity* assay to include a concentration range rather than specific levels for the standard and sample to make the assay consistent with the *Anti-factor IIa potency* assay.

Response: Comment incorporated.

Comment Summary #19: The commenter suggested increasing the *Anti-Factor IIa* standard curve range from “0.005 U/mL” to “0.05 U/mL” to allow the same sample dilutions to be used on the *Anti-Factor Xa* method.

Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider revisions upon receipt of supporting data.

Comment Summary #20: The commenter suggested revising the *Anti-factor IIa potency* method to allow for polyethylene glycol 6000 buffer concentrations between 0 to 1% to allow the 0.1% polyethylene glycol 6000 buffer for *Anti-factor Xa activity* to be used on the *Anti-factor IIa potency* analysis.

Response: Comment incorporated.

Comment Summary #21: The commenter indicated significant concerns with the repeatability and reproducibility of the *Anti-factor IIa potency* assay. The variability observed, when applied against the Heparin Lock Flush Solution limits of 90-120% labeled potency, has significant negative impact to the shelf life of currently approved and marketed Heparin Lock Flush syringes as it encompasses two-thirds of the label claim range.

Response: Comment not incorporated because inter-laboratory variability is an agreement between laboratories and is related to how well the USP Heparin Sodium for Assays Reference Standard compares with the test material and the precision of each laboratory.

Comment Summary #22: The commenter suggested revising the *Limit of galactosamine in total hexosamine* by including a linearity test to demonstrate detector linearity since the glucosamine peak will be roughly 100 times larger than the galactosamine peak area at the limit.

Response: Comment not incorporated because the *Limit of galactosamine in total hexosamine* uses a ratio.

Comment Summary #23: The commenter suggested expanding *Limit of galactosamine in total hexosamine* by allowing for different electrochemical detectors and/or lack of eluant generator.

Response: Comment not incorporated because users can demonstrate compliance by validating their equipment.

Comment Summary #24: The commenter suggested increasing the galactosamine (GalN) limit in the *Limit of galactosamine in total hexosamine* as it is unrealistic to reduce the Dermatan sulfate content below 3% without changing the internal composition and, to some extent, the biological activity of heparin.

Response: Comment not incorporated because heparin manufacturers have been producing heparin with the DS content below 1% consistently.

Comment Summary #25: The commenter suggested deleting the guard column from the *Limit of galactosamine in total hexosamine* because improved glucosamine peak shape and increased theoretical plates can be obtained without using the guard column.

Response: Comment incorporated.

Comment Summary #26: The commenter suggested that the *Limit of Galactosamine in Total Hexosamine* test does not determine the amount of free sugars, particularly glucosamine, in an intact (unhydrolyzed) sample. Thus, a heparin sample that would fail the limit test by small amount could be adulterated to pass the limit test by the addition of glucosamine. The commenter suggested measuring the intact heparin molecule instead of a method involving hydrolysis.

Response: Comment not incorporated because addition of 2% (w/w) glucosamine hydrochloride to heparin can easily be detected by ¹H NMR Spectroscopy.

Comment Summary #27: The commenter suggested revising the *Limit of galactosamine in total hexosamine standard solution* preparation as a 1:100 dilution, allowing for a more accurate pipetting of a smaller amount of standard solution avoiding possible errors in a quantitative transfer.

Response: Comment incorporated.

Comment Summary #28: The commenter suggested clarifying the *Absence of oversulfated chondroitin sulfate* acceptance criterion “No features” to mean a signal-to-noise ratio of 3 to 1.

Response: Comment not incorporated because General Chapter <1225> Validation of Compendial Procedures clarifies the Limit of Detection.

Comment Summary #29: The commenter suggested allowing industry additional time to evaluate the *Absence of oversulfated chondroitin sulfate* method since the required USP Reference Standards were not available for the Heparin Sodium *Proposed Interim Revision Announcement*.

Response: Comment not incorporated because all USP Reference Standards needed to perform this method are currently available.

Comment Summary #30: The commenters suggested lowering the *Nucleotidic impurities* specification to “Not More Than (NMT) 0.1%.”

Response: Comment not incorporated because supporting data was not provided.

Comment Summary #31: The commenter indicated that the *Nucleotidic impurities* lists negative absorbance readings for the majority of Heparin Active Pharmaceutical Ingredients (API’s) after the correction for light scattering at A260. The commenter suggested that USP evaluate the significance of these negative results and the applicability of the light scattering correction to this product.

Response: Comment not incorporated because the supporting data generated by USP do not mirror this finding.

Comment Summary #32: The commenters suggested lowering the *Protein impurities* specification to “NMT 0.25%.”

Response: Comment not incorporated because no supporting data was provided.

Comment Summary #33: The commenter suggested two changes to the *Protein impurities* assay: (1) adjust the concentrations of the standard solutions, and (2) remove a discrepancy between the described range of the standard curve and the acceptance criteria for “NMT 1.0% is found.”

Response: Comment incorporated.

Comment Summary #34: The commenter suggested specifying in the *Protein impurities* section the reading of samples within 10 minutes after the 30 minute incubation upon the addition of the *Diluted Folin-Ciocalteau’s Phenol Reagent*.

Response: Comment incorporated.

Comment Summary #35: The commenter suggested clarifying the *Protein impurities* acceptance criteria NMT 1.0% by adding “(w/w).”

Response: Comment incorporated.

Comment Summary #36: The commenter suggested including a solvent correction in the acceptance criteria for the *Anti-factor Ila Potency* test.

Response: Comment not incorporated because all Heparin API should comply with the residual solvent requirements (per General Chapter <467> Residual Solvents) as specifically stated in the monograph.

Comment Summary #37: The commenters suggested extending the comment period for the *Proposed Interim Revision Announcement* at least four weeks after the USP Reference Standards become available, with a parallel adjustment in the monograph official date, so that industry has adequate time to review, verify, and validate the USP Reference Standards to the monograph methods.

Response: Comment not incorporated because the Expert Committee determined that the USP Reference Standards required by the Heparin Sodium and Heparin Sodium Injection Monographs will become available in time for industry to prepare before the monographs become official.

Monograph/Section(s): Heparin Sodium Injection/Anti-Factor Ila Potency Assay
Expert Committee: Biologics and Biotechnology–Blood and Blood Products
No. of Commenters: 3

Comment Summary #1: The commenters suggested that the *Anti-factor IIa potency* labeled potency specification range should be increased to reflect the new method's capability. They suggested that the current specifications with the current test method, as a system, reduce industry ability to confidently release and maintain compliance to labeled claim for potency over product shelf life.

Response: Comment not incorporated.

Comment Summary #2: The commenter suggested that the current clotting assay remain a viable alternative method to the *Anti-factor IIa potency* method for Heparin Injection and Heparin Lock Flush Solution for a period of 12 months following official monograph and Lot M USP Heparin Sodium for Assays Reference Standard implementation.

Response: Comment not incorporated.

Monograph/Section(s): Nefazodone Hydrochloride/Identification

Expert Committee(s): Monograph Development-Psychiatrics and Psychoactives

No. of Commenter(s): 0

Reason for Revision #1: *Identification* test *B* was revised to change the solvent from water to methanol because of the slightly soluble nature of the drug substance in water.