



U.S. Pharmacopeia
The Standard of QualitySM

December 17, 2008

To: Members of the B&B Blood and Blood Products Expert Committee; Jean Huxsoll, Ph.D., Chair

From: Members of the Heparin Ad hoc Advisory Panel; Kristian Johansen, Ph.D., and Wesley Workman, Ph.D., Co-chairs

RE: Heparin Advisory Panel Recommendations, Meeting #16

Recommendation 1:

Revise the Heparin Sodium Injection monograph to replace the current sheep plasma clotting assay with the anti-factor IIa assay that has been added to the Heparin Sodium monograph.

Recommendation 2:

Revise the acceptance criteria for the potency of heparin sodium, calculated on the dried basis, from NLT 140 USP units/mg to NLT 180 USP units/mg. USP units become the same as international units and are based on anti-factor IIa activity.

Recommendation 3:

Revise the ratio of anti-factor Xa activity to anti-factor IIa potency calculation to read:

anti-factor Xa activity / anti-factor IIa potency

And revise the acceptance criteria to read 0.9-1.1, previously read 80%-120%.

Recommendation 4:

Move the anti-factor Xa activity assay to the identification section because it is not validated for potency. The assay is used for the calculation of the Xa/IIa ratio which an aspect of Heparin Sodium identification.

Recommendation 5:

Revisions to the reagents section proposal, with the change of antithrombin III to antithrombin are recommended.

Recommendation 6:

Revisions to the NMR section

- ◆ Changing of the word “peak” to “signal” throughout the NMR section
- ◆ Standard solution of heparin sodium in deuterium oxide with 0.02% TSP (w/v)
- ◆ N-acetyl heparin signal to noise ratio in the standard solution is at least 1000/1 in the region near 2ppm.
- ◆ Removal of the water presaturation step
- ◆ Shortening of the spectral window from 14 to -2, to 10 to -2 ppm.
- ◆ Removal of IdoA (signal 3)
- ◆ Addition of the language “[U]sing a 90 degree pulse with a 20 second delay” to the procedure section.
- ◆ Addition of the language “[N]o unidentified signals greater than 4% of the mean height of signals 1 and 2 are present in the following ranges: 0.10-2.00, 2.10-3.20, 5.70-8.00 ppm.”

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Recommendation 7:

Revisions to the SAX method:

- ◆ Deletion of the language “(for heparin sodium of porcine origin)” from section B; the method can also be used for heparins of bovine origin.
- ◆ Change of approximate retention times in the note to read 20 minutes for dermatan sulfate, 30 minutes for heparin sodium, and 50 minutes for oversulfated chondroitin sulfate.
- ◆ Change in the system suitability requirements, resolution section, to read “NLT 1.0 between the dermatan sulfate and the heparin peaks, and NLT 1.5 between the heparin and the oversulfated chondroitin sulfate.” Previously the distance between the heparin and oversulfated chondroitin sulfate peaks was 1.0.

Recommendation 8:

The European Pharmacopoeia monograph assay for Protamine Sulfate will be included in the *USP-NF* Protamine Sulfate monograph.

Recommendation 9:

The Advisory Panel moved to recommend the Heparin Sodium monograph as it was revised, reviewed, and finalized at the meeting, December 17, 2008 to the USP Biologics & Biotechnology: Blood and Blood Products Expert Committee and suggests its publication in *Pharmacopeial Forum* 35(2).