



U.S. Pharmacopeia
The Standard of QualitySM

April 25, 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 for the Revision of the Heparin Sodium Monograph

In response to the global heparin contamination issue, the Heparin Ad hoc Advisory Panel recommends a two stage approach to the revision of the Heparin Sodium and Heparin Calcium monographs. Stage 1 is to consider incorporation of the FDA recommended methods of ¹H 500 MHz NMR (Nuclear Magnetic Resonance; NMR) and Capillary Electrophoresis (CE) into the monograph. Stage 2 is to address longer-term monograph revisions, including the heparin potency assay and alternative impurity tests among others. Stage 2 activities will begin as soon as the immediate, short term revision needs have been addressed.

The Advisory Panel met April 24-25, 2008 at USP headquarters to address both Stages 1 and 2. The attached proposed monograph addresses the inclusion of the NMR and CE methodologies for detection of over-sulfated chondroitin sulfate (OS CS) and dermatan sulfate. It is presented for your consideration and adoption as monograph changes. The Advisory Panel's specific recommendations are that:

Recommendation 1: the two methods recommended by FDA of ¹H 500 MHz NMR (Nuclear Magnetic Resonance) and Capillary Electrophoresis be included in the monograph.

Recommendation 2: a briefing be appended to the monograph that a) reflects a two-stage approach (interim and long-term) and b) also indicates that Identification Tests A, B, and D apply to heparin sodium of all origins and that Identification Test C currently applies only heparin of porcine origin.

Recommendation 3: in the Identification section of the monograph, a 12 mg/ml concentration of Heparin Sodium test solution be used to assure a suitable amount of test solution is available because there is a fixed content in the reference standard material,.

Recommendation 4: a system suitability includes the specification of a ppm value for the N-acetyl signal of heparin, identified through the use of a reference standard solution on a daily basis.

Recommendation 5: the peak shape of the sample on the CE electropherogram is comparable with what is provided in the system suitability reference standard.

Recommendation 6: the limit of Dermatan Sulfate Impurity is 2.0%.

Recommendation 7: a) USP communicate the General Notices statement indicating that "...are prepared from ingredients that meet the requirements of the compendial monographs for those individual ingredients for which monographs are provided" and b) USP explore revising the definition statement of the enoxaparin sodium monograph to reflect that the starting material for enoxaparin sodium must comply with the requirements in the USP Heparin Sodium monograph.

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Recommendation 8: the Heparin Calcium monograph is revised to include the ^1H 500 MHz NMR method (the Capillary Electrophoresis method from the Heparin Sodium monograph is not suitable for Heparin Calcium. Alternative/additional tests will be addressed in Stage 2)

Recommendation 9: the following Stage 2 actions be considered:

1. Revisit identification tests and assure applicability across heparins
2. Address the heparin potency assay
3. Develop assays/tests for heparin purity
4. Revisit the 2.0% limit of dermatan sulfate with the intention of lowering it to 1.0%.
5. For Heparin Calcium, develop a dermatan sulfate limit methodology and a potency assay

Also:

The Advisory Panel will continue its work on the Stage 2 activities via a web meeting in June 2008 (date to be determined), participation in the June 19-20 jointly sponsored EDQM-USP-NIBSC Heparin Workshop in Strasbourg, and in its next face-to-face meeting August 7-8, 2008. The Advisory Panel will continue to invite Dr. Huxsoll to participate in its activities.

Note: This document has had minor editing after its original development by the Advisory Panel.