



U.S. Pharmacopeia
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Heparin Stage 2 Web Meeting #1 March 3, 2009 Frequently Asked Questions

1. When will the revised Heparin monographs become official?
 - ◆ We aim for the monographs to become official on August 1, 2009 after they have been approved by the USP B&B Blood and Blood Products Expert Committee. The final monographs will be published on the USP Web site prior to publication in USP's *Pharmacopeial Forum* (PF).
2. Will USP consider harmonizing some compendial tests with EP?
 - ◆ Dialogue has been, and continues to be, ongoing between EP, JP, and USP regarding harmonization of some compendial tests.
3. Is the validation work that USP has done available to the public?
 - ◆ Generally, USP does not publish validation work, though there are efforts to publish the work in the form of a peer reviewed article. If that occurs the article will be made available.
4. Will USP consider improving the sensitivity of the NMR test (per given experiment time) by shortening the delay time and determining the 'Ernst' angle? This would also require the inclusion of 'dummy' scans, prior to acquisition, in order to reach steady-state.
 - ◆ The USP Heparin Ad hoc Advisory Panel (AP) discussed the parameters in depth and the monograph reflects their decision. The sensitivity in the monograph test is sufficient to meet the requirements of the monograph.
5. If NMR provides a sensitive test for dermatan sulfate (DS) and oversulfated chondroitin sulfate (OSCS), what is the need for the ion exchange method?
 - ◆ The proposed Chromatographic Identity test is an orthogonal method that provides a clear separation of heparin from process impurities and OSCS.
6. Have outside laboratories evaluated these new methods in the Stage 2 proposal?
 - ◆ Industry and members of the AP have helped to evaluate the methods and the specifications.
7. Were the new specifications based on real-world data?
 - ◆ These were all data-driven decisions. The AP reviewed an extensive amount of past and current data from multiple lots of Heparin before deciding on the proposed specifications.
8. What data were generated to ensure the requirements are appropriate for the materials on the market?
 - ◆ We have reviewed batch release data from the Heparin industry and regulators. The AP also generated additional data using commercially available Heparins to test the proposed specifications.
9. How was the ratio specification of 0.9 to 1.1 (anti-factor Xa/anti-factor IIa) set, and is USP concerned that it will cause good samples to fail?
 - ◆ The specification was based on data from many commercial batches that were analyzed. We do not expect that it will cause good samples to fail.
10. Could the heparin signal in the 3.35-4.55 ppm region be over 200% signal height of mean of the signal heights of 1 & 2 (The blue box)?
 - ◆ USP has not seen many samples that have failed to meet this requirement. In the situation wherein a sample contains a large amount of residual solvent from the manufacturing process, there will be large solvent peaks in the region of 4.55 – 3.35 ppm. This will cause the sample to fail.
11. Can USP comment on the specific chromogenic substrates and other reagents to use for the assay?
 - ◆ USP can not recommend a specific substrate; there are many suitable ones on the market. Each laboratory should evaluate the substrate(s) based on the platform of choice.

Headquarters

12601 Twinbrook Parkway
Rockville, Maryland 20852
+1-301-881-0666

Europe/Middle East/Africa

Münchensteinerstrasse 41
CH-4052 Basel, Switzerland
+41 (0)61 316 30 10

USP-India Private Limited

ICICI Knowledge Park
Genome Valley
Labs 7-10, Phase III
Turkapally, Shameerpet
Ranga Reddy District
Hyderabad 500 078, A.P., India
+91-40-2348-0088

USP-China

Building 11
Lane 67 Libing Road
Zhangjiang Hi-Tech Park
Shanghai, 201203, China
+86-21-51370600

USP-Brazil

WTorre Technology Park
Avenida Ceci, 1600
Barverí
São Paulo, Brasil

12. Will USP consider lowering the magnetic field requirement in NMR to accommodate a 400MHz instrument?
 - ◆ The AP has decided, and has also been encouraged by the FDA, to set the magnetic field strength requirement at NLT 500 MHz. It is at the regulator's discretion to consider data from lower-field instruments.
13. Does the revised NMR method allow OSCS as long as it is present at less than 4% of the mean of signal height of 1 and 2?
 - ◆ If there are any signals in the ¹H NMR spectrum consistent with OSCS that cannot be proven not to be OSCS, the sample fails, regardless of the signal height.
14. For the Chromatographic Identity test (IDENTIFICATION B), did USP use an ion chromatography system or a regular HPLC system during validation?
 - ◆ An ion chromatography system was used.
15. Does the 4% limit criterion eliminate the confusion caused by the ¹³C satellite peak at 2.17 ppm in the NMR?
 - ◆ Yes, it does eliminate confusion. Most manufacturers run it with ¹³C decoupled.
16. The proposed Chromatographic Identity test requires determination of the relative standard deviation from three (3) replicates while USP <621> *Chromatography* calls for five (5) replicates.
 - ◆ The monograph requirements always supersede the general chapter requirements. Follow the monograph requirements.
17. What is the correlation between galactosamine (GalN) and dermatan sulfate (DS)? In other words, if GalN is 1%, what would be DS content?
 - ◆ LIMIT OF GALACTOSAMINE IN TOTAL HEXOSAMINE is the test for total galactosamine, not just dermatan sulfate, so a correlation is not intended.
18. Since the comment deadline is May 15, having the various USP standards available at the end of April only provides 2 weeks to try out the methods. Can the comment period be extended to verify the method (as FDA requires)?
 - ◆ There are no plans for the comment period to be extended.
19. Will future USP Reference Standards (RS) be calibrated against the WHO International Standards or against current USP RS?
 - ◆ The proposed USP Heparin Sodium RS, Lot M, will be released by the time the revised monograph becomes official (now planned for August 2009). This material will be calibrated against the current International Standard for Unfractionated Heparin to bring the USP Heparin Unit into harmony with the International Unit (IU). Future lots will be assayed against both the IS and the USP Reference Standard.
20. Has USP shown a true 1:1 ratio between Anti-factor Xa and IIa activities?
 - ◆ Based on data available to USP, the ratio of Anti-factor Xa activity and Anti-factor IIa potency falls within the specifications stated in the monograph.