Heparin Calcium

Change to read:

» Heparin Calcium is the calcium salt of sulfated glycosaminoglycans present as a mixture of heterogeneous molecules of mixed mucopolysaccharide nature varying in molecular weights. It is present in mammalian tissues and is usually obtained from the intestinal mucosa or other suitable tissues of domestic mammals used for food by humans. •The sourcing of heparin material must be specified in compliance with applicable regulatory requirements. The manufacturing process must be validated to demonstrate clearance and inactivation of relevant infectious and adventitious agents (e.g., viruses, TSE agents). See *Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin* ⟨1050⟩ for general guidance on viral safety evaluation.•(RB 18-Jun-2008) It is purified to retain a combination of activities against different fractions of the blood clotting sequence. It is composed of polymers of alternating derivatives of •α-• (RB 18-Jun-2008) D-glucosamine (*N*-sulfated, *O*-sulfated, or *N*-acetylated) and uronic acid (•α-•(RB 18-Jun-2008) L-iduronic acid or •β-• (RB 18-Jun-2008) D-glucuronic acid) joined by glycosidic linkages. The component activities of the mixture are in ratios corresponding to those shown by the USP Heparin Sodium •for Assays• (RB 1-Oct-2009) Reference Standard. Some of these components have the property of prolonging the clotting time of blood. This occurs through the formation of a complex of each component with the plasma proteins antithrombin III and heparin cofactor II to potentiate the inactivation of thrombin. Other coagulation proteases in the clotting sequence, such as activated factor X (factor X_a), are also inhibited. The potency of Heparin Calcium, calculated on the dried basis, is not less than •180• (RB 1-Oct-2009) USP Heparin Units in each mg, and not less than 90.0 percent and not more than 110.0 percent of the potency stated on the label. Heparin Calcium is essentially free from sodium.

•• (RB 1-Oct-2009)

Packaging and storage—Preserve in tight containers, and store at a temperature below 40°, preferably at room temperature.

Labeling—Label it to indicate the tissue and the animal species from which it is derived.

Change to read:

USP Reference standards ⟨11⟩**—***USP Endotoxin RS. USP Heparin Sodium •for Assays• (RB 1-Oct-2009) RS. •USP Heparin Sodium Identification RS.•(RB 18-Jun-2008) •USP Oversulfated Chondroitin Sulfate RS.•* (RB 1-Oct-2009)

Change to read:

Identification—

•A: *^{1}H NMR spectrum* (see *Nuclear Magnetic Resonance* ⟨761⟩)—

Standard solution—Prepare a solution of USP Heparin Sodium Identification RS at not less than 20 mg per mL in deuterium oxide with 0.02% (w/v) deuterated trimethylsilylpropionic (TSP) acid sodium salt.

System suitability solution—Prepare 1% (w/w) USP Oversulfated Chondroitin Sulfate RS in *Standard solution*.

Sample solution—Prepare a solution of Heparin Calcium at not less than 20 mg per mL in deuterium oxide with 0.02% (w/v) deuterated TSP.

Procedure—Using a pulsed (Fourier transform) NMR spectrometer operating at NLT 500 MHz for ^{1}H, acquire a free induction decay (FID) using NLT 16 scans using a 90° pulse and 20 second delay. Record the ^{1}H NMR spectra of the *Standard solution* and *System suitability solution* at 25°. Collect the ^{1}H NMR spectrum with a spectral window of at least 10 to −2 ppm and without spinning. The number of transients should be adjusted until the signal-to-noise ratio of the *N*-acetyl heparin signal in the *Standard solution* is at least 1000/1 in the region near 2 ppm. The *Standard solution* shall be run at least daily when *Sample solutions* are being run. For all samples, the TSP methyl signal should be set to 0.00 ppm. The chemical shift for the *N*-acetyl resonance of heparin and oversulfated chondroitin sulfate in the *System suitability solution* should be observed at 2.05 ± 0.02 and 2.16 ± 0.03 ppm, respectively. Record the ^{1}H NMR spectrum of the *Sample solution* at 25°. The chemical shift for the *N*-acetyl resonance of heparin in the *Sample solution* should be observed at 2.05 ± 0.02 ppm. No features associated with oversulfated chondroitin sulfate are found between 2.12 and 3.00 ppm.

B: It responds to the flame test for *Calcium* ⟨191⟩.•(RB 1-Oct-2009)

Bacterial endotoxins ⟨85⟩**—**It contains not more than 0.03 Endotoxin Unit per USP Heparin Unit.

Sterility ⟨71⟩ (where it is labeled as sterile)—It meets the requirements.

pH ⟨791⟩**:** between 5.0 and 7.5, in a solution (1 in 100).

Loss on drying ⟨731⟩**—**Dry it in vacuum at 60° for 3 hours: it loses not more than 5.0% of its weight.

Residue on ignition ⟨281⟩**:** between 28.0% and 41.0%.

Protein—To 1 mL of a solution (1 in 100) add 5 drops of trichloroacetic acid solution (1 in 5): no precipitate or turbidity forms.

Heavy metals, *Method II* ⟨231⟩**:** 0.003%.

Change to read:

Anti-factor X_a activity—Proceed as directed in the test for *Anti-factor X_a activity* under *Heparin Sodium*, except to use Heparin Calcium instead of Heparin Sodium to prepare the •*Sample solutions.*• (RB 1-Oct-2009) The specified results are obtained.

Nitrogen content, *Method I* ⟨461⟩**:** between 1.3% and 2.5%, calculated on the dried basis, the procedure for *Nitrates and Nitrites Absent* being used.

Change to read:

Assay—Proceed as directed in the *Assay* under *Heparin Sodium,* except to use Heparin Calcium solution to prepare the •*Sample solutions.*•(RB 1-Oct-2009)