- B. Braun's Supplier Recall of Heparin API Prompts Voluntary Recall of Heparin Solutions (3/21/2008)
- American Health Packaging Announces a Recall of Approximately 1,400 Units of Heparin Sodium Vial Products as Part of Broader Baxter Recall (3/20/2008)
- Baxter to Proceed with Recall of Remaining Heparin Sodium Vial Products (2/28/2008)
- Baxter Issues Urgent Nationwide Voluntary Recall of Heparin 1,000 Units/ml 10 and 30ml Multi-Dose Vials (1/25/2008)

Screening Methods (3/6/2008)

Please send all test results to the U.S. FDA.

- Impurity Evaluation of Heparin Sodium by Capillary Electrophoresis
- Impurity Evaluation of Heparin Sodium by ^{1}H-NMR Spectroscopy (updated 4/8/2008)

In early February, after learning about a spike in adverse events involving this product, FDA launched a far ranging investigation in both the United States and abroad. This included inspecting Baxter's domestic facilities, examining Heparin product in the United States and sending a team of experts to China to conduct a comprehensive inspection of the Changzhou SPL facility that makes the active ingredient for this drug.

While the FDA has yet to determine the root cause of these adverse events, we have found a Heparin-like compound that is not Heparin present in some of the Heparin Active Pharmaceutical Ingredient (API) produced by Scientific Protein Labs, which maintains a facility in Wisconsin in addition to the Changzhou plant.

This contaminant is present in significant quantities, accounting for 5 to 20 percent of the total mass of each sample tested. It reacts like Heparin in many tests, which is why the traditional release tests did not detect it.

At this point, we don't know how the Heparin-like compound got into the Heparin Active Pharmaceutical Ingredient, but we are continuing to aggressively investigate the situation.

We don't yet have proof that this contaminant is causing the adverse events. There is an association, but not a direct causal link at this time.

To ensure that all is being done to provide a safe supply of this life-saving drug, we are releasing information on two tests that manufacturers and regulators can use to screen for this contaminant.

The two methods include proton nuclear magnetic resonance (H-1 NMR) and capillary electrophoresis (CE). The tests are to be used for ALL Heparin Sodium API prior to batch release. The API material is considered contaminated if there is a doublet peak at 2.1 ppm in H-1 NMR and a shoulder peak in CE, as illustrated in the two attachments. Heparin sodium API must contain only a single peak (singlet) at 2.1 ppm in NMR and a single peak in CE. It is recommended that both screening methods (H-1 NMR and CE) be used in addition to the regulatory and/or compendial specification requirements.

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Date created: February 11, 2008, updated April 9, 2008

Impurity Evaluation of Heparin Sodium by Capillary Electrophoresis

Instrument:	Hewlett Packard 3D-CE equipped with diode array detector or equivalent
Capillary:	Bare fused silica capillary, internal diameter 50μm 64.5cm-total length, 56cm-effective length
Column temp.:	25°C
Detection wavelength:	200nm (band width 10nm)
Polarity:	Negative
Voltage:	30 kV
Injection:	50 mbar pressure for 10 seconds
Filter:	Cellulose acetate membrane filters (0.22μm)
Separation Time:	15 minutes
Electrolyte:	36mM Phosphate buffer (pH 3.5): Transfer 1.0g of monobasic sodium phosphate, monohydrate to a beaker and add 195mL of Milli-Q water. Adjust pH with phosphoric acid to pH 3.5. Transfer the solution into 200 mL volumetric flask and dilute to the volume with Milli-Q water. Filter the buffer with a membrane filter. It recommended to degas buffer before use.
Test solution:	Prepare a Heparin sample concentration of approximately 10 mg/mL in Milli-Q water. Filter the sample solution. Between each sample run, flush the capillary for 2 min. with filtered Milli-Q water and 2 min. with filtered electrolyte. Introduce the sample onto the capillary by hydrodynamic injection.
Specification:	The electropherogram of test solution does not exhibit a sharp distinguishable peak in front of the main heparin peak. The migration time of heparin in the test solution is about 5.7 min. See attached for examples.

Reference:

1. Private communication, Baxter study number 41010
2. R.P. Patel, C. Narkowica, J.P. Hutchinson, E.F. Hilder, G.A. Jacobson, A simple CE method for the rapid separation and determination of intact low molecular weight and unfractionated heparins, Journal of Pharmaceutical and Biomedial Analysis 46 (2008) 30-35

Figure 1: Electropherogram of a sample with an extra peak ("Fail")

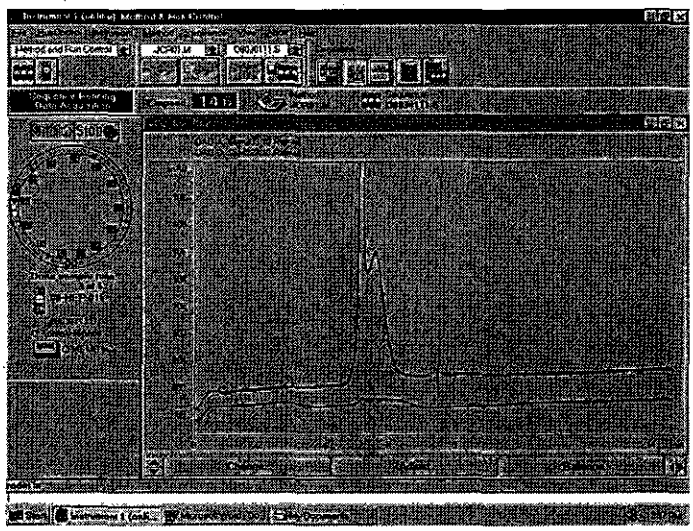
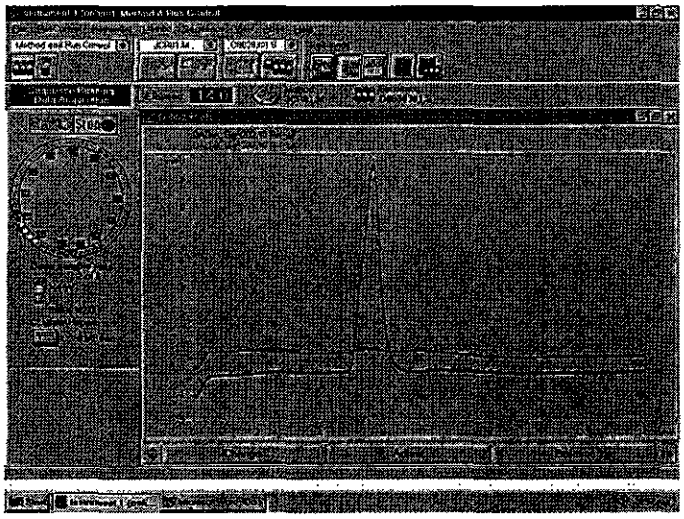


Figure 2: Electropherogram of control sample ("Pass")



Impurity Evaluation of Heparin Sodium by ^{1}H-NMR Spectroscopy

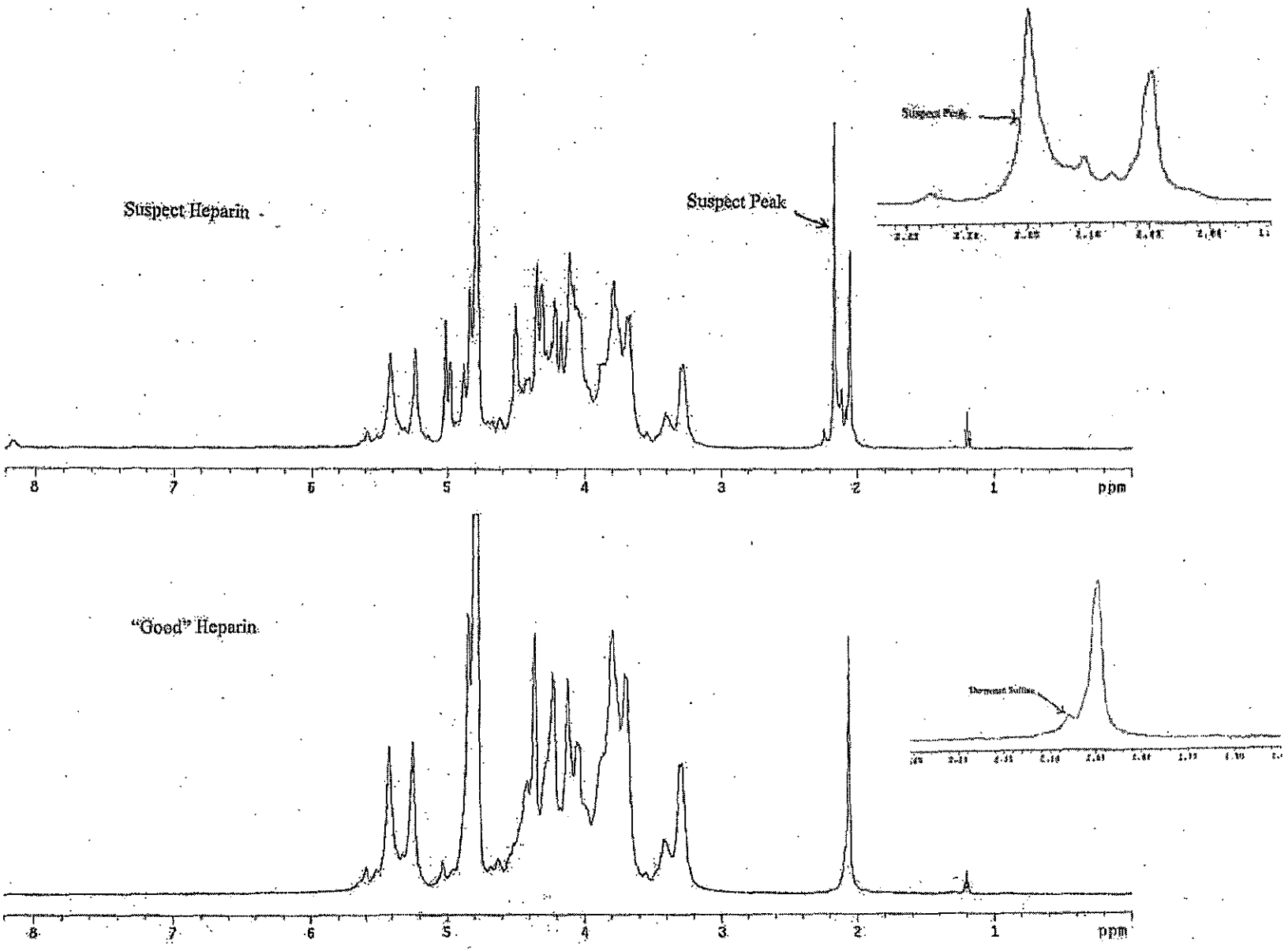
Instrument:
500 MHz NMR, less than 500MHz can be used if appropriately qualified material shows good separation between the N-acetyl protons of over sulfated chondroitin sulfate, dermatan sulfate and heparin sodium

Reagents:
Solvent: D_2O (Deutered water)
Internal reference standard: TSP (tri-methyl-silyl propionate, sodium salt) to be referenced at 0.00 ppm.

Preparation of Test solutions:
Weigh between 10 and 40 mg of heparin sodium into a 5 mm NMR tube and dissolve in 0.6 ml of D_2O spiked with 0.05 to 0.10% by weight TSP. Sample may require several minutes of constant agitation to dissolve.

^{1}H-NMR analysis:
Collect ^{1}H-NMR spectrum on a 500 MHz NMR instrument.
Spectral parameters should include no less than 16 transients, 90 degree pulse width, acquisition time of at least one second, time between transients of 20 seconds and a spectral window of 8000 hz. The number of transients should be adjusted until the signal-to-noise is at least 200/1 in the region near 2 ppm.
The sample should be run at 25 °C.

Criteria:
The N-acetyl protons of heparin should show a single peak at 2.04 ppm (± 0.02ppm). A small dermatan sulfate peak, corresponding to N-acetyl protons of dermatan sulfate, may show near 2.08 ppm. **No peak should be visible at 2.15 ±0.02 ppm.**


Suspect Heparin
Suspect Peak
8
7
6
5
4
3
2
1
ppm
"Good" Heparin
8
7
6
5
4
3
2
1
ppm