平成２０年４月２２日　安全対策調査会
参考資料　１－２

事　務　連　絡
平成２０年３月１０日

各都道府県衛生主管部（局）薬務主管課　御中

厚生労働省医薬食品局
監視指導・麻薬対策課
安　全　対　策　課

ヘパリンナトリウム製剤等の品質の確保の徹底等について

今般、米国ＦＤＡ等により、米国において、昨年１２月以降、米国バクスター社製ヘパリン製剤投与後にアレルギー等の重篤な副作用の発生の増加が認められ、順次、自主回収が進められていること、また、当該事象の原因は調査中であるものの、ヘパリンナトリウム製剤に使用される原薬（以下「ヘパリン原薬」という。）中に、通常ヘパリン原薬に含まれていない不純物としてヘパリン様物質の混入（５～２０％）が確認されたこと等が公表されたところである。

また、ドイツにおいても同様に、ヘパリンナトリウム製剤の投与後にアレルギー等の副作用が多数発生していることが確認され、ヘパリンナトリウム製剤の回収が進められているところである。

このような状況を考慮し、ヘパリンナトリウム製剤、ヘパリンカルシウム製剤、ダルテパリンナトリウム製剤、パルナパリンナトリウム製剤及びレビパリンナトリウム製剤（以下「ヘパリン製剤等」という。）の製造販売業者に対してヘパリン製剤等の品質確保及び安全性に関する情報の収集・提供の徹底のため、下記のとおり適切な措置を採るよう指示しているので、ご承知いただくとともに貴管下関係業者等の適切な指導方ご配慮願います。

記

１．ヘパリン製剤等の品質確保の徹底

ヘパリン製剤等に係る製造販売業者又は製造業者は次に掲げる事項を実施し、製品の品質の確保を図ること。

（１）当該製剤に使用する原薬やその動物由来の原材料について、動物の原産地、組織の入手方法、原材料作製機関名、原薬製造施設等を把握すること。

（２）製剤及び原薬の製造所における製造管理及び品質管理の方法について、原材料の品質管理を含め、その適合状況を確認すること。また、その結果に応じ、必要により適切な措置を講ずること。

（３）当該製剤の原薬及び製剤の製造にあたっては、出荷前に、承認書等で規定される事項の確認に加え、ヘパリン様物質の混入がないことを適切な試験検査によって確認すること。ヘパリン様物質に関する試験検査については、当面、米国ＦＤＡが公表した試験検査方法を参考とすること。万一、当該物質の混入などの異常が認められた場合には、出荷停止・自主回収等の措置をとるとともに、速やかにその旨を監視指導・麻薬対策課へ報告すること。

(参考)

米国ＦＤＡのＨＰ

http://www.fda.gov/cder/drug/infopage/heparin/default.htm

２．安全性に関する情報の収集・提供の徹底

（１）ヘパリン製剤等について、軽微なものも含めたアレルギー等の副作用の平成１９年度における発現状況について、各医療機関の医療関係者より聴き取り調査を行うこと。

（２）ヘパリン製剤等の添付文書の重大な副作用に記載されているショック等の副作用に十分に注意の上使用するよう、あらためて医療関係者に情報提供し、注意喚起の徹底を図ること。

（３）（１）及び（２）の実施状況に関して、以下の事項について本年３月２４日（月）（事務連絡により別途指示のあった製剤については、別途指示のあった日）までに安全対策課あて報告すること。

①平成 19 年度に納入実績のある医療機関数

②情報提供及び調査を実施した医療機関数

③平成 19 年度の出荷本数（平成１９年○月～平成○年○月；集計の期間を記載）

④アレルギー等の副作用の発現状況の内訳

・増加傾向と回答した医療機関数；　　施設

・変化なしと回答した医療機関数；　　施設

・減少傾向と回答した医療機関数；　　施設

以上

Information on Heparin Sodium Injection (Baxter)

Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vial of heparin sodium for injection, and their heparin lock flush solutions.

- Public Health Update: Recall of Heparin Sodium for Injection (2/28/2008)
- FDA-483 on Heparin (2/28/08)
- Public Health Advisory (2/11/2008)
- Question and Answers (2/11/2008)
- FDA News (2/11/2008)
- Baxter to Proceed with Recall of Remaining Heparin Sodium Vial Products (2/28/08)
- Baxter Issues Urgent Nationwide Voluntary Recall of Heparin 1,000 Units/ml 10 and 30m Multi-Dose Vials (1/25/2008)
- Transcripts of FDA Press Conferences on Adverse Events Associated with Baxter Healthcare Corporation's Multiple-Dose Vials of Injectable Heparin (2/28/2008, 2/18/200 and 2/11/2008)

Screening Methods (3/6/2008)

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

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 SPI 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 Pharmaceutica 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 mus 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.

If you test Heparin and detect a contaminant, please contact FDA at: cderrecalls@fda.hhs.gov or call 301-796-3358.

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Date created: February 11, 2008, updated March 6, 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")

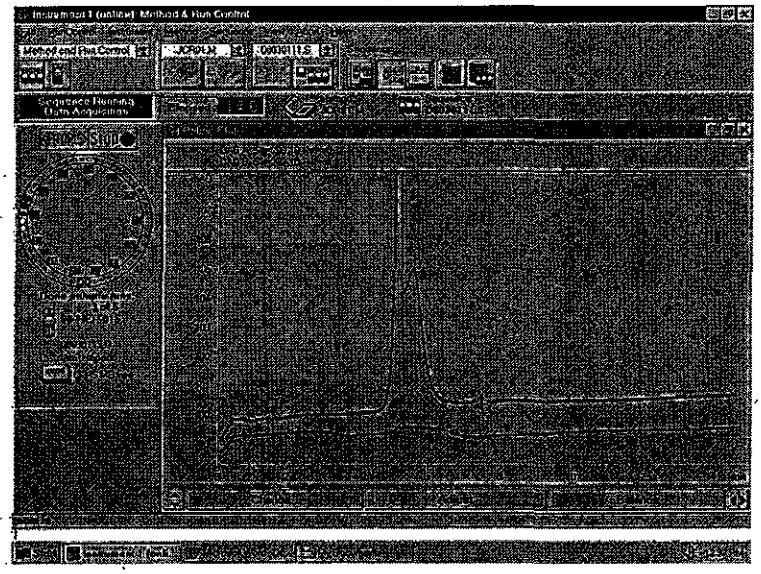
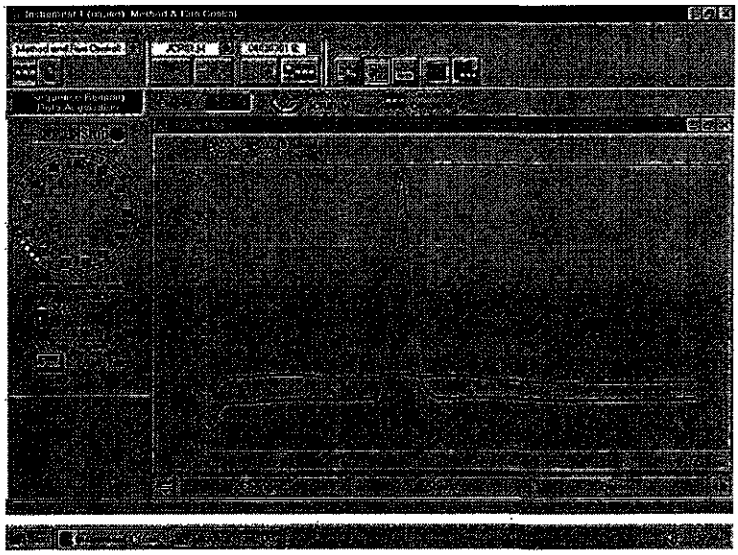


Figure 2: Electropherogram of control sample ("Pass")



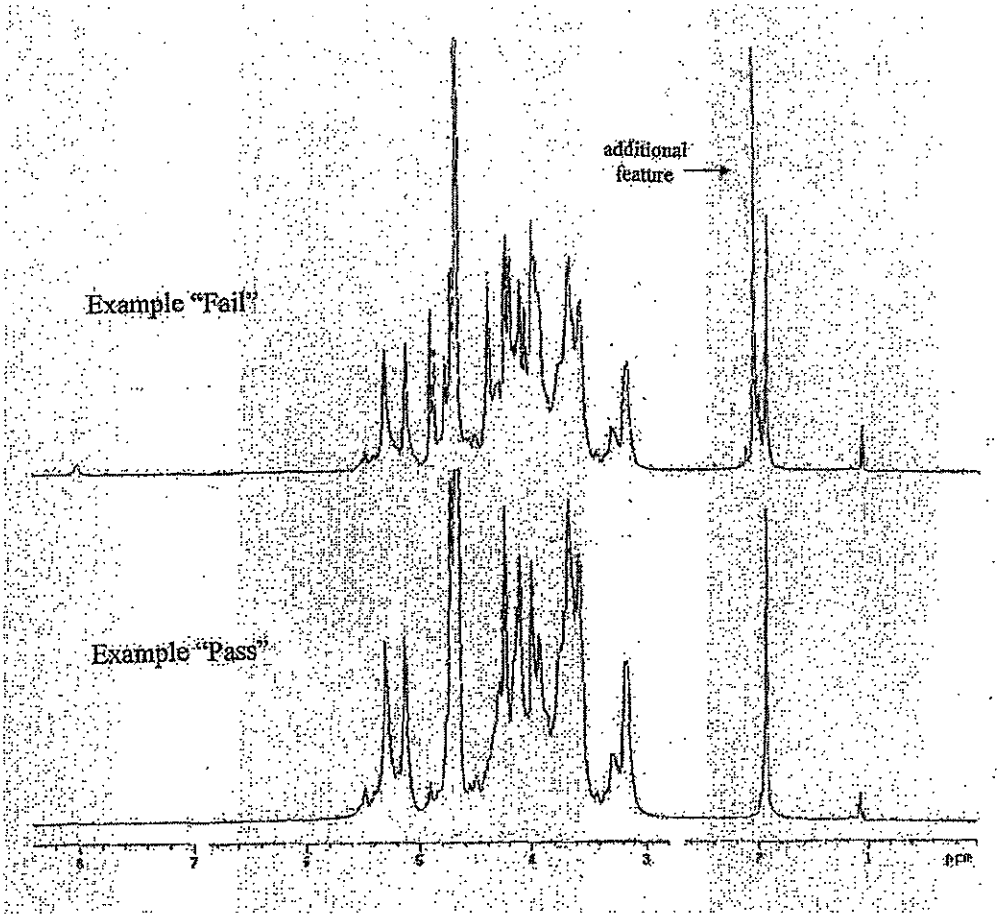
Impurity Evaluation of Heparin Sulfate by ^{1}H-NMR Spectroscopy

Instrument: 500 MHz NMR
Reagent: D_2O

Preparation of Test solutions: Weigh 25 mg of heparin sulfate into a 5 mm NMR tube and dissolve in 0.6 ml of D_2O. Sample may require several minutes 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, approximately 40 degree pulse width, acquisition time of at least one second, time between transients of 4 seconds and a spectral window of 8000 hz.
The sample should be run at 25 °C.

Specification: The region from 1.9 - 2.1 ppm shows the presence of a primary singlet.
There are no secondary features between 1.5 – 3.0 ppm (see example spectra.)



Information on Heparin Sodium Injection

Please report all adverse events associated with heparin to MedWatch

Serious injuries and deaths have been associated with the use of heparin, a blood-thinning drug that contained active pharmaceutical ingredient (API) from China. The adverse events have included allergic or hypersensitivity-type reactions, with symptoms such as low blood pressure, shortness of breath, nausea, vomiting, diarrhea, and abdominal pain.

In February 2008, Baxter Healthcare Corporation recalled multi-dose and single-dose vials of heparin sodium for injection, as well as HEP-LOCK heparin flush products. After launching a far-ranging investigation, FDA scientists identified a previously unknown contaminant in the heparin. The agency is continuing to aggressively investigate the situation.

FDA's Role (3/14/2008)

- Heparin, Adverse Reactions
- Heparin, Analyzing the Contaminant
- Heparin, Import Alert

Adverse Event Reports (4/8/2008)

- Information on Adverse Event Reports and Heparin

Notice to Manufacturers/Initial Distributors of Medical Devices (4/9/2008)

- Important Notice to Manufacturers and Initial Distributors of Medical Devices That May Contain Heparin Or Are Heparin-Coated

Heparin Test Results

Please send all test results to the U.S. FDA at: cderrecalls@cder.fda.gov or call 301-796-3358.

Please provide the following information regarding heparin testing:

1. Name
2. Company
3. Telephone number
4. Email address
5. Lot # of heparin sample
6. Date heparin sample was manufactured
7. Source of Heparin: API, Finish Product, Crude/Bulk, or Other
8. Proton NMR Results (FDA Web Page Method): Two Peaks (Yes/No) – Date performed
9. Capillary Electrophoresis (FDA Web Page Method): Two Peaks (Yes/No) – Date performed
10. Additional Tests performed
11. Comments on results of test data
12. Conclusion: FAIL (Suspect or Atypical) or PASS (Not Suspect or Typical)
13. Heparin Sample associated with increased Adverse Events (Yes/No/Unknown)

Inspectional Observations

- FDA-483 on Heparin (2/28/2008)

News and Press Conferences

- FDA News (2/11/2008)
- Transcripts of FDA Press Conferences on Adverse Events Associated with Baxter Healthcare Corporation's Multiple-Dose Vials of Injectable Heparin

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Public Health Advisories and Updates

- Public Health Update: Recall of Heparin Sodium for Injection (2/28/2008)
- Public Health Advisory (2/11/2008)

Questions and Answers

- Updated Questions and Answers on Heparin Sodium Injection (Baxter) (3/7/2008)
- Question and Answers (2/11/2008)

Recalls

- Covidien Initiates Voluntary Recall of Pre-Filled Syringes Containing Heparin (3/28/2008)

- 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)

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

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PDF requires the free Adobe Acrobat Reader

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.

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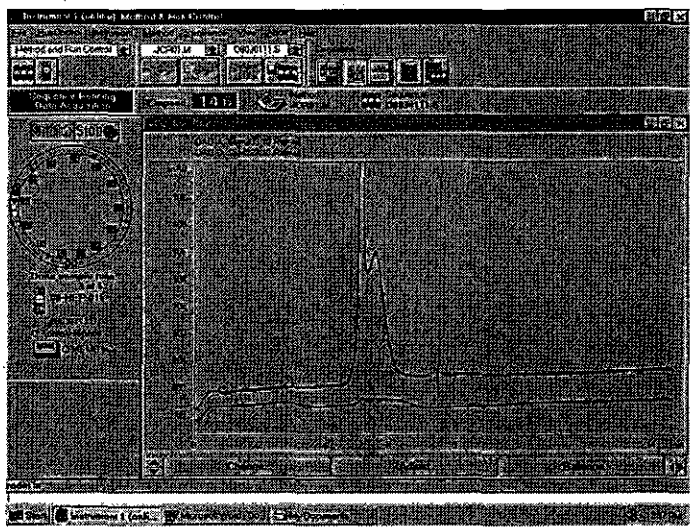
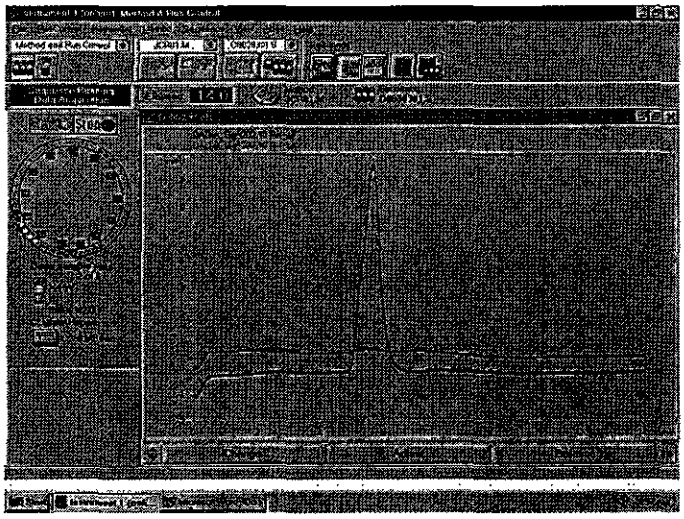


Figure 2: Electropherogram of control sample ("Pass")



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

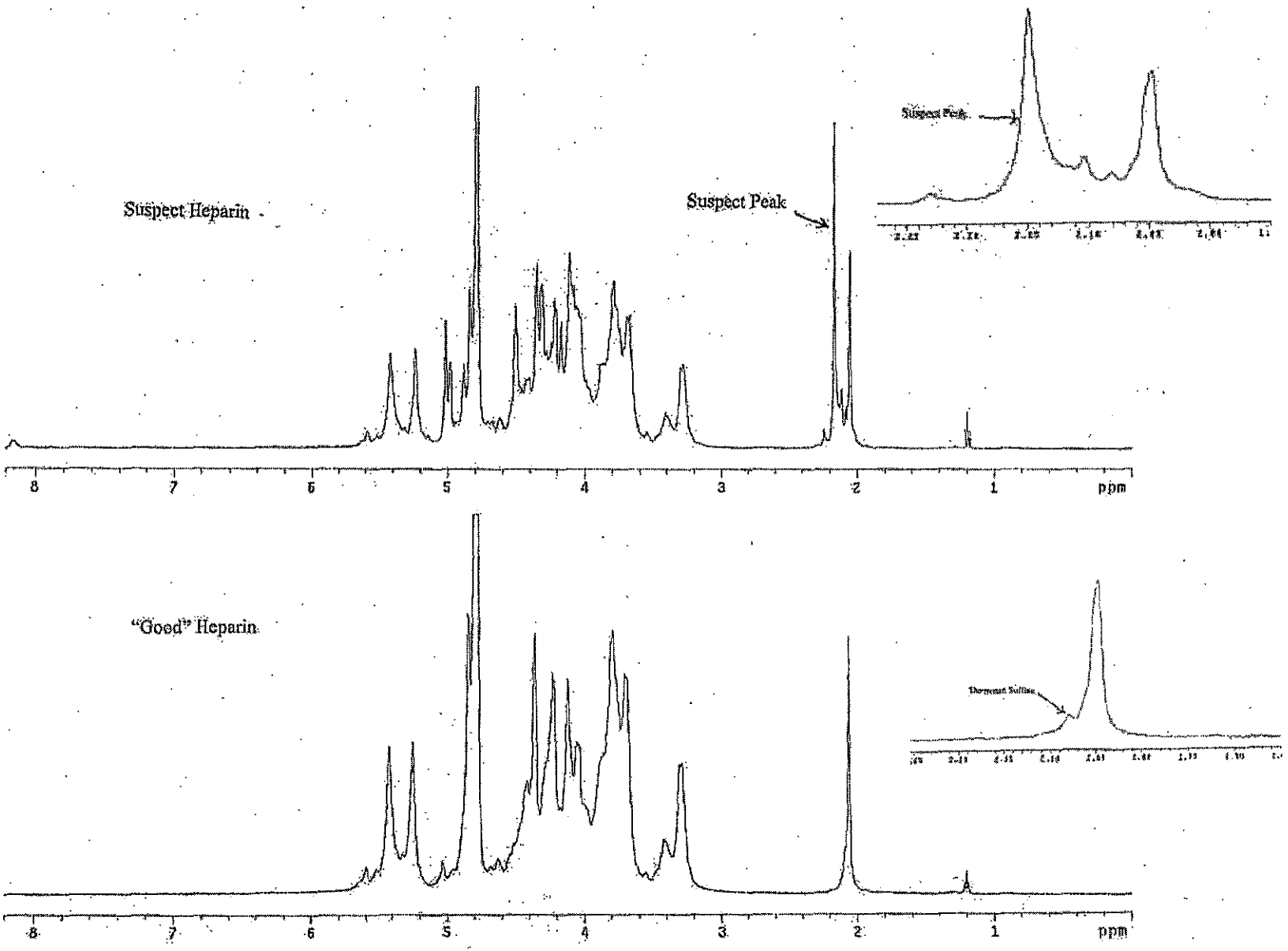
Instrument:
500 MHz NMR, less than 500MHz can be used if appropriately qualified material shows good separation between the N-acetyl protons of over sulfated chondroitin sulfate, dermatan sulfate and heparin sodium

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
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