

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201370Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

Amendment to Cross-Discipline Team Leader  
For Heparin Sodium NDA 201370

<b>Date</b>	June 28, 2011
<b>From</b>	Ali Al-Hakim, Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	201370
<b>Applicant</b>	Pfizer Inc.
<b>Date of Submission</b>	March 08, 2010
<b>PDUFA Goal Date</b>	July 29, 2011
<b>Proprietary Name / Established Name</b>	Heparin Sodium, USP Injection
<b>Dosage forms / Strength</b>	2,000U per 2 mL vial, (1000U/mL, single use vial, preservative free) 5,000U per (b)(4) vial (5000U/mL, multi use vial) 10,000U per 10mL vial (1000U/mL, multi-use vial) 50,000U per 10 mL vial, (5000U/mL multi-use vial) 10,000U per (b)(4) vial (10000U/mL multi-use vial).
<b>Proposed Indication(s)</b>	<ul style="list-style-type: none"> <li>• Prophylaxis and treatment of venous thromboembolism</li> <li>• Atrial fibrillation with embolization</li> <li>• (b)(4) treatment of acute and chronic consumption coagulopathies</li> <li>• Prevention of clotting in arterial and cardiac surgery</li> <li>• Prophylaxis and treatment of peripheral arterial embolism</li> <li>• Anticoagulant use in transfusion and dialysis procedures (b)(4)</li> </ul>
<b>Recommended</b>	Approval

Original Cross-Discipline Team Leader (CDTL) memo for Heparin Sodium NDA 201370 dated March 25, 2011 concluded that this NDA can not be approved from the CMC perspective because of the “WITHHOLD” overall recommendation issued by office of Compliance on March 04, 2011. However, Office of Compliance has updated its recommendation in the Establishment Evaluation System (EES) and issued “ACCEPTABLE” overall recommendation for this NDA on June 27, 2011. Therefore, the NDA is recommended for approval.

Ali Al-Hakim, Ph.D  
Branch Chief, Division III  
Office of New Drug Quality Assessment  
OPS-CDER-FDA

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06/28/2011

## Cross-Discipline Team Leader Review

<b>Date</b>	March 15, 2011
<b>From</b>	Ali Al-Hakim, Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	201370
<b>Applicant</b>	Pfizer Inc.
<b>Date of Submission</b>	March 08, 2010
<b>PDUFA Goal Date</b>	April 09, 2011
<b>Proprietary Name / Established Name</b>	Heparin Sodium, USP Injection
<b>Dosage forms / Strength</b>	2,000U per 2 mL vial, (1000U/mL, single use vial, preservative free) 5,000U per (b)(4) vial (5000U/mL, multi use vial) 10,000U per 10mL vial (1000U/mL, multi-use vial) 50,000U per 10 mL vial, (5000U/mL multi-use vial) 10,000U per (b)(4) vial (10000U/mL multi-use vial).
<b>Proposed Indication(s)</b>	<ul style="list-style-type: none"> <li>• Prophylaxis and treatment of venous thromboembolism</li> <li>• Atrial fibrillation with embolization</li> <li>• (b)(4) treatment of acute and chronic consumption coagulopathies</li> <li>• Prevention of clotting in arterial and cardiac surgery</li> <li>• Prophylaxis and treatment of peripheral arterial embolism</li> <li>• Anticoagulant use in transfusion and dialysis procedures (b)(4)</li> </ul>
<b>Recommended</b>	Complete response

### 1. Introduction

This NDA was submitted as 505b2. The sponsor of the NDA is Pfizer Inc. Pfizer proposes to introduce commercial product utilizing heparin sodium derived from porcine intestinal tissue. The source of the heparin sodium will be the Pfizer facility which is the supplier for several currently marketed heparin drug products in the US (DMF 2712). Pfizer (Pharmacia Hepar) Franklin, Ohio facility will be responsible for the production and quality control of heparin sodium drug substance (DMF 2712) and has been the main supplier of heparin for the commercially-manufactured porcine sourced heparin sodium injection products for NDA 017346 which was approved in 1972. However, Pfizer reported that this NDA was discontinued in May 1992 for commercial reasons. Pfizer has another NDA Heparin Sodium 004570 (Pharmacia & Upjohn, a wholly owned subsidiary of Pfizer). However, this NDA was a bovine based drug product. NDA 004570 is an active NDA, which was first approved in February of 1942. Pfizer has maintained relevant reporting obligations for this NDA, although the product has not been marketed since 2002 because in early 2000, the agency requested that all bovine sourced NDAs, including this one, should be removed from the market due to the BSE safety concerns.

## 2. Background

The proposed drug product, heparin sodium injection USP is a sterile solution for intravenous or subcutaneous administration and will be available in five different strengths as preserved or as preservative free formulations:

- a. 2,000U per 2 mL vial, (1000U/mL, single use vial, preservative free)
- b. 5,000U per (b) (4) vial (5000U/mL, single use vial)
- c. 10,000U per 10mL vial (1000U/mL, multi-use vial)
- d. 50,000U per 10 mL vial, (5000U/mL multi-use vial)
- e. 10,000U per (b) (4) vial (10000U/mL single-use vial).

With the exception of 2000U/2mL vial presentation, all the proposed heparin sodium presentations contain benzyl alcohol as preservative. (b) (4)

The pH of the drug product is approximately 7 to be compatible with physiological solution.

All the above presentations are supplied as single vial pack or as 25 vial packs. The product will be stored at 20-25°C.

## 3. Chemistry, Manufacturing and Control (CMC)

### Drug Substance and Drug Product

The drug substance, heparin sodium is derived from porcine intestinal tissue; it is a sodium salt of sulfated glycosaminoglycans with a molecular weight ranging from 6 to 30KDa. It is a negatively charged molecule. Heparin sodium is composed of polymers of alternating derivatives of  $\alpha$ -D-glucosamine (N-sulfated, O-sulfated, or N-acetylated) and uronic acid ( $\alpha$ - L-iduronic acid or  $\beta$ -D-glucuronic acid) joined by glycosidic linkages. Representation of various heparin units is provided below.

(b) (4)

The CMC information for the drug substance was provided in Pfizer's DMF No. 2712. The Applicant provided adequate reference to their Type I DMF 2712 for information pertaining to the drug substance, Heparin Sodium USP. The DMF contains the necessary information related to manufacturing, characterization, physical and biological properties, manufacture, process controls, analytical methods, specifications, validation, container closure system, reference standard and stability data for heparin sodium USP. The NDA contains specification for accepting the drug substance, which conforms to the current USP heparin sodium acceptance criteria. The specifications include tests for appearance, identity ( $^1\text{H-NMR}$  and chromatographic retention time, Anti-factor Xa to IIa activities, test for sodium), test for inorganic impurities (heavy metals, residue on ignition (b) (4) test for organic impurities (Protein and nucleotidic impurities, residual solvents and Galactosamine in Total Hexosamine), and

potency assay. In addition, specific tests such as pH, loss on drying and bacterial endotoxin are provided as part of the specification.

Heparin sodium injection potency is determined by Anti-Factor IIa assay. (b) (4)

The NDA contains adequate and appropriate descriptions of the manufacture, characterization, controls and quality of the Heparin Sodium which meet the current USP heparin sodium. DMF 2712 was reviewed and found acceptable to support the NDA. The drug substance has (b) (4) months retest period.

The manufacturing process for heparin sodium injection utilizes (b) (4)

The proposed specification conforms to heparin sodium injection USP monograph. (b) (4) all test methods (Potency, Bacterial Endotoxin, Particulate Matter, pH, Sterility, Volume in Container, and Identification) used for testing heparin sodium injection are USP methods.

Sufficient stability data have been provided to support an expiry period of 24 months for the drug product stored at recommended room temperature conditions.

#### 4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. Todd Palmby, reported in his review that no nonclinical study reports were submitted with this NDA, rather an integrated literature review was provided. Published pharmacology studies show inhibition of coagulation factors by heparin *in vitro* and *in vivo*, which impinge on the processes of thrombosis and fibrosis. Heparin can inhibit various coagulation factors, including factor IX, factor X, thrombin and factor XIII.

Reports of toxicology studies conducted with heparin indicate effects consistent with the pharmacologic activity. Studies in mice, rats and rabbits show changes in coagulation factors at doses lower than the recommended clinical dose. In addition, heparin-induced thrombocytopenia has been reported in mice following subcutaneous administration. Thrombocytopenia is also an adverse reaction reported for clinical use of heparin.

Heparin Sodium Injection is available as preservative-free or preserved with benzyl alcohol. There are reports indicating cases of "gasping syndrome" in neonates and low-birth weight neonates that received benzyl alcohol dosages >99 mg/kg/day. This information has been added to the label. Presence of benzyl alcohol may be of potential risk to the fetus; a preservative-free heparin should be used during pregnancy.

Dr. Palmby concluded that the application is recommended for approval.

## 5. Clinical Pharmacology

The reviewer of the clinical pharmacology section of the NDA, Dr. Bahru Habtemariam, reported that the porcine sourced product for this NDA was the same material used under Pfizer NDA 17-346, which was approved based on two bioequivalence type studies where the anticoagulation properties of the porcine sourced product (test) was compared to the bovine sourced product (reference) under Pfizer NDA 4-570 in healthy, state prison, subjects. The studies were conducted in 1971 and the bioequivalence analyses did conform to current standards.

Dr. Habtemariam indicated that ONDQA-Biopharm has been consulted regarding the need for bridging bioequivalence studies in order to approve a porcine sourced product. ONDQA-Biopharm colleague Patrick Marroum stated that bioequivalence studies between the porcine and bovine sourced products are not necessary to approve the porcine sourced product. Therefore, no additional clinical pharmacology analysis were performed for the present 505(b)(2) submission. In the current NDA, the label was reformatted according to the Physician Labeling Rule (PLR). Most of the clinical pharmacology aspects of the label did not change in content and the drug interaction section was updated to include newer drugs that could interact with heparin.

Dr. Habtemariam concluded that the application is acceptable from clinical pharmacology perspective

## 6. Microbiology

The microbiology reviewer, Ms. Denise Miller, reported that the application is recommended for approval from a quality microbiology standpoint for the manufacture and (b) (4) of Heparin Sodium for Injection in various strengths and vial sizes as described in the NDA.

## 7. Clinical/Efficacy

The Clinical reviewer, Dr. Min Lu, reported that this NDA is 505 (b)(2) application and the sponsor relied entirely on the previous findings of efficacy and safety of Heparin Sodium products under NDA 4-570 and NDA 17-346. Upon the Division's request, the sponsor has provided heparin sodium product labeling for NDA 4-570 and NDA 17-346 and also provided an annotated labeling with literature references for the proposed heparin sodium injection for this NDA. No new clinical efficacy or safety data were submitted in this NDA application.

Dr. Lu reported that there were no clinical efficacy data submitted for review. The sponsor relied on the previous Agency's findings of efficacy of Heparin Sodium products under NDA 4-570 (bovine-based heparin sodium product) and NDA 17-346 (porcine-based heparin sodium product) as listed drugs for Heparin Sodium Injection for this NDA.

## 8. Safety

Dr. Lu reported that there were no clinical safety data submitted for review. The sponsor relied on the previous Agency's findings of safety of Heparin Sodium products under NDA 4-570 (bovine-based heparin sodium product) and NDA 17-346 (porcine-based heparin sodium product) as listed drugs for Heparin Sodium Injection for this NDA. The NDA 4-570 is still active and the product has been discontinued from market since 2002 and the NDA 17-246 was withdrawn in 1994.

Safety was not identified as a reason for the product discontinuation for these two NDA heparin products.

The sponsor provided literature references for the overall safety of Heparin Sodium. Heparin sodium has been marketed for more than 70 years and the safety profile of heparin has been well characterized based on the clinical experience. The adverse effects associated with the use of heparin include hemorrhagic complications, immune-mediated heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT), thrombocytopenia, hepatic enzyme elevation, hypersensitivity reactions, osteopenia and alopecia. The sponsor included heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT) under WARNINGS and PRECAUTIONS section of Labeling which is consistent with the Agency's recommendation for other marketed heparin products.

Dr. Kathy Robie Suh, medical team leader, concurred with Dr. Lu's recommendation from a clinical perspective that this application should be approved.

## **8. Postmarket Experience**

The proposed Heparin Sodium Injection under this NDA is not currently marketed in any country.

## **9. Advisory Committee Meeting**

This product was not discussed at an Advisory Committee meeting.

## **10. Pediatrics**

Ms. Jeanine Best, the reviewer from the Pediatric and Maternal Health Staff reported that adequate and well-controlled clinical trials with heparin have never been conducted in pediatric patients. Pediatric dosing recommendations were initially extrapolated from use in adults and have evolved over time with long-term clinical experience in children. PMHS-Pediatric Team noted that the pediatric dosing guidelines provided in this 505(b)(2) heparin sodium injection labeling were outdated and not consistent with current published dosing guidelines. As requested, the Sponsor provided updated pediatric dosing guidelines that are consistent with current clinical practice guidelines. PMHS-Pediatric Team has developed standard pediatric use language warning against the use of benzyl alcohol-containing products in neonates and infants, as the amount of benzyl alcohol that can lead to toxicity in these age groups is unknown. Generally, the benzyl alcohol warning language and/or cross-references should be placed in the Warnings and Precautions section and *Pediatric Use* subsection of labeling. In products such as Heparin Sodium Injection, when there are available benzyl-alcohol free formulations, a contraindication against the use of the benzyl alcohol-containing formulations in neonates and infants should be placed in labeling, rather than a warning against use.

## **11. Other Relevant Regulatory Issues**

### **Manufacturing Facilities**

Initial cGMP recommendation for this NDA dated January 05, 2011 was acceptable. However, the EES was updated on March 14, 2011 with a "Withhold" cGMP recommendation made by the Office of Compliance for the manufacturing facilities as indicated in the Establishment Evaluation System (EES).

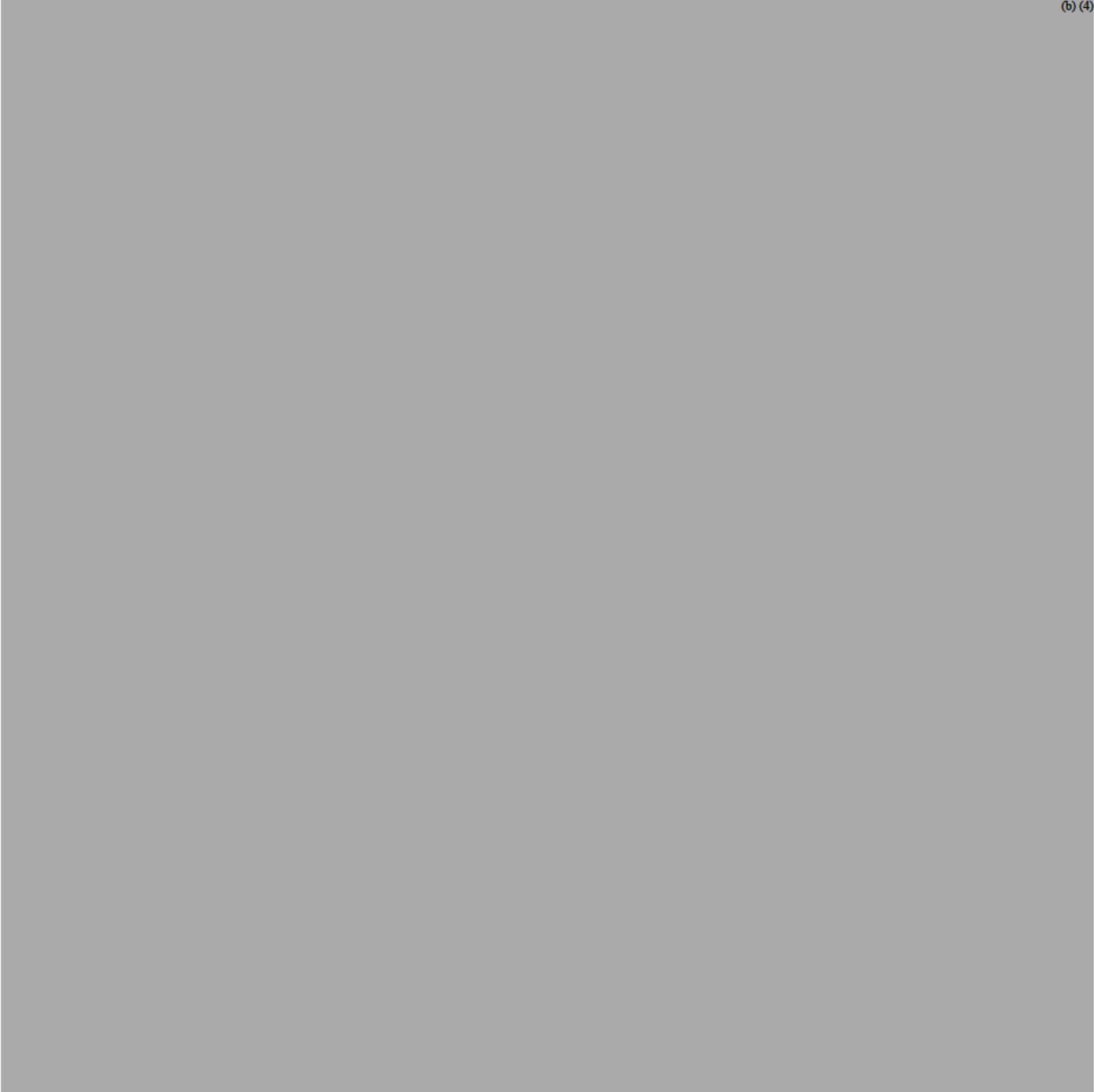
## 12. Labeling

With respect the drug product label, Dr. Iris Masucci, from Office of Medical Policy for the Study of Endpoints and Label Development is currently working with the review division regarding finalization the labeling revisions. The labeling revisions are still ongoing and the final version has not been finalized yet.

Regarding the labeling issues related to the package insert, container labels and carton, the labeling reviewer, Scott Dallas, RPH, from division of Medication Errors and Prevention Analysis, noted that areas where information on the consolidated package insert, container labels and carton labeling could be improved to minimize the potential for medication errors. Comments and recommendations for revisions that aim at reducing the risk of future medication errors were communicated to the applicant. Responses were received from the sponsor and they are currently being evaluated.

**Proposed Vial label for the 1.000 and 5.000 Units are provided below.**

(b) (4)



Cross Discipline Team Leader Review  
NDA 201370

**Overall Conclusion**

The NDA can not be approved from the CMC perspective because of the **"WITHHOLD"** overall recommendation issued by office of Compliance for some of the manufacturing sites. This conclusion supersedes previous reviews recommendations related to EES based on the updated recommendation.

Ali Al-Hakim, Ph.D  
Branch Chief, Division III  
Office of New Drug Quality Assessment  
OPS-CDER-FDA

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ALI H AL HAKIM  
03/25/2011