

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201370Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Ann. T. Farrell, M.D., Acting Division Director
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	201370
<b>Supplement #</b>	
<b>Applicant Name</b>	Pfizer, Inc.
<b>Date of Submission</b>	4/11/11
<b>PDUFA Goal Date</b>	10/11/11
<b>Proprietary Name / Established (USAN) Name</b>	Heparin Sodium
<b>Dosage Forms / Strength</b>	Vials for Injection Preserved with benzyl alcohol: 1,000; 5,000; and 10,000 units/mL Preservative-free 1,000 units/mL
<b>Proposed Indication(s)</b>	Prophylaxis and treatment of venous thromboembolism Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation (b) (4) treatment of acute and chronic consumption coagulopathies Prevention of clotting in arterial and cardiac surgery Prophylaxis and treatment of peripheral arterial embolism Anticoagulant use in transfusion, extracorporeal circulation, and dialysis procedures
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Min Lu, M.D./Kathy Robie-Suh, M.D./Ph.D.
Statistical Review	Kallappa Koti, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Todd Palmby, Ph.D./Haleh Saber, Ph.D.
CMC Review/OBP Review	Muthukumar Ramaswamy, Ph.D./Ali Al-Hakim, Ph.D.
Microbiology Review	Denise A. Miller
Clinical Pharmacology Review	Bahru Habtemariam, Ph.D./Julie Bullock, Ph.D. and Patrick Marroum, Ph.D.
CDTL Reviews	Ali Al-Hakim, Ph.D.
OSE/DMEPA	Scott Dallas, Rh. /Carol Holquist, RPh
Other	Iris Masucci Pharm.D., BCPS (DDMAC), Jeanine Best, MSN, RN, PNP/Hari Sachs, M.D. (PMHS-Peds), Richardae Araojo, Pharm.D./Karen Feibus, M.D. (PMHS-Maternal Health),

# Signatory Authority Review Template

## 1. Introduction

NDA 201743 is a 505 b2 application for heparin sodium derived from porcine mucosa which was originally submitted to the Agency on March 8, 2010. The Agency filed the application and granted a standard review. The Agency sent a Complete Response Letter due to problems uncovered during an inspection. The applicant responded to the CR letter on April 11, 2011.

Heparin sodium was initially approved in 1939.

## 2. Background

Dr. Lu's first cycle review summarizes important background information for this product including the reliance on safety and effectiveness established for NDA 4-570.

From her review she states:

*Heparin sodium under NDA 4-570 (Pharmacia &Upjohn, a wholly owned subsidiary of Pfizer) was first approved in February of 1942. Heparin sodium was derived from bovine lung tissue. The NDA is still active and the product has been discontinued from market since 2002. Heparin Sodium under NDA 4-570 is listed as a discontinued drug product in the Orange Book.*

Her review has the following additional important historical information regarding indications for the current submission.

*Heparin sodium was first approved by the FDA on February 9, 1939, for prevention and treatment of postoperative thrombosis and embolism. A review of heparin sodium (formerly called Sodium Heparin) efficacy was conducted for the FDA by the National Academy of Sciences-National Research Council (NAS/NRC), Drug Efficacy Study Group in accordance with the Drug Efficacy Study Implementation (DESI), which intended to classify all pre-1962 drugs that were already on the market as either effective, ineffective, or needing further study. In 1970, FDA evaluated reports received from the NAS/NRC and concluded that heparin sodium (under NDAs 5-521, 4-570, 5-264, 3-895, and 0-552) is effective for the prophylaxis and treatment of venous thrombosis and its extension; for prophylaxis and treatment of pulmonary embolism; in atrial fibrillation with embolization; for diagnosis and treatment of chronic consumptive coagulopathies (coagulation consumptive coagulopathy); as an anticoagulant in blood transfusions and in blood samples for laboratory purposes; for prevention of clotting in arterial and heart surgery; and for prevention of cerebral thrombosis in the evolving stroke (35 Federal Register [FR], 16608, October 24, 1970).*

*FDA further reviewed and evaluated additional data and amended the original FR to change the effectiveness classification of the 'probably effective' and some 'possibly*

*effective' indications to 'effective' (37 FR, 492, January 12, 1972). These additional indications included: as an adjunct in the treatment of coronary occlusion with acute myocardial infarction; as an adjunct in the prophylaxis and treatment of peripheral arterial embolism; for prevention of recurrent arterial embolism; for arterial occlusion due to embolism; and as an anticoagulant in extracorporeal circulation and dialysis procedure.*

*Heparin sodium under NDA 17-346 (formerly Parke-Davis, a wholly-owned subsidiary of Warner-Lambert and Pfizer) was approved for several strengths of the Steri-Dose\_syringe in May 1973. Heparin sodium was derived from porcine intestinal mucosa. The NDA application was withdrawn in 1994. Heparin Sodium under NDA 17-346 is a discontinued drug product in the Orange Book. No documents are identified that indicate that the reason for the withdrawn was due to safety, efficacy, or false data. The sponsor indicated that Parke-Davis discontinued marketing the product for commercial reasons.*

*NDA 17-346 included data from two clinical studies comparing the anticoagulation activity (determined by coagulation time, prothrombin time, prothrombin consumption time, and recalcified plasma clotting time) of intravenous single doses each of heparin sodium injection, USP (porcine-based) and a marketed heparin product (sodium heparin injection, USP, Upjohn, bovine-based). A total of 50 normal volunteers were involved in these crossover studies. There were no statistically significant differences in whole blood clotting time, recalcified plasma clotting time, 1-stage plasma prothrombin clotting time, and prothrombin consumption between the Parke-Davis and Upjohn drugs. The NDA 17-346 was approved in May 1973. The NDA application was withdrawn in 1994.*

*The Agency's finding of efficacy and safety of heparin sodium for NDA 4-570 and NDA 17-346 is reflected in the product labeling under these two NDA applications. In 1983, FDA provided updated guideline for the professional labeling of Heparin Sodium Injection and set forth the Indications and Dosage and Administration sections for heparin sodium (48 FR, 50167, October 31, 1983). The Indications were set forth as follows:*

- \_Anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension;*
- \_(In a low-dose regimen) for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdominothoracic surgery or who for other reasons are at risk of developing thromboembolic disease;*
- \_Prophylaxis and treatment of pulmonary embolism;*
- \_Atrial fibrillation with embolization;*
- \_Diagnosis and treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation);*
- \_Prevention of clotting in arterial and heart surgery;*
- \_Prophylaxis and treatment of peripheral arterial embolism; and*
- \_As an anticoagulant in blood transfusions, extracorporeal circulation, and dialysis procedures and in*

blood samples for laboratory purposes.

The following indications were not included in the recommended guideline:

(b) (4)

(b) (4)

### 3. CMC/Device

From Dr. Ramaswamy's first cycle review:

*From CMC perspective, the NDA application is recommended for approval. The Office of Compliance has determined that the compliance status of all manufacturing sites associated with this application is acceptable.*

*A 24 month expiration period is recommended for the proposed drug product packaged in (b) (4) glass vials with a (b) (4) stopper and stored at USP controlled room temperature.*

However, just prior to the approval action, the Office of Compliance issued a recommendation to withhold approval based on information from an inspection. The applicant was informed of the results of the inspection. In the April 11, 2011 cover letter the applicant chose to remove the sites failing inspection from the application.

In this submission, the applicant has chosen to remove the sites which failed inspection in the last cycle. The Chemistry, Manufacturing and Controls current CDTL review dated June 2011 states the following:

*Original Cross-Discipline Team Leader (CDTL) memo for Heparin Sodium NDA 201370 dated March 15, 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.*

### 4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies provided in this submission. The pharmacology/toxicology review team reviewed the submission and participated in labeling review. No issues that would preclude approval were identified.

### 5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified. A biowaiver was granted.

## **6. Clinical Microbiology**

No issues that would preclude approval were identified.

## **7. Clinical/Statistical-Efficacy**

No new clinical data was submitted. Drs. Lu and Robie-Suh reviewed the labeling.

## **8. Safety**

The major safety issues associated with Heparin sodium are hemorrhagic complications and heparin-induced thrombocytopenia and thrombosis which have been part of the product labeling for many years. No new safety issues have been identified.

## **9. Advisory Committee Meeting**

This product is not a NME.

## **10. Pediatrics**

This product is a 505 b2. The Pediatric and Maternal Health Staff have participated in all labeling negotiations for their areas of expertise.

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

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

The labeling was reviewed by all disciplines and consultant staff.

## **13. Decision/Action/Risk Benefit Assessment**

- Recommended regulatory action  
Approval
- Risk Benefit Assessment  
This is a 505 b2 application.
- Recommendation for Post marketing Risk Management Activities  
Routine post-marketing surveillance
- Recommendation for other Post marketing Study Requirements/  
Commitments  
None

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/s/  
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ANN T FARRELL  
07/14/2011