CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201370Orig1s000

MEDICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 8, 2011

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader
Division of Hematology Products

Subject: NDA 201370, resubmission April 11, 2011
Heparin Sodium Injection (heparin sodium, USP)
Sponsor: Pfizer, Inc.
235 East 42nd Street
New York, NY 10017-5755

To: NDA 201370

This is the second review cycle for this 505(b)(2) application for a new Heparin Sodium Injection product derived from porcine intestine. The presentations include several containing benzyl alcohol as a preservative and one preservative-free presentation. The first cycle review of the NDA found the application acceptable from a clinical viewpoint. However, manufacturing facilities inspection identified deficiencies that precluded approval and a Complete Response (CR) letter was issued on April 7, 2011. Labeling review was not completed at that time. In the current resubmission the sponsor has responded to the identified deficiencies deleting the two heparin supplier sites where deficiencies were found. The Amended Cross-Discipline Team Leader Review by Dr. Ali Al-Hakim (6/28/2011) comments that Office of Compliance has updated its recommendation in the Establishment Evaluation System and issued "ACCEPTABLE" overall recommendation for this NDA on June 27, 2011 and therefore the NDA is recommended for approval. No new clinical information is included in the resubmission.

Clinical review of the original application and the resubmission was conducted by Dr. Min Lu (reviews finalized 3/9/2011 and 6/23/2011). Clinical review during the current cycle has focused on updating and optimizing presentation of the drug product labeling information in the Physician's Labeling Rule (PLR) format. Consultative reviews during this cycle were provided by the Pediatric and Maternal Health Staff with particular attention to concerns for use of benzyl alcohol preservative-containing formulations in pediatric patients and pregnant or nursing women (Jeanine Best, finalized 6/29/11 and 6/15/11). Final labeling recommendations and wording have been developed through labeling discussions involving all disciplines and final wording in the labeling is being negotiated with the sponsor.

From a clinical viewpoint the application is acceptable for approval with agreed upon labeling.

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/s/

KATHY M ROBIE SUH
07/08/2011

DIVISION OF HEMATOLOGY PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA	201370/SD23
Sponsor:	Pfizer Inc.
Drug name:	Heparin Sodium Injection
Indication:	Prophylaxis and treatment of Venous Thromboembolic Events
Route of administration:	Intravenous Injection
Submission:	Resubmission/Complete Response
Date submitted:	April 11, 2011
Date received:	April 11, 2011
Review completed:	June 23, 2011
Reviewer:	Min Lu, M.D., M.P.H.

The original NDA was submitted as a 505(b) (2) application on March 8, 2010. The Division issued a Complete Response Letter on April 7, 2011 citing deficiencies in the facilities inspections in manufacture of the crude heparin suppliers. There were no clinical deficiencies. Labeling comments were not provided.

The sponsor has submitted a response on April 11, 2011 stating that the sponsor will not use the two heparin suppliers where inspection deficiencies were identified. This will be reviewed by FDA Office of New Drug Quality Assessment and the Office of Compliance. No new clinical information is included in this resubmission.

During this review cycle, Pediatric and Maternal Health Staff recommended to use their standard language for heparin formulations containing benzyl alcohol in the pediatric population under WARNINGS and PRECAUTIONS for all heparin product labeling and indicated that a Contraindication for benzyl alcohol-containing heparin products is not warranted because there may be need for the use of heparin in an emergency situation where a benzyl alcohol free formulation of heparin is unavailable. The recommended language has been discussed during the Division's labeling meetings and agreed upon by the reviewers with some revisions.

The labeling should incorporate the above recommended changes. The application is acceptable for approval from a clinical viewpoint. The approvability of the NDA will be

contingent upon the assessment of the sponsor's response by FDA Office of New Drug Quality Assessment and the Office of Compliance.

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/s/

MIN LU
06/23/2011

KATHY M ROBIE SUH
06/23/2011

Concur. In working to present the label in PLR format, during labeling discussions the review team revised and updated the wording and information included in the label to enhance accuracy, clarity and utility.

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	201370
Applicant Name	Pfizer, Inc.
Date of Submission	March 8, 2010
PDUFA Goal Date	April 9, 2011
Proprietary Name / **Established (USAN) Name**	Heparin Sodium
Dosage Forms / Strength	Vials for Injection Preserved with benzyl alcohol: 1,000; 5,000; and 10,000 units/mL Preservative-free 1,000 units/mL
Proposed Indication(s)	Prophylaxis and treatment of venous thromboembolism Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation [redacted] (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
Action/Recommended Action for NME:	**Complete Response**

Material Reviewed/Consulted 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 Rothman, 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, Pharm.D. Patrick Marroum, Ph.D.
DDMAC	
DSI	N/A
CDTL Review	Ali Al-Hakim, Ph.D.
OSE/DMEPA	Scott Dallas, Rh. / Carol Holquist, R. Ph.

OSE/DDRE	
OSE/DSRCS	
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),

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

NDA 201743 is a 505 b2 application for heparin sodium derived from porcine mucosa which was submitted to the Agency on March 8, 2010. The Agency filed the application and granted a standard review. The review clock was extended due to the submission of additional CMC data.

Heparin sodium was initially approved in 1939. Heparin sodium has approval for the following indications:

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

2. Background

Dr. Lu's 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 inarterial 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 anadjunct 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)

The notice also set forth the entire Dosage and Administration section with guideline on

3. CMC/Device

There were no issues identified that preclude approval.
From Dr. Ramaswamy's 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.*

On March 17, 2011, the Office of Compliance sent an email with the following information:

1. Firm Name and Address:

(b) (4)

Please be advised of the following change to the initial site status as a result of a full review of the Establishment Inspection Report (EIR) and inspectional exhibits. The initial OC decision In January 5, 2011 was based on the findings documented in the FDA-483. At the time the decision was made, the EIR was not available for OC review. Upon receipt and review of the EIR and supportive documentation these documents revealed systemic cGMP deficiencies as follows: deficient investigations of customer complaints, contract laboratories not qualified, lack of sample traceability, (b) (4) *Based on these significant quality issues, OC has changed the facility status to non-acceptable. Because the specific site has been found non-acceptable, OC recommends withhold to the application including this supplier.*

2. Firm Name and Address:

(b) (4)

Please be advised of the following change to the initial site status as a result of a full review of the Establishment Inspection Report (EIR) and inspectional exhibits. The initial OC decision In January 5, 2011 was based on the Field initial classification of NAI. Upon receipt and review of the EIR and supportive documentation these documents revealed systemic cGMP deficiencies as follows: deficient investigations of customer complaints, contract laboratories not qualified, release of crude heparin sodium lots using results provided by the contract laboratory via e-mail, text messaging or phone without reviewing and approving the actual results documentation from the laboratory. Based on these significant quality issues, OC has changed the facility status to non-acceptable. Because the specific site has been found non-acceptable, OC recommends withhold to the application including this supplier.

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.

11. Other Relevant Regulatory Issues

12. Labeling

All disciplines made recommendations for labeling which were incorporated.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Complete Response

- Risk Benefit Assessment

N/A

- Recommendation for Post marketing Risk Management Activities

  None

- Recommendation for other Post marketing Study Requirements/ Commitments

  None

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/s/

ANN T FARRELL
04/07/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 10, 2011

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader
Division of Hematology Products

Subject: NDA 201370, submitted March 8, 2010
Heparin Sodium Injection (heparin sodium, USP)
Sponsor: Pfizer, Inc.
235 East 42nd Street
New York, NY 10017-5755

To: NDA 201370

This is the first review cycle for a 505(b)(2) application for a new Heparin Sodium Injection product derived from porcine intestine. The presentations include several containing benzyl alcohol as a preservative and one preservative-free presentation. The sponsor references its NDA 17-346 for porcine sourced heparin (which was withdrawn apparently for non-safety reasons in 1994) and its NDA 4-570 for bovine-sourced heparin which is still active. The application relies upon the Agency's previous findings of safety and efficacy for heparin sodium. Literature references for the overall safety of heparin were provided. No new clinical trials for efficacy and safety have been conducted.

Clinical:
The primary Clinical Review of the application was conducted by Dr. Min Lu (March 9, 2011). Please see Dr. Lu's review for details of the regulatory history of the approval of heparin sodium products. Heparin sodium injection was first approved by the FDA in 1939. The sponsor's referenced product under NDA 4-570 was approved in 1942. Efficacy of Heparin Sodium Injection USP was established under the Drug Efficacy Study Implementation (DESI) process with a finding of efficacy for several antithrombotic indications published in the Federal Register in 1970. The Indications and Dosage and Administration sections of the Heparin Sodium Injection USP labeling were published along with announcement of availability of an updated guideline for the professional labeling for Heparin Sodium Injection USP in the Federal Register in 1972. The approved indications are:

- 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 clinical review commented that the safety profile of heparin has been well-characterized based on the clinical experience. As indicated in Dr. Lu's review the main safety issues with Heparin Sodium Injection and low molecular weight heparin (LMWH) products are hemorrhagic complications and immune-mediated heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT) associated with the treatment.

Dr. Lu's review concludes that the "Risk benefit analysis is the same as for the listed Heparin Sodium Injection product. Heparin Sodium Injection, derived from porcine intestinal mucosa, is an effective anticoagulation in the indicated patient populations with an acceptable safety profile" and from the clinical perspective recommended approval of the application. I concur with that assessment.

This heparin sodium product is the first to have its label presented in the Physician's Labeling Rule (PLR) format. The clinical review found the sponsor's submitted PLR labeling reflects the approved text from NDA 4-570 with added safety information for heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT), and Fatal Medication Errors subsections under WARNINGS AND PRECAUTIONS. The additions were found to be acceptable and recommendations were made to reword some sections of the labeling for clarity and also to update some sections (including, but not limited to, geriatric, pediatric, and pregnancy subsections) following current guidance. The Pediatric Team of the Pediatric and Maternal Health Staff (PMHS) (Jeannine Best, 10/6/2010) provided comments for the labeling, making recommendations to update the recommended dosing for pediatric patients and to adequately reflect the warnings for benzyl alcohol exposure in neonate infants and ensure proper selection of a benzyl alcohol-free formulation in these populations. The Maternal Health Team of the PMHS (Richardae Araojo, Pharm.D., 10/6/2010) reviewed the label and made recommendations for the Pregnancy and Nursing Mothers sections of the labeling. The recommendations were discussed among the review team and communicated to the sponsor and the labeling was revised accordingly. See Dr. Lu's review for details of the areas for modifications.

Chemistry:
Chemistry, Manufacturing and Controls (CMC) information was reviewed by Ali Al Hakim, Ph.D. (2/14/2011). The application references the information in the sponsor's DMF for Heparin Sodium USP. The CMC review found the information for the drug substance and the manufacturing, specifications and stability to be acceptable and recommended for approval from a CMC perspective.

Other Information:
The Pharmacology/Toxicology review of the application conducted by Todd Palmby, Ph.D. (3/4/2011) commented that no nonclinical studies were submitted to support the application, rather an integrated literature review was provided. The submission was found adequate and approval was recommended for the proposed indications. The review also provided recommendations for relevant sections of the labeling.

The Clinical Pharmacology review was conducted by Bahru Habtemariam, Pharm.D. (3/4/2011). No new clinical pharmacology data were submitted in the application. The Clinical Pharmacology review indicated that the sponsor's porcine-sourced heparin product (NDA 17-346, withdrawn for non-safety reasons) referenced for this application had been approved based on in vivo bioequivalence studies comparing it to active NDA 4-570 bovine-sourced heparin (also referenced for this application). The review commented that ONDQA-Biopharm had determined that bridging bioequivalence studies were not needed to approve the porcine sourced product. The ONDQA-Biopharm comment stated, "No invivo bio studies are needed because the formulation is exactly the same and the active ingredient is considered to be the same eve though it is from 2 different sources. The manufacturing process is identical and it is administered by IV. Therefore the studies that are included are not required and can be considered supportive." No additional clinical pharmacology analyses were performed and the NDA was found acceptable from clinical pharmacology perspective. Recommendations for labeling included reformatting for PLR and updating the drug interactions information.

Conclusions and Recommendations:
I concur with Dr. Lu's primary review recommendation that from a clinical perspective this application for Heparin Sodium Injection USP should be approved. Approved indications should be the same as those for currently marketed Heparin Sodium Injection products. The labeling should be generally the same in content as that for the other approved heparin sodium products, with the format updated to conform to PLR requirements. The labeling for approved heparin products includes information regarding dosing and use of heparin sodium in pediatric patients and warnings regarding benzyl alcohol. The Pregnancy, Nursing Mothers and Pediatric Use sections of the labeling should be revised and updated as recommended by the PMHS.

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/s/

KATHY M ROBIE SUH
03/12/2011

CLINICAL REVIEW

Application Type	NDA 505 (b)(2)
Application Number(s)	201370
Priority or Standard	Standard
Submit Date(s)	March 8, 2010
Received Date(s)	March 9, 2010
PDUFA Goal Date	April 9, 2011
Division/Office	DHP/OODP
Reviewer Name(s)	Min Lu, M.D., M.P.H.
Review Completion Date	March 2, 2010
Established Name	Heparin sodium
(Proposed) Trade Name	Heparin Sodium Injection USP
Therapeutic Class	Anticoagulant
Applicant	Pfizer Inc.
Formulation(s)	Injection • Preserved with benzyl alcohol: 1,000; 5,000; and 10,000 units/mL • Preservative-free 1,000 units/mL
Dosing Regimen	Various dosing regimens for different indications
Indication(s)	• 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
Intended Population(s)	Patients with medical conditions under listed indications

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical perspective, this reviewer recommends approval for this application.

1.2 Risk Benefit Assessment

This is a 505(b)(2) application. Risk benefit analysis is the same as for the listed Heparin Sodium Injection product. Heparin Sodium Injection, derived from porcine intestinal mucosa, is an effective anticoagulation in the indicated patient populations with an acceptable safety profile.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

N/A. This is a 505(b)(2) application.

1.4 Recommendations for Postmarket Requirements and Commitments

N/A. This is a 505(b)(2) application.

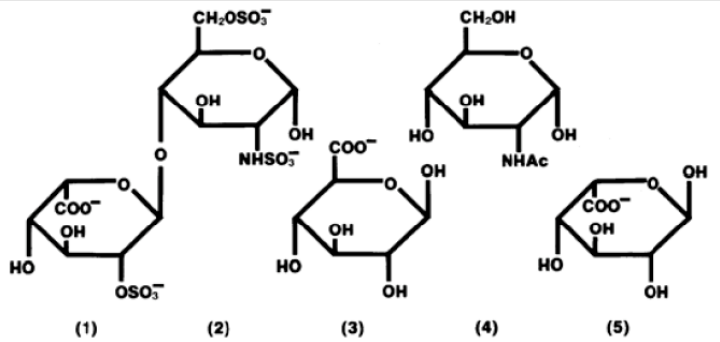
2 Introduction and Regulatory Background

2.1 Product Information

Heparin is a heterogenous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans with anticoagulant properties. Heparin sodium is composed of polymers of alternating derivatives of α-D-glucosamine (N-sulfated, O-sulfated, or N-acetylated) and O-sulfated uronic acid (α-Liduronic acid or β -D-glucuronic acid) joined by glycosidic linkages.

Heparin Sodium Injection is a sterile solution of heparin sodium derived from porcine intestinal mucosa, standardized for anticoagulant activity, in water for injection. It is to be administered by intravenous or deep subcutaneous routes. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

Structure of Heparin Sodium (representative subunits):



The proposed formulations of heparin sodium include several formulations preserved with benzyl alcohol and one preservative-free formulation.

For heparin sodium preserved with benzyl alcohol, the following are the proposed strengths and presentations:

- 1,000 units/mL (vial: 10,000 units in 10 mL)
- 5,000 units/mL (vials: 5,000 units in 1 mL and 50,000 units in 10 mL)
- 10,000 units/mL (vial: 10,000 units in 1 mL).

The strength of preservative-free formulation is 1,000 Units/mL (vial: 2,000 in 2 mL).

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently available treatments that have been approved by FDA for indications similar to those of heparin sodium

Approved Products	Indications
Lovenox (enoxaparin sodium)	Prophylaxis of DVT in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness; Treatment of acute DVT with or without PE; Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction; Treatment of acute ST-segment elevation myocardial infarction [STEMI] managed medically or with subsequent percutaneous coronary intervention
Fragmin (dalteparin sodium)	Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction; Prophylaxis of DVT in abdominal surgery, hip replacement surgery or medical patients with severely restricted mobility during acute illness; Extended treatment of symptomatic venous thromboembolism to reduce the recurrence in patients with cancer.
Arixtra (Fondaparinux sodium)	Prophylaxis of DVT in patients undergoing hip fracture surgery (including extended prophylaxis), hip replacement surgery, knee replacement surgery, or abdominal surgery; Treatment of DVT or acute pulmonary embolism (PE) when administered in conjunction with warfarin.
Coumadin (warfarin sodium)	Prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism; Prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement;

	To reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.
Argatroban	Prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia; As an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).
Innohep (tinzaparin sodium injection)	Treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium
Angiomax (bivalirudin)	As an anticoagulant in patients: With unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA); Undergoing percutaneous coronary intervention (PCI) with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) as in the REPLACE-2 study; With, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), undergoing PCI.
REFLUDAN [lepirudin (rDNA) for injection]	Anticoagulation in patients with heparin-associated thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications.
Iprivask	Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.
PRADAXA (dabigatran etexilate mesylate)	To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

Current heparin sodium injections available in U.S.

Applications	**Strengths**	**Companies**
NDA 17-029	1,000 Units/mL	APP Pharms
	10,000 Units/mL	
	20,000 Units/mL	
NDA 17-037	1,000 Units/mL	Baxter Healthcare
	5,000 Units/mL	
	10,000 Units/mL	
NDA 17-651	5,000 Units/mL	APP Pharms
ANDA 88100	5,000 Units/mL	Hospira
ANDA 90571	1,000 Units/mL	Hospira
	5,000 Units/mL	
	10,000 Units/mL	
ANDA 90808	1,000 Units/mL	Sagent Pharms
	5,000 Units/mL	
	10,000 Units/mL	
ANDA 90809	20,000 Units/mL	Sagent Pharms

2.4 Important Safety Issues with Consideration to Related Drugs

The main safety issues with Heparin Sodium Injection and low molecular weight heparin (LMWH) products are hemorrhagic complications and immune-mediated heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT) associated with the treatment.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On June 15, 2009, Pharmacia & Upjohn Company (Pharmacia)/Pfizer requested a meeting to discuss their proposal to re-introduce Heparin Sodium drug product to the U.S. market under NDA 4-570. On July 23, 2009, the Agency commented in a teleconference that the Sponsor's proposed prior approval supplement was not appropriate because NDA 4-570 was bovine-sourced heparin while the proposed would be porcine-sourced heparin. The Agency recommended that the Sponsor submit either a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) for the porcine-sourced heparin.

On December 2, 2009, a Pre-NDA meeting was held regarding the NDA application (PIND 106887). The Agency agreed that a 505(b)(2) application cross-referencing existing applications for Clinical and Non-Clinical historical data would be appropriate. The Agency also expected (and the sponsor accepted) that Pfizer test all stability, commercial, and validation batches associated with this NDA using new USP reference standard (Heparin Sodium USP Monograph issued on October 01, 2009) so that product quality consistency can be assured. FDA CMC recommended additional stability data would be needed and the application should clearly provide information about all drug product and component manufacturers. This may include heparin API manufacturer(s) and crude heparin manufacturer(s), as well as all manufacturers involved between crude manufacturing and the final API, the drug product manufacturer(s), and testing laboratories. The Agency reminded the Sponsor that all testing sites in the Drug Master File (DMF) should meet current good manufacturing practices (CGMP).

2.6 Other Relevant Background Information

The Pfizer (Pharmacia Hepar) Franklin, Ohio facility is responsible for the production and quality control of heparin sodium drug substance (DMF 2712) and has been the main supplier of heparin for several of the commercially-manufactured heparin sodium injection products.

3 Ethics and Good Clinical Practices

N/A. No clinical trials have been conducted for this NDA application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Chemistry, Manufacturing, and Controls (CMC) Review. On November 12, 2010 the sponsor submitted a major amendment to this application to provide additional stability data requested by FDA CMC reviewer. Manufacturing sites for crude heparin (b) (4) and drug substance and product were requested to be inspected.

4.2 Clinical Microbiology

See Microbiology Review.

4.3 Preclinical Pharmacology/Toxicology

See Pharmacology/Toxicology Review. No new pharmacology/toxicology studies have been conducted for this application.

4.4 Clinical Pharmacology

See also Clinical Pharmacology Review. No new clinical pharmacology studies have been conducted for this application.

5 Sources of Clinical Data

This is a NDA 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.

6 Review of Efficacy

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.

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.

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)

The notice also set forth the entire Dosage and Administration section with guideline on dosage schedules for different indications.

The heparin sodium products in U.S. adopted the recommended Indications and Dosage and Administration sections in their labels after this FR notice from the Agency. Heparin sodium products under NDA 4-570 and NDA 17-346 were also adopted the Agency's guideline for the Indications and Dosage and Administration sections.

7 Review of Safety

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.

The sponsor provided a 120-day safety update that included a review of published literature on heparin exposure during pregnancy and lactation upon the Agency's request. The sponsor included 15 literature publications describing over 700 women who received UFH during pregnancy. FDA Maternal Health Team [CDER Pediatric and Maternal Health Staff (PMHS)] has reviewed this literature and concluded that there did not appear to be increased risks of adverse maternal or fetal effects in those who received heparin and also noted that some of these studies were conducted retrospectively and included small sample sizes (See review by Richardae Araojo, Pharm.D., 9/27/2010).

The proposed Heparin Sodium Injection in the application includes strengths preserved with benzyl alcohol and a preservative-free formulation. For formulations preserved with benzyl alcohol, each mL of the 1000 and 5000 USP Units contains 9.45 mg benzyl alcohol. Benzyl alcohol has been known to cause severe metabolic acidosis, encephalopathy, and respiratory depression with gasping, leading to the death of premature infants. Although the amount of benzyl alcohol at normal therapeutic doses of Heparin Sodium Injection is substantially lower than those reported in association with the "gasping syndrome" (99 to 234 mg/kg, Gershanik J, et al, NEJM 1982; 307:1384-8), premature and low-birthweight infants, and patients who receiving high dosages may be more likely to develop toxicity. FDA Pediatric Team (CDER PMHS) has recommended Heparin Sodium Injection preserved with benzyl alcohol to be contraindicated in neonates, infants, pregnant women, or nursing mothers (See review by Jeanine Best, 9/28/2010).

8 Postmarket Experience

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

(b) (4)

The Periodic Adverse Drug Experience Report for Heparin (heparin sodium) Injection under NDA 004570 covering the reporting period from February 6, 2009 through February 5, 2010 included 37 15-day alert reports and 1 non-15-day alert reports. The 37 reports included 23 initial reports and 14 follow-up reports. There were 29 reported from foreign countries and 8 from U.S. AEs reported during this reporting period in more than 1 case were heparin-induced thrombocytopenia (10 cases), deep vein thrombosis (3 cases), and dyspnea (2 cases). The sponsor indicated that the sources of heparin in these AE reports were not usually available; therefore, AEs in reports may or may not be related to heparin from the sponsor.

9 Appendices

9.1 Literature Review/References

See 9.2 labeling recommendations for related literature review/references.

9.2 Labeling Recommendations

The sponsor has submitted labeling which has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR). The submitted labeling reflects the approved text from NDA 4-570 with added safety information for heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT), and Fatal Medication Errors subsections under WARNINGS AND PRECAUTIONS.

The following are clinical recommendations for the proposed labeling:

- Indications and Usage: rewording to provide clarity for each indication.
- Dosage and Administration: updating the section to reflect current use of heparin in clinical settings.
- Contraindications section: adding HIT/HITTS, known hypersensitivity to pork products to this section. Also, heparin sodium injection preserved with benzyl alcohol should not be used in neonates, infants, pregnant women and nursing mothers.
- Warnings and Precautions section: rewording the heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT) subsection to be consistent with Agency's previous recommendations. This section should be reordered according to importance.
- Adverse Reactions section: rewording to provide clarity in this section.

- Use in Special Population: updating pregnancy, nursing mother, pediatric use and geriatric use sections following current guidance.
- Patient Counseling Information: adding hemorrhage and HIT/HITT information under this section.

In response to the Agency's request for information, the sponsor submitted the following publications to support the current dosing recommendations under Dosage and Administration:

1. Geerts WH, et al, Prevention of Venous Thromboembolism, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), CHEST 2008; 133:381S–453S.
2. Hirsh J, et al, Parenteral Anticoagulants, American College of Chest Physicians-Evidence-Based Clinical Practice Guidelines (8th Edition), CIIEST 2008; 133:141S-159S)
3. Kearon C, et al, Antithrombotic Therapy for Venous Thromboembolic Disease, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), CHEST 2008; 133:454S–545S
4. Deykin D, Indications and Techniques for the Use of Heparin in the Treatment of Thromboembolism, World J Surg 1978; 2:39-43
5. Gravlee GP, et al, Heparin Management Protocol for Cardiopulmonary Bypass Influences Postoperative Heparin Rebound but not Bleeding, Anesthesiology 1992; 393-401
6. Ovrum E, et al, Heparinized cardiopulmonary bypass circuits and low systemic anticoagulation: An analysis of nearly 6000 patients undergoing coronary artery bypass grafting, J Thorac Cardiovasc Surg 2010;1-5

(b) (4)

(b) (4)

The sponsor also added dosing recommendation if specific manufacturer's recommendation was not available under 2.10 Extracorporeal Dialysis. The current heparin labeling doesn't provide a specific dose for patients undergoing extracorporeal dialysis. The proposed dose of 25–30 IU/kg followed by an infusion rate of 1500–2000 IU/h is based on average pharmacodynamic data published in literature (Ouseph R, et al, Anticoagulation for Intermittent Hemodialysis, Seminars in Dialysis 2000; 13: 181-7).

The sponsor added section 2.9 Converting to Dabigatran to provide instruction for patients converting from heparin use to recently approved oral anticoagulant, dabigatran.

The sponsor has also revised section 2.1 Preparation for Administration to provide a list of certain substances incompatible with Heparin in infusion solutions as requested by the Agency with a reference (The AHFS Handbook of Injectable Drugs, 16th edition, 2011).

The sponsor added anti-Xa level monitoring in patients who developed heparin resistance under section 5.6 Heparin Resistance under Warnings and Precautions based on the recommendations from current clinical practice guidelines (Hirsh J, et al. Parenteral Anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008; 133(suppl):141S–159S).

The sponsor has revised the 8.1 Pregnancy, 8.2 Nursing Mothers, and 8.4 Pediatric Use as recommended by FDA Pediatric and Maternal Health Staff following current guidance (See review by Richardae Araojo, Pharm.D. dated 9/27/2010 and Jeanine Best dated 9/28/2010). The sponsor also revised 8.5 Geriatric Use to be consistent with 21CFR 201.57.

The above additions in the labeling are acceptable. The exact wording of the labeling in the PLR format has been reviewed and commented upon by all disciplines during the labeling meetings. The comments have conveyed to the sponsor and the sponsor has revised originally submitted labeling as requested.

9.3 Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIN LU
03/08/2011

KATHY M ROBIE SUH
03/09/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 201370 **Applicant: Pfizer Inc.** **Stamp Date: March 9, 2010**

Drug Name: Heparin Sodium Injection **NDA/BLA Type: NDA 505 (b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			x	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	
11.	Has the applicant submitted a benefit-risk analysis for the product?			x	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(2) Sponsor cited reference drugs: NDA 4-570 Heparin Sodium, and NDA 17-346 Heparin Sodium Clinical evaluation of the application will rely on information in the public domain (i.e., labels for other approved heparin sodium injections, DESI findings of safety and efficacy for heparin sodium, published literature).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to			x	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				
EFFICACY				(See comment for #12).	
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			x	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY				**(See comment for #12)**	
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			x	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			x	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?			x	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			x	

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Min Lu, M.D., M.P.H. 4/19/2010

Reviewing Medical Officer Date

Kathy Robie Suh, M.D., Ph.D. 4/19/2010

Clinical Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201370	ORIG-1	PFIZER INC	HEPARIN SODIUM INJECTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIN LU
04/20/2010

KATHY M ROBIE SUH
04/20/2010