CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201370Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	201370
Supporting document/s:	23
Applicant's letter date:	April 11, 2011
CDER stamp date:	April 11, 2011
Product:	Heparin Sodium Injection
Indication:	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
Applicant:	Pfizer Inc.
Review Division:	Division of Hematology Products
Reviewer:	Todd R. Palmby, PhD
Supervisor/Team Leader:	Haleh Saber, PhD
Division Director:	Ann Farrell, MD
Project Manager:	Marcus Cato, MBA

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Any information or data necessary for approval of NDA 201370 that Pfizer does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 201370.

Reference ID: 2965248

1 Executive Summary

1.1 Introduction

This is a class 2 resubmission of a 505(b)(2) application for Heparin Sodium Injection sourced from porcine intestinal tissue. A complete response (CR) letter was issued for the original NDA submission; deficiencies were not related to any Pharmacology/Toxicology studies. A Pharmacology/Toxicology review was completed for the original submission on March 4, 2011. Refer to that review for non-clinical information relating to Heparin Sodium Injection.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical information was included with this resubmission.

1.3 Recommendations

1.3.1 Approvability

We recommend approval of Heparin Sodium Injection for the proposed indications.

1.3.3 Labeling

The package insert for Heparin Sodium Injection that was revised during the review of the original NDA was modified further with this resubmission. Recommendations were made by the FDA in order to convey consistent safety information for Heparin product labels regarding the presence of benzyl alcohol in some preparations as a preservative. Refer to the review of the current resubmission by the Pediatric and Maternal Health Staff for recommendations regarding the presence of benzyl alcohol.

During the current review cycle, section 8.1 Pregnancy of the package insert was revised to reflect an accurate comparison of the IV heparin dose used in a published animal study and the maximum human daily dose of Heparin Sodium Injection. The maximum human daily dose of Heparin Sodium Injection is 60,000 units/day, which is equivalent to 1,000 units/kg/day for a 60 kg person. In the published animal study, a dose of 10,000 units/kg/day IV heparin administered to pregnant rats and rabbits during the period of organogenesis resulted in increased resorptions in both species. This dose is 10 times greater based on body weight than the maximum human daily dose of 1,000 units/kg/day. Refer to the Pharmacology/Toxicology review of the original NDA submission for a review of this published non-clinical embryo-fetal toxicity study.

The following is the final revised version of section 8.1 of the package insert:

Under **FULL PRESCRIBING INFORMATION**:

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C

Reference ID: 2965248

There are no adequate and well controlled studies on heparin use in pregnant women. In published reports, heparin exposure during pregnancy did not show evidence of an increased risk of adverse maternal or fetal outcomes in humans. Heparin sodium does not cross the placenta, based on human and animal studies. Administration of heparin to pregnant animals at doses higher than the maximum human daily dose based on body weight resulted in increased resorptions. Use heparin sodium during pregnancy only if the potential benefit justifies the potential risk to the fetus.

If available, preservative-free HEPARIN SODIUM INJECTION is recommended when heparin therapy is needed during pregnancy. There are no known adverse outcomes associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration; however, the preservative benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants *[see Use in Specific Populations (8.4].*

In a published study conducted in rats and rabbits, pregnant animals received heparin intravenously during organogenesis at a dose of 10,000 units/kg/day, approximately 10 times the maximum human daily dose based on body weight. The number of early resorptions increased in both species. There was no evidence of teratogenic effects.

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/s/

TODD R PALMBY
06/24/2011

HALEH SABER
06/24/2011

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	201370
Supporting document/s:	1, 7
Applicant's letter date:	March 8, 2010
CDER stamp date:	March 9, 2010
Product:	Heparin Sodium Injection
Indication:	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
Applicant:	Pfizer Inc.
Review Division:	Division of Hematology Products
Reviewer:	Todd R. Palmby, PhD
Supervisor/Team Leader:	Haleh Saber, PhD
Division Director:	Ann Farrell, MD
Project Manager:	Marcus Cato, MBA

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Any information or data necessary for approval of NDA 201370 that Pfizer does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 201370.

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1 Executive Summary

1.1 Introduction

This 505(b)(2) application is submitted for Heparin Sodium Injection sourced from porcine intestinal tissue. The Applicant is relying on the FDA's previous findings of safety and effectiveness for a heparin (porcine) product for which the NDA (17346) has been withdrawn for reasons other than safety. Data included in NDA 17346, and accompanying DMFs, along with another active NDA (4570) for a heparin sourced from bovine lung tissue, are owned by the Applicant of the current NDA. Heparin is a DESI product, and as such has not previously been approved under the current NDA standards for approval. Consequently, there has been little nonclinical toxicology studies of heparin.

1.2 Brief Discussion of Nonclinical Findings

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.

The potential for embryo-fetal toxicity associated with heparin treatment was assessed by a literature review. Heparin does not appear to cross the placenta in animal models or in humans, thus it is of reduced concern that heparin can result in direct effects on embryo-fetal development. However, a published report of an embryofetal development toxicity study conducted in rats and rabbits with high molecular weight heparin concluded that heparin could, perhaps indirectly, affect embryo-fetal development. In this study, increased early resorptions occurred in rats and rabbits that received 10,000 units/kg/day intravenous heparin during organogenesis. This dose is approximately 1/6 the maximum human daily dose. There was no evidence of teratogenic effects.

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 (see section 8.4 Pediatric Use). Presence of benzyl alcohol may be of potential risk to the fetus; a preservative-free heparin should be used during pregnancy (see section 8.1 Pregnancy).

The 1000, 5000 and 10000 units per mL preparations of Heparin Sodium Injection preserved with benzyl alcohol contain 9.45 mg benzyl alcohol per mL. The maximum volume of Heparin Sodium Injection that is indicated for human use is 60

mg/day (i.e., 60,000 units/day dose with the 1,000 units/mL formulation). This dose and formulation will deliver 567 mg/day of benzyl alcohol.

1.3 Recommendations

1.3.1 Approvability

We recommend approval of Heparin Sodium Injection for the proposed indications.

1.3.3 Labeling

The following sections of the package insert for Heparin Sodium Injection were modified from the original version with input from the Pharmacology/Toxicology team and represent the FDA recommendations:

(b) (4)

2 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

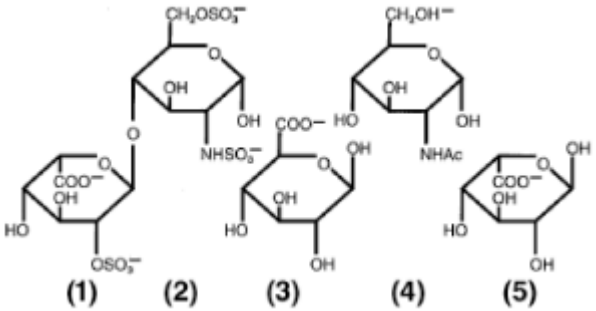
(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number
9041-08-1
Generic Name
Heparin Sodium
Code Name
PNU-1394, CI-767
Molecular Weight
Typically between 6 and 30 kDa
Structure or Biochemical Description

Figure 1: Heparin Sodium Subunits



representative subunits

Heparin sodium is a glycosaminoclycan with anticoagulant properties, and is a heterogeneous mixture of variably sulfated polysaccharide chains composed of repeating units of d-glucosamine and either l-iduronic or d-glucuronic acids. Heparin sodium is synthesized in mast cells of animal tissue, particularly in the liver, lung or gut. Heparin sodium that is the subject of this application is isolated from porcine intestinal tissue.

Pharmacologic Class
anticoagulant

2.2 Relevant INDs, NDAs, and DMFs

NDA 17346, NDA 4570, DMF 2712, (b) (4)

2.3 Drug Formulation

Table 1: Heparin Sodium Formulations

Name of Ingredient	Function	1,000 units Heparin sodium	1,000 units Heparin sodium, preservative free	5,000 units Heparin sodium	5,000 units Heparin sodium	10,000 units Heparin sodium
Fill Volume (mL)		10	2	1	10	1
Heparin Sodium (porcine intestinal tissue)	Active	1,000 units	1,000 units	5,000 units	5,000 units	10,000 units
Sodium Chloride		(b) (4)				
Benzyl Alcohol	Preservative	94.5 mg	-	9.45 mg	94.5 mg	9.45 mg

Formulations also contain water for injection (vehicle), and sodium hydroxide or hydrochloric acid (pH adjustment).

2.5 Comments on Impurities/Degradants of Concern

Degrandants:

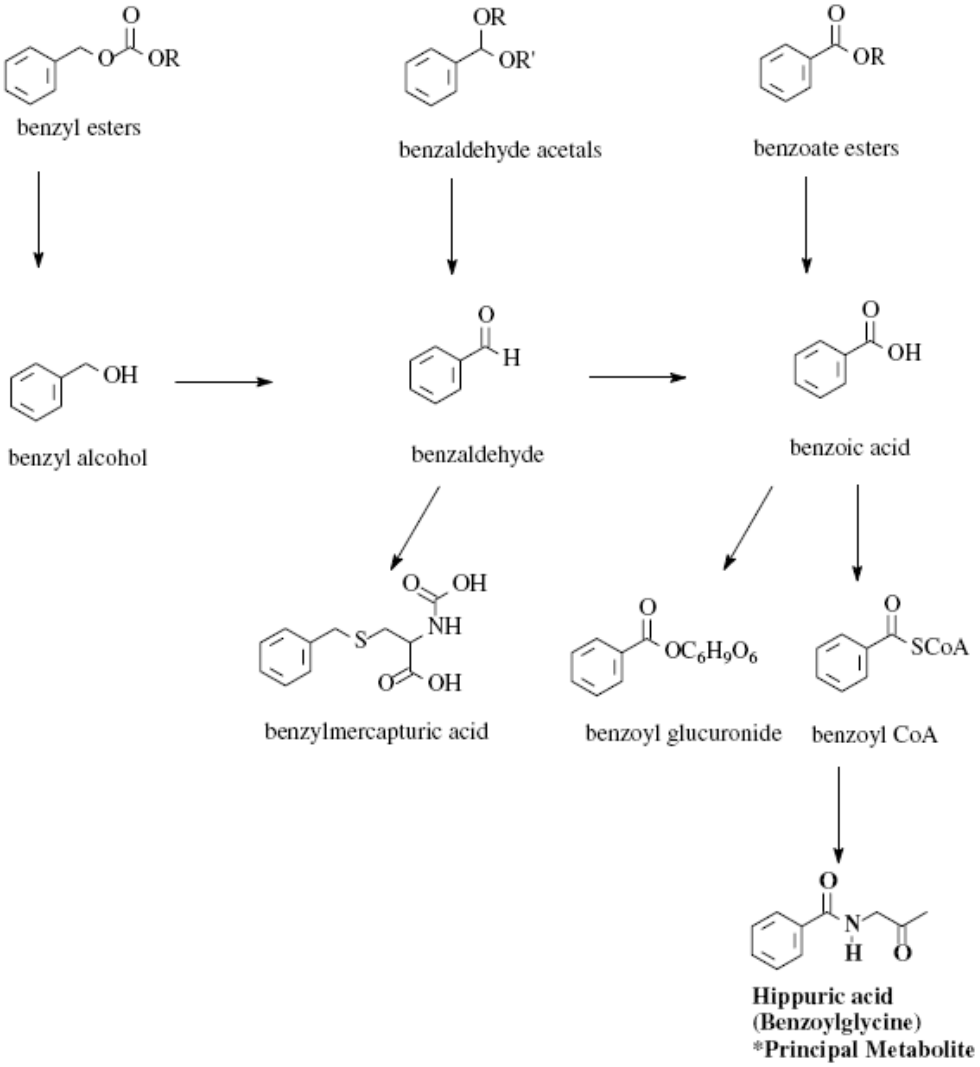
Benzyl alcohol is added to some formulations of Heparin Sodium Injection as a preservative. The Applicant proposes to control the levels of (b) (4) (b) (4) impurities in the benzyl alcohol only, not in the drug product. (b) (4) (b) (4) is a degradation product of benzyl alcohol as well as a metabolite (b) (4) of benzyl alcohol in many species including humans. The Applicant assessed the safety of (b) (4) (b) (4)

(b) (4)

Therefore, the previous exposure of subjects to (b) (4) by direct consumption or through metabolism of benzyl alcohol provides sufficient safety for the worst case scenario of (b) (4) as a degradant in the Heparin Sodium Injection drug product. The (b) (4) content in the Heparin Sodium Injection drug product up to a level of (b) (4) is acceptable from a Pharmacology/Toxicology perspective.

(b) (4)

Figure 2: Metabolism of benzyl derivatives



(Figure excerpted from Applicant's package)

Leachables:

There were four leachables detected in Heparin Sodium Injection. The total daily intake (TDI) of these leachables were reported by the Applicant based on their presence in lot 9AP09 [redacted] (b) (4) following 9 months of storage stability testing at 25°C/60%RH (**Error! Reference source not found.**) and the maximum volume of administration.

Table 2: Maximum levels of leachables in Heparin Sodium Injection (b) (4)

(b) (4)

(b) (4)

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Heparin Sodium injection is indicated for:

- 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

Recommended Adult Dosages:

Therapeutic Anticoagulant Effect with Full-Dose Heparin†

Deep	Initial Dose	333 units/kg subcutaneously

(b) (4)

Subcutaneous (Intrafat) Injection *Use a different site for each injection*	Every 12 hours	250 units/kg subcutaneously
Intermittent IV Injection	Initial Dose	10,000 units
	Every 4 to 6 hours	5,000 to 10,000 units
Continuous IV Infusion	Initial Dose	5,000 units
	Continuous	20,000 to 40,000 units/24 hours
† Based on 150 lb. (68 kg) patient. Adjust dose based on laboratory monitoring.		

• Cardiovascular Surgery

Intravascular via Total Body Perfusion	Initial Dose	≥150 units/kg; adjust for longer procedures

• Low-dose Prophylaxis of Postoperative Thromboembolism

Deep Subcutaneous (Intrafat) Injection	Initial Dose	5,000 units 2 hours before surgery
	Every 8 to 12 hours	5,000 units

• Extracorporeal dialysis

Intravascular via Extracorporeal Dialysis	25 to 30 units/kg followed by infusion rate of 1,500 to 2,000 units/hour if manufacturers' recommendations are not available

2.7 Regulatory Background

The Applicant states in the submission that it wishes to re-enter the market with a porcine-derived Heparin Sodium Injection drug product in the United States as a result of recent market and supply chain issues with certain manufacturers. Pfizer (Pharmacia Hepar) has a Franklin, Ohio facility that is responsible for the production of heparin drug substance (DMF 2712) and has been a supplier of heparin for multiple heparin products approved in the US. NDA 17346, held by Pfizer (formerly Parke-Davis, a wholly-owned subsidiary of Warner-Lambert and Pfizer), was for a porcine-based drug product, which was originally filed in 1972 and subsequently approved for several strengths of the Steri-Dose™ syringe in 1973. Parke-Davis discontinued marketing this product for commercial reasons. In May, 1992, NDA 17346 was withdrawn for reasons that did not involve the safety of the product. NDA 4570, held by Pfizer (Pharmacia & Upjohn, a wholly owned subsidiary of Pfizer) was for a bovine-based drug product, which is an active NDA first approved in 1942 with maintained relevant reporting obligations. Heparin under NDA 4570 has not been marketed since 2002. The current application is for heparin derived from porcine intestinal tissue produced at the Franklin, Ohio Pfizer facility.

On July 23, 2009, the Applicant met with FDA regarding the regulatory pathway for the Pfizer porcine-derived heparin sodium drug product. On December 2, 2009, a pre-NDA meeting was held between the Applicant and FDA.

The Applicant decided to submit a 505(b)(2) application for porcine-derived heparin sodium in which it cross-references two NDAs, NDA 4570 (bovine) and NDA 17346 (porcine). The information in both of these cross-referenced NDAs is currently owned by subsidiaries of the Applicant.

3 Studies Submitted

No nonclinical studies were submitted.

4 Pharmacology

No pharmacology studies were submitted.

The blood coagulation system involves multiple coagulation pathways which include many factors that are important *in vivo*. The activated protease, factor X, converts prothrombin into thrombin, and thereby initiates thrombosis. Once activated, thrombin itself can convert fibrinogen into activated fibrin monomers, forming a gel, which is the endpoint of *in vitro* coagulation assays. The fibrin monomers are initially bound to each other noncovalently, but subsequent activation of factor XIII catalyzes a transglutamination reaction that cross-links adjacent fibrin monomers to enhance the strength of the clot.

Heparin is a glycosaminoglycan that is produced by mast cells and stored in secretory granules. Heparin catalyzes the antithrombin inhibition of multiple coagulation proteases. Antithrombin is synthesized in the liver and is present in human plasma at approximately 2.6 μM. Antithrombin inhibits activated coagulation factors, including thrombin, factor X and factor IX, but has little activity against factor VII. Antithrombin inhibits these proteases via a specific Arg-Ser peptide on the reactive site of antithrombin and becomes trapped as a stable 1:1 complex. When heparin plasma concentration is 0.1 to 1 units/mL, antithrombin rapidly inhibits thrombin, factor IX and factor X (half lives < 0.1 second). Both thrombin and antithrombin bind to heparin, which increases the rate of this interaction and inhibition by 1,000 fold. Heparin is released once thrombin is bound to antithrombin. Heparin can therefore inhibit thrombosis through inhibiting the conversion of prothrombin to thrombin by factor X. Further inhibition of coagulation by heparin is achieved by inhibiting active thrombin and reducing the conversion of fibrinogen to fibrin. Moreover, heparin can inhibit the stabilization of fibrin clots by inhibiting fibrin cross-linking by factor XIII [11].

5 Pharmacokinetics/ADME/Toxicokinetics

No studies were submitted.

[11] Goodman and Gilman's The Pharmacological Basis of Therapeutics. In: Brunton LL, editor. 11th ed. New York: McGraw-Hill; 2006: p. 1470-4.

6 General Toxicology

No studies were submitted.

Published reports of toxicology studies conducted with heparin demonstrate that the majority of findings are consistent with the pharmacological activity. In single dose rat models of thrombosis, the lowest intravenous dose of heparin that induced changes in clotting factors was 2.3 units/kg[12]. In a separate study, hemorrhagic changes occurred at single doses of 12 units/kg intravenous injection in rabbits, while changes in clotting factors and thrombocytopenia were reported at single doses of 35 to 250 units/kg intravenous injection[13]. Heparin administered via a single subcutaneous injection of 3000 units/kg heparin was associated with changes in liver and clotting factors in the rat[14]. A dose of 200 units/kg/day heparin for 3 days in mice resulted in changes in clotting factors[15]

7 Genetic Toxicology

No studies were submitted.

8 Carcinogenicity

No studies were submitted.

9 Reproductive and Developmental Toxicology

No studies were submitted.

Publications were referenced by the Applicant that included information about the potential for heparin to cause embryo-fetal toxicity. It appears unlikely that heparin can cause direct effects on embryo-fetal development due to multiple studies demonstrating a lack of placental transfer. There are multiple published reports of clinical and nonclinical studies regarding the ability of heparin to cross the placenta during pregnancy.

One study was conducted in 6 pregnant guinea pigs administered heparin into the vena cava. Prior to administration, a midline abdominal incision was made and the uterus was opened and individual fetuses surrounded by amniotic sacs were floated in saline solution. Four to 6 fetuses were present in each pregnant female; blood samples were obtained once per fetus at varying intervals before and after heparin administration to the mother. The thrombin times were measured before and 5, 10, 15 and >15 minutes following heparin administration. The thrombin times in the fetuses were unaffected by administration of heparin up to the last time-point examined. A subsequent human study measured whole blood clotting time, thrombin time, plasma recalcification time and the plasma prothrombin time in mothers and infants in control or

[12] Lorrain, J., et al. (2002) *J Pharm Exp Ther*; **304**: 567-574.
[13] Drozd, N.N., et al. (1996) *Exp Clin Pharmacol*; **59**: 30-33.
[14] Copple, B.L., et al. (2002) *Toxicol Appl Pharmacol*; **180**: 186-196.
[15] Takahashi, H., et al. (2005) *Brit J Pharmacol*; **146**: 333-343.

experimental groups. Values from infants of the experimental groups did not differ significantly from the control group[16].

In a study conducted in sheep, the placental transport of low molecular weight heparin (CY222) in comparison to standard heparin was examined. Standard and low molecular weight heparin were labeled with ^{125}I, and administered to pregnant sheep at gestational day 108-119. One to three days after administration of an intravenous bolus injection of 5000 anti-factor X units of ^{125}I-labeled standard heparin or low molecular weight heparin, nine serial blood samples were collected over 4 hours from the mother and fetus. Radioactivity, anti-factor X activity and activated partial thromboplastin times (APTT) were measured. At therapeutic levels of standard and low molecular weight heparins in the mother, there was no detectable radioactivity or anticoagulant effects in the fetus[17].

Multiple clinical studies have demonstrated that heparin does not cross the placenta in humans. In a study in 21 women administered heparin between the 15th and 23rd week of pregnancy, there was no evidence for the passage of heparin or low molecular weight heparin across the placental barrier[18]. Two studies also concluded that two different low molecular weight heparins, LHN-1 and CY 216, do not cross the placental during the second or third trimester of pregnancy, respectively[19,20].

One study conducted in sheep assessed whether the low molecular weight heparin, Pharmuka-10169, could alter the fetal coagulation system. The Pharmuka-10169 was ^{125}I-labeled and injected into pregnant sheep. Labeled Pharmuka-10169 was found not to cross the placenta, but it did affect fetal coagulation. In vitro, Pharmuka-10169 catalyzed the inhibition of thrombin but not factor X by sheep plasma and was not neutralizable by protamine sulphate. These effects were attributed to the enhanced neutralization of thrombin by heparin cofactor II. Therefore, it was concluded that Pharmuka-10169 does not cross the placenta, but did induce the release of an endogenous dermatan sulphate-like substance which altered fetal coagulation[21].

In a toxicity study heparin was added to culture media of post-implantation rat embryos undergoing organogenesis *in vitro*. Heparin caused defective folding and closure of neural folds in the embryos between gestation days 9.5 and 10.5[22]. This finding is of little significance due to the lack of placental transfer of heparin in humans.

In an embryo-fetal toxicity study, high molecular weight heparin was administered intravenously at 1,000, 3,000 or 10,000 units/kg/day to pregnant rats from gestational day 7-14, and to pregnant rabbits from gestational day 7-16. There were no observed effects in either species at 1,000 or 3,000 units/kg/day. Rats receiving 10,000 units/kg had 33 early resorptions out of 151 implantations as compared to the control group that had 12 early resorptions out of 169 implantations. Four dams in the 10,000 units/kg group accounted for 80% of the early resorptions. Rabbits treated with 10,000 units/kg

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[16] Flessa, H.C., et al. (1965) *Am J Obst Gynec*; **93**(4): 570-573.
[17] Andrew, M., et al. (1985) *Brit J Haematol*; **59**: 103-108.
[18] Mätzsch, T., et al. (1991) *Bloo Coag Fibrin*; **2**: 273-278.
[19] Omri, A., et al. (1989) *Thrombosis and Haemostasis*; **61**: 55-56.
[20] Forestier, F., et al. (1987) *Thrombosis and Haemostasis*; **57**: 234.
[21] Andrew, M., et al. (1986) *Thrombosis and Haemostasis*; **55**: 342-346.
[22] Kesby, G.J. (2000) *Toxicol and Applied Pharmacol*; **163**: 60-66.

had 81 early resorptions out of 191 implantations compared to 6 early resorptions out of 69 implantations in control animals. There were no malformations observed that would suggest the potential for teratogenicity. However, signs of slight developmental delays were noted in the 10,000 units/kg group[23].

The presence of benzyl alcohol as a preservative in some of the preparations of Heparin Sodium Injection poses a potential risk to the fetus. The benzyl alcohol-containing formulation is contraindicated in pregnant women. The preservative free formulation is considered Category C and may be administered to pregnant women if the potential benefit justifies risk to the fetus.

10 Special Toxicology Studies

No studies were submitted.

[23] Lehrer, S.B., Becker, B.A. (1974) *Teratology*; **9**: A-26-A-27.

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/s/

TODD R PALMBY
03/02/2011

HALEH SABER
03/04/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201370 **Applicant:** Pfizer **Stamp Date:** 03/09/2010

Drug Name: heparin sodium **NDA/BLA Type:** 505(b)(2)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable; Separate toxicology studies were not conducted with this drug substance.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable; Separate toxicology studies were not conducted with this drug substance.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable; No pharm/tox study reports were submitted with this NDA.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			This will be a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes___

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

None at this time.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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

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