

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201370Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW

NDA# 201370
Drug Heparin sodium Injection
Formulation Injection
Type Original NDA
Sponsor Pfizer Inc
Letter Date March 8, 2010
Reviewer/Team Leader Patrick Marroum, Ph.D.

Background:

Pfizer Inc is submitting this application to seek approval of a new porcine intestinal tissue Heparin for the following indications:

- (b) (4) prophylaxis and treatment of venous thrombosis (b) (4)
- (b) (4)
- (b) (4)
- (b) (4) treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation);
- Prevention of clotting in arterial and cardiac surgery;
- Prophylaxis and treatment of peripheral arterial embolism;
- (b) (4) anticoagulant in blood transfusions, extracorporeal circulation, and dialysis procedures (b) (4)

The compositional formula for the various proposed Heparin injection strengths are included in Appendix I.

Waiver:

According to the 21CFR 320.22 (b)

For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

- (1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

COMMENTS:

Since the composition of this Heparin for Injection formulation is identical to an already approved drug product (NDA17346), this new formulation qualifies for an in vivo bioavailability waiver as per the CFR.

RECOMMENDATION

The Office of New Drug Quality Assessment has reviewed this submission and recommends granting an in vivo bioavailability/bioequivalence waiver based on CFR 21320.22(b).

Patrick Marroum, Ph. D.
Office of New Drug Quality Assessment

Date _____

cc: Dorantes, Al-Hakim.

APPENDIX I

**Table 2.3.P.1-1. Composition of Heparin Sodium Injection, USP, 1000 U/mL
Pfizer Code¹ 52003/EDP 401051**

Name of Ingredients	Reference to Standard	Function	Composition (x/mL)	Unit Formula (mg/10 mL vial) [§]
Heparin Sodium (porcine intestinal tissue)	USP/Pfizer DMF (b) (4)	Active	1,000 units	10,000 units
Sodium Chloride	USP	(b) (4)	9.00 mg	(b) (4)
Benzyl Alcohol	NF/Ph. Eur.		9.45 mg	
Water for Injection	USP	Vehicle	q.s.	q.s.
Sodium Hydroxide	Pfizer	pH Adjustment		(b) (4)
Hydrochloric Acid	Pfizer	pH Adjustment		(b) (4)
			Fill Volume Target (mL)	(b) (4)
			Fill Volume (label claim) (mL)[‡]	10
Vial			10 mL	
Stopper				
Metal Seal/Flip Top Cap				
(b) (4)				

**Table 2.3.P.1-4. Composition of Heparin Sodium Injection, USP, 10,000 U/mL
Pfizer Code 52010/EDP 401039**

Name of Ingredients	Reference to Standard	Function	Composition (x/mL)	Unit Formula (mg/1 mL vial)§
Heparin Sodium (porcine intestinal tissue)	USP/Pfizer DMF (b) (4)	Active	10,000 units	10,000 units
Sodium Chloride	USP	(b) (4)	(b) (4)	(b) (4)
Benzyl Alcohol	NF/Ph. Eur.		9.45 mg	
Water for Injection	USP	Vehicle	q.s.	q.s.
Sodium Hydroxide	Pfizer	pH Adjustment		(b) (4)
Hydrochloric Acid	Pfizer	pH Adjustment		(b) (4)
Fill Volume Target (mL)				(b) (4)
Fill Volume (label claim) (mL)‡				1
Vial	(b) (4)			(b) (4)
Stopper				
Metal Seal/Flip Top Cap				
				(b) (4)

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/s/

PATRICK J MARROUM
04/06/2011

Clinical Pharmacology Review

NDA	201-370/SN0/SDN 1
Submission Date:	8 March 2010
Brand Name:	Heparin Sodium
Generic Name:	Heparin Sodium
Formulation:	Solution for injection
OCP Reviewers:	Bahru A Habtemariam, Pharm.D.
OCP Team Leader:	Julie Bullock, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 5
OND Division:	Division Hematology Products
Sponsor:	Pfizer
Submission Type; Code:	505(b)(2)
Dosing regimen:	see Appendix A
Indications	Anti-coagulation (see Appendix A)

NDA 201-370^(b)₍₄₎ is a 505(b)(2) application for a porcine sourced heparin submitted by Pfizer. For the current submission Pfizer has referenced two of its own previous NDAs as described below:

- NDA 4-570: A bovine sourced drug product, the original NDA was approved in February 1942. NDA 4-570 is still an active NDA, for which the sponsor has maintained relevant reporting obligations. However, the product has not been marketed since 2002.
- NDA 17-346: This original NDA was approved in May 1973 for a porcine sourced heparin product. NDA 17-346 was withdrawn without prejudice in May 1992, apparently for commercial reasons.

The porcine sourced product under NDA 17-346 was approved based on two bioequivalence type studies where the anticoagulation properties of the porcine sourced product (test) was compared to the bovine sourced product (reference) under NDA 4-570 in healthy, state prison, subjects. The studies were conducted in 1971 and the bioequivalence analyses did conform to current standards.

We consulted ONDQA-Biopharm regarding the need for bridging bioequivalence studies in order to approve a porcine sourced product. ONDQA-Biopharm colleague Patrick Marroum stated that bioequivalence studies between the porcine and bovine sourced products are not necessary to approve the porcine sourced product (see email in Appendix C). Therefore, no additional clinical pharmacology analysis were performed for the present 505(b)(2) submission.

In the current NDA, the label was reformatted according to the Physician Labeling Rule (PLR). Much of clinical pharmacology aspects of the label did not change in content. The drug interaction section (Section 7) was updated to include newer drugs that could interact with heparin (see Appendix B).

Recommendation:

NDA 201-370 is acceptable from clinical pharmacology perspective.

Bahru A Habtemariam, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

Julie Bullock, Pharm.D.
Team Leader
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **M Cato**; MTL - **KM Robie Suh**; MO - **M Lu**
DCP-5: Reviewers - **B Habtemariam**, TL - **J Bullock**, DDD - **B Booth**,
DD - **A Rahman**

APPENDIX A – HEPARIN INDICATIONS & DOSE

Heparin indicated for:

- Prophylaxis and treatment of venous thrombosis and pulmonary embolism;
- Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation;
- (b) (4) treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation);
- Prevention of clotting in arterial and cardiac surgery;
- Prophylaxis and treatment of peripheral arterial embolism;
- Anticoagulant use in blood transfusions, extracorporeal circulation, and dialysis procedures.

The recommended dose for Heparin depends on route and frequency. The recommended dosing regimens for adults are:

METHOD OF ADMINISTRATION	FREQUENCY	RECOMMENDED DOSE*
Deep Subcutaneous (Intrafat) Injection	Initial Dose	333 units/kg subcutaneously
	Every 12 hours	250 units/kg subcutaneously
Intermittent Intravenous Injection	Initial Dose	10,000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection, USP
	Every 4 to 6 hours	5,000 to 10,000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride Injection, USP
Continuous Intravenous Infusion	Initial Dose	5,000 units by IV injection
	Continuous	20,000 to 40,000 units per 24 hours in 1,000 mL of 0.9% Sodium Chloride Injection, USP (or in any compatible solution) for infusion

* Based on 150 lb (68 kg) patient

APPENDIX B – LABELING

7 DRUG INTERACTIONS

7.1 Drugs Enhancing Heparin Effect

- Drugs that interfere with platelet aggregation – These drugs (e.g., systemic salicylates, NSAIDs including celecoxib and ibuprofen, glycoprotein IIb/IIIa antagonists, thienopyridines, dipyridamole, hydroxychloroquine, dextran) may induce bleeding. Use heparin sodium with caution in patients receiving such agents.
- Antithrombin III (human) – The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. Thus, in order to reduce the risk of bleeding, reduced dosage of heparin is recommended during treatment with antithrombin III (human).

7.2 Drugs Decreasing Heparin Effect

Digitalis, tetracyclines, nicotine, nitrates, and antihistamines may partially counteract the anticoagulant action of heparin sodium. Monitor patients' coagulation tests appropriately.

APPENDIX C – EMAIL FROM ONDQA BIOPHARM

From: Marroum, Patrick J
Sent: Thursday, May 20, 2010 7:29 AM
To: Bullock, Julie; Farrell, Ann T; Booth, Brian P
Cc: Boocker, Nancy; Sitlani, Jay; Schneider, Kay; Christl, Leah A; Jamison, Janet; Weiner, Janice; Cato, Marcus; Al Hakim, Ali H; Dorantes, Angelica
Subject: RE: Draft Filing ltr: NDA 201370: Pfizer: Heparin Sodium

Julie:

No in vivo bio studies are needed because the formulation is exactly the same and the active ingredient is considered to be the same even though it is from 2 different animal 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.

Patrick

From: Bullock, Julie
Sent: Wednesday, May 19, 2010 9:59 AM
To: Farrell, Ann T; Booth, Brian P
Cc: Boocker, Nancy; Sitlani, Jay; Schneider, Kay; Christl, Leah A; Jamison, Janet; Weiner, Janice; Cato, Marcus; Marroum, Patrick J; Al Hakim, Ali H
Subject: RE: Draft Filing ltr: NDA 201370: Pfizer: Heparin Sodium

>>It is unclear whether these "bridging" studies are considered supportive information or whether the Division considers this data necessary to approval of a 505(b)(2) application for heparin.

I am still waiting for our ONDQA biopharm group to decide on if these in-vivo bridging studies are needed to link bovine vs. porcine sourced products. I brought this to ONDQA's attention and Patrick Marroum was notified of this issue in April.

<< Message: RE: >>

Once we hear their verdict I will know if these bridging studies are supportive vs. necessary. If they are not necessary the sponsor should submit a biowaiver to excuse them from in-vivo BE/comparison studies.

Thanks,
Julie

Julie M. Bullock, Pharm.D.
Team Leader, Oncology/Hematology
Office of Clinical Pharmacology
julie.bullock@fda.hhs.gov
Tele: 301.796.1509

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/s/

BAHRU A HABTEMARIAM
03/04/2011

JULIE M BULLOCK
03/04/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA 201370 is a 505(b)(2) application where the sponsor (pfizer) is referencing two of its own previously approved NDAs. Brief descriptions of the reference NDAs are provided below:

- NDA 017346: This was a porcine based product. The original NDA application was filed in March 1972 and subsequently approved for several strengths of the Steri-Dose™ syringe in May 1973. Marketing of NDA 017346 was discontinued for commercial reasons, and subsequently withdrawn in May 1992.
- NDA 004570: This was a bovine based drug product approved in February 1942. NDA 004570 is an active NDA. Pfizer has maintained relevant reporting obligations for this NDA, although the product has not been marketed since 2002.

For the current NDA, heparin will be derived from porcine intestinal tissue, similar to NDA 017346.

	Information		Information
NDA/BLA Number	201370	Brand Name	Heparin Sodium
OCP Division (I, II, III, IV, V)	5	Generic Name	Heparin Sodium
Medical Division	Oncology	Drug Class	Hematology
OCP Reviewer	Bahru A Habtemariam, Pharm.D	Indication(s)	Prophylaxis and treatment of venous thrombosis , Prevention of postoperative DVT and pulmonary embolism, Prophylaxis and treatment of pulmonary embolism , Atrial fibrillation with embolization , (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 and dialysis (b) (4)
OCP Team Leader	Julie Bullock, Pharm.D	Dosage Form	Subcutaneous and Intravenous Injections
Pharmacometrics Reviewer	NA	Dosing Regimen	Subcutaneous and Intravenous
Date of Submission	March 8, 2010	Route of Administration	Subcutaneous and Intravenous
Estimated Due Date of OCP Review	9/1/2010	Sponsor	Pfizer Inc
Medical Division Due Date	January 9, 2011	Priority Classification	Standard
PDUFA Due Date	January 9, 2011		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	2	2	The sponsor submitted synopses of two (767-1 and 767-2) pharmacodynamic equivalence studies. However, the sponsor did not submit full study reports, study protocols, and raw datasets.
Tabular Listing of All Human Studies				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		2	2	
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	36	36	
Total Number of Studies	2	2	2	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			The sponsor submitted synopses of two pharmacodynamic equivalence studies. However, these analyses are not acceptable by current standards.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		X		
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?		X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology 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. **For the referenced bioequivalence studies (studies 767-1 and 767-2), the sponsor needs to submit the study protocols, clinical study reports, and raw data. The datasets need to be submitted in SAS transport format.**

Bahru A. Habtemariam, Pharm.D.
Reviewing Clinical Pharmacologist

April 21, 2010
Date

Julie Bullock, Pharm.D.
Team Leader/Supervisor

April 21, 2010
Date

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

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/s/

BAHRU A HABTEMARIAM
04/22/2010

JULIE M BULLOCK
04/22/2010