

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201370Orig1s000

CHEMISTRY REVIEW(S)

NDA 201307

Heparin Sodium (heparin sodium, USP) Injection

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Pfizer Inc.
Address: 235 East 42nd Street,
New York, NY 10017-5755

Indication:

- Prophylaxis and treatment of venous thromboembolism
- 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 procedures (b) (4)

Presentation: With the exception of 2000U/2mL vial presentation, all the proposed heparin sodium presentations contain benzyl alcohol as preservative. Three of the above presentations, (preservative free 2000U per 2mLvial and preserved 10000U or 50000U per 10mLvial) are packaged in Type I glass (b) (4) vial capped with grey (b) (4) stopper and aluminum seal. The remaining two presentations (5000U per (b) (4) vial and 10000 Units per (b) (4) vial) are packaged in (b) (4) Type I glass vial capped with grey (b) (4) stopper, and aluminum over seal.

Establishments Evaluation Report (EER) Status: Acceptable

Consults:	EA -	Acceptable
	Statistics -	N/A
	Methods Validation -	Not recommended
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm Toxicology -	Acceptable

Original Submission: February 10, 2010
Re-submissions: N/A
Post-Approval CMC Agreements: None at this time.

Drug Substance

The drug substance, heparin sodium, is derived from porcine intestinal tissue and is a sodium salt of sulfated glycosaminoglycans with a molecular weight ranging from 6 to 30KDa. It is a negatively charged molecule. Heparin sodium is composed of polymers of alternating derivatives of α -D-glucosamine (N-sulfated, O-sulfated, or N-acetylated) and uronic acid (α -L-iduronic acid or β -D-glucuronic acid) joined by glycosidic linkages. (b) (4)

Representation of various heparin units is provided below. (b) (4)

The Applicant provided adequate reference to their Type I DMF 2712, which contains CMC information for the drug substance, Heparin Sodium USP. . The DMF contains the necessary information related to manufacturing, characterization, physical and biological properties, manufacture, process controls, analytical methods, specifications, validation, container closure system, reference standard and stability data for heparin sodium USP. The NDA contains specification for accepting the drug substance, which conforms to the current USP heparin sodium acceptance criteria. The acceptance criteria include tests for **appearance, identity (1 H-NMR and chromatographic retention time, Anti-factor Xa to IIa activities, test for sodium), test for inorganic impurities (heavy metals, residue on ignition and nitrogen), test for organic impurities (Protein and nucleotidic impurities, residual solvents and Galactosamine in Total Hexosamine), and potency assay.** In addition, specific tests such as pH, loss on drying and bacterial endotoxin are provided as part of the specification.

DMF 2712 was reviewed and found acceptable to support the NDA. The drug substance has (b) (4) months retest period.

Conclusion: Drug substance is adequate.

Drug Product:

(b) (4)

(b) (4)

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

Sufficient stability data have been provided to support an expiry period of 24 months under recommended room temperature conditions.

Conclusion: Drug product is adequate

Overall Conclusion: From CMC point of view, the NDA is recommended for approval.

Ali Al-Hakim, Ph.D.
Branch Chief, Division III
ONDQA/CDRR/FDA

Proposed vial labels for the 1,000 and 5,000 and 10,000 Units are provided in the next page.

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

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/s/

ALI H AL HAKIM
02/17/2011

NDA 201370

Heparin Sodium (heparin sodium, USP) Injection

Pfizer Inc.

**Muthukumar Ramaswamy, Ph.D.
Division of Hematology Products (HFD 160)**

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Chemistry Review Data Sheet

1. NDA 20-1370

2. REVIEW #: 2

3. REVIEW DATE: 1-24-11

4. REVIEWER: Muthukumar Ramaswamy, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
PIND 106887 - Pre-NDA meeting minutes	12/03/2009
Initial Quality Assessment for NDA 201370	04/22/2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original application	
Amendment/001	3/8/10
Amendment /002	4/16/10
Amendment/003	4/16/10
Amendment/005	7/29/10
Amendment/009	8/19/10
Amendment/009	10/13/10
Amendment/013	11/12/10
Amendment/017	01/21/11

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc
Address:	235 East 42 nd Street, New York, NY 10017-5755
Representative:	Tricia Douglas
Telephone:	212 733-6289

8. DRUG PRODUCT NAME/CODE/TYPE:

Executive Summary Section

1. Proprietary Name: Heparin Sodium Injection
2. Non-Proprietary Name (USAN): Heparin Sodium Injection USP
3. Code Name/# (ONDC only): 700
4. Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: Type 1/4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Conditions treated by anticoagulation

11. DOSAGE FORM: Sterile solution for injection

12. STRENGTH/POTENCY: 2000Units/vial (1000U/mL); 10,000Units/vial (1000U/mL), 5000Units/vial (5000U/mL), 50000 Units/vial (5000U/mL) and 10000units/vial (10,000 U/mL)

13. ROUTE OF ADMINISTRATION: Injection (IV, SC)

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Chemical Name: Heparin Sodium.
Molecular weight: ~ 6 to 30 kDa.
 Structural Formula: “It is composed of polymers of alternating derivatives of α -D-glucosamine (N-sulfated, O-sulfated, or N-acetylated) and uronic acid (α - L-iduronic acid or β –D- glucuronic acid) joined by glycosidic linkages.”

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
02712	II	Pharmacia and Upjohn	Heparin Sodium USP	1	Adequate	08/31/2009	Reviewed by Art Shaw, Ph.D.
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	06/08/10	Reviewed for dimensions and specifications by Muthukumar Ramaswamy, Ph.D. See page 30-32 of this

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(b) (4)	III	(b) (4)	1	Adequate	1/21/10	NDA Reviewed by Sharon Kelly
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¹ Action codes for DMF Table: <http://darrrts.fda.gov:7777/darrrts/ViewDocument?documentId=090140af801b3f2c>

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	1/5/11	
Pharm/Tox	Acceptable	9/30/10	Pharm Tox Reviewer, Todd Palmby was consulted on the levels of potential impurities such as (b) (4) that may be present in the drug product
LNC	NA		
EA	NA		
Microbiology	Acceptable	NA	Review in DARRTS pending - Denise Miller.

Executive Summary Section

The Chemistry Review for NDA 20-1370

The Executive Summary**I. Recommendations**

- A. Recommendation and Conclusion on Approvability:
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 .

- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable :**
None

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

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

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

With the exception of 2000U/2mL vial presentation, all the proposed heparin sodium presentations contain benzyl alcohol as preservative. Three of the above presentations, (preservative free 2000U per (b) (4) vial and preserved 10000U or 50000U per 10mLvial) are packaged in Type I glass (b) (4) vial capped with grey (b) (4) stopper and aluminum seal. The remaining two presentations (5000U per (b) (4) vial and 10000 Units per (b) (4) vial) are packaged in (b) (4) Type I glass vial capped with grey (b) (4) stopper, and aluminum over seal.

All presentations except the high potency formulation (10000U/mL) contain sodium chloride (b) (4). The pH of the drug product is approximately 7 to be compatible with physiological solution. All the above presentations are supplied as single vial pack or as 25 vial packs. The product will be stored at 20-25°C.

The drug substance, heparin sodium is derived from porcine intestinal tissue and is a sodium salt of sulfated glycosaminoglycans with a molecular weight ranging from 6 to 30KDa. It is a negatively charged molecule. Heparin sodium is composed of polymers of alternating derivatives of α -D-glucosamine (N-sulfated, O-sulfated, or N-acetylated) and uronic acid (α - L-iduronic acid or β -D-glucuronic acid) joined by glycosidic linkages. (b) (4)

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

(b) (4)

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(b) (4)

B. Description of How the Drug Product is Intended to be Used

Heparin sodium injection is an anticoagulant and is intended for subcutaneous or intravenous administration and should not be used for intramuscular injection. Heparin sodium injection will be available as preserved or as preservative free formulations. Do not administer the HEPARIN SODIUM INJECTION formulation preserved with benzyl alcohol to neonates and infants. When heparin therapy is needed in neonates and infants, use a preservative-free formulation.

The drug products should be inspected visually for particulate matter and discoloration prior to administration. Heparin Sodium Injection should not be mixed with certain drugs. Heparin Sodium Injection is incompatible with certain substances in solution (e.g., alteplase, amikacin sulfate, atracurium besylate, ciprofloxacin, cytarabine, daunorubicin, droperidol, erythromycin lactobionate, gentamicin sulfate, idarubicin, kanamycin sulfate, mitoxantrone HCl, polymyxin B sulfate, promethazine HCl, streptomycin sulfate, tobramycin sulfate). Package insert should be consulted for additional information related to dosage and administration.

C. Basis for Approvability or Not-Approval Recommendation

The NDA contains adequate chemistry, manufacturing, control (CMC) information for Heparin Sodium Injection, USP and is recommended for approvable from CMC perspective for the following reasons.

The Applicant provided adequate reference to their Type I DMF 2712 for information pertaining to the drug substance, Heparin Sodium USP. The DMF contains general information, characterization, physical and biological properties, manufacture, process controls, analytical methods, specifications, validation, container closure system, reference standard and stability data for heparin sodium USP. The NDA contains specification for accepting the drug substance, which conforms to the current USP heparin sodium acceptance criteria.

The NDA contains CMC information for 5 different presentations, which are differentiated by their preservative content (with or without benzyl alcohol) or potency (1000 to 10000U/mL) or by the packaging configuration (single or multi-use vials). The proposed drug products will be filled in (b) (4) or 10 mL Type I glass vials and sealed with (b) (4) stopper and aluminum over seal. The product of different strength will be differentiated by cap/over seal color

Presentations			
Strength	Vial Size (mL)	Stopper	Cap/Overseal Color
1000 units (preservative-free)	2	13 mm	Violet
1000 units	10	13 mm	Salmon
5000 units	(b) (4)	13 mm	Orange Peel
5000 units	10	13 mm	Orange Peel
10000 units	(b) (4)	13 mm	Medium Brown

All excipients used in the drug product are non-animal derived. All presentations except the 10000 units/vial (10000U/mL) contain sodium chloride (b) (4). All presentations contain WFI and may contain sodium hydroxide or hydrochloric acid which is added for pH adjustment to achieve a pH of 5.0 to 7.5.

The NDA describes composition of the drug product, batch formula and batch sizes of all strengths, and provides a description of the manufacturing process and controls of critical process parameters. The choice of benzyl alcohol as an antimicrobial preservative and the proposed concentrations of preservative in the formulation (9.45 mg/mL) are based on historical data. The drug product will be manufactured at Pharmacia Upjohn Facility in Kalamazoo, Michigan. A maximum batch size of (b) (4) is proposed for 1000

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and 5000 U/mL strength preservative containing drug products. A smaller batch size (b) (4) is proposed for 1000 U/mL (preservative free) and 10,000 U/mL drug products.

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

The NDA describes (b) (4) validation and process control information (microbiological control) for various stages (b) (4)

The Applicant has demonstrated the compatibility and stability of heparin sodium injection following dilution in 0.9% Sodium Chloride Injection USP (b) (4) at two final heparin concentrations (b) (4). The compatibility study was assessed by parameters such as appearance, visible particulates, (b) (4) and a relative potency for heparin using the USP biological assay. This study encompasses a range of dosing regimens and all potential excipients in the compatibility assessment.

The NDA contains specifications for the proposed product and the proposed specification conforms to heparin sodium injection USP monograph. (b) (4) all test methods (Potency, Bacterial Endotoxin, Particulate Matter, pH, Sterility, Volume in Container, and Identification) used for testing heparin sodium injection are USP methods. The in-house test method proposed for benzyl alcohol is capable of analyzing related impurities such as (b) (4) and the proposed test method validation for this method is adequate. Per additional discussion with the Agency the shelf-life specification for benzyl alcohol content will be revised to (b) (4) of the nominal content. The NDA contains information on container closure integrity of the packaging system.

The NDA contains batch analysis results for 18 batches. The potency of the two (2) out of the 18 lots were assayed per current USP monograph using Anti-Factor IIa methodology and the remaining lots were assayed per (b) (4) clotting factor assay.

To support the Application for the proposed heparin sodium USP injection product, the Applicant relies on data from confirmatory stability batches, supporting stability data from validation batches along with freeze thaw data and historical information for bovine lung derived heparin. The Applicant has used a bracketed stability study design to evaluate the stability of preservative containing heparin product. The bracketing approach covers factors such as high and low potency heparin formulation, batch size, and crude heparin source (b) (4). To augment the confirmatory stability study design, the Applicant has agreed with the Agency to place one additional batch of 5000U/mL preserved heparin formulation on registration stability program.

The NDA contains 12-18 months of long-term and 6 months of accelerated data from confirmatory stability for 6 batches of **preserved heparin product (1000U/ml, 5000U/mL and 10000U/mL)** packaged in the proposed commercial packaging system and the stability data met all proposed acceptance criteria.

The Application contains 12-18 months of long-term stability data for 5 batches (4 batches from the original Confirmatory stability study and one (1) validation batch from validation study) of preservative-free 1000U/ml heparin formulation packaged in (b) (4) (*non-commercial container*). The stability

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data for the above five (5) batches of preservative-free product in non-commercial container met all **except pH** attributes. The Applicant has investigated the event and as a corrective measure implemented (b) (4) vials for packaging the preservative free 1000U/mL product. *The NDA application also contains 9 months of long-term and 6 months accelerated stability data for 2 batches of preservative free 1000U/mL heparin formulation packaged in (b) (4) vials..* The long-term stability data for the above two batches (b) (4) met all stability attributes including pH (b) (4)

The above stability batches are stored at 30°C /75% RH (long-term storage condition) and 40°C/75% RH (accelerated storage conditions). Note that the recommended storage condition for the product will be 20° to 25° C (68° to 77°F) [USP Controlled Room Temperature].

The batches enrolled in stability were evaluated for appearance (appearance, color and clarity), potency, particulate matter, pH, sterility and preservative content (benzyl alcohol, if applicable). For product packaged in multi-use vials (10 mL), antimicrobial effectiveness testing was performed. The stability batches were initially tested with the (b) (4) assay while the later time points utilized the Anti-factor IIa assay.

In addition, the NDA contains 12 days (b) (4) data to support temperature excursion and the temperature recycling study used preservative free heparin product packaged in (b) (4) vials. The NDA also contains 60 month stability data for bovine lung derived heparin (supportive stability studies).

Based on the stability data for batches stored at intermediate and accelerated storage conditions, **an expiration period of 24 months is recommended for the proposed product packaged in (b) (4) glass vials with a (b) (4) stopper stored at USP controlled room temperature (20° to 25° C) (68° to 77°F).**

Post approval stability commitment:

The Applicant has committed to place first three commercial scale batches of the lowest strength and highest strength product on stability per applicable protocol and stated that annual production batches will be selected at a rate of one lot per year per strength for stability testing per the protocol. The products will be monitored for appearance, particulate matter, potency, pH, benzyl alcohol (if applicable), and sterility.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Same date as draft review

Chemistry Team Leader Name/Date

Project Manager Name/Date

C. CC Block

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/s/

MUTHUKUMAR RAMASWAMY
01/27/2011

ALI H AL HAKIM
01/28/2011

NDA 201370

Heparin Sodium (heparin sodium, USP) Injection

Pfizer Inc.

Muthukumar Ramaswamy, Ph.D.
Division of Hematology Products (HFD 160)

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Chemistry Review Data Sheet

1. NDA 20-1370

2. REVIEW #: 1

3. REVIEW DATE: 06-15-10

4. REVIEWER: Muthukumar Ramaswamy, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
PIND 106887 - Pre-NDA meeting minutes	12/03/2009
Initial Quality Assessment for NDA 201370	04/22/2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original application	3/8/10
Amendment/001	3/8/10
Amendment /002	4/16/10
Amendment/003	4/16/10

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc
Address:	235 East 42 nd Street, New York, NY 10017-5755
Representative:	Tricia Douglas
Telephone:	212 733-6289

8. DRUG PRODUCT NAME/CODE/TYPE:

1. Proprietary Name: Heparin Sodium Injection
2. Non-Proprietary Name (USAN): Heparin Sodium Injection USP
3. Code Name/# (ONDC only): 700
4. Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: Type 1/4

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- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Conditions treated by anticoagulation

11. DOSAGE FORM: Sterile solution for injection

12. STRENGTH/POTENCY: 2000Units/vial (1000U/mL); 10,000Units/vial (1000U/mL), 5000Units/vial (5000U/mL), 50000 Units/vial (5000U/mL) and 10000units/vial (10,000 U/mL)

13. ROUTE OF ADMINISTRATION: Injection (IV, SC)

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

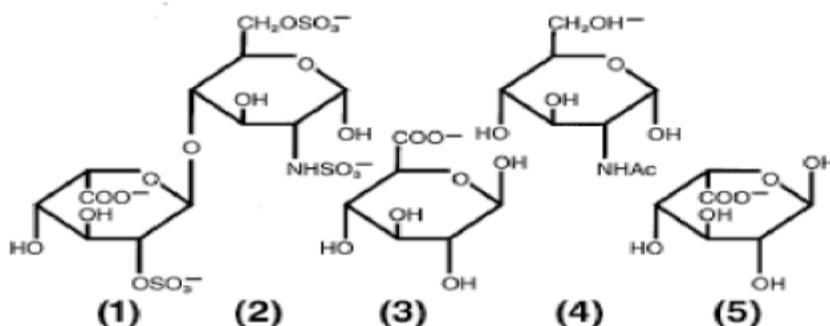
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Heparin Sodium.

Molecular weight: ~ 6 to 30 kDa.

Structural Formula: "It is composed of polymers of alternating derivatives of α -D-glucosamine (N-sulfated, O-sulfated, or N-acetylated) and uronic acid (α -L-iduronic acid or β -D-glucuronic acid) joined by glycosidic linkages."

Representative subunit structure is shown below:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
02712	II	Pharmacia and Upjohn	Heparin Sodium USP	1	Adequate	08/31/2009	Reviewed by Art Shaw,

Executive Summary Section

(b) (4)	III	(b) (4)	4	Adequate	06/08/10	Ph.D. Reviewed for dimensions and specifications by Muthukumar Ramaswamy, Ph.D. See page 30-32 of this NDA
	III		1	Adequate	1/21/10	Reviewed by Sharon Kelly
	V		7	To be completed Micro. Staff	NA	To be reviewed by Microbiology Staff

¹ Action codes for DMF Table: <http://darrts.fda.gov:7777/darrts/ViewDocument?documentId=090140af801b3f2c>

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	pending		
Pharm/Tox	NA		
LNC			
EA	NA		
Microbiology	Review pending	NA	NA

Executive Summary Section

The Chemistry Review for NDA 20-1370

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability:** Approvable pending resolution of outstanding CMC related issues (Chemistry and microbiology) and acceptable recommendation from Office of Compliance
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable :** none

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product, heparin sodium injection USP will be available in five different presentations for intravenous administration or for subcutaneous administration. The strengths and potencies of these five presentations are as follows: 2000U/vial (Potency:1000 U/mL), 10000 units/vial (Potency:1000U/mL), 5000Units/vial (Potency: 5000U/mL), 50,000Units/vial (Potency: 5000U/mL) and 10000 Units/vial (Potency:10,000U/mL).

The 1000 (b)(4) U/mL presentations will be available as single (b)(4) dose presentations in Type I clear glass (b)(4) or 10 mL vial sealed with grey (b)(4) stopper and aluminum over seal and plastic flip-off. The (b)(4) multi-use 5000U/ml presentation and multi-dose 1000 U/mL presentation contain benzyl alcohol as preservative. The NDA also contains information on a preservative free 1000U/mL vial presentation, which is packaged in Type I clear glass 2 mL vial sealed with grey (b)(4) stopper and aluminum over seal. All presentations except the 10000U/mL (b)(4) use vials contain sodium chloride (b)(4). The pH of the drug product is approximately 7 to be compatible with physiological solution. All the above presentations are supplied as single vial pack or as 25 vial packs. The product should be stored at 20-25°C.

The drug substance, heparin sodium is a sodium salt of sulfated glycosaminoglycans derived from porcine intestinal tissue with a molecular weight ranging from 6 to 30KDa. It is a negatively charged molecule. Heparin sodium is composed of polymers of alternating derivatives of α -D-glucosamine (N-sulfated, O-sulfated, or N-acetylated) and uronic acid (α -L-iduronic acid or β -D- glucuronic acid) joined by glycosidic linkages. (b)(4)

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

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B. Description of How the Drug Product is Intended to be Used

Heparin sodium Injection is intended for the following indications:

-
-
-
-
-
-
-

Heparin sodium injection is intended for Subcutaneous or intravenous administration and should not be used for intramuscular injection. The drug products should be inspected visually for particulate matter and discoloration prior to administration. Heparin Sodium Injection should not be mixed with certain drugs.

C. Basis for Approvability or Not-Approval Recommendation

The NDA contains chemistry, manufacturing, control (CMC) information for Heparin Sodium Injection, USP. The drug product is a (b) (4) sterile solution of heparin sodium derived from porcine intestinal tissue. The NDA cross-references Type I DMF 2712 for a description of general information, characterization, physical and biological properties, manufacture, process controls, analytical methods, specifications, validation, container closure system, reference standard and stability of heparin sodium USP. The NDA contains specification for heparin sodium, which conforms to the current USP heparin sodium acceptance criteria. With the exception of (b) (4)

(b) (4) Heparin sodium is tested in accordance with USP monograph procedures. The potency is determined by Anti-Factor IIa assay using a USP reference standard. The assay measures the anticoagulant activity of heparin.

The NDA contains CMC information for different strengths (2000, 5000, 10000, 50000 or 10000 units/vial) of drug products, Heparin Sodium Injection, USP. With the exception of 2000U/vial presentation (1000U/mL, preservative free product), all products will contain benzyl alcohol as preservative. All presentations except the 10000 units/vial (10000U/mL) contain sodium chloride (b) (4). All presentations contain WFI, and sodium hydroxide or hydrochloric acid as needed for pH adjustment to achieve a pH of 5.0 to 7.5. All presentations except the 10000 units/mL contain sodium chloride (b) (4). All excipients used in the drug product are non-animal derived.

Presentations			
Strength	Vial Size (mL)	Stopper	Cap/Overseal Color
1000 units (preservative-free)	2	13 mm	Violet
1000 units	10	13 mm	Salmon
5000 units	(b) (4)	13 mm	Orange Peel
5000 units	10	13 mm	Orange Peel
10000 units	(b) (4)	13 mm	Medium Brown

The drug products will be filled in (b) (4) 10 mL Type I glass vials and sealed with (b) (4) (b) (4) stopper and aluminum over seal. The product of different strength will be differentiated

Executive Summary Section

by cap/over seal color. The NDA contains letters of authorization from [REDACTED]

(b) (4)
(b) (4)

The NDA describes composition of the drug product, batch formulas for all strengths, batch size, and a description of the manufacturing process control of critical process. The drug product will be manufactured at Pharmacia Upjohn Facility in Kalamazoo, Michigan. The NDA provides a letter of authorization fo [REDACTED]

(b) (4)

A maximum batch size of [REDACTED] (b) (4) is proposed for 1000 and 5000 U/mL strength preservative containing product. A smaller batch size [REDACTED] (b) (4) is proposed for 1000 U/mL (preservative free) and 10,000 U/mL product. The manufacturing process for heparin sodium injection utilizes [REDACTED] (b) (4)

(b) (4)

(b) (4)

[REDACTED] (b) (4) The choice of benzyl alcohol as an antimicrobial preservative and the proposed concentrations of preservative in the formulation (9.45 mg/mL) are based on historical data. The NDA contains information on container closure integrity of the packaging system. The adequacy of the microbiological controls will be assessed by the Microbiology Staff.

The NDA has evaluated the compatibility of potential diluent excipients and stability of heparin sodium injection following dilution in 0.9% Sodium Chloride Injection USP [REDACTED] (b) (4) at two final heparin concentrations [REDACTED] (b) (4) to encompass the range of dosing regimens and all potential excipients in the compatibility assessment. Compatibility was evaluated by measuring appearance, visible particulates, [REDACTED] (b) (4) and a relative potency for heparin using the USP biological assay.

The NDA contains specifications for heparin sodium injection USP. With the exception of test method for assaying benzyl alcohol, all test methods used for heparin sodium injection (Potency, Bacterial Endotoxin, Particulate Matter, pH, Sterility, Volume in Container, and Identification) are USP methods. The test method for benzyl alcohol is an in-house method. The test method is not specific for analyzing related impurities such as [REDACTED] (b) (4) and the proposed test method validation for the determination of benzyl alcohol.in adequate.

Executive Summary Section

The NDA contains batch analysis results for 18 batches. The potency of the two lots out of the 18 lots were assayed per current USP monograph using Anti-Factor IIa methodology and rest of the lots were assayed per (b) (4) clotting factor assay.

The NDA also contains stability information for 12 batches. The NDA contains 6 months long-term and accelerated stability data for the following:

- a) 4 batches of preservative free 2000U/vial (1000U/ml) heparin presentation
- b) 3 batches of 10,000U/vial (10000U/ml) heparin (with preservative)
- c) 1 batch each of 5000U/vial (Single-use) and 50000U/vial (multi-use) vial
- d) 1 batch of 10000U/ vial (1000U/mL, preserved).

The batches enrolled in stability are stored at 30°C /75% RH (long term storage condition) and 40°C/75% RH (accelerated storage condition). The proposed stability design uses a bracketing approach, covering high and low potency heparin formulation, batch size, and crude heparin source (b) (4). The study design also uses a matrixing approach with respect to time points. The NDA states that the stability studies were performed per ICH guideline Q1A(R2). The stability batches were made at (b) (4) of the proposed commercial scale at Pfizer Kalamazoo, Michigan and packaged in (b) (4) glass vials at Pfizer Kalamazoo, Michigan.

The stability samples were evaluated for appearance (appearance, color and clarity), potency, particulate matter, pH, sterility and preservative content (benzyl alcohol, if applicable). For product packaged in multi-use vials (10 mL), antimicrobial effectiveness testing was performed. The stability program for the first 10 lots was initially tested with the (b) (4) assay while the last two batches utilize the Anti-factor IIa assay. Pfizer is qualifying the chromogenic Anti-factor IIa assay. The NDA did not contain a time line for switching all stability samples from the current (b) (4)-based clotting assay to Anti-factor IIa.

The NDA states that data from the confirmatory ICH stability study demonstrates that there are no significant trends in any of the measured parameters, with the exception of pH results for the preservative free formulation. pH data for preservative-free presentation exceeded the acceptance limit at the 6 month stability point.

The NDA states that the use of (b) (4)

Recently, the Applicant has added two additional batches, 9AP11 and 9AP12, in their confirmatory ICH stability program. In addition, the NDA contains (b) (4) 60 month stability data for bovine lung derived heparin (supportive stability studies).

Based on the 6 months stability data for 10 batches from the confirmatory ICH program and supporting 60 months stability data from historical batches, the firm is proposing an expiration period is 24 months when stored at controlled room temperature for the product packaged in (b) (4) glass vials with a (b) (4) stopper. The firm should provide additional 6 months of stability data to meet the minimum required stability data for an NDA application. A 24 month expiration can not be granted at this stage.

The proposed storage conditions for this product is 20° to 25° C (68° to 77°F) [USP Controlled Room Temperature].

Post approval stability commitment:

Executive Summary Section

The Applicant has committed to place first three commercial scale batches of the lowest strength and highest strength product on stability per applicable protocol and stated that annual production batches will be selected at a rate of one lot per year per strength for stability testing per the protocol. The products will be monitored for appearance, particulate matter, potency, pH, benzyl alcohol (if applicable), and sterility.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Same date as draft review
Chemistry Team Leader Name/Date
Project Manager Name/Date

C. CC Block

31 pages has been withheld in full as B(4) CCI/TS
immediately following this page

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/

MUTHUKUMAR RAMASWAMY
06/29/2010

ALI H AL HAKIM
06/30/2010

ONDQA Initial Quality Assessment
Muthukumar Ramaswamy, Ph.D., Division of Pre-marketing Assessment, Branch 2

NDA: 201370

Applicant: Pfizer, Inc.

Stamp Date: 9-Mar-2010

PDUFA Date: 9-Jan-2011

Proposed Proprietary Name: Heparin Sodium

Established Name: Heparin Sodium Injection USP

Dosage form and strength: Sterile solution for injection; 1,000, 5,000 and 10,000 U/mL

Route of Administration: Injection

Indication: Conditions treated by anti-coagulation

PAL: Eldon Leuzinger, Ph.D. ONDQA

ONDQA Fileability Recommendation: Acceptable for filing

Primary reviewer: Muthukumar Ramaswamy, Ph.D.

Time goals:

- Initial Quality Assessment in DARRTS: by 23-April 2010
- Chemistry filing memo in DARRTS: by 23-April 2010
- Filing Decision: 23-April 2010
- Filing review issues, "Day 74": 22-May-2010
- Mid-cycle meeting: "month 5": 9-Aug-2010
- Wrap Up Meeting: 5 Dec. 2010
- Complete Primary and secondary review: 05-Dec-2010; 12-Dec-2010

Relevant DMFs:

DMF 2712: Heparin sodium (porcine intestinal tissue) from Pfizer Inc.

(b) (4)

***CONSULTS/ CMC RELATED
REVIEWS***

COMMENT

Biopharmaceutics

Biowaiver request may be needed. Clinical team to initiate consult request

CDRH or CBER

Not Applicable

EA

Categorical exclusion request will be assessed by Primary Reviewer.

EES

EER was created and sent to Compliance by Tu-van Lambert, ONDQA, PM

OSE

Labeling consult request will be sent as part of DMEP's request.

Methods Validation

Validation may be requested of FDA labs after test methods are finalized

Microbiology

Endotoxin, sterility, (b) (4)

Pharm/Tox

May Not Be Not Applicable

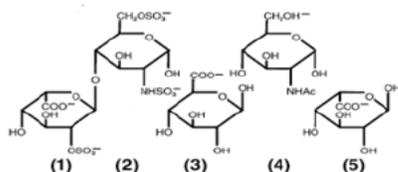
Labeling and Nomenclature

OSE/DMEPA

ONDQA Initial Quality Assessment
Muthukumar Ramaswamy, Ph.D., Division of Pre-marketing Assessment, Branch 2

Summary:

Pfizer Inc. has filed an electronic NDA for heparin sodium injection derived from porcine intestinal tissue in eCTD format with labeling provided in SPL format. The product is intended to be administered by intravenous or deep subcutaneous routes. The Clinical Division has assigned a 10 months review cycle for this NDA. This NDA is filed as a 505(b)(2) applications. Pfizer has referenced two of its legacy NDA applications for safety and/ or effectiveness: NDA 017346 for heparin derived from porcine tissue (Parke-Davis, a subsidiary of Pfizer Inc.) and NDA 004570 for heparin derived from bovine and porcine (Pharmacia and Upjohn, a subsidiary of Pfizer Inc). NDA 017346 was withdrawn without prejudice in May 1992. Pfizer NDA 004570 was first approved in February of 1942 for bovine based drug product and is active.



Drug Substance:

Heparin sodium is a heterogeneous mixture of variably sulfated polysaccharide chains composed of repeating units of d-glucosamine and either l-iduronic or d-glucuronic acids. The Pfizer is sourcing heparin from Pharmacia Hepar Inc., Franklin, Ohio, which utilizes crude heparin isolated from pork intestinal tissue (Attachment 1 contains a list of crude heparin suppliers) for manufacturing the active pharmaceutical ingredient (API). The Pfizer facility at Franklin, Ohio is responsible for the production and quality control of heparin sodium drug substance. The DMF 2172 was cross-referenced by NDA 017346, and NDA 004570. Pfizer has been the main supplier of heparin for several of the commercially-manufactured heparin sodium injection products.

Table 2.3.S-1. Specification for Heparin Sodium, USP

Attribute	Test Method	Acceptance Criterion
Identification		
¹ H-NMR Spectrum (Test A)	USP <761>	(b) (4)
Identification (Chromatographic) (Test B)	USP	
Anti-Factor Xa to Anti-Factor IIa Ratio (Test C)	USP	
Identification (Sodium) (Test D)	USP <191>	
Assay		
Anti-Factor IIa Potency	USP	
Inorganic Impurities		(b) (4)

Best Available Copy

ONDQA Initial Quality Assessment
Muthukumar Ramaswamy, Ph.D., Division of Pre-marketing Assessment, Branch 2

The NDA references DMF 2712 for the following information related to the drug substance: General information, characterization, physical and biological properties, manufacture, process controls, analytical methods, specifications, validation, container closure system, reference standard and stability. The proposed specification for heparin sodium (reproduced from the NDA above) conforms to the current USP heparin sodium acceptance criteria. With the exception of (b) (4)

(b) (4) Heparin sodium is tested in accordance with the analytical procedures USP monograph.

Critical Issues: None noted. Adequacy of the DMF 2712 to meet current USP specifications will be determined during review.

Drug Product:

The proposed drug product, Heparin Sodium Injection, USP, is a (b) (4) sterile solution of heparin sodium derived from porcine intestinal tissue. The potency is determined by Anti-Factor IIa assay using a USP reference standard based on units of heparin activity per milligram. (b) (4)



The NDA proposes to manufacture three different concentrations (1000, 5000 or 10000 units/mL) of Heparin Sodium Injection, USP in five different presentations. The 1000 and 5000 U/mL strength vials are available in single use (b) (4) size vials) and multi-use format (10 mL size vials). The 10000 U/mL vial will be available as single use vials.

With the exception of 1000 U/mL single-use vials, all other presentations (multi-use 1000U/ml, single and multi-use 5000U/ml vials, and single-use 10,000U/mL) contain preservative (benzyl alcohol). The preservative-free product is identical compositionally to the preserved 1000 U/mL product except for the removal of benzyl alcohol. All presentations contain WFI, and sodium hydroxide or hydrochloric acid as needed for pH adjustment to achieve a pH of 5.0 to 7.5. All presentations except the 10000 units/mL contain sodium chloride (b) (4)

Composition of Heparin Sodium Injection, USP (unit formula for various presentations)							
Strength			1000U/mL		5000U/mL		10000U/mL
Name of Ingredients	Reference to Standard	Function	multi-use (mg/10 mL vial)§	Single-use (mg/2 mL vial)	Single-use (mg/1 mL vial)	multi-use (mg/10 mL vial)	Single-use (mg mL vial) (b) (4)
Heparin Sodium (porcine intestinal tissue)	USP/Pfizer r DMF 2712	Active	10,000 units	2,000 units	5,000 units	50,000 units	10,000 units (b) (4)
Sodium Chloride	USP	(b) (4)	(b) (4)				
Benzyl Alcohol	NF/Ph. Eur.	Preservative					
Water for Injection	USP	(b) (4)					
Sodium Hydroxide	Pfizer	pH Adjustment					
Hydrochloric Acid	Pfizer	pH Adjustment					
Fill Volume Target (mL)							
Fill Volume (label claim) (mL)			10	2	1	10	1 (b) (4)

ONDQA Initial Quality Assessment
Muthukumar Ramaswamy, Ph.D., Division of Pre-marketing Assessment, Branch 2

Heparin sodium injection, USP will be contained within USP Type 1 (b)(4) glass vials with (b)(4) stoppers and over sealed with a metal seal with a plastic flip-off cap. The NDA contains letters of authorization from (b)(4)

Presentations			
Strength	Vial Size (mL)	Stopper	Cap/Overseal Color
1000 units (preservative-free)	2	13 mm	Violet
1000 units	10	13 mm	Salmon
5000 units	(b)(4)	13 mm	Orange Peel
5000 units	10	13 mm	Orange Peel
10000 units	(b)(4)	13 mm	Medium Brown

Sections 3.2.P.1 and 3.2.P.2 describe composition of the drug product and the pharmaceutical development history. Batch formulas for all strengths, a description of the manufacturing process control of critical process are described under 3.2.P.3.2.3., 3.2.P.3.3 and 3.2.P.3.4 respectively. A maximum batch size of (b)(4) is proposed for 1000 and 5000 U/mL strength preservative containing product. A smaller batch size (b)(4) is proposed for 1000 U/mL (preservative free) and 10,000 U/mL product.

The NDA describes the manufacturing process for heparin sodium injection and utilizes (b)(4)

The NDA states that manufacturing process parameters were derived from (b)(4)

The NDA describes (b)(4) validation information under process validation section. The NDA states that the drug product is manufactured in controlled manufacturing areas in accordance with current good manufacturing practices (cGMP) and is routinely inspected by worldwide regulatory agencies.

Microbiological controls:

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

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/s/

MUTHUKUMAR RAMASWAMY
04/22/2010
IQA for NDA 201370

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04/22/2010