CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201370Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Pediatric and Maternal Health Staff Memorandum

Date: June 14, 2011 **Date Consulted:** June 1, 2011

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader – Pediatric Team
Pediatric and Maternal Health Staff

Lisa Mathis, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: Heparin Sodium Injection, USP, NDA 201-370 and NDA 17-029

Subject: Pediatric Use Labeling

Materials Reviewed: Heparin Sodium Injection, USP labeling

Consult Question: Please evaluate the language proposed for risks associated with benzyl alcohol in pregnancy, nursing mothers, and pediatric use.

INTRODUCTION

The Pediatric and Maternal Health Staff (PMHS) has been working with the Division of Hematology Products (DHP) in developing appropriate risk language for benzyl alcohol-containing heparin formulations, so that all heparin products which contain benzyl alcohol as a preservative have consistent labeling language.

This memorandum reflects the agreed upon pregnancy, nursing mothers, and pediatric use language for heparin products which contain benzyl alcohol as a preservative. Appendix A of this review provides a tracked-changes version of labeling that highlights the recommended PMHS revisions to the labeling for NDA 201-370 (PLR labeling format). The recommended language for heparin labeling in the old labeling format is incorporated in this review.

BACKGROUND

Pediatric Benzyl Alcohol Toxicity

Benzyl alcohol, 0.9% is an antimicrobial preservative widely used in a variety of drug products, especially those intended for multi-use, and in fluids for parenteral therapy. In 1982, two groups of investigators independently concluded that intravascular infusion or flush solutions containing benzyl alcohol, 0.9% caused severe metabolic acidosis, encephalopathy, and respiratory depression with gasping, leading to the death of 16 infants in neonatal intensive care units. This conclusion was based on the discovery of large amounts of benzyl alcohol and its metabolites, benzoic acid and hippuric acid, in the blood and urine of the affected neonates. The benzyl alcohol amounts found in the deceased neonates were in the lethal range for laboratory animals.[1,2]

In May 1982, FDA in conjunction with the American Academy of Pediatrics (AAP) and CDC issued a bulletin containing strong recommendations to warn pediatricians and hospital personnel against using fluids and diluents preserved with benzyl alcohol in newborn infants. In addition, the AAP recommended that medications containing benzyl alcohol also be avoided in newborn infants when possible.[3]

Benzyl alcohol toxicity occurs in infants, particularly in low birth-weight infants, because greater amounts of benzyl alcohol are received relative to body weight, and the metabolic and excretory pathways are still immature.[4]

DISCUSSION AND CONCLUSIONS

Adequate and well controlled studies with heparin have never been conducted in pregnant women, nursing mothers, or in pediatric patients; however use is fairly common. Pediatric dosing recommendations were initially extrapolated from use in adults and have evolved over

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[1] Gershanik J, Boecler B, Ensley H, et al. The gasping syndrome and benzyl alcohol poisoning, NEJM. 1982;301:1384

[2] Brown W, Buist N, Gipson H, et al. Fatal benzyl alcohol poisoning in a neonatal intensive care unit. Lancet. 1982;1:1250

[3] American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs. Benzyl Alcohol: Toxic Agent in Neonatal Units. Pediatrics. 1983;72(3):356-8

[4] Hiller J, Benda G, Rahatzad M, et al. Benzyl alcohol Toxicity: Impact on mortality and intraventricular hemorrhage among very low birth-weight infants. 1986;77(4):500-6

time with long-term clinical experience in children. The updated clinical pediatric dosing guidelines information should be consistent in all heparin products labeling.

PMHS has developed standard pediatric use language warning against the use of benzyl alcohol-containing products in neonates and infants, as the amount of benzyl alcohol that can lead to toxicity in these age groups is unknown. Warnings and Precautions regarding pediatric use and the use of benzyl alcohol-containing heparin formulations should be placed in all heparin product labeling. Recommendations to use benzyl alcohol free heparin formulations when available should be placed in the pregnancy, nursing mothers, and pediatric use sections of labeling. A Contraindication for benzyl alcohol-containing heparin products is not warranted because the use of heparin in an emergency situation where a benzyl alcohol free formulation of heparin is unavailable should not be discouraged.

The Sponsors should provide the amount of benzyl alcohol per heparin mg dose for each heparin product that contains benzyl alcohol as a preservative.

RECOMMENDATIONS
PMHS/DHP PLR-Format Heparin Labeling Recommended Revisions

HIGHLIGHTS OF PRESCIBING INFORMATION
----------WARNINGS AND PRECAUTIONS----------

- Benzyl Alcohol Toxicity: Preservative-free formulation recommended for neonates and infants. (5.2)

----------**USE IN SPECIFIC POPULATIONS**----------

- Pregnancy: Preservative-free formulation recommended. Limited human data in pregnant women. (8.1)
- Nursing Mothers: Preservative-free formulation recommended. Caution should be exercised when administered to a nursing woman. (8.3)
- Pediatric Use: Preservative-free formulation recommended in neonates and infants. Dosing recommendations based on clinical experience. (2.4, 8.4)

2 DOSAGE AND ADMINISTRATION
2.4 Pediatric Use
Preservative-free HEPARIN SODIUM INJECTION, when available, is recommended for use in neonates and infants

There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience. In general, the following dosage schedule may be used as a guideline in pediatric patients:

Initial Dose	75 to 100 units/kg (IV bolus over 10 minutes)
Maintenance Dose	Infants: 25 to 30 units/kg/hour; Infants < 2 months have the highest requirements (average 28 units/kg/hour)

	Children > 1 year of age: 18 to 20 units/kg/hour; Older children may require less heparin, similar to weight-adjusted adult dosage
Monitoring	Adjust heparin to maintain aPTT of 60 to 85 seconds, assuming this reflects an anti-Factor Xa level of 0.35 to 0.70.

5 WARNINGS AND PRECAUTIONS

5.2 Benzyl Alcohol Toxicity

Preservative-free HEPARIN SODIUM INJECTION, when available, is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients *[see Use in Specific Populations (8.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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 less than the maximum human daily dose 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 1/6 the maximum human daily dose. The number of early resorptions increased in both species. There was no evidence of teratogenic effects.

8.3 Nursing Mothers

If available, preservative-free HEPARIN SODIUM INJECTION is recommended when heparin therapy is needed during lactation. Due to its large molecular weight, heparin is not likely to be excreted in human milk, and any heparin in milk would not be orally absorbed by a nursing infant. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant. Exercise caution when administering Heparin Sodium Injection to a nursing mother *[see Use in Specific Populations (8.4)]*.

8.4 Pediatric Use

There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience *[see Dosage and Administration (2.4)]*.

Preservative-free HEPARIN SODIUM INJECTION, when available, is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Carefully examine all HEPARIN SODIUM INJECTION vials to confirm choice of the correct strength prior to administration of the drug. Pediatric patients, including neonates, have died as a result of medication errors in which HEPARIN SODIUM INJECTION vials have been confused with "catheter lock flush" vials *[see Warnings and Precautions (5.1)]*

PMHS Old Labeling-Format Heparin Labeling Recommended Revisions

(b) (4)

[redacted]

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(b) (4)

Additional PMHS Recommendations

1. Update the pediatric dosage and administration information in all heparin products labeling for consistency with current clinical practice dosing guidelines.

2. **P**rovide the amount of benzyl alcohol per heparin mg dose for each heparin product that contains benzyl alcohol as a preservative.

Appendix A – Tracked-Changes to PLR-Format Heparin Labeling, NDA 201370

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/s/

JEANINE A BEST
06/14/2011

Karen B FEIBUS
06/19/2011
I concur with the PLR and pre-PLR labeling recommendations presented in this review.

LISA L MATHIS
06/29/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 6, 2011
To:	Ann Farrell, MD, Acting Director Division of Hematology Products HFD-160
Thru:	Carol Holquist, RPh, Director Division of Medication Errors and Prevention and Analysis HFD-420
From:	Scott Dallas, RPh, Safety Evaluator Division of Medication Errors and Prevention and Analysis HFD-420
Subject:	3rd Amended DMEPA Heparin Labeling Review
Drug Name(s):	Heparin Sodium Injection, USP
Application Type / Number:	NDA 201370
Applicant/sponsor:	Pfizer Injectables
OSE RCM #:	2010 - 819

1 BACKGROUND

This review evaluates Pfizer's proposed revisions to the label and labeling that were submitted on April 1, 2011. The revisions were made in response to a March 29, 2011 FDA correspondence requesting Pfizer increase the prominence of the words "per mL" in the expression of potency and the "2 mL" in the total volume statement on the proposed 1,000 USP units per mL, 2 mL container label of Heparin Sodium Injection, USP.

2 MATERIAL REVIEWED

We reviewed the following labels and labeling:

- Proposed 1,000 USP units/mL, 2 mL container label (Appendix A) and carton labeling (Appendix B)
- Proposed 5,000 USP units/mL, 1 mL container label and carton labeling
- Proposed 10,000 USP units/mL, 1 mL container label and carton labeling
- Proposed 1,000 USP units/mL, 10 mL container label and carton labeling
- Proposed 5,000 USP units/mL, 10 mL container label and carton labeling

3 DISCUSSION

DMEPA's review of the container labels and carton labeling finds that Pfizer has proposed to revise all of the container labels and carton labeling for their heparin sodium injection products under this application. The prominence of the words "per mL" in the expression of potency and the "x mL" in the total volume statement appear to have been increased satisfactorily to have a prominence similar to the number "x,000" in the expression of potency. Increasing the prominence of these specific sections of text might help to decrease the potential for misinterpretation of the total drug content and the expression of potency in these products.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the container labels and carton labeling finds the proposed revisions to be acceptable. We have no other comments at this time.

If you have further questions or need clarifications, please contact Sue Kang, Project Manager, at 301-796-4216.

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/s/

SCOTT M DALLAS
04/06/2011

CAROL A HOLQUIST
04/06/2011

RPM FILING REVIEW- ADDENDUM

Please note the below revision shown in tracked changes

Application Information		
NDA # 201370 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Heparin Sodium Injection USP Established/Proper Name: Heparin Sodium derived from porcine intestinal tissue Dosage Form: Injection Strengths: 1000 units/mL (10 mL vial, BA) 1000 units/mL (2 mL vial) 5000 units/mL (1 and 10 mL vials) 10000 units/mL (1 mL vial)		
Applicant: Pfizer Inc. Agent for Applicant (if applicable): N/A		
Date of Application: March 8, 2010 Date of Receipt: March 9, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: January 9, 2011	Action Goal Date (if different):	
Filing Date: May 8, 2010	Date of Filing Meeting: April 19, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed Anticoagulant therapy (b) (4) [redacted] (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.htm and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		√		Not a new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			√	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			√	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***			√	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		√		

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Marcus Cato, M.B.A.
Regulatory Health Project Manager
Division of Hematology Products
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Janet Jamison, R.N., C.C.R.P.
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/s/

MARCUS A CATO
04/04/2011

JANET K JAMISON
04/04/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 18, 2011
To:	Ann Farrell, MD, Acting Director Division of Hematology Products HFD-160
Thru:	Carol Holquist, RPh, Director Division of Medication Errors and Prevention and Analysis HFD-420
From:	Scott Dallas, RPh, Safety Evaluator Division of Medication Errors and Prevention and Analysis HFD-420
Subject:	2nd Amended DMEPA Heparin Labeling Review
Drug Name(s):	Heparin Sodium Injection, USP
Application Type / Number:	NDA 201370
Applicant/sponsor:	Pfizer Injectables
OSE RCM #:	2010 - 819

1 BACKGROUND

This review evaluates Pfizer's proposed revisions to the package insert, labels and labeling that were submitted on March 9, 2011. The revisions were made in response to a February 25, 2011 FDA correspondence requesting Pfizer revise the package insert, container labels and carton labeling for their Heparin Sodium Injection, USP.

2 MATERIAL REVIEWED

We reviewed the package insert and the following labels and labeling:

- Proposed 1,000 USP Units/mL, 2 mL container label (Appendix A) and carton labeling (Appendix B)
- Proposed 5,000 USP Units/mL, 1 mL container label and carton labeling
- Proposed 10,000 USP Units/mL, 1 mL container label and carton labeling
- Proposed 1,000 USP Units/mL, 10 mL container label and carton labeling
- Proposed 5,000 USP Units/mL, 10 mL container label and carton labeling

3 DISCUSSION

DMEPA's review of the package insert, container labels and carton labeling finds Pfizer proposed revisions acceptable except for the proposed revisions to the 1,000 USP units per mL, 2 mL fill vial container label. DMEPA finds the proposed 1,000 USP units per mL container label still vulnerable to misinterpretation which could result in medication errors. Practitioners could misinterpret the revised label to think that 1,000 USP units of heparin are in 2 mL's , whereas the total drug content is actually 2,000 USP units per 2 mL. The increased potential for misinterpretation can be partially attributed to the small physical size of the label and complying with the USP heparin monograph which does not allow a total potency per total volume statement to appear on the label. In order to decrease the potential for misinterpretation it is critical for practitioners to identify that the expression of potency is written as "per mL" and the total volume in the vial is 2 mL's so practitioners can recognize and then calculate that the vial actually contains a total of 2,000 USP units of heparin. Thus, the prominence of the words "per mL" in the expression of potency and the "2 mL" in the volume statement needs to be increased to have a prominence similar to the number "1,000" in the expression of potency to help decrease the potential for misinterpretation. We would like to provide some potential label designs that prominently display the "1,000" and "per mL" in the expression of potency and "2 mL" in the total volume statements, so the applicant can evaluate and decide which design appears to effectively aid a practitioner to identify this critical information.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation identified the expression of potency and the total volume statement on the 1,000 USP units per mL, 2 mL fill container label could be improved to minimize the potential for medication errors. We provide comments and recommendations for revisions in Section 4.1 that aim at reducing the risk of future medication errors.

The Division of Medication Error Prevention and Analysis would appreciate feedback on the final outcome of this review. If you have further questions or need clarifications, please contact Sue Kang, Project Manager, at 301-796-4216.

4.1 COMMENTS TO THE APPLICANT

Our assessment of the container labels and carton and package labeling indicates that the proposed 1,000 USP units per mL, 2 mL fill vial label is vulnerable to misinterpretation and could result in medication errors. It appears a practitioner could still misinterpret the expression of potency and the total drug content on of the vial. The prominence of the words "per mL" in the expression of potency and the "2 mL" in the total volume statement needs to be increased to have a prominence similar to the number "1,000" in the expression of potency to help decrease the potential for misinterpretation. If a practitioner can identify the expression of potency as per mL,"**1,000** USP Units **per mL**", and the total volume statement as "**2 mL**", then the practitioner may be able to recognize that the total potency of the vial must be calculated and that the vial contains a total of 2,000 USP units of heparin rather than 1,000 USP units of heparin. Correctly identifying and interpreting these statements may decrease the probability of a medication error. Please evaluate the potential label designs presented below or propose another design for the 1,000 USP units per mL, 2 mL fill container label that appears to effectively aid a practitioner to identify this critical information.

a.

1,000 USP units **per mL**
2 mL Single Dose Vial

b.

1,000 USP Units
per mL
2 mL Single Dose Vial

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/s/

SCOTT M DALLAS
03/18/2011

CAROL A HOLQUIST
03/18/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 9, 2011
To:	Ann Farrell, MD, Acting Director Division of Hematology Products HFD-160
Thru:	Carol Holquist, RPh, Director Division of Medication Errors and Prevention and Analysis HFD-420
From:	Scott Dallas, RPh, Safety Evaluator Division of Medication Errors and Prevention and Analysis HFD-420
Subject:	Amended DMEPA Heparin Labeling Review
Drug Name(s):	Heparin Sodium Injection, USP
Application Type / Number:	NDA 201370
Applicant/sponsor:	Pfizer Injectables
OSE RCM #:	2010 - 819

1 BACKGROUND

This review evaluates Pfizer's revised consolidated package insert, container labels and carton labeling for Heparin Sodium Injection, USP.

2 MATERIAL REVIEWED

We reviewed the following labels and labeling:

- Proposed 5,000 USP Units/mL, 1 mL container label (Appendix A)
- Proposed 10,000 USP Units/mL, 1 mL container label (Appendix B)
- Proposed 1,000 USP Units/mL, 2 mL container label (Appendix C)
- Proposed 1,000 USP Units/mL, 10 mL container label (Appendix D)
- Proposed 5,000 USP Units/mL, 10 mL container label (Appendix E)

3 DISCUSSION

A review of the revised container labels and carton labeling indicates the applicant made major revisions to the labels and labeling submitted as part of their original submission on March 8, 2010. Revisions included the incorporation of additional or multiple colors on a larger portion of the labels and labeling and revising the presentation or format of some text. Our review of the revised labels and labeling has identified the following deficiencies.

3.1 PACKAGE INSERT LABELING

The consolidated package insert labeling has failed to incorporate and identify a usage type for the vials as either a single dose or multiple dose containers. We acknowledge that four of the proposed presentations contain benzyl alcohol as a preservative which may lead one to believe the product can be used for multiple dosing. However, we are unsure if the proposed vial stopper is acceptable for multiple needle penetrations which would be required for a multiple dose container. Thus, to help ensure the safe use of these heparin products, then the package insert labeling needs to clearly identify the usage type for each container as either single dose or multiple dose.

3.2 CONTAINER LABELS

3.2.1 Net Quantity Statement

The net quantity statement appears to lack prominence on the currently proposed container labels. The lack of prominence of the net quantity statement is most notable on the 1 mL and 2 mL fill vials. The lack of prominence of the net quantity statement is especially concerning with the 2 mL fill vial. The small physical size of the 1,000 USP units per mL, 2 mL fill volume product could easily be misinterpreted to contain only 1 mL based solely on healthcare providers conditioned and learned experience with vials of similar size and shape. If a healthcare provider misinterprets the contents as 1 mL and administers the entire

contents of the vial, then the patient could receive an overdose or double the dose of heparin. Therefore, healthcare providers need to be able to easily comprehend the expression of potency statement as 1,000 USP units per mL and read the net quantity statement as 2 mL in order to calculate and determine that the vial actually contains a total of 2,000 USP units of heparin. Although DMEPA is most concerned with the presentation of the net quantity statement with the 2 mL fill volume vial, it appears that the prominence of the net quantity statement could be increased on all the labels. We note that it may be difficult to increase the prominence of the net quantity statement based upon the proposed format of information and the small amount of physical space on the principal display panel. Thus, in order to create more space we would like to propose that porcine heparin statement needs to be relocated to the side panel. To accommodate additional space on the side panel DMEPA recommends removal of the Dosage and Use statement. The Dosage and Use statement occupies three lines of space and provides no useful information to a healthcare provider. These revisions should provide additional space to increase the prominence of the net quantity statement.

3.2.2 Cautionary Statement "Not for Lock Flush"

The applicant has incorporated the cautionary statement "NOT for Lock Flush" in all capital letters a vertical orientation along side the principal display panel of the container labels. The readability of this statement appears negatively affected by presenting the statement in a vertical orientation and in all capital letters "NOT FOR LOCK FLUSH". Healthcare providers should be able to quickly identify, read and interpret warning or cautionary statements. Thus, the presentation of this statement needs further revisions to increase its readability, and could be accomplished by utilizing a number of techniques, such as using mixed case lettering, mixing formatting (bolding, underlining, font size), reverse lettering or reorienting the statement to a horizontal position.

3.2.3 Single Dose and Multiple Dose Statements

The applicant has failed to incorporate and identify a usage type for the vials as either single dose or multiple dose. These statements are important to help ensure healthcare providers use the product in an acceptable manner. When the type of usage is determined for these containers, then an appropriate usage statement, single dose or multiple dose, needs to be incorporated onto the container label.

3.3 CARTON LABELING

The comments under Sections 3.2.1, and 3.2.3 are applicable to the carton labeling as well.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation has noted areas where information on the consolidated package insert, container labels and carton labeling could be improved to minimize the potential for medication errors. We provide comments and recommendations for revisions in Section 4.1 and 4.2 that aim at reducing the risk of future medication errors.

The Division of Medication Error Prevention and Analysis would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sue Kang, Project Manager, at 301-796-4216.

4.1 COMMENTS TO THE DIVISION

DMEPA notes the labels and labeling fail to identify a usage type for the containers as either single dose or multiple dose. When the type of usage is determined for these containers, then an appropriate usage statement, single dose or multiple dose, needs to be incorporated into the package insert, container, and carton labeling.

4.2 COMMENTS TO THE APPLICANT

Our assessment of the consolidated package insert, container labels and carton labeling indicates that the presentation of information is vulnerable to confusion and could result in medication errors. Therefore, we recommend the following changes or request that the applicant submit additional information to support the proposed container labels and carton labeling.

A. Package Insert Labeling

We recommend a usage type statement for the containers as either single dose or multiple dose needs to be incorporated into the package insert labeling.

B. Container Labels

1. Increase the prominence of the net quantity statement (i.e. 1 mL, 2 mL, and 10 mL). Increasing the prominence of the net quantity statement while keeping the statement in close proximity to the expression of potency may decrease the risk of misinterpretation of the total drug contents in the vial. To create more space on the principal display panel we recommend relocation of the "Derived from porcine intestinal tissue" statement to the side panel and deletion of the (b) (4) (b) (4) statements from the label. Multiple techniques could be considered to increase the prominence of the net quantity statement. Techniques could include increasing the font size of the net

quantity statement, inclusion of the net quantity statement into the boxing for the 1 mL and 2 mL vial fill size (see below) or some other or combination of techniques.

1,000 USP units per mL
2 mL per vial

2. We recommend increasing the readability of the cautionary statement and suggest revising format of the statement "NOT FOR LOCK FLUSH" to appear as "**NOT for Lock Flush**" or "**NOT for Lock Flush**". The proposed presentation of the statement in all capital letters and in a vertical orientation is difficult to read. If the recommended formatting revisions do not appear to satisfactory increase the readability of the cautionary statement, then other options should be explored, such as but not limited to increasing the font size, using a combination of bolding and unbolding, reverse lettering or revising the statement to a horizontal orientation.
3. We recommend that a usage type statement for the containers as either single dose or multiple dose needs to be incorporated onto the container labeling.

C. Carton Labeling (trays)

Recommendations listed as B.2., and B.3., are applicable to the carton labeling.

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/s/

SCOTT M DALLAS
02/08/2011

CAROL A HOLQUIST
02/08/2011

MEMORANDUM

To: **Marcus Cato**
Division of Hematology Products

From: **Iris Masucci, PharmD, BCPS, Office of Medical Policy**
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **October 22, 2010**

Re: **Comments on draft labeling for heparin sodium injection**
NDA 201370

We have reviewed the proposed label for heparin sodium injection (FDA version received 10/7/10) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

Please see attached label for recommended changes.

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/s/

IRIS P MASUCCI
11/19/2010

LAURIE B BURKE
12/14/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 5, 2010
To:	Ann Farrell, MD, Acting Director Division of Medical Imaging and Hematology Products, HFD-160
Thru:	Carol Holquist, RPh, Director Division of Medication Errors and Prevention and Analysis, HFD-420
From:	Scott Dallas, RPh, Safety Evaluator Division of Medication Errors and Prevention and Analysis, HFD-420
Subject:	DMEPA Heparin Label Review
Drug Name(s):	Heparin Sodium Injection, USP
Application Type / Number:	NDA 201370
Applicant/sponsor:	Pfizer Injectables
OSE RCM #:	2010 - 819

1 INTRODUCTION

This review evaluates the proposed consolidated package insert, container labels and carton labeling for Heparin Sodium Injection, USP under the NDA 201370 from a medication error safety perspective per a request from the Division of Medical Imaging and Hematology Products (DMIHP).

1.1 REGULATORY HISTORY

The applicant has initiated a new NDA according to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The applicant has cross referenced two NDA's which were NDA 4-570 a bovine based product which has not been marketed since 2002, and NDA 17-346 a porcine based product which was withdrawn without prejudice in May 1992. The applicant has stated their intent to re-enter the market with a porcine-derived heparin product because the applicant believes there is a potential lack of heparin injectable supply.

2 MATERIAL REVIEWED

We reviewed the following proposed labeling and labels:

- Consolidated package insert labeling
- Container label 1,000 USP Units/mL, 2 mL, preservative free (Appendix A)
- Container label 5,000 USP Units/mL, 1 mL, preserved with benzyl alcohol (Appendix B)
- Container label 10,000 USP Units/mL, 1 mL, preserved with benzyl alcohol (Appendix C)
- Container label 1,000 USP Units/mL, 10 mL, preserved with benzyl alcohol (Appendix D)
- Container label 5,000 USP Units/mL, 10 mL, preserved with benzyl alcohol (Appendix E)
- Carton labeling 1,000 USP units/mL with a 2 mL fill volume (Appendix F)
- Carton labeling 5,000 USP units/mL with a 1 mL fill volume (Appendix G)
- Carton labeling 10,000 USP units/mL with a 1 mL fill volume (Appendix H)
- Carton labeling 1,000 USP units/mL with a 10 mL fill volume (Appendix I)

- Carton labeling 5,000 USP units/mL with a 10 mL fill volume, preserved with benzyl alcohol (Appendix J)

3 DISCUSSION

Our evaluation indicates the applicant needs to revise their consolidated package insert, labeling and labels to minimize the potential for confusion and to optimize the safe use of these injectables. Some of the requested revisions will promote consistency between the applicant's proposed labels and labeling with other marketed heparin sodium injectable labels and labeling from different manufacturers. Also, additional revisions are necessary to ensure the proposed labels and labeling is in agreement with the USP monograph for Heparin Sodium Injection.

3.1 PACKAGE INSERT

3.1.1 Title - Statement of Identity

The applicant proposes to title and identify the products as (b) (4) (b) (4)

Identifying the product in this manner could be confusing to practitioners, because the practitioner may think that this product is different than then other heparin injectable products. However, this product should be equivalent to other heparin product derived from porcine intestinal mucosa. Thus, to prevent confusion between heparin products, the product needs to be identified by the USP monograph name.

3.1.2 Dosage Formulation Statement

The applicant proposes to include the statement (b) (4) (b) (The use of the word (b) (4) may not be appropriate to indicate there are two different formulations. The word "or" may help alert practitioners there are actually two dosage formulations. In addition, to help promote consistency between consolidated package inserts it may be appropriate to follow the format of an approved consolidated package insert. Thus, a statement similar to "Available as: Preservative Free **or** Contains Benzyl Alcohol" might be more consistent with another approved and marketed package insert by APP Pharmaceuticals.

3.1.3 Expression of Potency

The applicant proposes to express the potency in terms of Units/mL. However, the expression of potency needs to be in agreement with the USP monograph labeling requirement for Heparin Sodium Injection. Thus the potency needs to be expressed in terms of USP Units/mL.

3.1.4 How Supplied Section

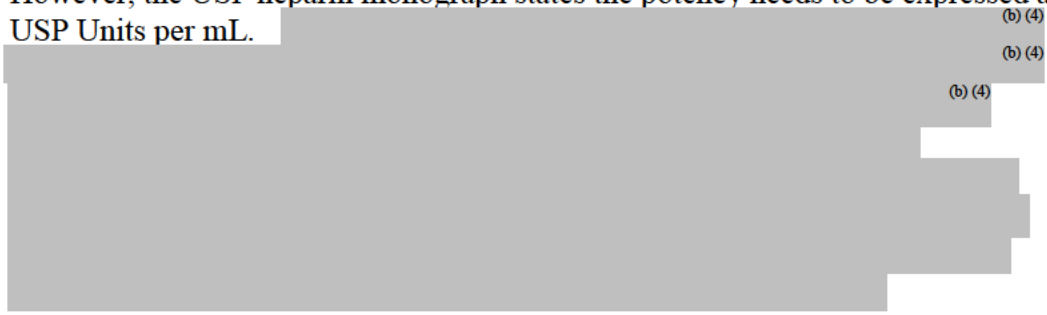
The applicant proposes to separate the two formulations using a table format in the How Supplied/Storage and Handling section. Although the table format appears to physically separate the two formulations the formulations can be further differentiated by bolding or highlighting the text "preservative free" and "benzyl alcohol".

3.2 CONTAINER LABELS AND CARTON LABELING

We noted the following with the proposed labels and labeling.

3.2.1 Expression of Potency

The applicant proposes to present the expression of potency as xx000 Units/mL. However, the USP heparin monograph states the potency needs to be expressed as USP Units per mL. (b) (4)



Additionally, the primary expression of potency displayed below the established name does not appear to be prominent enough to optimize the safe use of this product for all the labels except possibly the 2 mL vial. Thus, the prominence of the expression of potency below the established name needs to be increased on the labeling.

Moreover, the applicant proposes to present the expression of potency with reverse lettering on a colored background in the top portion of the label for the multiple dose vials. The presentation of the expression of potency in the top portion of the label is not consistent with other marketed heparin products. Presenting the most prominent expression of potency in the top portion of the label might be misinterpreted by practitioners to indicate that entire vial contains xxx units resulting in a 10 fold overdose.

Presenting the abbreviation USP with a capital letter U directly after the numeral 0 increases the risk the capital letter U might be misinterpreted for a numeral zero. This risk of misinterpretation can be decreased if the size of the letter U is reduced or further separated from the last numeral 0.

3.2.2 Cautionary Statement "Not for Lock Flush"

The applicant has not incorporated the cautionary statement "Not for Lock Flush" on the principal display panel of their labels and labeling. The FDA has requested that all manufacturers of Heparin Sodium Injection, USP vials include the

cautionary statement "NOT for Lock Flush" on their labels and labeling to help mitigate errors between concentrated heparin products and diluted or lock flush heparin products. Thus, the applicant needs to incorporate this statement on their labels and labeling to help ensure consistently with all marketed concentrated heparin products. The color red has been associated with warnings in this country. Therefore, the inclusion of the color red to the actual text or as a background color might help alert the practitioner that the purpose of the statement is to serve as a warning.

3.2.3 Benzyl Alcohol Warning Statement

The applicant proposes to include a statement printed in black type that reads (b) (4) This statement does not warn or alert the practitioner that this ingredient can be a hazard. Thus, this statement needs to be revised to be more consistent with another approved benzyl alcohol statement which reads "Warning: Contains Benzyl Alcohol". Inclusion of the word "warning" in the statement helps to alert the practitioner to determine what the potential hazard may be before administering the product. Other approved warning statements have also been printed in bolded red colored lettering. The color red has been associated with the concept of danger or warning in the U.S. Thus, the use of the color red with this statement might further alert the practitioner that the purpose of the statement is to warn the practitioner.

3.2.4 Total Volume Statement

The applicant proposes to place a total volume statement (b) (4) . Practitioners that normally dispense or administer heparin are probably more accustom to finding this statement on the lower portion of the label. Therefore, to be more consistent with other heparin sodium injection labels the total volume statement should be relocated to the lower portion of the label. In addition, the prominence of the statement needs to be increased so that practitioners can focus on the expression of potency and the total volume statement at the same time to help calculate the total drug contents of the vial.

3.2.5 Route of Administration Statement

The applicant proposes to present the route of administration statement on the side panel (b) (4) . If space permits, then we would prefer the route of administration statement appear on the principal display panel. The applicant has also proposed to include the negative statement (b) (4) We have attempted to limit the use of any negative statement, because practitioners can easily misinterpret the statement to indicate a positive intent. Thus, to decrease the risk of misinterpretation the negative route of administration statement should be removed from the label.

3.2.6 Dosage Statement

The applicant proposes to include a "Dosage and Use" statement that occupies 5 lines of space on the side panel. However, the proposed statement does not

provide the practitioner with any useful information and only decreases the amount of white space on the label. Therefore, it may be better to decrease or eliminate the amount of text devoted to the dosage statement, so that the readability of other information is enhanced.

3.2.7 "Rx only" Statement

The applicant proposes to include the "Rx only" statement on the principal display panel. Placement of this statement on the principal display panel increases the amount of clutter which can impair the readability of the label. Due to the limitations of space it would be acceptable to place this statement on the side panel if the readability of information on the principal display panel needs to be enhanced.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation notes areas where information on the consolidated package insert, container labels and carton labeling could be improved to minimize the potential for medication errors. We provide comments and recommendations for revisions in Section 4.1 that aim at reducing the risk of future medication errors.

The Division of Medication Error Prevention and Analysis would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sue Kang, Project Manager, at 301-796-4216.

4.1 COMMENTS TO THE APPLICANT

Our assessment of the consolidated package insert, container labels and carton labeling indicates that the presentation of information is vulnerable to confusion and could result in medication errors. Therefore, we recommend the following changes or request that the applicant submit additional information to support the proposed container labels and carton labeling.

A. Package Insert Labeling

1. Revise the title or statement of identity of the package insert to read "Heparin Sodium Injection, USP" (b) (4) [redacted]
2. Revise the proposed statement in the Highlights section (b) (4) [redacted] (b) (4) to appear as "Available as: Preservative Free **or** Contains Benzyl Alcohol", with the word "or" printed in bold.
3. Bold the statements "preservative free", and "benzyl alcohol" in the How Supplied section to help further differentiate the formulations.
4. Revise the expression of potency (b) (4) [redacted] to "USP units per mL" to be in agreement with the labeling requirement of the USP monograph for Heparin Sodium Injection.

5. Eliminate the numeral [redacted] from the designation [redacted] in the expression of potency (e.g. revise 5000 Units/1 mL to read 5,000 USP units/mL).
6. Revise the presentation of a number one thousand or greater to include a comma (e.g., the number 1000 should appear as 1,000).

B. Container Labels

1. Increase the prominence of the expression of potency statement appearing directly below the established name.
2. Revise the expression of potency statement to x,xxx USP units/mL to be in agreement with the USP monograph labeling requirement for Heparin Sodium Injection. Revise the statement in a method that decreases the risk the letter "U" in USP might be misinterpreted as a numeral zero. Possible methods to consider include decreasing the font size of the abbreviation USP, for example to ½ or ¾ the size of the numerals, including an additional space(s) between the last zero and the abbreviation USP, or by using a combination of bolding and unbolding to present the expression of strength. Other methods and techniques might also be evaluated.
3. Remove the reverse lettering expression of potency from the top portion of the multiple dose vials. The most prominent expression of potency for these multiple dose heparin product needs to be presented directly below the established name, unless the applicant has evidence to support their present proposal.
4. Include the cautionary statement "NOT for Lock Flush" on the principal display panel. The statement needs to appear as a unique or stand alone statement and not be embedded with other text. The cautionary statement needs to appear away from the route of administration statement and might appear above, below or to the side of other text on the principal display panel. In addition, we suggest the statement appear as a boxed format and include some red color, either for the lettering or as a background color in the boxed format.
5. Relocate the total volume statement to the lower portion of the label and below the expression of potency statement.
6. Revise the benzyl alcohol statement to appear with red colored lettering, possibly with a bolded font, and to read "Warning: Contains Benzyl Alcohol".
7. Relocate the route of administration statement to the principal display panel. If inclusion of this statement appears to decrease or hinder the readability of information on the principal display panel, then leave the statement on the side panel but increase the prominence of the route of administration.
8. Delete the [redacted] from the label.
9. We suggest that if additional blank or white space is needed on the principal display panel to reduce clutter and increase the readability of the information, then we suggest relocating the "Rx only" statement to the side panel.

10. We suggest if additional blank space or white space is needed on the side panel or to increase the area of the principal display panel, then we suggest decreasing the amount of text or eliminating the Dosage and Use statement.

C. Carton Labeling

Recommendations listed as B.1, 2, 4, 6, and 8 are applicable to the carton labeling.

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/s/

SCOTT M DALLAS
10/08/2010

CAROL A HOLQUIST
10/08/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pediatric and Maternal Health Staff – Pediatric Review

Date: September 28, 2010 **Date Consulted:** April 14, 2010

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader – Pediatric Team
Pediatric and Maternal Health Staff

Lisa Mathis, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: Heparin Sodium Injection, USP, NDA 201-370

Subject: Pediatric Use Labeling

Materials Reviewed: Heparin Sodium Injection, USP labeling

Consult Question: Please evaluate the current pediatric use labeling language in heparin sodium labeling for risks associated with benzyl alcohol.

INTRODUCTION

On March 8, 2010, Pfizer Inc. submitted a 505(b)(2) Application, NDA 201-370 for Heparin Sodium Injection (porcine derived) preserved with benzyl alcohol or preservative free formulations, as a 505(b)(2). The Referenced Listed Drug (RLD) is Phramacia & UpJohn's Heparin Sodium Injection, NDA 4-570 (discontinued). Submitted labeling reflects the approved text from NDA 4-570 with added safety information. In addition, the submitted labeling is in the Physician Lableing Rule (PLR) format.

Proposed indications for this 505(b)(2) Heparin Sodium Injection product include:

- Prophylaxis and treatment of venous thrombosis and pulmonary embolism;
- Prophylaxis and treatment of the 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;
- (b) (4) anticoagulant in blood transfusions, extracorporeal circulation, and dialysis procedures.

DHP consulted the Pediatric and Maternal Health (PMHS) Staff - Pediatric Team on April 14, 2010, to review the proposed pediatric use labeling.

This review provides PMHS – Pediatric Team's suggested revisions to the sponsor's proposed pediatric use information in Heparin Sodium Injection labeling. Appendix A of this review provides a tracked-changes version of labeling that highlights the recommended PMHS - Pediatric Team revisions.

BACKGROUND

Heparin Use in Children

Heparin is the most common anticoagulant drug used in children, and is mainly used for the treatment and prevention of thrombosis and for maintaining the patency of extracorporeal circuits and venous and arterial catheters. Adequate and well-controlled clinical trials have not been conducted with heparin in any pediatric age group and dosing recommendations, initially extrapolated from adult use are now based on long-term pediatric clinical experience. Andrew M and Michelson A, et al outline the following protocol for systemic heparin administration and adjustment for pediatric patients: [1]

[1] Andrew M, Michaleson A. Guidelines for antithrombotic therapy in pediatric patients. J Pediatrics . 1998;132(4):575-88

Pediatric Benzyl Alcohol Toxicity

Benzyl alcohol, 0.9% is an antimicrobial preservative widely used in a variety of drug products, especially those intended for multi-use, and in fluids for parenteral therapy. In 1982, two groups of investigators independently concluded that intravascular infusion or flush solutions containing benzyl alcohol, 0.9% caused severe metabolic acidosis, encephalopathy, and respiratory depression with gasping, leading to the death of 16 infants in neonatal intensive care units. This conclusion was based on the discovery of large amounts of benzyl alcohol and its metabolites, benzoic acid and hippuric acid, in the blood and urine of the affected neonates. The benzyl alcohol amounts found in the deceased neonates were in the lethal range for laboratory animals.[2,3]

In May 1982, FDA in conjunction with the American Academy of Pediatrics (AAP) and CDC issued a bulletin containing strong recommendations to warn pediatricians and hospital personnel against using fluids and diluents preserved with benzyl alcohol in newborn infants. In addition, the AAP recommended that medications containing benzyl alcohol also be avoided in newborn infants when possible.[4]

[2] Gershanik J, Boecler B, Ensley H, et al. The gasping syndrome and benzyl alcohol poisoning, NEJM. 1982;301:1384

[3] Brown W, Buist N, Gipson H, et al. Fatal benzyl alcohol poisoning in a neonatal intensive care unit. Lancet. 1982;1:1250

[4] American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs. Benzyl Alcohol: Toxic Agent in Neonatal Units. Pediatrics. 1983;72(3):356-8

Benzyl alcohol toxicity occurs in infants, particularly in low birth-weight infants, because greater amounts of benzyl alcohol are received relative to body weight, and the metabolic and excretory pathways are still immature.[5]

Pediatric Use Labeling

The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted.

PROPOSED SPONSOR LABELING (Dated August 9, 2010)

(b) (4)

[redacted]

[5] Hiller J, Benda G, Rahatzad M, et al. Benzyl alcohol Toxicity: Impact on mortality and intraventricular hemorrhage among very low birth-weight infants. 1986;77(4):500-6

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/s/

JEANINE A BEST
09/28/2010

HARI C SACHS
09/30/2010
I concur

LISA L MATHIS
10/06/2010

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Maternal Health Team Review

Date: September 27, 2010 **Date Consulted:** April 14, 2010

From: Richardae Araojo, Pharm.D.
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Through: Karen Feibus, MD
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Lisa Mathis, MD
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Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: Heparin Sodium Injection; NDA 201-370

Subject: Pregnancy and Lactation Labeling

Materials Reviewed: Pregnancy and Nursing Mother's subsections of proposed heparin labeling.

Consult Question: Please review the Pregnancy and Nursing Mother's subsections of heparin labeling.

INTRODUCTION

On March 8, 2010, Pfizer submitted a 505(b)(2) application (NDA 201-370) for Heparin sodium injection, derived from porcine intestinal tissue, to the Division of Hematology Products (DHP). The sponsor's proposed indications for heparin are:

- 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)

DHP requested the Maternal Health Team's (MHT) review of the Pregnancy and Nursing Mothers subsections of the sponsor's proposed Heparin labeling.

BACKGROUND

Heparin is an anticoagulant that acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot in inhibiting the activation of the fibrin stabilizing factor.

With regard to developmental toxicity, heparin is labeled with pregnancy category C based on a lack animal reproduction data and adequate and well controlled studies in pregnant women. However, unfractionated (and more recently low molecular weight) heparin has been widely used during pregnancy in the clinical setting for many years, and there is a wide body of literature available on heparin use during pregnancy. In a letter dated May 21, 2010, DHP requested that the sponsor provide (1) a review and analysis of published literature on heparin exposure during pregnancy and lactation, and (2) based on their analysis, recommend relevant language describing the data for inclusion in labeling.

On July 29, 2010, the sponsor submitted a response to the division's information request related to pregnancy and lactation. This review uses a tabular format to summarize the sponsor's review and analysis of published literature on heparin exposure during pregnancy and lactation and recommends revisions to the Pregnancy and Nursing Mothers subsections of the sponsor's proposed heparin labeling.

SUMBMITTED MATERIAL

On July 29, 2010, the sponsor submitted a 120-Day Safety Update for Heparin that included a review and analysis of published literature on heparin exposure during pregnancy and lactation. Provided below is a summary of the sponsor's submission.

Published Literature on Heparin Exposure during Pregnancy

The sponsor conducted a literature search on heparin exposure during pregnancy using Medline, Embase, Derwent, BIOSIS, CAB Abstracts and Current Contents through June 2010. The sponsor provided Table 1 below which summarizes relevant results from their literature search. Minor revisions were made to the sponsor's presentation of data when needed to provide clarification for the reader. The last column provides reviewer comments regarding each study.

Key (repeated at bottom of table): APS: antiphospholipid antibody syndrome; ASA: cetylsalicylic acid, aspirin; BMD: bone mineral density; Hx: history; IUGR: intrauterine growth restriction; LGA: large for gestational age; LMWH: low molecular weight heparin; NICU: neonatal intensive care unit; PROM: premature rupture of membranes; RPL: recurrent pregnancy loss; RR: risk ratio; sc: subcutaneous; SGA: small for gestational age; TM: trimester; UFH: unfractionated heparin; VTE: venous thromboembolism; *includes any bleeding; mostly minor; † Pregnancies with co-morbid conditions excluded

Table 1. Heparin Exposure in Pregnancy

	Number of Pregnancy Exposures	Pregnancy Outcomes	Infant Outcomes	Source	Reviewer comments:
1.	244 patients with therapeutic or prophylactic exposure (mean 62 days, 24,000 U/day) during pregnancy and/or first 6 weeks post partum	Pregnant: Thrombocytopenia: 10 (4%); Heparin induced thrombocytopenia (HIT): 0 Nonpregnant control: Thrombocytopenia: 26 (11%); HIT: 10 (4%)	*None reported*	Fausett, 2001	Retrospective cohort study comparing the incidence of HIT among 244 unfractionated heparin (UFH) treated pregnant women and 244 UFH treated nonpregnant women. Pregnant and nonpregnant women were identified by means of diagnosis related group and Current Procedural Terminology code searches at three medical centers in Utah. The incidence of HIT in the two groups was compared. Infant outcomes were not reported. The nonpregnant cohort was older than the pregnant cohort. The authors concluded that HIT is rare in pregnant women.
2.	100 pregnancies in 77 patients receiving heparin therapy	Significant bleeding: 2 Leg pain: 2	Prematurity: 8/91 (8.8%)† Spontaneous abortion: 1/30 (3.3%)† Stillbirth 3/93 (3.2%) Neonatal death: 1/90	Ginsberg, 1989	Retrospective cohort study of 100 pregnancies in 77 patients who received heparin for the prevention or treatment of venous thromboembolism (n=98) or for prosthetic heart valves (n=2). The study enrolled patients treated with heparin during pregnancy at three hospitals in Canada between January 1997 and

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
			(1.1%) Congenital malformation: 0†		December 1998. Patients were identified by medical records. Among the 100 pregnancies, heparin therapy was administered in 6 patients during the first trimester, in 2 during the second trimester, in 36 during the third trimester, in 28 during the second and third trimesters, in 1 during the first and second trimesters, and in 27 during all three trimesters. The mean duration of heparin therapy was 18 weeks (range, 0.75 to 42 weeks). Pregnancy outcomes: 9 premature births with normal outcomes, 1 premature birth resulting in a neonatal death at 25 weeks, 3 spontaneous abortions, 3 stillbirths, and one premature infant with Trisomy 21. The authors considered these rates of adverse fetal/neonatal outcomes similar to rates in published studies and rates in the hospitals studied. In addition, two episodes of significant maternal bleeding were reported - one postpartum and one during the second trimester. The authors concluded that heparin therapy during pregnancy is safe for the fetus and mother and that the frequency of maternal thrombotic recurrence is low.
3.	35 patients with high fetal umbilical artery flow ratio (systolic/diastolic)	*None reported*	None died, compared to 2 deaths in control group	Chu-Hong-Nu, 2005	Article in Chinese, abstract in English. Based on abstract, the study objective was to evaluate the efficiency of heparin on the ratio of peak systolic to least diastolic flow velocity (S/D) of umbilical artery flow velocity waveforms in second-trimester pregnancies. Sixty-seven pregnant women carrying 72 fetuses (5 twin gestations) with fetal umbilical artery flow S/D ratios greater than the 95th

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					percentage were divided into study and control groups. In the study group, 35 women carrying 38 fetuses were treated with heparin at a dose of 6250 U or 12,500 U + 5% glucose per day for a mean of 3.7 +/- 2.1 days (range 1 to 10 days). In the control group, 32 women with 34 fetuses were treated with dextrose (control) for a mean of 6.8 +/- 2.8 days (range 3 to 14 days). After treatment the S/D ratios were re-examined and compared between the two groups. The mean daily decrease in S/D ratio in the heparin group and control group was 0.37 ($t = 3.620$, $P < 0.01$) and 0.135 ($t = 3.061$, $P < 0.01$), respectively. There was a significant deference ($t = 1.998$, $P < 0.05$). The treatment time was significantly shorter in the heparin group than in the control ($t = 3.435$, $P < 0.01$). The effective rate was significantly higher in heparin group than in the control ($P < 0.01$). In the control group, there were 10 subjects with S/D ratios that continued to increase, and two fetuses died. No deaths occurred in the study group. The authors concluded that heparin can significantly decrease elevated S/D ratios of umbilical artery flow velocity waveforms in the second trimester of pregnancy, and it is effective in improving fetal outcomes.
4.	Prospective, single center trial; 50 gravidas with history of recurrent pregnancy loss and antiphospholipid	No significant difference in maternal outcomes.	Miscarriage: heparin/ASA – 20% ASA alone – 54% ($p<0.05$).	Kutteh, 1996	Prospective, single-center study to compare the use of low dose aspirin (ASA) alone to low-dose ASA and heparin to treat antiphospholipid antibody syndrome (APS). The study enrolled 50 patients with ≥ 3 spontaneous pregnancy losses and positive

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
	antibody syndrome alternatively assigned to ASA-alone or heparin and ASA (25 in each arm)		Live births: Heparin/ASA – 80%; ASA only – 46% ($p<0.05$)		antiphospholipid antibodies on two occasions. At the first confirmed pregnancy test, patients were alternatively assigned to receive daily low dose ASA (81mg/day) alone or with subcutaneous (sc) heparin (10,000 or 20,000 units/ml) every 12 hours until onset of labor. Heparin dosages were adjusted as needed to maintain 1.2 to 1.5 times the baseline PTT. Study treatment was restarted postpartum. There were 20 viable infants born to the 25 women treated with heparin plus low-dose aspirin (80%) compared with 11 viable infants from the 25 women who were treated with low-dose aspirin only (44%). The difference in rates of live births was significant ($p < 0.05$). There were no differences between the two groups in the estimated gestational age at birth, birth weight, or percentage of vaginal deliveries versus cesarean sections. There were no significant differences in maternal outcomes (gestational diabetes, minor bleeding, thrombocytopenia, preeclampsia or major bleeding). Five women treated with heparin plus ASA and 14 women treated with ASA alone had a spontaneous abortion after enrollment in the study. The authors concluded that heparin plus low-dose aspirin provides a significantly better pregnancy outcome than low-dose aspirin alone for APS associated recurrent pregnancy loss.
5.	28 women randomized to receive dalteparin or UFH to treat APS in	UFH: 4/13 (31%) live births Dalteparin: 9/13 (69%)	*None reported*	Stephenson, 2004	Randomized study comparing dalteparin to UFH for the treatment of APS in pregnancy. Between June 1998 and March 2001, the study enrolled women

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
	pregnancy	live births			with recurrent pregnancy loss or unexplained fetal demise and persistently positive antiphospholipid antibodies. A total of 28 women were randomized to receive ASA and dalteparin or UFH either preconceptionally or early in pregnancy. Among the 14 women in the dalteparin group, 13 conceived and there were 9 live births. Among the 14 women in the UFH group, 13 conceived and there were 4 live births. The remaining births resulted in miscarriage. The authors concluded that dalteparin used concomitantly with low dose ASA may be an effective alternative to UFH for the treatment of APS in pregnancy.
6.	53 pregnancies (51 singleton, 2 twin) with anti-phospholipid antibody syndrome treated with heparin	Route of delivery: 51% cesarean section, 49% vaginal delivery Outcomes: 27% fetal-placental disorders, 5.7% subchorionic hematoma, 1 PPROM @ 25 wks, No reports of 3rd trimester bleeding.	55 newborn infants. Mean birth weight 2,826g (range 800g – 4000g) 9%LGA, 1% SGA, Mean 5 minute APGAR- 9.6 (7-10) 12 NICU admissions, 3 of 4 IUGR neonates with placental infarction.	Ruffatti, 1998	Case series of 55 infants born to 53 antiphospholipid antibody (aPL) positive mothers who were treated with heparin calcium during pregnancy. Calcium heparin was self-administered subcutaneously 3 times daily at a dosage between 15,000 and 37,500 units. Treatment began at a mean estimated gestational age of 7.75 weeks ± 2.12 SD (range 5 - 15) and continued throughout pregnancy until delivery. There were 30 female infants and 25 male infants, including two sets of twins delivered between the 25^{th} and 40^{th} weeks gestation (mean 36.69 $\pm$ 2.91SD). One neonate was delivered before 30 weeks gestation, and 21 (39.62%) were delivered between 30 and 37 weeks gestation. Fetal-placental disorders were observed in 15 cases (27.27%) and

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					included growth retardation (n=5), oligohydramnios (n=4), growth retardation and oligohydramnios (n=3), abnormalities in placental circulation (n=1), and abnormal fetal heart rate (n=1). Maternal disorders occurred in 23 mothers and included: decreased antithrombin III (n=5), increased D-dimer (n=5), decreased antithrombin III with increased D-dimer (n=2), subchronic hematoma (n=3), premature rupture of membranes (n=3), hepatogestosis (n=2), preeclampsia (n=1), toxoplasmosis (n=1), and melanoma (n=1). In 2 women, fetal growth retardation occurred at 18 and 26 weeks gestation. When increased doses of heparin did not improve fetal growth, the women were started on intravenous Ig. Infant mean birth weight was 2.828 g ± 706.50 SD (range 800 - 4.000) and mean 5-minute Apgar score was 9.60 ± 0.68 SD (range 7 -10). Among the 55 infants, 43 were admitted to the nursery soon after delivery for times ranging between 3 and 13 days. Five of the infants (11.62%) had minor neonatal complications such as transient hyperbilirubinemia and/or hypoglycemia. No malformations were reported. Twelve infants (21.81%) were admitted to the neonatal intensive care unit for periods varying between 2 and 120 days (mean 30.33 ± 33.40 SD), after which the clinical course was normal. The authors reported that all neonates suffered from

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					complications due only to prematurity including transient tachypnea (n=3), mild pulmonary disease (n=5), respiratory distress (n=2), and prematurity alone (n=1). In addition, one of the 12 infants suffered from a number of problems all considered by the authors to be due to prematurity including respiratory distress syndrome, bronchopulmonary dysplasia, sepsis, disseminated intravascular coagulation, transient heart ischemia, intracranial hemorrhage, retinopathy, hyperbilirubinemia, and bilateral inguinal hernias. Signs of thrombosis or other aPL-related disorders were not observed in any of the newborns. During the follow-up period (infant age range between 1.33 and 5.66 years), none of the diseases suffered by the 55 children differed from those found in the normal pediatric population. In addition, none of the infants had aPL-related manifestations. The authors concluded that heparin calcium is an effective drug for the prevention of poor outcomes in newborns of aPL positive mothers.
7.	41 patients with Factor V Leiden or G20210A prothrombin gene mutation and history of prior adverse pregnancy outcome	80% reduction in risk of adverse pregnancy outcome compared to untreated pregnancies		Paidas, 2004	Paidas conducted an analysis of 41 patients (28 with Factor V Leiden and 13 with prothrombin G20210A gene mutations) with prior adverse pregnancy outcomes. The outcomes of pregnancies treated with antenatal heparin in the index pregnancy were compared to the outcomes of previous untreated pregnancies. The authors reported that pregnancies in which antenatal heparin was administrated had a nearly

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					80% reduction in the risk for overall adverse pregnancy outcome compared to untreated pregnancies (OR 0.21, 95% CI 0.11 0.39, P < 0.05). This persisted when first trimester losses were excluded (n= 111 total pregnancies, OR 0.46 95% CI 0.23, 0.94, P < 0.05). The authors concluded that antenatal heparin (UFH or LMWH) administration is associated with a lower rate of adverse pregnancy outcome in women with the Factor V Leiden or the prothrombin gene mutation G20210A who also had a history of poor pregnancy outcome.
8.	Case series; 2 patients with antithrombin III deficiency	1 uneventful delivery 1 surgical termination of pregnancy with "technical problems causing a loss of 300 – 400 mL blood" that was managed medically	1 uneventful delivery 1 pregnancy termination – indication not stated.	Brandt, 1981	Case report of two patients with antithrombin III (AT III) deficiency treated with scheparin for prolonged periods and purified antithrombin as needed. One patient received sc heparin (5,000 U twice daily) 3 weeks before anticipated delivery. During induction of labor the heparin was increased to 10,000 twice daily with ATIII infusion as needed. Delivery was uneventful with no abnormal bleeding. The neonatal outcome is not otherwise reported. The other patient with known AT III deficiency experienced two episodes of thrombosis early in pregnancy and subsequently terminated the pregnancy. Prior to procedure she received heparin 10,000 units sc twice daily and two courses of AT-III concentrate. The procedure had "technical problems" causing a loss of 300-400 ml blood and requiring oxytocin.
9.	123 patients with primary anti-phospholipid syndrome	BMD -3.7% at lumbar spine; -0.9% at femoral neck;	Not provided	Backos, 1999	Prospective study of bone mineral density (BMD) change during pregnancy and the puerperium in 123 women with primary antiphospholipid syndrome

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
	treated with ASA + low dose sc heparin: 46 UFH; 77 LMWH	no change at forearm. No fractures			treated with low-dose aspirin (75 mg) and sc low-dose heparin (46 UFH; 77 LMWH) 5,000 units every 12 hours. The mean duration of heparin treatment was 27 weeks. Lumbar spine, neck of femur and forearm BMD were measured at 12 weeks gestation, immediately postpartum, and 12 weeks postpartum. Of the 123 women, 119 (97%) received heparin until 34 weeks of pregnancy. Four women (3%) delivered between 32 and 34 weeks gestation. There were no heparin- induced bleeding complications, thrombocytopenia, hypersensitivity reactions, or symptomatic fractures. All women delivered live infants. BMD decreased by 3.7% ($P < 0.001$) at the lumbar spine and by 0.9% ($P < 0.05$) at the neck of femur. There was no significant change at the forearm. There was no significant difference in BMD changes between UFH and LMWH preparations. Baseline BMD measurements were osteopenic at the lumbar spine in 10 women and at the femoral neck in 8 women. Because of this, the authors questioned whether there was a decrease in BMD between starting heparin and the baseline measurement at 12 weeks gestation. The authors then measured BMD in a cohort of 9 women treated with aspirin and heparin prior to pregnancy and at 12 weeks gestation. The mean BMD increased by 1.8% ($p=0.01$) at the lumbar spine and by 1.1% (not significant) at the femoral neck between these two

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					time-points. The authors concluded that long-term heparin treatment during pregnancy is associated with a small but significant decrease in BMD at the lumbar spine and neck of femur. This finding is similar to that previously reported to occur in untreated pregnancies.
10.	Prospective matched cohort study: heparin = 25; matched controls = 25	Fracture = 0 Heparin-treated postpartum patients had BMD (dual photon densitometry) 0.082 gm/cm^2 lower than controls.	No data presented	Douketis et al, 1996	Prospective matched cohort study of lumbar spine bone density in postpartum women who received long term (>1 month) heparin therapy during pregnancy. Twenty-five women who received heparin during pregnancy and 25 matched controls underwent dual photon absorptiometry of the lumbar spine in the post-partum period. Indications for heparin included prior VTE (n=17), VTE in current pregnancy (n=4), prior VTE and lupus anticoagulant (n=2), prior VTE and Protein S deficiency (n=1), and mechanical heart valve (n=1). The patients were matched by age, weight and smoking status. None of the heparin treated patients developed symptoms suggestive of a fracture during the study or during the mean follow up period of 23.4 months. Breastfeeding was not mentioned. Heparin treated patients had lower bone density results than controls. The mean difference in bone density between matched pairs of heparin treated patients and control patients was 0.082 g/cm^2 (p = 0.0077). There were 6 matched pairs in which only the heparin-treated patient had a bone density below 1.0 g/ cm^2 compared to only one pair in which the control patient had a bone density below this level

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					(p = 0.089). The authors concluded that long-term heparin therapy in this study was associated with a significant reduction in bone density, although fractures were uncommon, and there was no significant correlation between lumbar bone density and the dose or duration of heparin. The outcomes of this study are confounded since it is not known whether the heparin treated group started with a lower BMD and therefore, if the authors chose an appropriate control group.
11.	Meta-analysis: UFH + ASA vs. ASA alone for RPL and APS (98 patients from 3 trials on UFH)	UFH+ASA: Less preeclampsia (RR 0.471) Preterm labor, no difference (RR 1.027)	UFH+ASA: More live births (74.27% vs. 55.83%; RR=1.301) Birth weight, no difference	Mak et al, 2010	Meta-analysis of five randomized controlled trials(published between 1996 and 2009) to assess whether heparin and aspirin is superior to aspirin alone in treating patients with recurrent pregnancy loss (RPL) and positive anti-phospholipid antibodies (aPL). The outcome measure for the meta-analysis was the proportion of pregnancies resulting in live births. Among the 334 patients in these trials, 171 received heparin and aspirin, and 163 were assigned to take aspirin only. The mean age of the participants was 33.38 years. Eighty-seven (13.4%) of the participants recruited in these trials had a history of recurrent early pregnancy and fetal losses, respectively, except for one study in which this information was not presented. None of the participants had a history of clinical vascular thrombosis. The overall live birth rates were 74.27% for heparin

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					and aspirin versus 55.83% for aspirin alone. Patients who received heparin and aspirin had significantly higher live birth rates (RR 1.301; 95% CI 1.040, 1.629) than aspirin alone. There were no significant differences in preeclampsia, preterm labor and birth weight between the groups. The authors concluded that the combination of heparin and aspirin is superior to aspirin alone in achieving more live births in patients with positive aPL antibodies and RPL.
12.	Case series; 10 patients sc heparin 15,000 or 30,000 IU daily	Preeclampsia: 2 cases No report of bleeding complications	10 live born neonates; 3 with respiratory distress syndrome	Ruffatti and Scapinello, 1996	Case series of 10 pregnant women with a history of at least 2 spontaneous abortions and positive for anticardiolipin antibodies (aCL). No patients had lupus anticoagulant activity. During pregnancy, the patients were treated with calcium heparin in doses varying between 15,000 and 30,000 IU daily (mean gestational age at start of heparin therapy was 10.8 weeks). Maternal problems that occurred during pregnancy included decreased free protein S and increased D-dimer (n=1), increased D-dimer (n=3), and decreased ATIII (n=2). In addition, two patients developed hepatogestosis in the third trimester. Fetal problems that occurred included oligohydramnios and growth retardation (n=1), oligohydramnios and reduced fetal movements (n=1), oligohydramnios (n=3), and abnormal fetal heart rate (n=1). All pregnancies delivered between the 31st and 38th

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					weeks (mean 35.6), birth weight range 1720g – 3660g. Maternal or fetal problems led to delivery in eight cases. No bleeding complications were reported, but minor events occurred (bruising, rashes, minor epistaxis). Seven of the ten neonates had normal perinatal courses and 3 experienced respiratory distress and required ventilator support for a few days after which their clinical course was normal. The authors did not state whether the 3 neonates that experienced respiratory distress were born prematurely. No malformations were observed. Six of the nine placentas examined (66.6%) showed signs of thrombotic events. The authors concluded that calcium heparin is effective and well tolerated; although it did not prevent minor maternal and fetal problems the outcomes were favorable.
13.	Retrospective chart review of 92 pregnant women treated with UFH: 62 adjusted dose 30 fixed-dose	Maternal hemorrhage 20 (19.4%)* Transfusion 2 (1.9%) VTE 2 (1.9%) Preeclampsia 6 (5.8%)	Fetal demise 8 (7.8%)	Clark et al, 2009	Retrospective study to review treatment, indication, and maternal and fetal outcomes in pregnant women who received anticoagulants at Kaiser Permanente in Colorado. Between January 1, 1998 and March 31, 2005, 93 mothers were prescribed an anticoagulant during 103 pregnancies. Among these women, one contributed three pregnancies and eight contributed two pregnancies. Maternal age range was 21 to 42 years. Most patients had a high body mass index at the time of pregnancy. Indications for anticoagulation included VTE prophylaxis (53.4%), history of pregnancy loss (29.1%), acute VTE (16.5%), and history of cerebral vascular accident (1.0%). The majority of patients

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					received UFH (89.3%), while others received LMWH (5.8%) or were switched between the two during pregnancy (4.9%). There were no maternal deaths. Fetal demise occurred in 8 cases (7.8%) at a median of 14 weeks gestation (range 7 to 22 weeks). No fetal demise occurred in pregnancies treated for acute VTE or history of CVA. Pulmonary embolism occurred in 2 women (one antepartum while receiving dalteparin and one postpartum while receiving warfarin). Maternal hemorrhage occurred in 19% (20/103) of the pregnancies. Hemorrhage was predominantly vaginal (n = 13) or related to a cesarean incision (n = 4). Most bleeding occurred in the postpartum period, including 2 episodes requiring blood transfusion. Two patients had subchorionic placental hematoma and one patient developed a subconjunctival hemorrhage. The fetus survived in each case. Other maternal complications included preeclampsia (n=6) and oligohydramnios (n=3). The authors concluded that maternal and fetal adverse events were infrequent in the study population and that UFH remains a viable treatment option during pregnancy.
14.	Prospective observational study: 25 consecutive pregnancies with Hx fetal loss and 7 with early DVT (UFH=23)	Successful pregnancy outcome 16/23 (69.6%)	Live births 17 Spontaneous abortion 6	Ghosh et al, 2008	The authors followed 32 consecutive pregnant women with thrombophilia and a history of recurrent fetal loss or DVT. Twenty-three women were treated with UFH and 9 with LMWH. Of the UFH treated patients, 16 of 23 resulted in a live birth and the remaining resulted in

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
					spontaneous abortion at varied gestational ages. All women treated with LMWH during pregnancy had live births and no spontaneous abortions. No treatment related side effects occurred and postpartum blood loss was within the normal range. The authors concluded that both UFH and LMWH were effective.
15.	Retrospective chart review: UFH or LMWH for acute VTE (UFH=12; LMWH=11)	UFH, n=12: Minor bleed: 2 (17%) Recurrent VTE: 1 (9%)	UFH, n=12: Fetal loss 1 (8%)	Malcolm et al, 2002	Retrospective chart review of all women treated for acute VTE in pregnancy at a Hospital in Canada from January 1990 to December 1999. Twenty-three cases were identified in which 12 were treated with UFH and 11 treated with LMWH. Maternal and fetal outcomes were similar between the two groups. In the UFH group, 2 mothers experienced minor bleeding, one mother had a VTE recurrence, and there was 1 fetal loss at 32 weeks gestation. The fetal loss occurred in a woman treated for DVT with UFH from 10 weeks gestation. Fetal autopsy revealed that the cause of death was placental infarction secondary to thrombosis of placental vessels. The authors concluded that LMWH can be effectively used for acute VTE in pregnancy and there is no difference in complication rate between LMWH and UFH. However, their sample size was limited.
16.	Retrospective chart review: 57 pregnancies in 46 women (adjusted-dose	Hematuria: 2 (3.5%) Allergic reaction: 3 (5.3%)	Preterm delivery: 10 (discharged in good health)	Perry et al, 1991	Retrospective review of 57 pregnancies in 46 women treated with UFH at a hospital in Pennsylvania. The indications for UFH use were multiple pregnancy loss, previous thromboembolic

Table 1. Heparin Exposure in Pregnancy					
	Number of Pregnancy Exposures	**Pregnancy Outcomes**	**Infant Outcomes**	**Source**	**Reviewer comments:**
	UFH; mean dose 25,500 IU SC daily)		Fetal loss: 5		event, and others not specified. Patients received subcutaneous UFH 25,500 IU daily (average) for an average of 20.3 weeks. There were no reported cases of clinically significant osteoporosis or thrombocytopenia. Gross hematuria occurred in 2 cases, but there were no cases of excess blood loss at delivery. There were 3 reported cases of allergic reactions. The authors reported a 26.3% rate of adverse fetal outcomes, which included 10 preterm births prior to 36 weeks and 5 fetal losses (first and second trimester). All preterm infants were later discharged in good health, and all fetal losses occurred in women with co-morbid conditions. The authors concluded that heparin is safe when used cautiously.

Key: APS: antiphospholipid antibody syndrome; ASA: cetylsalicylic acid, aspirin; BMD: bone mineral density; Hx: history; IUGR: intrauterine growth restriction; LGA: large for gestational age; LMWH: low molecular weight heparin; NICU: neonatal intensive care unit; PROM: premature rupture of membranes; RPL: recurrent pregnancy loss; RR: risk ratio; sc: subcutaneous; SGA: small for gestational age; TM: trimester; UFH: unfractionated heparin; VTE: venous thromboembolism;
*includes any bleeding; mostly minor; † Pregnancies with co-morbid conditions excluded

In addition to the articles summarized above, the sponsor referenced another publication by Ruffatti and colleagues, which is summarized below:

- **Ruffatti A, Orsini A, Di Lenardo L, et al. A prospective study of fifty-three consecutive calcium heparin treated pregnancies in patients with antiphospholipid antibody-related fetal loss. Clin Exp Rheumatol 1997; 15(5):499-505.**

  Prospective study to evaluate the efficacy and safety of calcium heparin administered alone for the prevention of fetal loss related to antiphospholipid antibodies (aPL). Fifty-three consecutively ascertained pregnancies (51 singleton, two twin) were followed in 53 patients who had a history of at least two consecutive miscarriages during the first trimester and/or one fetal death during the second or third trimesters. All patients had at least two positive aPL tests more than eight weeks apart before pregnancy or a positive aPL test at the beginning of pregnancy. Patients were treated with calcium heparin alone, self-administered subcutaneously three times daily at dosages varying between 15,000 and 37,500 units. Treatment was started soon after a sonogram demonstrated a live embryo (mean gestational age 7.75 weeks) and was continued throughout pregnancy until labor.

  Only minor side effects of heparin (bruising or rashes at injection site, minor epistaxis, and eosinophilia) were observed. The authors reported that all pregnancies ended favorably with 27 delivered by cesarean section and 26 vaginal deliveries. There were no congenital malformations reported; however, maternal/fetal problems included: IUGR (n=5), oligohydramnios (n=4), IUGR and oligohydramnios (n=3), abnormalities in placental circulation (n=1), IUGR, oligohydramnios, and abnormalities in placental circulation (n=1), and abnormal fetal heart rate (n=1).

  The authors concluded that calcium heparin administered alone is effective in achieving the delivery of viable infants and is well tolerated.

Based on the data presented above, the sponsor concluded that UFH is generally considered safe for the fetus and should be used as necessary for maternal indications. In addition, the sponsor states that the management of thrombophilia, thromboembolic complications, and anticoagulant therapy during pregnancy has been extensively reviewed and recommendations are provided in the 8th Edition of the American College of CHEST Physicians Guidelines.

Reviewer comments:

- *Based on the data presented above, among over 700 women who received UFH during pregnancy there did not appear to be increased risks of adverse maternal or fetal effects. This reviewer notes that some of these studies were conducted retrospectively and included small sample sizes. However, in many cases, treatment with UFH resulted in improved maternal and fetal outcomes.*

Published Literature on Heparin Exposure during Lactation

The sponsor states that for most antithrombotic agents, data on breastfeeding are limited. In addition, because of heparin's high molecular weight and strong negative charge, UFH does not pass into breast milk and can be safely given to nursing mothers.

Sponsor's Proposed Labeling Related to Pregnancy and Lactation

(b) (4)

[redacted]

DISCUSSION AND CONCLUSIONS

Heparin is an anticoagulant that inhibits reactions that lead to blood clotting and formation of fibrin clots. Heparin is currently labeled as pregnancy category C based on a lack animal reproduction data and adequate and well controlled studies in pregnant women. Historically, unfractionated heparin (UFH), and more recently low molecular weight heparin, have been used as standard antithrombotic therapy for pregnant women with venous thromboembolism and thrombophilias. Heparin has also been used in the clinical setting to reduce pregnancy wastage in women with recurrent pregnancy loss and antiphospholipid antibody syndrome. Because UFH has a large molecular weight, it does not cross the placenta or enter human milk.

The sponsor submitted a review of published literature on UFH use during pregnancy which was summarized in this review. These data showed that among over 700 women who received UFH during pregnancy there did not appear to be increased risks of adverse maternal or fetal effects. This reviewer notes that some of these studies were conducted retrospectively and included small sample sizes. However, in many cases, treatment with UFH resulted in improved maternal and fetal outcomes.

Based on the data presented in this review, the MHT recommends inclusion of relevant human data in heparin labeling. Provided below are the MHT's recommended revisions to the

Pregnancy and Nursing Mothers subsections of Heparin labeling based on relevant published data on heparin use during pregnancy.

RECOMMENDATIONS

1. The MHT recommends the following language for the Highlights, Pregnancy, and Nursing Mothers sections of heparin labeling. A track changes, word version of labeling will be forwarded to the division.

Highlights

----------CONTRAINDICATIONS----------

- Do not use heparin sodium injection preserved with benzyl alcohol in neonates, infants, pregnant women, or nursing mothers. When heparin therapy is needed in these populations, use Heparin Sodium Injection preservative free (4.2).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Limited human data. May cause fetal harm. Use preservative-free formulation (8.1).
- Nursing Mothers: Exercise caution. Use preservative-free formulation (8.3).

4 CONTRAINDICATIONS

4.2 The use of Heparin Sodium Injection, USP (porcine), preserved with benzyl alcohol is contraindicated in:

- Neonates, infants, pregnant women, and nursing mothers. Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. When heparin therapy is needed in these populations, use Heparin Sodium Injection preservative free *[see Use in Specific Populations (8.1, 8.3, 8.4)]*.

8.1 Pregnancy

Do not administer Heparin Sodium Injection, USP (porcine), preserved with benzyl alcohol to pregnant women *[see Contraindications (4.2) and Use in Specific Populations (8.3, 8.4)]*. When heparin therapy is needed during pregnancy, use Heparin Sodium Injection, USP (porcine), preservative free.

Pregnancy Category C (Heparin Sodium Injection, USP (porcine), preservative free)

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 less than the maximum human daily dose resulted in increased

resorptions. Use preservative-free heparin sodium during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 1/6 the maximum human daily dose. The number of early resorptions increased in both species. There was no evidence of teratogenic effects.

8.3 Nursing Mothers

Do not administer Heparin Sodium Injection, USP (porcine), preserved with benzyl alcohol, to nursing mothers *[see Contraindications (4.2) and Use in Specific Populations (8.4)]*. When heparin therapy is needed during lactation, use Heparin Sodium Injection, USP (porcine), preservative free.

It is unlikely that heparin is excreted in human milk because of its large molecular weight, and any heparin in milk would not be orally absorbed by a nursing infant. Exercise caution when administering Heparin Sodium Injection, USP (porcine), preservative free, to a nursing mother.

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/s/

RICHARDAE T ARAOJO
09/28/2010

Karen B FEIBUS
09/28/2010
I agree with the review of data, conclusions, and recommendations contained in this review.

LISA L MATHIS
10/06/2010

Division of Hematology Products
(DHP)

REGULATORY PROJECT MANAGEMENT LABELING REVIEW

Application Number: NDA 201370

Name of Drug: Heparin Sodium Injection USP

Sponsor: Pfizer Inc.

Materials Reviewed: Package Insert (PI)

Supporting Document Number: 1
Submission Date: March 8, 2010
Receipt Date: March 9, 2010

Background and Summary

Pfizer submitted NDA 201370 on March 8, 2010, (received March 9, 2010) for the following indications:

•Anticoagulant therapy in prophylaxis and treatment of venous thrombosis (b) (4) ;

• (b) (4)

• Prophylaxis and treatment of pulmonary embolism;
• Atrial fibrillation with embolization;
• (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)

Package Insert

The submitted PI generally follows the PLR format. The following comments should be conveyed to the sponsor:

I. GENERAL

A. You submitted two separate PIs one with preservative and one for preservative free.

Reviewer Comment: You should submit a single, all inclusive, package insert (to include Preservative Free presentations and Benzyl Alcohol presentations) with appropriate warnings and language.

II. HIGHLIGHTS OF PRESCRIBING INFORMATION section

B. The drug name in the title line reads "**HEPARIN SODIUM INJECTION,** (b) (4)

Reviewer Comment: Revise the title line to: "HEPARIN SODIUM INJECTION." (b) (4)

C. The Highlights exceeded one-half page.

Reviewer Comment: The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

D. In the "**DOSAGE AND ADMINISTRATION**" section, you included both a tabular format and free text.

Reviewer Comment: You should present all dosing regimens using a tabular format to enhance accessibility of information.

E. In the "**WARNINGS AND PRECAUTIONS**" section, you listed a number of warnings.

Reviewer Comment: In both the FPI and the Highlights, List W&P in decreasing order of importance (i.e., reflecting the relative public health significance).

F. In the "**ADVERSE REACTIONS**" section, you state "contact Pfizer at (1-800-438-1985 (b) (4)

Reviewer Comment: A general link company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].

III. FULL PRESCRIBING INFORMATION: CONTENTS section

G. You did not include the following section: "**15 REFERENCES.**"

Reviewer Comment: In both the FPI Contents and the FPI, Include the section heading "15 REFERENCES." In the FPI, list the references included on page 12 of your proposed package insert.

IV. FULL PRESCRIBING INFORMATION section

H. In the "**WARNINGS AND PRECAUTIONS**" section, you listed a number of warnings.

Reviewer Comment: See E above.

I. "**ADVERSE REACTIONS**" section.

Reviewer Comment: Include following statement: "The following adverse reactions have been identified during post approval use of Heparin Sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

J. You included the revision date on page 11 of your proposed package insert.

Reviewer Comment: The revision date at the end of highlights replaces the "revision" or "issued" date at the end of the prescribing information. The revision date should not appear in both places.

K. You included the phrase (b) (4) on page 10 of your proposed package insert.

Reviewer Comment: This statement is not required for the prescribing information, only container and carton labels.

Conclusions

1. The above comments should be sent to the sponsor.

2. The entire label should be reviewed by the review team, including the SEALD team.

_____
Marcus Cato, M.B.A.
Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

_____
Janet Jamison
Chief, Project Management Staff (Acting)
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Drafted: Cato. M/ May 10, 2010
Finalized: Cato. M/ May 12, 2010
Filename: N201370-0510109LblRev.doc
RPM LABELING REVIEW

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

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/s/

MARCUS A CATO
05/12/2010

JANET K JAMISON
05/12/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: April 30, 2010

To: Marcus Cato, MBA – Regulatory Project Manager
Division of Hematology Products (DHP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 201370
DDMAC labeling comments for Heparin Sodium Injection, USP

DDMAC has reviewed the proposed product labeling (PI) and proposed carton and container labeling for Heparin Sodium Injection, USP (Heparin) (preservative and preservative-free) dated March 8, 2010, and submitted for consult on April 14, 2010.

We offer the following comments.

Highlights

Use in Specific Populations

1. Should information from the Pediatric Use section of the full prescribing information describing deaths due to medication errors in this patient population be included in Highlights as well?

Full Prescribing Information

Indications and Usage

1. What is the rationale for placing the phrase, [redacted] (b) (4) in parentheses? We recommend either deleting the parentheses or deleting the phrase altogether. For example, the current Heparin PI contains the phrase, “Low dose regimen” without parentheses.

Carton and Container Labeling

We have reviewed the proposed carton and container labeling and have no comments at this time.

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

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/s/

MICHELLE L SAFARIK
04/30/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201370 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Heparin Sodium Injection USP Established/Proper Name: Heparin Sodium derived from porcine intestinal tissue Dosage Form: Injection Strengths: 1000 units/mL (10 mL vial, BA)† 1000 units/mL (2 mL vial) 5000 units/mL (1 and 10 mL vials)† 10000 units/mL (1 mL vial)†		
Applicant: Pfizer Inc. Agent for Applicant (if applicable): N/A		
Date of Application: March 8, 2010 Date of Receipt: March 9, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: January 9, 2011	Action Goal Date (if different):	
Filing Date: May 8, 2010	Date of Filing Meeting: April 19, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): □ Anticoagulant therapy [redacted] (b) (4)		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.***	☒ Standard ☐ Priority

If a tropical disease priority review voucher was submitted, review classification is Priority.	☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): PIND 106887	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	√			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	√			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***		√		More follow up needed
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		√		
If yes, explain in comment column.			√	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			√	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	√			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		√		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		√		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		√		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		√		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***		√		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		√		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		√		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		√		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			√	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	√			
Index: Does the submission contain an accurate comprehensive index?	√			
Is the submission complete as required under 21 CFR 314.50	√			

(*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		√		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			√	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	√			
Are all establishments and their registration numbers listed on the form/attached to the form?	√			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	√			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	√			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	√			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with	√			

authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				

Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			√	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	√			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	√			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			√	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	√			

<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		√		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	√			No OSE proprietary name review needed.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	√			
Is the PI submitted in PLR format?	√			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			√	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	√			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			√	
REMS consulted to OSE/DRISK?			√	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	√			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label			

	☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			√	

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			√	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			√	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			√	
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***			√	

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		√		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** December 2, 2009 ***If yes, distribute minutes before filing meeting***	√			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		√		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 19, 2010

BLA/NDA/Supp #: NDA 201370

PROPRIETARY NAME: Heparin Sodium Injection USP

ESTABLISHED/PROPER NAME: Heparin Sodium derived from porcine intestinal tissue

DOSAGE FORM/STRENGTH: Injection; 1000 units/mL (10 mL vial, BA)†
1000 units/mL (2 mL vial)
5000 units/mL (1 and 10 mL vials)†
10000 units/mL (1 mL vial)†

APPLICANT: Pfizer Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): □ Anticoagulant therapy (b) (4)

BACKGROUND: N/A

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Cato, Marcus	Y
	CPMS/TL:	Jamison, Janet	Y
Cross-Discipline Team Leader (CDTL)	Dr. Ali Al Hakim		Y
Clinical	Reviewer:	Lu, Min	Y
	TL:	Robie Suh, Kathy M	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Habtemariam, Bahru	Y
	TL:	Bullock, Julie	Y
Biostatistics	Reviewer:	Koti, Kallappa	Y
	TL:	Rothmann, Mark D	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Palmby, Todd	Y
	TL:	Saber, Haleh	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	

Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Ramaswamy, Muthukumar	Y
	TL:	Al Hakim, Ali H	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Miller, Denise	Y
	TL:	Langille, Stephen	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Perrella, Frank	Y
	TL:	Rivera Martinez, Edwin	N
OSE/DMEPA (proprietary name)	Reviewer:	N/A	
	TL:	N/A	
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:	N/A	

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**: None	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No Studies were conducted	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Bioequivalence data may not be needed	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**: None	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: None	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: • Need to request ALL Crude Heparin Sources (names, addresses, etc.) for EES • Will need additional Stability data	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**: Need to request ALL Crude Heparin Sources (names, addresses, etc.) for EES	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**: N/A	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Ann Farrell **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

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/

MARCUS A CATO
04/22/2010

JANET K JAMISON
04/22/2010