

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201370Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 201370

SUPPL # N/A

HFD # 161

Trade Name Heparin Sodium Injection USP

Generic Name Heparin Sodium derived from porcine intestinal tissue

Applicant Name Pfizer Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:



Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

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Name of person completing form: Marcus Cato  
Title: Regulatory Health Project Manager  
Date: 07/13/11

Name of Office/Division Director signing form: Ann T. Farrell  
Title: Director, Division of Hematology Products (Acting)

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARCUS A CATO  
07/14/2011

ANN T FARRELL  
07/21/2011

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 201370 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: DHP PDUFA Goal Date: Stamp Date: 4/11/2011  
10/11/2011

Proprietary Name: Heparin Sodium Injection USP

Established/Generic Name: Heparin Sodium derived from porcine intestinal tissue

Dosage Form: Injection

Applicant/Sponsor: Pfizer Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 6  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:**

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

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)  
 No: Please check all that apply:  
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)  
 Deferred for some or all pediatric subpopulations (Complete Sections C)  
 Completed for some or all pediatric subpopulations (Complete Sections D)  
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)  
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)  
 (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A:</b> Fully Waived Studies (for all pediatric age groups)
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Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:  
 Disease/condition does not exist in children  
 Too few children with disease/condition to study  
 Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.**

*additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

*If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.**

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:**

**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)  
 No: Please check all that apply:  
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)  
 Deferred for some or all pediatric subpopulations (Complete Sections C)  
 Completed for some or all pediatric subpopulations (Complete Sections D)  
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)  
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)  
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:  
 Disease/condition does not exist in children  
 Too few children with disease/condition to study  
 Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)
- Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.**

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

**This page was completed by:**

*{See appended electronic signature page}*

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 6/2008)**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARCUS A CATO  
07/12/2011

Heparin Sodium Injection, USP

1.3.3 Debarment Certification

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Pfizer Inc. 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.

Tricia Douglas, MS, RAC

 H-10-2010

Manager, Worldwide Regulatory Strategy

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 201370 BLA # N/A	NDA Supplement # N/A BLA STN # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Heparin Sodium Injection USP Established/Proper Name: Heparin Sodium derived from porcine intestinal tissue Dosage Form: Injection		Applicant: Pfizer Inc. Agent for Applicant (if applicable): Tricia S. Douglas Manager, Worldwide Regulatory Strategy
RPM: Marcus Cato		Division: DHP
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>N/A</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>N/A</p> <p>If no listed drug, explain.</p> <p><input checked="" type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input checked="" type="checkbox"/> Other (explain) This application relies on DESI findings</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: 07-21-11</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>October 11, 2011</u></li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  <input type="checkbox"/> None    CR, 04-07-11

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>2</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Carbohydrates/polysaccharides/Glycosaminoglycans/heparin</p> <p> <input type="checkbox"/> Fast Track  <input type="checkbox"/> Rolling Review  <input type="checkbox"/> Orphan drug designation         </p> <p> <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Direct-to-OTC         </p> <p>           NDAs: Subpart H  <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I  <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>           BLAs: Subpart E  <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H  <input type="checkbox"/> Approval based on animal studies         </p> <p>           REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input checked="" type="checkbox"/> REMS not required         </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	07-21-11
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP 07-21-11, CR 04-7-11
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	07-21-11
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	03-08-10
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	APP_11-22-2010

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	04-1-11
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	N/A
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 05-12-10 <input checked="" type="checkbox"/> DMEPA 10-8-10; 2-8-11; 3-18-11, 4-6-11 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 4-30-10 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews MHT 10-6-10; 6-29-11; Peds 10-6-10, 6-15-11; SEALD 12-14-10
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	4-22-10, 4-4-11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) 7-14-11, 4-6-11
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input type="checkbox"/> Not a (b)(2) 7-14-11
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Not new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA.</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters (except action letters), emails, faxes, telecons)</i>	3-19-10,5-21-10,6-29-10,7-15-10, 9-16-10,9-20-10,10-29-10,11-3-10, 11-22-10,1-5-11,2-1-11, 2-5-11,2-25-11, 4-6-11, 4-21-11(2), 6-15-11, 7-11-11
❖ Internal memoranda, telecons, etc.	1-27-10, 10-5-10, 5-5-11
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 12-16-09
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	7-29-09, 10-20-09
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	N/A
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	N/A
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7-14-11, 4-7-11
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3-25-11, 6-28-11
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	03-12-11, 7-8-11
• Clinical review(s) <i>(indicate date for each review)</i>	4-20-10, 3-9-11, 6-23-11
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	N/A 3-9-11
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4-22-10, 3-4-11
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4-22-10, 3-4-11
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4-20-10, 3-4-11, 6-24-11
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4-20-10, 3-4-11, 6-24-11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
<b>❖ Product Quality Discipline Reviews</b>		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None 2-17-11
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 4-22-10, 6-30-10, 1-28-11, 4-6-11
<b>❖ Microbiology Reviews</b>		<input type="checkbox"/> Not needed 4-9-10, 3-4-11
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i></b>		<input checked="" type="checkbox"/> None
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		6-30-10 (page 39-40)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
<b>❖ Facilities Review/Inspection</b>		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup>)</i>		Date completed: 6-28-11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i></b>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/  
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MARCUS A CATO  
07/21/2011

## Cato, Marcus

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**From:** Cato, Marcus  
**Sent:** Thursday, July 14, 2011 3:24 PM  
**To:** Cato, Marcus  
**Subject:** FW: NDA 201370 - cleared for action

---

**From:** Duvall Miller, Beth A  
**Sent:** Thursday, July 14, 2011 8:20 AM  
**To:** Cato, Marcus  
**Cc:** Kim, Tamy  
**Subject:** NDA 201370 - cleared for action

Hi Marcus,

After reviewing the various responses to the emails regarding this application, your previous clearance from a 505(b)(2) perspective still applies with the following two caveats:

- Per Janice Weiner's 7/12/11 email: 'The question regarding therapeutic equivalence would not impact 505(b)(2)-related clearance issues, but should be resolved around the time that an action is taken on the application.'
- Reviews should document the appropriate reason for granting a biowaiver issue – this was the subject of several separate email strings in April 2011.

Finally, make sure you have made the corrections to your 505(b)(2) assessment that were listed below in my 4/6/11 email before archiving in DARRTS. Thanks,

Beth

*Beth Duvall-Miller*

Team Leader, Regulatory Affairs Team  
CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

---

**From:** Duvall Miller, Beth A  
**Sent:** Wednesday, April 06, 2011 4:29 PM  
**To:** Cato, Marcus  
**Cc:** Weiner, Janice; Kim, Tamy  
**Subject:** NDA 201370 - cleared for CR action

Hi Marcus,

Your application has been cleared for action from a 505(b)(2) perspective contingent upon the biowaiver issue having been addressed (the subject of several separate email strings). We also note that DHP and ONDQA previously confirmed that there is no need to rely upon the withdrawn NDA for bovine-sourced heparin.

Please make the following changes to your 505(b)(2) assessment but hold off on archiving in DARRTS until you are nearing an approval action. We will need to clear

your application again during subsequent review cycle(s) so please let me know when the resubmission arrives.

- Q1: Response should be 'yes'. Please also delete the comment under your response (b) (4)
- Q4: Response to 'a' should be 'yes'; response to 'b' should be 'no'. Skip 'c'.
- Q6: Remove the text under the table, i.e., leave this response entirely blank.
- Q8: Leave all responses blank since there is no reliance on a listed drug (i.e., the listed drugs are being cross-referenced, not relied-upon)
- Q10: Response should be 'no' since the 5,000 units/mL is a new presentation.
- Q11: Leave responses blank.
- Q12: Leave blank since there are no listed drugs relied-upon in this application.
- Q14: Deselect 'no relevant patents' statement. Select 'Paragraph II certification' since Pfizer did submit a Para II certification in their application. But please include a comment under that selection to say that patent certification was not necessary since Pfizer was cross-referencing their own application.

Beth

*Beth Duvall-Miller*

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

## Cato, Marcus

---

**From:** Cato, Marcus  
**Sent:** Monday, July 11, 2011 2:30 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** NDA 201370 INFORMATION REQUEST

**Importance:** High

**Attachments:** IRLab-0414-1-0-pkg-insert-track.doc

Dear Ms. Douglas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We are reviewing the product labeling in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

### PACKAGE INSERT LABELING

1. Submit a revised package insert for NDA 201370 with revisions to the sections, as shown in the attached labeling. Additions and deletions are denoted in tracked changes format as well as double underline and ~~strike through~~ letters.



IRLab-0414-1-0-pkg  
-insert-trac...

Please provide a revised package insert by **COB Wednesday July 13, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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/s/  
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MARCUS A CATO  
07/11/2011

## Cato, Marcus

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**From:** Cato, Marcus  
**Sent:** Wednesday, June 15, 2011 11:46 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** NDA 201370 INFORMATION REQUEST

**Attachments:** IR-lab-0414-1-0-pkg-insert (6-13-11).doc

Dear Ms. Douglas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We are reviewing the product labeling in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

### PACKAGE INSERT LABELING

1. Submit a revised package insert for NDA 201370 with revisions to the sections, as shown in the attached labeling. Additions and deletions are denoted in tracked changes format as well as double underline and ~~strike through~~ letters.



IR-lab-0414-1-0-pk  
g-insert (6-...

Please provide a revised package insert by **COB Monday June 20, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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/s/  
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MARCUS A CATO  
06/15/2011

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** Wednesday, April 27, 2011  
**TIME:** 1:00 – 1:45 PM, EST  
**LOCATION:** White Oak Building 22  
**APPLICATION:** NDA 201370  
**DRUG NAME:** Heparin Sodium Injection, USP  
**TYPE OF MEETING:** Teleconference

**MEETING CHAIR:** Eric Duffy, Ph.D.,

**MEETING RECORDER:** Marcus Cato, M.B.A.

### **FDA ATTENDEES:**

#### OFFICE OF PHARMACEUTICAL SCIENCE/ OFFICE OF NEW DRUG QUALITY ASSESSMENT/ DIVISION OF NEW DRUG QUALITY ASSESSMENT

Eric Duffy, Ph.D., Division Director  
Ali H. Al-Hakim, Ph.D. Branch Chief, Office of New Drug Quality Assessment  
Deborah Mesmer, Regulatory Project Manager, Quality

#### OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS DIVISION OF HEMATOLOGY PRODUCTS

Ann Farrell, M.D., Director (Acting)  
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader  
Min Lu, M.P.H., M.D., Clinical Reviewer  
Marcus Cato, M.B.A., Regulatory Health Project Manager  
Diane Leaman, Safety Regulatory Health Project Manager

#### OFFICE OF COMPLIANCE/ DIVISION OF MANUFACTURING AND PRODUCT QUALITY

Frank Perrella, Ph.D., Product Reviewer  
Cesar Matto, Compliance Officer  
Milva Melendez, Compliance Officer

### **EXTERNAL CONSTITUENT ATTENDEES:**

Jacqueline D. Schumacher - Global CMC, Pfizer  
Fred Haller - Manufacturing, Pfizer  
Joe Heissler - Safety, Pfizer  
Doug Ross - Medical, Pfizer  
Wesley E. Workman - Quality Operations, Pfizer  
Tricia Douglas - Regulatory Lead, Pfizer

## BACKGROUND:

On April 7, 2011, the Division of Hematology Products issued a complete response letter citing facility inspection deficiencies at both the (b) (4) manufacturing facilities for NDA 201370. In a submission dated April 11, 2011, Pfizer submitted correspondence stating:

Pfizer will not use the following crude heparin suppliers, which are currently included within DMF (b) (4). Our current, planned commercial supply chain does not necessitate their inclusion. Pfizer commits not to use crude heparin from the above referenced suppliers in commercial product. The updated Letter of Authorization reflects these changes. Furthermore, the Pfizer facility in Ohio (subject of DMF 2712) has appropriate quality systems in place to differentiate the incoming crude from these suppliers and the resultant purified heparin sodium.

In e-mail correspondence dated April 14, 2011, the sponsor clarified that it intended to remove the suppliers from the NDA only and not from the DMF. After receipt of the acknowledgement letter Pfizer requested clarification on the implications that withdrawing the two suppliers from the DMF (2712) would have on the NDA application (201370).

## MEETING OBJECTIVES:

(b) (4)

## DISCUSSION POINTS:

- FDA obtained confirmation that Pfizer was authorized to represent Hepar and that confidential information could be discussed.
- Pfizer explained that the NDA (201370) includes a letter of authorization to DMF 2712. Pfizer has updated DMF 2712 and submitted correspondence to NDA 201370 describing its intent to exclude crude heparin supplied from (b) (4). This would be accomplished by its quality systems (Material Resource Planning (MRP)). Pfizer briefly described the system. Pfizer stated that batches from the different suppliers would not be comingled.
- FDA advised Pfizer that it should submit both a detailed description and the actual procedures (MRP) that would be used to segregate and exclude crude heparin supplied from the two sites.
  - Pfizer should submit an amendment to the DMF with this information and correspondence to the NDA cross-referencing the DMF amendment.
- Pfizer inquired about what deficiencies were found at the two sites and how it might safeguard against them in the future. FDA mentioned that it was not at liberty to speak on specific cases under review, but described the general nature of the inspection process and why there might be delays in Pfizer receiving more information. FDA assured Pfizer that follow-up with the manufacturers would be clearer as the process nears completion.
- Pfizer asked about withdrawal of (b) (4) from DMF 2712 and the possibility of reinstating these suppliers at a later date. FDA stated that withdrawal of the suppliers from DMF 2712

would simplify things. Reinstating the suppliers could be accomplished via normal regulatory procedures for amending a DMF.

- FDA advised that the review timeline would remain unchanged but it is interested in expeditiously completing its review. Pfizer stated that the DMF and NDA amendments would be submitted within a few days.

**DECISIONS (AGREEMENTS) REACHED:**

Pfizer will amend the DMF and NDA application by the end of the week to add details of the MRP and the actual procedures to the DMF and cross reference to the NDA.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

No unresolved issues or issues requiring further discussion.

**ACTION ITEMS:**

Pfizer will amend the DMF and NDA application by the end of the week.

**ATTACHMENTS/HANDOUTS:**

No attachments or handouts provided.

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/s/  
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MARCUS A CATO  
05/05/2011

ERIC P DUFFY  
05/05/2011



NDA 201370

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Douglas:

We acknowledge receipt on April 11, 2011, of your April 11, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection USP.

We consider this a complete, class 2 response to our April 7, 2011, action letter. Therefore, the user fee goal date is October 11, 2011.

If you have any questions, call me at (301) 796-3903.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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MARCUS A CATO  
04/21/2011

**Cato, Marcus**

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**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Thursday, April 14, 2011 4:01 PM  
**To:** Cato, Marcus  
**Cc:** Lambert, Tu-Van  
**Subject:** RE: Heparin NDA 201370

Dear Marcus,

We are removing the suppliers from the NDA only – I need to contact my CMC colleagues to get an answer to your second question. I will be in touch shortly

*Regards,  
Tricia*

*Tricia S. Douglas*

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
219/9/S14

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**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Thursday, April 14, 2011 3:53 PM  
**To:** Douglas, Tricia S  
**Cc:** Lambert, Tu-Van  
**Subject:** RE: Heparin NDA 201370  
**Importance:** High

Hi Tricia,

We have received your response. we have the following clarifying questions:

Will these facilities (b) (4) be withdrawn from the application as well as the DMF? The language used is not clear to whether you are withdrawing the sites or simply committing to not using material from these sites. Also, please clarify if the Pfizer Ohio faculty is indeed still receiving the crude heparin from these sites.

Best,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)

(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Thursday, April 14, 2011 11:19 AM  
**To:** Cato, Marcus  
**Subject:** Heparin NDA 201370  
**Importance:** High

Dear Marcus,

Just checking in on the status of the response submitted to the Complete Response Letter. Please share any feedback you may have. Many thanks in advance

*Regards,  
Tricia*

*Tricia S. Douglas*

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

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219/9/S14

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/s/  
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MARCUS A CATO  
04/21/2011

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Wednesday, March 30, 2011 7:44 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

With regard to the requested carton labeling changes; does the Agency object to applying these revisions to all presentations, for consistency?

*Regards,*  
*Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)  
[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
219/9/S14

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Tuesday, March 29, 2011 9:04 AM  
**To:** Douglas, Tricia S  
**Subject:** NDA 201370 Information Request

Hi Tricia,

We are reviewing your NDA submission and would like to request a written response to the attached request for information. A hard copy of this letter should follow in the mail. If possible, please reply with revised labels by **COB Friday, April 1, 2011**.

Please feel free to contact me directly, should you have any questions. **Please confirm receipt of this message.**

Kind Regards,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
[Marcus.Cato@fda.hhs.gov](mailto:Marcus.Cato@fda.hhs.gov)

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**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, March 29, 2011 1:34 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

With regards to the USPI please clarify the purpose of the approval date in the Highlights section. Is this the a general approval date for all Heparins or is the original approval date for Pfizer Heparin. If it is the latter, then it should be 1942. Please confirm.

Also, section 17 cross references section 7 – Pfizer believes that the cross reference should be section 7.1 ( more specific and accurate) – please confirm your concurrence.

Looking forward to your response and thanks in advance

*Regards,  
Tricia*

*Tricia S. Douglas*

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
219/9/S14

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Tuesday, March 29, 2011 12:46 PM  
**To:** Douglas, Tricia S  
**Subject:** RE: NDA 201370 Information Request

yes

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, March 29, 2011 12:46 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Hi Marcus,

It seems like our tracked changes from the last revision/submission were not accepted. New revisions by FDA are in red while Pfizer's previous revisions are in blue. Can we assume that our previous revisions are accepted (blue)?

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
219/9/S14

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Tuesday, March 29, 2011 9:04 AM  
**To:** Douglas, Tricia S  
**Subject:** NDA 201370 Information Request

Hi Tricia,

We are reviewing your NDA submission and would like to request a written response to the attached request for information. A hard copy of this letter should follow in the mail. If possible, please reply with revised labels by **COB Friday, April 1, 2011**.

Please feel free to contact me directly, should you have any questions. **Please confirm receipt of this message.**

Kind Regards,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
[Marcus.Cato@fda.hhs.gov](mailto:Marcus.Cato@fda.hhs.gov)

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## Cato, Marcus

---

**From:** Cato, Marcus  
**Sent:** Tuesday, March 29, 2011 9:20 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: From FDA - Heparin DMF Information request

Dear Ms. Douglas,

I apologize if you were caught off-guard by the recent DMF request.

1. Does this impact our PDUFA goal?

I am not in a position to comment on how this request affects your goal date other than state that it does not change or modify it.

2. Why are we receiving this information request so close to the PDUFA goal date? It is dated 3/10/11 and we received it 3/25/11

The information request (hard copies) are mailed via the US-mail system. It is often our practice to e-mail letters so that they arrive in advance of the hard copy, however, this is done as a courtesy and we are not always able to do so.

3. We tried to stay in close contact with the Division regarding expected information requests, were you aware of this?

I was not aware of this letter.

4. I spoke with the CMC PM with the same concerns and she explained that she would provide feedback from the review management team, can you do the same?

I will touch base with her. It is the same review team so I will let her be the point of contact for the requested feedback.

5. What is the status of the expected minor revisions to the USPI and carton labeling?

The requested revisions to the USPI and container labeling were sent a little while ago.

Thanks

~Marcus

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-----Original Message-----

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Monday, March 28, 2011 11:13 AM  
**To:** Cato, Marcus  
**Cc:** Lambert, Tu-Van  
**Subject:** FW: From FDA - Heparin DMF Information request  
**Importance:** High

Dear Marcus,

Please see attached Information Request that we receive Friday afternoon. We have the following concerns and hope that you can provide some insight;

1. Does this impact our PDUFA goal?
2. Why are we receiving this information request so close to the PDUFA goal date? It is dated 3/10/11 and we received it 3/25/11
3. We tried to stay in close contact with the Division regarding expected information requests, were you aware of this?
4. I spoke with the CMC PM with the same concerns and she explained that she would provide feedback from the review management team, can you do the same?
5. What is the status of the expected minor revisions to the USPI and carton labeling?

Thank you in advance and I hope to hear from you soon

Regards,  
Tricia

Tricia S. Douglas  
Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

tricia.douglas@pfizer.com  
219/9/S14

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Tuesday, March 29, 2011 9:22 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

This would need to be an official submission, I think our e-mails crossed as I just sent a reply when this one came in.

Warmly,

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, March 29, 2011 9:19 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request

Dear Marcus,

Thank you for your email. Do we need to submit an official submission or is email OK?

Can you share any insight on my email and voice message from yesterday and this morning? Thank in advance and looking forward to your response as we are approaching our PDUFA goal date of April 9, 2011

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
219/9/S14

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]

**Sent:** Tuesday, March 29, 2011 9:04 AM  
**To:** Douglas, Tricia S  
**Subject:** NDA 201370 Information Request

Hi Tricia,

We are reviewing your NDA submission and would like to request a written response to the attached request for information. A hard copy of this letter should follow in the mail. If possible, please reply with revised labels by **COB Friday, April 1, 2011**.

Please feel free to contact me directly, should you have any questions. **Please confirm receipt of this message.**

Kind Regards,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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## Cato, Marcus

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Monday, March 28, 2011 11:13 AM  
**To:** Cato, Marcus  
**Cc:** Lambert, Tu-Van  
**Subject:** FW: From FDA - Heparin DMF Information request

**Importance:** High

**Attachments:** dmfin001.PDF



dmfin001.PDF (90 KB)

Dear Marcus,

Please see attached Information Request that we receive Friday afternoon. We have the following concerns and hope that you can provide some insight;

1. Does this impact our PDUFA goal?
2. Why are we receiving this information request so close to the PDUFA goal date? It is dated 3/10/11 and we received it 3/25/11
3. We tried to stay in close contact with the Division regarding expected information requests, were you aware of this?
4. I spoke with the CMC PM with the same concerns and she explained that she would provide feedback from the review management team, can you do the same?
5. What is the status of the expected minor revisions to the USPI and carton labeling?

Thank you in advance and I hope to hear from you soon

Regards,  
Tricia

Tricia S. Douglas  
Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

tricia.douglas@pfizer.com  
219/9/S14

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Thursday, March 24, 2011 9:13 AM  
**To:** 'Douglas, Tricia S'  
**Cc:** Newman, Tyree  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

It is not currently necessary for Pfizer to submit another waiver request. FDA withdraws the 3/16/11 information request.

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Wednesday, March 23, 2011 9:59 AM  
**To:** Cato, Marcus  
**Cc:** Newman, Tyree  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

Is there an update on the below? We are approaching our PDUFA goal date of April 9, 2011 and we would like to avoid any delays if possible.

Also is there an update on the minor revisions to the USPI and carton labeling?

Thanks in advance, looking forward to your response

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017

4/6/2011

Reference ID: 2928992

212- 733-6189 office

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[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Wednesday, March 16, 2011 2:49 PM  
**To:** Douglas, Tricia S  
**Cc:** Newman, Tyree  
**Subject:** NDA 201370 Information Request

Hi Tricia,

We are reviewing your NDA submission and would like to request a written response to the below request for information. If possible, please reply by **COB Friday, March 18, 2011**.

Regarding the biowaiver request you submitted: In your request, the basis you provided for requesting the waiver does not apply here. Submit another waiver request citing the appropriate criteria under 21 CFR 320.22 for which you are seeking a waiver from the requirements.

Please feel free to contact me directly, should you have any questions. **Please confirm receipt of this message.**

Kind Regards,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
[Marcus.Cato@fda.hhs.gov](mailto:Marcus.Cato@fda.hhs.gov)

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4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Thursday, March 17, 2011 4:26 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

I am working internally on a clarification of the below request. You may disregard the Friday deadline.

Kindly,

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Wednesday, March 16, 2011 9:02 PM  
**To:** Cato, Marcus  
**Cc:** Newman, Tyree  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

Can you clarify whether the issue is with the CFR citation being incorrect or the inclusion of the legacy product information – hope to hear from you soon and thank you in advance

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Wednesday, March 16, 2011 2:49 PM

4/6/2011

Reference ID: 2928992

**To:** Douglas, Tricia S  
**Cc:** Newman, Tyree  
**Subject:** NDA 201370 Information Request

Hi Tricia,

We are reviewing your NDA submission and would like to request a written response to the below request for information. If possible, please reply by **COB Friday, March 18, 2011**.

Regarding the biowaiver request you submitted: In your request, the basis you provided for requesting the waiver does not apply here. Submit another waiver request citing the appropriate criteria under 21 CFR 320.22 for which you are seeking a waiver from the requirements.

Please feel free to contact me directly, should you have any questions. **Please confirm receipt of this message.**

Kind Regards,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Monday, March 14, 2011 10:18 PM  
**To:** Cato, Marcus  
**Subject:** Heparin NDA carton labeling  
**Importance:** High

Dear Marcus,

We recently discovered that our carton labels signature line read [REDACTED] (b) (4) – they should read Pfizer Inc.

We believe this is a minor amendment – should we amend the art work and submit now or (since we are approaching our PDUFA date) is it better to submit this an annual reportable change post approval?

Looking forward to your response – thanks in advance

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Monday, February 28, 2011 3:45 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High  
**Attachments:** quality-query-q6.pdf; cover-letter.pdf; pharmaceutical-development-drug-product.pdf

Dear Marcus,

To clarify question number one below – “inclusion of the net quantity statement into the boxing for the 1 mL and 2 mL vial fill size” for all vial sizes (1 mL, 2 mL and 10 mL, not just the 1 and 2 mL).

Also, Please see attached correspondences where we state that the only formulation/presentation that is not multiple use is the 1000 U/mL preservative free. Could this be an oversight (i.e. requested revisions to the USPI)

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda,hhs.gov]  
**Sent:** Monday, February 28, 2011 2:29 PM  
**To:** Douglas, Tricia S  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

Please see below.

Is it reasonable for us to make the following requested revision on all labels?

Consider 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

**Response.** The correspondence from the FDA stated the prominence of the net quantity statement should be increased on the container (vial) labels. The letter did not indicate that this issue had to be addressed on the carton labeling. If they want to they of course can change the carton labeling, but we didn't request them change

4/6/2011

Reference ID: 2928992

Cato, Marcus

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Monday, February 28, 2011 3:45 PM  
**To:** Cato, Marcus  
**Subject:** Heparn info Request  
**Importance:** High  
**Attachments:** quality-query-q6.pdf; cover-letter.pdf; pharmaceutical-development-drug-product.pdf

Dear Marcus,

Please see attached correspondence

*Regards,  
Tricia*

**Tricia S. Douglas**

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** (b) (6)  
**Sent:** Monday, February 28, 2011 3:27 PM  
**To:** Douglas, Tricia S  
**Cc:** (b) (6)  
**Subject:** URGENT: FOR DISCUSSION WITH MARCUS  
**Importance:** High

Tricia,

We dug into our correspondences with the FDA. We received a question at the end of June. Our specific response is attached.

Cover letter to FDA  
Query 6 (June 29 correspondence)  
Updated Pharm Dev to reflect information in response.

Clearly we state that the only formulation/presentation that is not multiple use is the 1000 U/mL preservative free.

Can you check with Marcus to ensure that he and his colleagues were aware of this response?

(b) (6)



**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Monday, February 28, 2011 2:29 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

Please see below.

Is it reasonable for us to make the following requested revision on all labels?  
Consider 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

**Response.** The correspondence from the FDA stated the prominence of the net quantity statement should be increased on the container (vial) labels. The letter did not indicate that this issue had to be addressed on the carton labeling. If they want to they of course can change the carton labeling, but we didn't request them change it. The sponsor has included part of our comment with techniques to consider in order to increase the prominence. The sponsor can decide which technique or techniques are needed to increase the prominence of the net quantity statement while keeping the statement in close proximity to the expression of potency.

To clarify, Not for Lock Flush should not be written vertically – correct?

**Response.** We noted the proposed presentation of the statement is difficult to read. We did not specifically state the statement could not be in a vertical orientation. Although generally presenting text in a vertical orientation decreases the readability of this information. To increase the readability of the statement we did recommended presenting the statement in one of the two formats that have been approved for other products. If the sponsor does not feel the readability of the statement is still not satisfactory after revising the format of statement, then the sponsor should consider other techniques and methods, one of which would be to revise the statement to a horizontal orientation.

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Monday, February 28, 2011 9:42 AM  
**To:** Cato, Marcus  
**Cc:** Newman, Tyree  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

4/6/2011

Reference ID: 2928992

Dear Marcus,

Is it reasonable for us to make the following requested revision on all labels?

Consider 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

To clarify, Not for Lock Flush should not be written vertically – correct?

Also, will we need to submit SPL?

I hope to hear from you soon and thank you in advance

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]

**Sent:** Friday, February 25, 2011 2:29 PM

**To:** Douglas, Tricia S

**Cc:** Newman, Tyree

**Subject:** NDA 201370 Information Request

**Importance:** High

Hi Tricia,

We are reviewing your NDA submission and would like to request a written response to the attached request for information. A hard copy of this letter should follow in the mail. If possible, please reply with revised labels by next **12:00 PM Friday, March 4, 2011**.

Please feel free to contact me directly, should you have any questions. **Please confirm receipt of this message.**

Kind Regards,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
[Marcus.Cato@fda.hhs.gov](mailto:Marcus.Cato@fda.hhs.gov)

4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Friday, February 18, 2011 1:27 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: Heparin NDA 201370

Hi Tricia,

thank you for your note. I will be sending you are request for further labeling revisions(not extensive) sometime next week for both PI and carton/container.

Have a nice weekend.

Kindly

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Friday, February 18, 2011 8:46 AM  
**To:** Cato, Marcus  
**Subject:** Heparin NDA 201370  
**Importance:** High

Dear Marcus,

I hope all is well.

I wanted to check in on the status of the NDA, for example, could we expect an action letter soon? Are there further revisions expected?

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

4/6/2011

Reference ID: 2928992

## Cato, Marcus

---

**From:** Cato, Marcus  
**Sent:** Saturday, February 05, 2011 1:54 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** NDA 201370 Information Request

**Importance:** High

**Attachments:** MClab-0414-1-0-pkg-insert-pfizer-track IR(2-5-11).doc

Dear Ms. Douglas,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We are reviewing the product labeling in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

### PACKAGE INSERT LABELING

1. Submit a revised package insert for NDA 201370 with revisions to the sections, as shown in the attached labeling. Additions and deletions are denoted in tracked changes format.



MClab-0414-1-0-pk  
g-insert-pfiz...

Please reply with revised labels by next **COB Wednesday, February 9, 2011**.

Please feel free to contact me should you have any questions.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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

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

MARCUS A CATO  
02/05/2011

Cato, Marcus

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Friday, February 04, 2011 11:55 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Hi Marcus,

We may have a delay in obtaining specific the exposure data due to generics being available so we are requesting a 1 week extension for our response. I hope to hear from you soon

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Thursday, February 03, 2011 1:27 PM  
**To:** Douglas, Tricia S  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Hi Tricia

yes

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Thursday, February 03, 2011 11:34 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

We have Heparin that we market in two other countries but it is not the same as our Heparin proposed in the NDA. My understanding of the request is that you would like the requested information on these two Heparins – please confirm

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Tuesday, February 01, 2011 11:23 AM  
**To:** Douglas, Tricia S  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

If you have Heparin Sodium marketed in other countries you should provide strengths and presentations of marketed heparin sodium, marketing history, and the requested post-marketing information.

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, February 01, 2011 10:58 AM  
**To:** Cato, Marcus

**Subject:** RE: NDA 201370 Information Request

Dear Marcus,

After some initial research we may have other approvals - we need to determine if it is indeed the same product. Can you clarify what you consider the same as our proposed product?

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)  
[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]

**Sent:** Tuesday, February 01, 2011 12:02 AM

**To:** Douglas, Tricia S

**Subject:** NDA 201370 Information Request

Dear Ms. Douglas,

We are reviewing your application and have the following request for additional information:

1. Provide a statement regarding if your proposed heparin product has been approved in other countries. If so, provide the safety summary of postmarketing experience from other countries. The information should include estimated exposure, adverse events, and relevant regulatory actions..

Please respond to this request on or before **Monday, February 7, 2011**.

Please feel free to contact me directly, should you have any questions.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
[Marcus.Cato@fda.hhs.gov](mailto:Marcus.Cato@fda.hhs.gov)

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4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Tuesday, February 01, 2011 11:23 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

If you have Heparin Sodium marketed in other countries you should provide strengths and presentations of marketed heparin sodium, marketing history, and the requested post-marketing information.

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, February 01, 2011 10:58 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request

Dear Marcus,

After some initial research we may have other approvals - we need to determine if it is indeed the same product. Can you clarify what you consider the same as our proposed product?

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Tuesday, February 01, 2011 12:02 AM

**To:** Douglas, Tricia S  
**Subject:** NDA 201370 Information Request

Dear Ms. Douglas,

We are reviewing your application and have the following request for additional information:

1. Provide a statement regarding if your proposed heparin product has been approved in other countries. If so, provide the safety summary of postmarketing experience from other countries. The information should include estimated exposure, adverse events, and relevant regulatory actions..

Please respond to this request on or before **Monday, February 7, 2011**.

Please feel free to contact me directly, should you have any questions.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Tuesday, February 01, 2011 11:23 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

If you have Heparin Sodium marketed in other countries you should provide strengths and presentations of marketed heparin sodium, marketing history, and the requested post-marketing information.

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, February 01, 2011 10:58 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request

Dear Marcus,

After some initial research we may have other approvals - we need to determine if it is indeed the same product. Can you clarify what you consider the same as our proposed product?

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Tuesday, February 01, 2011 12:02 AM

4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Tuesday, February 01, 2011 12:02 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** NDA 201370 Information Request

Dear Ms. Douglas,

We are reviewing your application and have the following request for additional information:

1. Provide a statement regarding if your proposed heparin product has been approved in other countries. If so, provide the safety summary of postmarketing experience from other countries. The information should include estimated exposure, adverse events, and relevant regulatory actions..

Please respond to this request on or before **Monday, February 7, 2011**.

Please feel free to contact me directly, should you have any questions.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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/s/  
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MARCUS A CATO  
02/01/2011

## Lambert, Tu-Van

---

**From:** Lambert, Tu-Van  
**Sent:** Wednesday, January 05, 2011 3:12 PM  
**To:** 'Douglas, Tricia S'  
**Cc:** Al Hakim, Ali H; Cato, Marcus  
**Subject:** NDA 201370 CMC Information Request

Hi Tricia,

Happy New Years. Hope your 2011 year is off to a good start.

Please provide responses to the following CMC information request.

- 1- Revise the shelf life of benzyl alcohol specification for the drug product to (b) (4) of the initial value
- 2- Include a specification for (b) (4) level of NMT (b) (4) in the drug product
- 3- Provide any additional stability data for the drug product, if available

Feel free to contact me if you have any questions.

Warmly,

Tu-Van Le Lambert  
Product Quality Regulatory Health Project Manager  
ONDQA/OPS/CDER  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 21, Room 2625  
Silver Spring, MD 20993  
Phone: (301) 796-4246  
Fax: (301) 796-9748

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/s/  
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ALI H AL HAKIM  
01/05/2011

## MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE: November 01, 2010 – March 30, 2011  
APPLICATION NUMBER: NDA 201370

BETWEEN:

Name: Tricia S. Douglas  
Manager, Worldwide Regulatory Strategy  
e-mail: tricia.douglas@pfizer.com  
Representing: Pfizer Inc.

AND

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

SUBJECT: Information Requests/General Correspondence

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Monday, December 20, 2010 5:35 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: Heparin NDA 201370 carton labeling

Dear Ms. Douglas,

Please submit an amendment to your application with the revised labels that you suspect may be infringing. Please articulate which aspects you were concerned about and why. Please also state if you tried to implement this aspect/presentation to address a safety issue or in response to a safety issue.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Wednesday, November 17, 2010 11:42 AM  
**To:** Cato, Marcus  
**Subject:** Heparin NDA 201370 carton labeling  
**Importance:** High

Dear Marcus,

I left you a voice message yesterday regarding an urgent issue with the vial/carton labeling submitted on Friday November 12, 2010. It was recently discovered that we need to revise some of the labels as we are potentially infringing on a trade mark. Please let me know your thoughts as soon as possible as we plan to submit an amendment hopefully this week. Many thanks in advance for your attention to this matter.

*Regards,*  
*Tricia*

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Wednesday, November 17, 2010 3:54 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: Heparin NDA 201370 carton labeling  
**Importance:** High

Hi Tricia,

Thank you for your call and followup e-mail. Unfortunately we are having some internal discussion and I will not be able to get back to you today regarding your inquiry. I will try to give you a call tomorrow to provide advice. In the mean time, I would recommend that you all not plan to resubmit this week.

Warmly,

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Wednesday, November 17, 2010 11:42 AM  
**To:** Cato, Marcus  
**Subject:** Heparin NDA 201370 carton labeling  
**Importance:** High

Dear Marcus,

I left you a voice message yesterday regarding an urgent issue with the vial/carton labeling submitted on Friday November 12, 2010. It was recently discovered that we need to revise some of the labels as we are potentially infringing on a trade mark. Please let me know your thoughts as soon as possible as we plan to submit an amendment hopefully this week. Many thanks in advance for your attention to this matter,

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Friday, November 12, 2010 3:05 PM  
**To:** Douglas, Tricia S; Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

Please be advised that there was an error in the 1000 units label. The color around the strength should have been (b) (4). This change will be reflected in the official submission which will go out shortly.

*Regards,*  
*Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Douglas, Tricia S  
**Sent:** Friday, November 05, 2010 11:58 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request

Dear Marcus,

Please see attached pdfs of the carton labeling. An official submission will follow next week

*Regards,*  
*Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Friday, November 05, 2010 11:24 AM  
**To:** Douglas, Tricia S  
**Subject:** RE: NDA 201370 Information Request

4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, November 09, 2010 8:26 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

Is there any update on the clinical (dosage and administration) issue below? We are working diligently to provide a response on Friday so this bit of information would assist us greatly. Many thanks in advance!

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Friday, November 05, 2010 11:24 AM  
**To:** Douglas, Tricia S  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

Please see below (clinical to come)...

The following citation for the published embryofetal developmental toxicology study in rats and rabbits referenced in the pregnancy section (8.1) was provided in your package and referenced in the submitted Nonclinical Overview.

Lehrer SB, Becker BA. Effects of heparin on fetuses of pregnant rats and rabbits. *Teratology* 1974;9:A26.

Thanks

~Marcus

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**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Tuesday, November 09, 2010 10:46 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

In your proposed labeling, under D&A section, for extracorporeal dialysis it stated "Follow equipment manufacturers' operating directions carefully". We deleted that because no specific dose was provided. If you can provide a specific dose for this indication, we may add it in D&A section.

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, November 09, 2010 8:26 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

Is there any update on the clinical (dosage and administration) issue below? We are working diligently to provide a response on Friday so this bit of information would assist us greatly. Many thanks in advance!

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)  
[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Friday, November 05, 2010 11:24 AM  
**To:** Douglas, Tricia S

4/6/2011

Reference ID: 2928992

**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

Please see below (clinical to come)...

The following citation for the published embryofetal developmental toxicology study in rats and rabbits referenced in the pregnancy section (8.1) was provided in your package and referenced in the submitted Nonclinical Overview.

Lehrer SB, Becker BA. Effects of heparin on fetuses of pregnant rats and rabbits. *Teratology* 1974;9:A26.

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Thursday, November 04, 2010 9:38 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

We have some questions regarding the revisions to the USPI;

- Can you provide a citation for the study referenced in the pregnancy section (8.1) of the USPI (rat tox study)?
- Please provide a rationale for removal of the extracorporeal dialysis section from the dosage and administration section

We hope to hear from you soon and thank you advance for your assistance.

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)  
[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

4/6/2011

Reference ID: 2928992

---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, November 02, 2010 1:15 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Hi Marcus,

In the tracked changes version of the USPI, we noticed that you replaced Heparin Sodium with Drug Name. We do not have a proprietary name so we would like to keep Heparin Sodium as the drug name, do you agree?

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

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[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, November 02, 2010 11:20 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

We are requesting a 2 week extension to go through the USPI. We have started an extensive review and we have noticed some discrepancies. It will take some time to review the entire document including the (b) (4). Please let us know your thoughts on an extension. Many thanks in advance

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Monday, November 01, 2010 1:46 PM  
**To:** Douglas, Tricia S  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Hi Tricia,

please see below..

Thanks

~Marcus

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---

4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Tuesday, November 02, 2010 1:19 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

Thats fine. We are still having internal discussion regarding how(exactly) the drug should be listed in the PI as there are some special PLR considerations. We will get back to soon regarding how it should read in the PI

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, November 02, 2010 1:15 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Hi Marcus,

In the tracked changes version of the USPI, we noticed that you replaced Heparin Sodium with Drug Name. We do not have a proprietary name so we would like to keep Heparin Sodium as the drug name, do you agree?

*Regards,*  
*Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

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685/18/15

4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Monday, November 01, 2010 1:39 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

Can we submit and email and follow up with an official submission during the following week.

Also, we have come up with a couple options to address FDA's concern's and to help avoid medication errors. We would like to submit both for review, do you agree?

*Regards,  
Tricia*

*Tricia S. Douglas*

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Friday, October 29, 2010 3:22 PM  
**To:** Douglas, Tricia S  
**Subject:** RE: NDA 201370 Information Request

Hi Tricia,

please see your information request letter attached. A hard copy should follow in the mail. If possible, please reply with revised labels by next COB Friday, November 5 2010.

Thanks

~Marcus

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4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Cato, Marcus  
**Sent:** Monday, November 01, 2010 1:46 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Hi Tricia,

please see below..

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Monday, November 01, 2010 1:39 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

Can we submit and email and follow up with an official submission during the following week. ....yes this should be fine

Also, we have come up with a couple options to address FDA's concern's and to help avoid medication errors. We would like to submit both for review, do you agree? (does this mean you have two different proposed carton/container labels? I believe it should be ok to submit both proposals, however I will confirm with the team and send you a seperate e-mail)

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

4/6/2011

Reference ID: 2928992

---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, October 12, 2010 12:55 PM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

Regarding a response to the Information Request for the Heparin vial labels, is there a status update on when we will receive comments back? I recall that you mentioned the end of September or early October was when we should have received feedback. We would like to proactively address any issues that we feel may lead to medication errors in accordance with recent industry developments in vial labeling - but we would like to receive feedback from the Agency on the Information Request first.

Looking forward to hearing from you soon.

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
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235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

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[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Thursday, July 15, 2010 4:48 PM  
**To:** Douglas, Tricia S  
**Subject:** NDA 201370 Information Request

Dear Ms. Douglas,  
Please find attached an electronic copy of your IR letter. A hard copy should follow in the mail.  
<<NDA 201370IR.pdf>>  
Please feel free to contact me directly, should you have any questions.  
Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
[Marcus.Cato@fda.hhs.gov](mailto:Marcus.Cato@fda.hhs.gov)

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4/6/2011

Reference ID: 2928992

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Thursday, September 23, 2010 10:56 AM  
**To:** Cato, Marcus  
**Subject:** Heparin planned DMF amendment - NDA 201370  
**Importance:** High

Dear Marcus,

As we are planning the DMF amendment does the NDA also need an amendment to reflect this? My initial thought is no, since the NDA is not yet approved, can you confirm? Many thanks in advance.

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

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[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, September 21, 2010 9:22 AM  
**To:** Cato, Marcus  
**Subject:** NDA 201307 - Heparin Sodium DMF amendments  
**Importance:** High

Dear Marcus,

Pfizer is planning to submit two DMF amendments. The purpose of these amendments is to remove (b) (4) as a crude supplier and add (b) (4) as a new (b) (4) crude supplier. Supply from (b) (4) is already being used by (b) (4) in the (b) (4) and has been procured by our Franklin facility.

Will this affect our pending application? I hope to hear from you soon and thank you in advance for your attention to this matter.

*Regards,  
Tricia*

***Tricia S. Douglas***

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office (b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

## Cato, Marcus

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Monday, July 26, 2010 9:49 AM  
**To:** Cato, Marcus  
**Subject:** FW: Heparin Vials - photos of vials  
**Attachments:** DSCN5520.jpg; DSCN5517.jpg; DSCN5518.jpg; DSCN5519.jpg

Hi Marcus,

The information request for the vial presentations was forwarded to you along with an official letter for your files on Friday. Here are some pictures of the vials forwarded to you. The 74 day letter response should be submitted today ( we had some issues with our Reg Ops department last week)

*Regards,*  
*Tricia*

*Tricia S. Douglas*

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
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4 pages of draft labeling has been withheld in full as B(4)  
CCI/TS immediately following this page

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

---

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

---

/s/

---

MARCUS A CATO  
09/16/2010

## Cato, Marcus

---

**From:** Cato, Marcus  
**Sent:** Wednesday, August 11, 2010 3:18 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** NDA 201370 Information Request

Dear Ms. Douglas,

We are reviewing your labeling submitted on August 9, 2010, and have noted that you have not provided detailed annotations for all sections of the labeling. Please provide the following information:

1. Provide annotations for all sections of the proposed labeling. If the section information is based on the labeling of listed drugs you should indicate it in the annotations, these annotations should be as specific as possible about the source of the labeling statements.
2. Please provide the last version of labeling for the listed drugs (NDA 17-346 and NDA 4-570).

Please respond to this request on or before Wednesday, **August 25, 2010**.

Please feel free to contact me directly, should you have any questions.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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## Cato, Marcus

---

**From:** Cato, Marcus  
**Sent:** Tuesday, June 29, 2010 10:17 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** RE: heparinfda review letter

Ms. Douglas,

The comments in the letter were regarding format of the PI rather than content. We would request that in your response you include a references section as described (omitting any references you feel are not necessary).

Thanks

~Marcus

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-----Original Message-----

From: Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
Sent: Friday, June 25, 2010 9:29 AM  
To: Cato, Marcus  
Subject: FW: heparinfda review letter  
Importance: High

Dear Marcus,

We would like some clarification to item 21 in the above referenced letter. We are requested to add section 15 with references from page 12 of our annotated USPI. These references include Pfizer internal Safety reports, FDA Medwatch, and journal articles. Is it absolutely necessary for us to add these references?

Thanks in advance and I look forward to your feedback.

Regards,  
Tricia

Tricia S. Douglas  
Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Tuesday, June 08, 2010 11:28 AM  
**To:** Cato, Marcus  
**Subject:** Re: NDA 201370 Filing Communication

Hi Marcus,

We don't have an exact date but we are looking at sometime around the end of July.

You should be receiving the submission with the protocols, study reports, and SAS data sets within the next couple of days

Thanks,

TD

-----  
Sent using BlackBerry

---

**From:** Cato, Marcus <Marcus.Cato@fda.hhs.gov>  
**To:** Douglas, Tricia S  
**Sent:** Tue Jun 08 11:24:18 2010  
**Subject:** RE: NDA 201370 Filing Communication

Hi Tricia,

we have a team meeting today, just wanted to know if you all had a target response date?

Thanks

~Marcus

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---

**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Thursday, May 27, 2010 9:00 AM  
**To:** Cato, Marcus  
**Subject:** RE: NDA 201370 Filing Communication

Hi Marcus,

Thank you for your email. I have scheduled an internal meeting with the required disciplines to provide responses as soon as we can.

9/16/2010

*Regards,  
Tricia*

*Tricia S. Douglas*

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

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[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Tuesday, May 25, 2010 10:24 AM  
**To:** Douglas, Tricia S  
**Subject:** NDA 201370 Filing Communication

Dear Ms. Douglas,

Please find attached an electronic copy of your filing letter. A hard copy should follow in the mail.

<<NDA 201370File.pdf>>

Please feel free to contact me directly, should you have any questions.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
[Marcus.Cato@fda.hhs.gov](mailto:Marcus.Cato@fda.hhs.gov)

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9/16/2010

**Cato, Marcus**

---

**From:** Douglas, Tricia S [Tricia.Douglas@pfizer.com]  
**Sent:** Friday, April 23, 2010 8:55 AM  
**To:** Cato, Marcus  
**Subject:** RE: New NDA 201370 Information Request  
**Importance:** High

Dear Marcus,

We have run into some issues with the conversion to SAS.

It seems we will need longer than one week (approximately one month). There are no electronic versions and the images are of poor quality, the tables must be build from listings which are not conducive to easy transcription and conversion, therefore the transcription and QC will be tedious and take much longer than the requested timeline. Then they still need to be converted from XLS to SAS.

Does FDA desire all or limited variables; e.g., demographics, treatment and the coagulation parameters? If only coagulation parameters are needed, this should probably take a week or two less.  
Does FDA have a desired SAS Format Specification other than transport file? Since this is being build by hand, we'd prefer to give them what they want in the desired format.

Thank you in advance and I hope to hear from you soon.

*Regards,  
Tricia*

*Tricia S. Douglas*

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

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[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

---

**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Thursday, April 22, 2010 2:59 PM  
**To:** Douglas, Tricia S  
**Subject:** RE: New NDA 201370 Information Request

yes that should be fine

Thanks Much

~Marcus

9/16/2010

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**From:** Douglas, Tricia S [mailto:Tricia.Douglas@pfizer.com]  
**Sent:** Thursday, April 22, 2010 2:48 PM  
**To:** Cato, Marcus  
**Subject:** RE: New NDA 201370 Information Request

Hi Marcus,

We will convert the data sets in the study reports. This will not be complete until next week, so the amendment can be submitted no earlier than the end of next week. Is that feasible?

*Regards,  
Tricia*

*Tricia S. Douglas*

Manager, Worldwide Regulatory Strategy  
Established Products  
Pfizer Inc.  
235 East 42nd St.  
New York, NY 10017  
212- 733-6189 office

(b) (6)

[tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com)  
685/18/15

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**From:** Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]  
**Sent:** Wednesday, April 21, 2010 2:42 PM  
**To:** Douglas, Tricia S  
**Subject:** RE: New NDA 201370 Information Request

Hi Tricia,

Yes please submit this information as an amendment to your NDA.

Additionally, if the individual patient listings for PK data is in an appendix in tabular format you should manually type it in and submit to us as .xpt files.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-2050 (phone)  
(301) 796-9849 (fax)

9/16/2010

## Cato, Marcus

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**From:** Cato, Marcus  
**Sent:** Thursday, April 15, 2010 10:51 AM  
**To:** 'Douglas, Tricia S'  
**Subject:** New NDA 201370 Information Request

**Importance:** High

**Follow Up Flag:** Follow up  
**Flag Status:** Blue

Ms. Douglas,

We are reviewing your new NDA and would like to request a prompt written response to the below request for information (Please respond to this request on or before Monday April 19, 2010):

**For studies 767-1 and 767-2, submit study protocols, raw datasets, and clinical study reports. The datasets should be submitted in sas transport file formats.**

Please feel free to contact me directly, should you have any questions.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-2050 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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## Cato, Marcus

---

**From:** Cato, Marcus  
**Sent:** Friday, March 19, 2010 3:47 PM  
**To:** 'tricia.douglas@pfizer.com'  
**Subject:** NDA 201370 NDA ACKNOWLEDGMENT

**Attachments:** NDA 201370ACK.pdf; NDA Review critique list.doc

NDA 201370

### NDA ACKNOWLEDGMENT

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Douglas:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Heparin Sodium Injection USP. Please find attached your acknowledgment letter. A hard copy should follow in the mail.



NDA



NDA Review

1370ACK.pdf (26 K critique list.doc (...)

Please also find the CDER Quality Assessment tool for your use in preparing submissions and during the review cycle.

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.  
Regulatory Project Management  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-2050 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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TU-VAN L LAMBERT  
03/10/2011

ALI H AL HAKIM  
03/10/2011

Reference ID: 2916592

Reference ID: 2928992



NDA 201370

## INFORMATION REQUEST

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Douglas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We also refer to your submissions dated April 16, July 29(2), August 9, 25, October 7, and November 12, 2010; January 10, February 9, and March 9, 2011, containing revised product labeling.

We are reviewing the product labeling in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

### PACKAGE INSERT LABELING

1. Submit a revised package insert for NDA 201370 with revisions to the sections, as shown in the attached labeling. Additions and deletions are denoted in tracked changes format.

### CONTAINER LABELING

2. 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.

<b>1,000</b> USP units <b>per mL</b> <b>2 mL</b> Single Dose Vial
--

b.

<b>1,000</b> USP Units <b>per mL</b> <b>2 mL</b> Single Dose Vial
---

If you have questions, call me at (301) 796-3903.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure - Revised Package Insert

9 pages of draft labeling has been withheld in full as B(4) CCI/  
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/s/  
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MARCUS A CATO  
03/29/2011



NDA 201370

## INFORMATION REQUEST

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Douglas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We also refer to your submissions dated April 16, July 29(2), August 9, 25, October 7, and November 12, 2010; January 10, and February 9, 2011, containing revised product labeling.

We are reviewing the product labeling in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

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 you submit additional information to support the proposed container labels and carton labeling.

### PACKAGE INSERT LABELING

1. Submit a revised package insert for NDA 201370 with revisions to the sections, as shown in the attached labeling. Additions and deletions are denoted in tracked changes format.

### CONTAINER LABELING

2. 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) Consider 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).

**1,000** USP units per mL  
**2** mL per vial

3. 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.
4. We recommend a usage type statement as either single dose or multiple dose needs to be incorporated onto the container labeling, and the statement “Discard unused portion” needs to be incorporated on the side panel of the single dose products.

### **CARTON LABELING**

5. Requests 3 and 4 above are applicable to the carton labeling.

If you have any questions, call me at (301) 796-3903.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure - Revised Package Insert

9 pages of draft labeling has been withheld in full as B(4)  
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/s/  
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MARCUS A CATO  
02/25/2011



NDA 201370

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street  
New York, NY 10017

Dear Ms. Douglas:

Please refer to your March 8, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

On November 12, 2010, we received your November 12, 2010, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 9, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 9, 2011.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, M.D.  
Director (Acting)  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/  
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ANN T FARRELL  
11/22/2010



NDA 201370

## INFORMATION REQUEST

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Douglas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We also refer to your submissions dated July 29(2), August 9, 25, and October 7, 2010, containing revised product labeling.

We are reviewing the product labeling in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

### PACKAGE INSERT LABELING

1. Submit a revised package insert for NDA 201370 with revisions to the sections, as shown in the attached labeling. Additions and deletions are denoted in tracked changes format.

### CONTAINER LABELING

2. Increase the prominence of the expression of potency statement appearing directly below the established name.
3. 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 that 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  $\frac{1}{2}$  or  $\frac{3}{4}$  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.

5. 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.
6. Relocate the total volume statement to the lower portion of the label and below the expression of potency statement.
7. Revise the benzyl alcohol statement to appear with red colored lettering, possibly with a bolded font, and to read “Warning: Contains Benzyl Alcohol”.
8. 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.
9. Delete the [REDACTED] (b) (4)
10. 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.
11. 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.

## CARTON LABELING

12. Requests 2, 3, 5, 7 and 9 above are applicable to the carton labeling.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, M.D.  
Director (Acting)  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure - Revised Package Insert

Reference ID: 2857466

10 pages of draft labeling has been withheld in full as B(4)  
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/s/  
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ANN T FARRELL  
10/29/2010

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** Friday, October 1, 2010  
**TIME:** 9:30 – 10:00 AM, EST  
**LOCATION:** White Oak Building 21  
**APPLICATION:** NDA 201370  
**DRUG NAME:** Heparin Sodium Injection, USP  
**TYPE OF MEETING:** Teleconference

**MEETING CHAIR:** Ali H. Al-Hakim, Ph.D.

**MEETING RECORDER:** Tu-Van Le Lambert, M.S.

### FDA ATTENDEES:

Ali H. Al-Hakim, Ph.D. – Branch Chief, Office of New Drug Quality Assessment (ONDQA)  
Muthukumar Ramaswamy, Ph.D. – Product Quality Reviewer, ONDQA  
Tu-Van Le Lambert, M.S. – Product Quality Regulatory Project Manager, ONDQA

### EXTERNAL CONSTITUENT ATTENDEES:

Jacqueline D. Schumacher - Global CMC, Pfizer  
Nancy J. Harper - Pharmaceutical Development, Pfizer  
Eileen K. Bohler - Analytical Sciences, Pfizer  
Deborah K. Long - Quality Operations, Pfizer  
Wesley E. Workman – PGM, Pfizer  
Kathleen Collins-Novikov - Regulatory Lead, Pfizer

### BACKGROUND:

On August 19, 2010, the Applicant submitted Quality Information in response to the Information Request the Agency sent on June 29, 2010. Upon further review of this submission, additional clarification on the drug product stability data provided was requested.

### MEETING OBJECTIVES:

To request for additional data for the drug product stability program to support the use of the matrixing/bracketing strategy for stability for all strengths in the application.

### DISCUSSION POINTS:

- The Agency stated that the three months stability data for the 1000 units/mL dosage form does not support the proposed 24 months expiry period. The Agency requested that more

batch data of the 6-9 months stability timepoints be submitted to support this expiry period. The Applicant agreed to do so.

- The Agency stated that the proposed matrixing and bracketing protocols in this application does not comply with ICH Q1D. It is especially important to provide complete data since the preservative-free presentation has a new container closure system. The data package the Applicant provided to support this strategy was not acceptable to support the matrixing/bracketing strategy.
- The Agency requested that the Applicant provide data for three batches each of high and low strengths for a given container-closure system as provided in ICH Q1D.
- The Agency stated that because of the bracketing and matrixing strategy performed, the Applicant may not be performing regular sterility testing to support the expiry dating. The Applicant acknowledged this and offered to provide supportive data in a post-approval supplement.
- The Agency requested 2-3 batches stability data for each drug product presentation to support the proposed stability program for this application. Nine months of stability data is needed, 12 months stability data provided by the end of the review cycle, and 6 months stability data at accelerated conditions. Complete stability data needs to be provided in order to complete the CMC review.
- When the Agency asked when additional stability data will be available, the Applicant replied that data should be available by mid-November. The Agency requested that this data be provided at that time in order to finalize the review on time. The Applicant agreed to do so.

**DECISIONS (AGREEMENTS) REACHED:**

No final decisions or agreements were made in this teleconference.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

No unresolved issues or issues requiring further discussion.

**ACTION ITEMS:**

The Applicant will provide additional drug product stability data as requested by the Agency.

**ATTACHMENTS/HANDOUTS:**

No attachments or handouts provided.

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/s/

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TU-VAN L LAMBERT  
10/05/2010

ALI H AL HAKIM  
10/05/2010

## Cato, Marcus

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**From:** Cato, Marcus  
**Sent:** Monday, September 20, 2010 4:16 PM  
**To:** 'Douglas, Tricia S'  
**Subject:** Heparin, NDA 201370, Pediatric Use labeling Information Request

**Importance:** High

Ms. Douglas,

We are reviewing your new NDA and would like to request a prompt written response to the below request for information (Please respond to this request on or before **COB September 21, 2010**) for time, please reply by e-mail in addition to submitting an amendment to the application:

The pediatric use information in your proposed heparin labeling includes outdated pediatric dosing guidelines in subsection 2.2 of the labeling. Your pediatric dosing guidelines are not consistent with current guidelines listed in publications and textbooks.

**Submit current pediatric dosing guidelines as well as the rationale and source of dosing guidelines.**

Please feel free to contact me directly, should you have any questions.

Kindly,

Marcus Cato, M.B.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-3903 (phone)  
(301) 796-9849 (fax)  
Marcus.Cato@fda.hhs.gov

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/s/

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MARCUS A CATO  
09/20/2010

Pfizer Inc  
235 East 42nd Street  
New York, NY 10017-5755  
Tel 212 733-6189 Fax 212 672-7605  
Email tricia.douglas@pfizer.com



## Pfizer Medical

19 August 2010

Rafel (Dwayne) Rieves, M.D., Director  
ATTN: Central Document Room  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Medical Imaging and Hematology Products  
5901-B Ammendale Rd.  
Beltsville, MD 20705-1266

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WRITTEN CONSENT OF PFIZER INC.

**Re: NDA 201370 Heparin Sodium (heparin sodium, USP) Injection**  
**Response to FDA Information Request (CMC)**

Dear Dr. Rieves,

Reference is made to our original New Drug application (NDA) 201370 submitted under section 505(b) (2) of the Food Drug and Cosmetic Act on March 8, 2010. Reference is also made to the information request letter issued by the Agency on June 29, 2010 and received by Pfizer on July 08, 2010. This information request was specific to the Chemistry Manufacturing and Controls (CMC) section of NDA 210370. The purpose of this submission is to provide the Agency with the requested information.

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To facilitate review, included in this submission are; the responses to the queries and the following updated Module 2.3 and 3 sections:

Module 2.3 (Quality Overall Summary)	Module 3 (Quality)
2.3.S Drug Substance	3.2.S.4.1 Specification
2.3.P.2 Pharmaceutical Development	3.2.P.2.1 Components of the Drug Product 3.2.P.2.2 Drug Product
2.3.P.5 Control of Drug Product	3.2.P.5.1 Specification 3.2.P.5.2 Analytical Procedures 3.2.P.5.3 Validation of Analytical Procedures 3.2.P.5.6 Justification of Specification

Application Number	Submission Sequence	Approximate Size of Submission	Index of Media Units
201370	0009	16 MB	Gateway

This submission is being submitted in electronic common technical document (eCTD) format, in accordance with the ICH and FDA guidance on electronic submissions. The submission has been scanned for viruses using McAfee VirusScan Enterprise Version 8.7.0i and is virus free. For issues regarding the technical use of this electronic submission, please contact [REDACTED] (b) (6)

Pfizer considers the information submitted for NDA 201370 to be complete and ready for review. Pfizer is committed to respond to the **reviewers' questions promptly and to work** with the Division as needed to facilitate this review.

If you have any questions regarding this submission, please contact me at 212 733 6189 or by e-mail [tricia.douglas@pfizer.com](mailto:tricia.douglas@pfizer.com) or send a facsimile to 212 672 7605.

Sincerely,

Tricia Douglas, MS, RAC  
Worldwide Regulatory Strategy  
Pfizer Medical

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/s/  
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MARCUS A CATO  
04/06/2011



NDA 201370

**INFORMATION REQUEST**

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Douglas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection USP.

We are reviewing the Labeling section of your submission and have the following sample request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Submit samples of your proposed heparin sodium presentations in the final packaging configuration (all 5 presentations).

Submit **all samples** to the following address:

Marcus Cato  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 5241  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20903

Please respond to the above request on or before July 30, 2010.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, M.D.  
Director (Acting)  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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

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/s/

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ANN T FARRELL  
07/15/2010



NDA 201370

**INFORMATION REQUEST**

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Douglas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We also refer to your March 8, 2010 submission, containing the new drug application (NDA) for Heparin Sodium Injection, USP.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4)

2. Include a specification for the appearance of heparin sodium USP drug substance.
3. Provide batch analysis results for heparin sodium lots 80739, 80750, 80751, 80753, 80760, and 80801 in a tabular format.

(b) (4)

5. Your method validation data for benzyl alcohol determination method does not indicate that it was specific for detecting the following impurities in benzyl alcohol: (b) (4)  
(b) (4) Provide the following:
  - a) Provide a copy of the Certificate of Analysis for a batch of benzyl alcohol used for manufacturing drug product used in process validation.
  - b) Develop and validate a method for detecting these impurities in benzyl alcohol excipient and drug product.
  - c) Propose and justify a specification for accepting of each of the above impurities in benzyl alcohol excipient and drug product
6. Justify the need for preservative in the single-use 5000U/mL and 10000U/mL heparin sodium formulation.

7. Submit all proposed changes [REDACTED] (b) (4) as a post-approval supplement or consult the Agency for appropriate filing strategy after completing all required studies.

10. Provide the following information:

- a. A copy of quantitative extractable and leachable assessment for the heparin sodium injection stored in the proposed container/closure system. A copy of the [REDACTED] (b) (4) Customer Service Report CS0078, Section 4.3, which demonstrated compatibility of the stopper with preservatives

- d. Provide a summary of all available USP/Ph. Eur. data to support the safety of the proposed container closure system

12. Your proposed specification for drug product is inadequate. Include additional specifications for sodium chloride content, visual inspection (container/closure integrity by appearance, clarity and color).
13. To meet the labeling requirements specified under USP heparin sodium injection monograph, include a label verification specification.
14. An information request letter was sent out to the DMF holder for DMF 2712.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Project Manager, at (301) 796-4246.

Sincerely,

*{See appended electronic signature page}*

Ali H. Al-Hakim, Ph.D.  
Branch Chief  
Office of New Drug Quality Assessment  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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

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/s/

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ALI H AL HAKIM  
06/29/2010



NDA 201370

**FILING COMMUNICATION**

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Collins:

Please refer to your new drug application (NDA) dated March 8, 2010, received March 9, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Heparin Sodium Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 9, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 9, 2010.

During our filing review of your application, we identified the following potential review issues:

**PRODUCT QUALITY**

1. Your stability section contains only 6 month real-time stability data for the primary stability batches. As per ICH Q1A(R2) guidelines, the long-term testing should cover a minimum of 12 month's duration on at least three primary batches at the time of submission.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

### **PRODUCT QUALITY**

1. Provide 12 months real time stability data for preserved and preservative free heparin formulations in the proposed container closure system.

2. Justify the rationale for the proposed (b) (4)

[Redacted]

[Redacted] (b) (4)

4. Identify by batch number and strength/vial size the stability batches (b) (4)

[Redacted]

5. Provide a time line for implementing the Anti-factor IIa potency assay for stability samples

6. Confirm that information about all drug substance and drug product component manufacturers and related testing facilities have been submitted to the appropriate applications (i.e. relevant NDAs and DMFs). Provide the date of submission for this information to the applications.

We remind you that for each establishment named in your application include the full corporate name of the facility, FEI number, specific address, contact person (name, title, phone number, and email address), and specific information on the type of manufacturing operation at the facility, including the type of testing (if applicable). Each facility must be ready for inspection so that the inspection may be planned as soon as possible.

### **MICROBIOLOGY**

7. Regarding the sterility test, USP <71> requires the method suitability test demonstrating that the chosen method is suitable for the product. Provide the report.

8. Regarding the endotoxin test, USP <85> requires that the product be tested for interfering factors using the chosen technique. Provide the report.

9. In the application, a brief summary of the (b) (4) was provided. Provide the complete (b) (4) report.
10. In the application, Preservative Effectiveness per USP <51> was performed in the stability program. The lowest acceptable concentration during the shelf life for the preservative is (b) (4). Was a validation study performed in which the lowest level of preservative is supported by the Preservative Effectiveness test? If so provide this report. If not, justify.

(b) (4)

## **NON-CLINICAL**

12. Provide a revised List of Literature References, specifically referring to citations made within the general toxicology, carcinogenicity, reproductive and developmental toxicity and other toxicity studies/immunogenicity sections of the Nonclinical Overview for databases within ExPub (i.e. references 3 and 5). Replace references for ExPub databases with references for individual published literature. Submit all references for our review.

## **PREGNANCY AND LACTATION**

13. Provide a review of published literature on heparin exposure during pregnancy and lactation in your 120-Day Safety Update. Details of the information that should be included in this review are provided below.

### Pregnancy

Because of the wide body of literature available, focus on review and analysis of epidemiologic data including case control, case series, and cohort studies on heparin exposure during pregnancy and the associated pregnancy and infant outcomes. In addition, provide the following:

- Literature references
- Number of pregnancy exposures
- Pregnancy outcomes (e.g., still birth, live birth, spontaneous abortion, other adverse events)
- Infant outcomes

### Lactation

It is not known if human data are available on heparin use during lactation. Provide a summary and analysis of any available published literature on heparin use during lactation including:

- Literature references
- Number of exposures
- Maternal dose
- Heparin concentration(s) in milk (if available include assay limit)
- Infant serum heparin concentration(s), if reported

- Effects on infant coagulation profiles, if available
- Estimated infant daily dose of heparin from exposure in human milk

14. Based on your review and analysis of the published literature, recommend relevant language describing data on heparin exposure during human pregnancy and/or lactation for inclusion in labeling. Limitations of the data should be described.

## LABELING

### GENERAL

15. You submitted two separate package inserts (PIs) one with preservative and one for preservative free.

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

### HIGHLIGHTS OF PRESCRIBING INFORMATION section

16. The drug name in the title line reads [REDACTED] (b) (4)

FDA Comment: Revise the title line to: **“HEPARIN SODIUM INJECTION.”** [REDACTED] (b) (4)

17. The Highlights exceeded one-half page.

FDA 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)]

18. In the **“DOSAGE AND ADMINISTRATION”** section, you included both a tabular format and free text.

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

19. In the **“WARNINGS AND PRECAUTIONS”** section, you listed a number of warnings.

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

20. In the **“ADVERSE REACTIONS”** section, you state “contact Pfizer at (1-800-438-1985

[REDACTED] (b) (4)

FDA 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)].

FULL PRESCRIBING INFORMATION: CONTENTS section

21. You did not include the following section: “**15 REFERENCES.**”

FDA 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.

FULL PRESCRIBING INFORMATION section

22. In the “**WARNINGS AND PRECAUTIONS**” section, you listed a number of warnings.

FDA Comment: See 19 above.

23. “**ADVERSE REACTIONS**” section.

FDA 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.”

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

FDA 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.

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

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

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, MD  
Director (Acting)  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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

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/s/

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ANN T FARRELL  
05/21/2010



NDA 201370

**NDA ACKNOWLEDGMENT**

Pfizer Inc.  
Attention: Tricia Douglas, M.S., RAC  
Manager, Worldwide Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Douglas:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Heparin Sodium Injection USP

Date of Application: March 8, 2010

Date of Receipt: March 9, 2010

Our Reference Number: NDA 201370

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 8, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me at (301) 796-3903.

Sincerely,

*{See appended electronic signature page}*

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

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

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/s/

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MARCUS A CATO  
03/19/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

PIND 106,887

MEETING MINUTES

Pfizer Inc./Pharmacia and Upjohn, Inc.  
Attention: Kathleen Collins  
Manager, Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Collins:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Heparin Sodium Injection.

We also refer to the teleconference between representatives of your firm and the FDA on December 2, 2009. The purpose of the meeting was to discuss your proposal to introduce commercial heparin sodium product utilizing heparin sodium derived from porcine intestinal tissue.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3903.

Sincerely,

*(See appended electronic signature page)*

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

Enclosure  
-Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** December 2, 2009, 3:00 PM- 4:00 PM EST  
**Meeting Location:** WO conference room 1311, building 22  
**Application Number:** PIND 106,887  
**Product Name:** Heparin Sodium Injection  
**Sponsor/Applicant Name:** Pfizer Inc./Pharmacia and Upjohn, Inc.  
**Meeting Chair:** Dr. Dwaine Rieves  
**Meeting Recorder:** Mr. Marcus Cato

### FDA ATTENDEES

#### OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director  
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader, Hematology  
Ann Farrell, M.D., Acting Deputy Director  
Marcus Cato, M.B.A, Regulatory Health Project Manager  
Ronald Honchel, Ph.D., Pharmacology/Toxicology Reviewer  
Min Lu, M.D., M.P.H., Clinical Reviewer

#### OFFICE OF PHARMACEUTICAL SCIENCE / OFFICE OF NEW DRUG QUALITY ASSESSMENT/

Ali Al Hakim, Ph.D., Branch Chief  
Tu-Van Lambert, Regulatory Health Project Manager  
Muthukumar Ramaswamy, Ph.D., Product Quality Reviewer  
Arthur Shaw, Ph.D., Product Quality Reviewer

#### OFFICE OF COMPLIANCE/ DIVISION OF MANUFACTURING AND PRODUCT QUALITY

Rick Friedman, M.S., Director  
Frank Perrella, Ph.D., Product Reviewer  
Carmelo Rosa, M.S., Team Leader  
Anthony Charity, M.S., Consumer Safety Officer

### SPONSOR ATTENDEES

Jackie Schumacher, Regulatory Lead - Sterile Injectables  
Wes Workman, PhD, Biopharm Quality Assurance

Nancy Harper, PhD, Pharmaceutical Sciences  
Sue McGrath, Quality Operations, Franklin OH (API)  
Joe Heissler, Safety and Risk Management  
Doug Ross, MD, MBA, Global Medical  
William McConnell, Drug Safety R&D (nonclinical)  
Debbie Long, Quality Operations, Kalamazoo MI (DP)  
Kate Collins, US Regulatory  
Stacey Boushelle, Regulatory CMC

## 1.0 BACKGROUND

In a letter dated June 15, 2009, Pharmacia & Upjohn Company (Pharmacia)/Pfizer requested a meeting to discuss their proposal to re-introduce Heparin Sodium drug product to the U.S. market under NDA 4-570.

In a teleconference between the Sponsor and FDA on July 23, 2009, FDA commented that the Sponsor's proposed, prior approval supplement, submission strategy was not appropriate. NDA 4-570 provided FDA approval to market bovine-sourced heparin. The Sponsor then proposed to market porcine-sourced heparin. FDA stated it expected the Sponsor to submit either a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) for the porcine-sourced heparin since it regards this product as importantly different from bovine sourced heparin; hence, the porcine-sourced heparin is a new drug. FDA advised the Sponsor to discuss its submission strategy internally and submit a request for a pre-NDA meeting.

In a submission dated October 21, 2009, the Sponsor submitted a meeting package with questions to the Agency, as follow-up to the July 23, 2009, teleconference. On December 1, 2009, FDA sent the Sponsor, via e-mail, draft responses to the questions raised in the October 21, 2009, submission (See Sponsor questions and responses below).

### MEETING OBJECTIVES:

To discuss the proposal to introduce commercial heparin sodium product utilizing heparin sodium derived from porcine intestinal tissue.

## 2. DISCUSSION

### Question 1 and Question 2

The sponsor acknowledged and accepted the FDA response (see below).

### Question 3

FDA asked the sponsor to clarify its statement:

1. (b) (4) RH – This condition will only be tested to support CRT labeled storage condition, if required, due to an issue with samples at the long-term storage condition

2. (b) (4) RH – This condition serves at the long-term storage condition for all climatic zones; see ICH Q1A(R2) and Q1F. This condition may also serve as the accelerated condition for the (b) (4) RH condition.

The Sponsor responded that the test will be performed at the (b) (4) condition unless an issue arises as it is the more conservative approach. However, as an alternative, it will use the (b) (4) test condition.

The Sponsor acknowledged and accepted the FDA advice and agreed to provide separate stability protocols in its application according to international conference on harmonization (ICH) guidelines.

Question 4

FDA emphasized its expectation that the Sponsor provide sufficient information for all potential drug product and component manufacturers. The Sponsor should audit the potential suppliers of heparin sodium to ensure compliance prior to submission of the application. FDA reminded the Sponsor that all testing sites in the Drug Master File (DMF) should meet current good manufacturing practices (CGMP). FDA requested a full, itemized, listing of all test sites along with detailed information relevant to each site (including the testing to be done). FDA reiterated that the Sponsor should ensure all suppliers are in compliance with FDA standards and have been audited. The Sponsor clarified that (b) (4) a supplier currently under import alert, was removed from the list of suppliers, and added that an amended DMF was submitted.

Question 5

The Sponsor acknowledged and accepted the FDA response.

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

**4.0 ACTION ITEMS**

Action Item/Description	Owner	Due Date
The Sponsor to address all FDA recommendations in its application.	Sponsor	N/A

**5.0 ATTACHMENTS AND HANDOUTS**

Sponsor Questions and FDA Responses

**Meeting Date:** December 2, 2009

**Time:** 3:00 – 4:00 PM EST

**Type:** Clinical, CMC, Guidance, (Type C)

**Product:** Heparin Sodium Injection, USP

**Sponsor:** Pfizer Inc./Pharmacia and Upjohn, Inc.

**Purpose:** To discuss the proposal to re-introduce heparin sodium drug product to the US market.

**Introductory Comment:** This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **December 2, 2009**, between **Pfizer** and FDA. This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

**Sponsor Questions and FDA Response:**

**QUESTION 1**

*In light of FDA's recommendation that such a change be filed as a 505(b)(2) application does the Agency agree with Pfizer's proposal to cross-reference existing applications for the Clinical and Non-Clinical historical data, along with an updated Quality section?*

**FDA Response:**

**Your proposal to cross-reference DMF 2712 for drug substance and NDA, N4-570 towards prior experience with related drug product is reasonable. Adequacy of information will be determined based on information provided at the time of NDA review.**

**We agree that a 505(b)2 application cross-referencing existing applications for Clinical and Non-Clinical historical data should be appropriate.**

**QUESTION 2**

*Considering that the Pfizer product will be released after testing against the new USP reference standard, are there any measures that Pfizer should further take to differentiate from products available and tested against the "old" USP standard?*

**FDA Response:**

**The Agency expects that Pfizer test all stability, commercial, and validation batches associated with this NDA using new USP reference standard (Heparin Sodium USP Monograph issued on October 01, 2009) so that product quality consistency can be assured.**

**Pfizer should work out this issue of differentiating the lots manufactured and released against old standard vs. new standard separately with the Agency. The issue will be resolved consistent with the approach the Agency has taken to address this issue for other manufacturers.**

**<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm185913.htm>**

**QUESTION 3**

*Does the Agency agree with Pfizer's proposal regarding stability data to be included in the application?*

**FDA Response:**



The Agency also agrees with your approach conducting stability studies under 3 different temperature storage conditions (b) (4) to meet ICH Q1A (R2) and Q1F guidelines.

**QUESTION 4**

*How can Pfizer best collaborate with the Office of Compliance and ONDQA to expedite relevant GMP/Pre-Approval Inspections for the Heparin Sodium Injection drug product, if required?*

**FDA Response:**

The application should clearly provide information about all drug product and component manufacturers. This may include heparin API manufacturer(s) and crude heparin manufacturer(s), as well as all manufacturers involved between crude manufacturing and the final API, the drug product manufacturer(s), and testing laboratories. There may be other manufacturers involved in the manufacture of the drug product; the previous list is not all-inclusive. Information for each establishment named in an application should include the full corporate name of the facility, FEI number, specific address, contact person (name, title, phone number, and email address), and specific information on the type of manufacturing operation at the facility, including the type of testing (if applicable). Each facility must be ready for inspection upon application submission so that the inspection may be planned as soon as possible.

**QUESTION 5**

*Pfizer proposes to cross reference existing literature for the non-clinical and clinical sections of the application. Does the Agency agree with this approach?*

**FDA Response:**

We agree that cross-referencing existing literature for the Clinical and Non-Clinical sections of the application should be appropriate.

**Additional FDA Comment:**

Please be aware that the proposed package insert should be consistent with the format described in the Physician Labeling Rule (PLR) of January 2006.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

IND-106887

GI-1

PHARMACIA AND  
UPJOHN CO

HEPARIN SODIUM

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/s/  
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MARCUS A CATO  
12/16/2009

## RECORD OF TELEPHONE CONVERSATION

DATE: October 26, 2009  
APPLICATION NUMBER: NDA 201370

### BETWEEN:

Name: Kathleen Collins-Novikov  
Global Strategy Lead for CV and Metabolic Products  
Worldwide Regulatory Affairs

e-mail: Kathleen.Collins-Novikov@pfizer.com  
  
Trish Douglas  
Regulatory Affairs

Representing: Pfizer Inc

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager  
Division of Medical Imaging and Hematology Products  
HFD-160

SUBJECT: Information to include in upcoming application.

### DISCUSSION:

Ms. Collins introduced Ms. Douglas as the new point of contact for the NDA.  
The sponsor asked the following questions:

We are planning to submit the NDA in eCTD format. Should we include a form 3674?  
**FDA response:** Yes

Should we include a field copy certification?  
**FDA response:** I will check and get back to you.

Should we include a patent certification? Are patent certification and patent information the same thing?  
**FDA response:** Yes. I will check and get back to you.

Should we include a product bibliography? What is it? What is its format?  
**FDA response:** I will check and get back to you.

Should we include SPL?  
**FDA response:** Yes

Should we include a right of reference authorization?  
**FDA response:** Yes

Should we include a statement *Not applicable* were appropriate?  
**FDA response:** Yes

We are referencing to previously approved NDAs. Should include archival copies?  
**FDA response:** No. Please note that a 505(b)(2) application makes reference to FDAs finding of safety and efficacy and can rely on investigations not conducted by or for the applicant and for which the applicant does not have a right of reference.

We are planning to submit the NDA in eCTD format. Should we include a paper archival copy?  
**FDA response:** No

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

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/s/  
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MARCUS A CATO  
01/27/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 4-570

**MEETING DENIED**

Pharmacia & Upjohn Company  
Attention: Kathleen Collins  
Manager, Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms Collins:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection USP.

We also refer to your October 16, 2009, correspondence requesting a meeting to discuss your planned filing strategy for a heparin sodium injection drug product derived from porcine intestinal tissue. We are denying the meeting because it was submitted to NDA 4-570.

For administrative reasons, we cannot process this request under your NDA. Please resubmit this request under Pre-Investigational New Drug Application (PIND) number 106,887.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

*(See appended electronic copy of this page)*

Kyong "Kaye" Kang, Pharm.D.  
Chief, Project Management Staff  
Division of Medical Imaging and Hematology  
Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-4570

GI-1

PHARMACIA AND  
UPJOHN CO

HEPARIN SODIUM

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/s/

KYONG A KANG  
10/20/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 4-570

**MEETING REQUEST CANCELED**

Pharmacia & Upjohn Company  
Attention: Kathleen Collins  
Manager, Regulatory Strategy  
235 East 42nd Street,  
New York, NY 10017

Dear Ms. Collins:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection USP.

We also refer to the teleconference between representatives of your firm and the FDA on July 23, 2009. The purpose of the meeting was to discuss your June 15, 2009, meeting request and your proposed, prior approval supplement, submission strategy.

We further refer to the meeting we scheduled for July 30, 2009, in response to your June 15, 2009, meeting request. We are cancelling this meeting because we regard your proposed submission strategy (the topic of discussion) as inappropriate. If you wish to schedule another meeting, you must submit a new meeting request.

A copy of the official minutes of the teleconference is attached for your information.

If you have any questions, call me at (301) 796-3603.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure - Meeting Minutes

**MEMORANDUM OF TELECONFERENCE MINUTES**

**MEETING DATE:** July 23, 2009  
**TIME:** 2:00 PM – 2:30 PM EST  
**LOCATION:** CDER WO Bldg22 conf rm 2157  
**APPLICATION:** NDA 4-570  
**SPONSOR:** Pharmacia and Upjohn, Inc.,  
**DRUG NAME:** Heparin sodium injection, USP  
**TYPE OF MEETING:** Type C

**MEETING CHAIR:** Dr. Dwaine Rieves

**MEETING RECORDER:** Mr. Marcus Cato

**FDA ATTENDEES:**

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/  
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director  
Marcus Cato, M.B.A., Regulatory Health Project Manager  
Diane V Leaman, Safety Regulatory Health Project Manager  
Kyong (Kaye) Kang, Pharm.D., Chief, Project Management Staff

**EXTERNAL ATTENDEES:**

PFIZER INC./PHARMACIA AND UPJOHN, INC.,

Kathleen Collins, Manager, Regulatory Strategy  
Corinne Gamper, Senior Director, Regulatory Strategy

**BACKGROUND:**

In a letter dated June 15, 2009, Pharmacia & Upjohn Company (Pharmacia) requested a meeting to discuss their proposal to re-introduce Heparin Sodium drug product to the U.S. market.

**MEETING OBJECTIVES:**

To discuss the June 15, 2009, meeting request and proposed, prior approval supplement, submission strategy.

**DISCUSSION POINTS:**

FDA commented that Pharmacia's proposed, prior approval supplement, submission strategy was not appropriate. NDA 4-570 provided FDA approval to market bovine-sourced heparin. Pharmacia now proposes to market porcine-sourced heparin. FDA expects Pharmacia to submit

either a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) for the porcine-sourced heparin since we regard this product as importantly different from bovine-sourced heparin; hence, the porcine-sourced heparin is a new drug. FDA advised Pharmacia to discuss its submission strategy internally and submit a request for a pre-NDA meeting. Pharmacia agreed.

Pharmacia stated that it originally viewed such a submission as a Chemistry, Manufacturing, and Controls (CMC) change. FDA emphasized that changing to porcine-sourced heparin may require different dosing, a different manufacturing processes, and may have different immunogenicity consequences. Pharmacia agreed.

**DECISIONS (AGREEMENTS) REACHED:**

- FDA will cancel the meeting scheduled for July 30, 2009
- Pharmacia will discuss submission options internally and submit a request for a pre-NDA meeting

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

- None

**ACTION ITEMS:**

- None

**ATTACHMENTS/HANDOUTS:**

- None

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 4570	GI 1	PHARMACIA AND UPJOHN CO	HEPARIN SODIUM

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/s/

MARCUS A CATO  
07/29/2009