

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201811Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # **201811**

SUPPL #

HFD # **161**

Trade Name **Argatroban**

Generic Name

Applicant Name **Fresenius Kabi USA, LLC.**

Approval Date, If Known **March 23, 2015**

### **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.

**N/A**

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:

**N/A**

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?

N/A

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



Investigation #2

YES

Explain:

!

!

! NO

! 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: **Beatrice Kallungal, BS**

Title: **Senior Regulatory Project Manager**

Date: **March 20, 2015**

Name of Office/Division Director signing form: **Ann T. Farrell, MD**

Title: **Division Director**

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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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BEATRICE A KALLUNGAL  
03/20/2015

ANN T FARRELL  
03/23/2015

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # <b>201811</b> BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: N/A Established/Proper Name: <b>Argatroban Injection</b> Dosage Form: <b>Injection</b>		Applicant: <b>Fresenius Kabi USA, LLC</b> Agent for Applicant (if applicable): N/A
RPM: <b>Beatrice Kallungal</b>		Division: <b>Division of Hematology Products</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)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>          Date of check: <b>March 18, 2015</b></p> <p><i>Note: 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.</i></p>
✓ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <b>March 23, 2015</b></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		CR 2/28/2014 (Cycle 4) CR 4/5/2013 (Cycle 3) CR 7/23/2012 (Cycle 2) CR 2/24/2011 (Cycle 1)
❖ 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 _____.		<input type="checkbox"/> Received

The Application Information Section is (only) a checklist. The Contents of Action Package Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Application Characteristics <sup>3</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only): <b>5S</b>  <i>(confirm chemical classification at time of approval)</i></p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  <input type="checkbox"/> Breakthrough Therapy designation             </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 type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required             </p> <p>Comments:</p>	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
❖ Public communications (approvals only)	
<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>Indicate what types (if any) of information were issued</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?</li> <li>If so, specify the type</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ 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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

<sup>3</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.

<b>CONTENTS OF ACTION PACKAGE</b>	
<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) 3/23/2015 (Cycle 5, Approval); 2/28/2014 (Cycle 4, CR); 4/5/2013 (Cycle 3, CR); 7/23/2012 (Cycle 2, CR); 2/24/2011 (Cycle 1, CR)
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
• Most recent draft labeling ( <i>if it is division-proposed labeling, it should be in track-changes format</i> )	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 1/23/2015
❖ 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
• Most-recent draft labeling ( <i>if it is division-proposed labeling, it should be in track-changes format</i> )	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ 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> )	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) ( <i>indicate date(s)</i> )	N/A
• Review(s) ( <i>indicate date(s)</i> )	
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	<b>RPM: 3/18/2015; 6/5/2012</b> <b>DMEPA: 3/4/2015; 12/13/2010</b> DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> None SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None <b>Other: CMC: 3/9/2015;</b> <b>PMHS: 9/20/2010; 7/27/2010</b>

### Administrative / Regulatory Documents

<ul style="list-style-type: none"> <li>❖ RPM Filing Review<sup>4</sup>/Memo of Filing Meeting (<i>indicate date of each review</i>)</li> <li>❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</li> </ul>	<p><b>RPM Filing Review: N/A</b></p> <p><b>505 (b)(2):</b>  <b>3/5/2015 (cycle 5);</b>  <b>3/22/2013 (cycle 3);</b>  <b>6/4/2012 (cycle 2);</b>  <b>6/1/2010 (cycle 1)</b></p>
❖ 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: This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	<p><b>Cycle 5: 3/20/2015, 3/19/2015, 3/18/2015, 3/10/2015, 2/10/2015, 2/6/2015;</b>  <b>Cycle 4: 9/26/2013;</b>  <b>Cycle 3: 1/14/2013, 10/24/2012, 10/16/2012; Cycle 2: 6/13/2012, 6/4/2012, 6/1/2012, 4/26/2012, 4/23/2012, 2/10/2012; Cycle 1: 10/05/2010, 9/14/2010, 7/2/2010, 6/29/2010, 6/22/2010; 5/04/2010; 4/29/2010; 4/19/2010</b></p>
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	<b>Telecon 11/19/2011 (Cycle 1)</b>
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	N/A

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<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> )	3/16/2015 (Cycle 5); 2/28/2014 (Cycle 4); 3/26/2013 (Cycle 3); 7/20/2012 (Cycle 2); 2/24/2011 (Cycle 1)
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	3/13/2015 (Cycle 5); 2/5/2014 (Cycle 4); 3/21/2013 (Cycle 3); 7/20/2012 (Cycle 2); 2/16/2011 (Cycle 1)
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<b>Cosigned reviews dated:</b> 2/11/2015 (Cycle 5); 1/31/2014 (Cycle 4); 1/7/2013 (Cycle 3); 6/29/2012 (Cycle 2); 2/9/2011 (Cycle 1)
• Clinical review(s) ( <i>indicate date for each review</i> )	2/11/2015 (Cycle 5); 1/31/2014 (Cycle 4); 1/7/2013 (Cycle 3); 6/29/2012 (Cycle 2); 2/9/2011 (Cycle 1)
• 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 type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	N/A The Applicant indicated that since there are no clinical studies conducted/submitted with this application, no financial disclosure is applicable.
❖ 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"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (<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

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<b>Cosigned reviews dated:</b> 2/26/2015 (Cycle 5); 2/16/2011 (Cycle 1)
Clinical Pharmacology review(s) (indicate date for each review)	2/26/2015 (2) (Cycle 5); 1/30/2014 (Cycle 4); 3/22/2013 (Cycle 3); 4/30/2012 (Cycle 2); 2/16/2011 (Cycle 1)
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)	<b>Cosigned reviews dated:</b> 3/10/2015 (Cycle 5); 1/11/2013 (Cycle 3); 6/4/2012 (Cycle 2); 2/2/2011 (Cycle 1)
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	3/10/2015 (Cycle 5); 2/5/2014, 1/30/2014 (Cycle 4); 1/11/2013 (Cycle 3); 6/4/2012 (Cycle 2); 2/2/2011 (Cycle 1)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
<ul style="list-style-type: none"> <li>• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> No separate review	
<ul style="list-style-type: none"> <li>• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>	<b>Cosigned reviews dated:</b> 3/9/2015 (Cycle 5); 1/30/2014 (Cycle 4); 3/19/2013 (Cycle 3); 7/6/2012 (Cycle 2); 2/16/2011 (Cycle 1)	
<ul style="list-style-type: none"> <li>• Product quality review(s) including ONDQA biopharmaceuticals reviews <i>(indicate date for each review)</i></li> </ul>	<b>CMC:</b> 3/9/2015 (Cycle 5); 1/30/2014 (Cycle 4); 3/19/2013 (Cycle 3); 7/6/2012 (Cycle 2); 2/16/2011, 5/26/2010 (Cycle 1)  <b>Biopharmaceuticals:</b> 3/10/2015 (Cycle 5); 2/4/2014 (Cycle 4); 4/24/2012 (Cycle 2)	
❖ Microbiology Reviews <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 (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	2/25/2015 (Cycle 5); 1/31/2014 (Cycle 4); 2/25/2013 (Cycle 3); 6/29/2012 (Cycle 2); 1/13/2011 (Cycle 1)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None	
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A	
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	<b>See CMC reviews signed:</b> 1/30/2014 (Cycle 4); 3/19/2013 (Cycle 3); 7/6/2012 (Cycle 2); 2/15/2011 (Cycle 1)	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup></i> )	Date completed: <b>2/25/2015 (Cycle 5 - acceptable);</b> <b>1/18/2013 (Cycle 3 - withhold)</b> <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</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.

**Day of Approval Activities**

❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: • Notify the CDER BT Program Manager	<input type="checkbox"/> Done <b>N/A</b> ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): • Notify the Division of Online Communications, Office of Communications	<input type="checkbox"/> Done <b>N/A</b>
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done <b>N/A</b>
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done <b>N/A</b>
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done <b>N/A</b>
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

**From:** [Kallungal, Beatrice](mailto:Kallungal.Beatrice)  
**To:** [Jenna.Holm@fresenius-kabi.com](mailto:Jenna.Holm@fresenius-kabi.com)  
**Cc:** [Jeremy.Rybicki@fresenius-kabi.com](mailto:Jeremy.Rybicki@fresenius-kabi.com); [Kallungal, Beatrice](mailto:Kallungal.Beatrice)  
**Subject:** RE: NDA 2010811, Argatroban - Draft package insert with FDA's revisions - 03/20/2015 - PLEASE RESPOND  
**Date:** Friday, March 20, 2015 4:22:38 PM  
**Attachments:** [NDA 201811\\_package insert\\_03202015.doc](#)

---

Hi Jenna,

Thank you for your response. We seek your agreement on the attached revised labeling. Please note that we have removed the changes related to pregnancy and lactation labeling rule (PLLR).

Please respond by **10 am Monday, March 23, 2015**.

Thanks,

Beatrice Kallungal  
Senior Regulatory Health Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OHOP  
WO22, Room 2354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-9304 (phone)  
(301) 796-9845 (fax)  
E-Mail: [beatrice.kallungal@fda.hhs.gov](mailto:beatrice.kallungal@fda.hhs.gov)

**From:** Jenna.Holm@fresenius-kabi.com [mailto:Jenna.Holm@fresenius-kabi.com]  
**Sent:** Thursday, March 19, 2015 4:22 PM  
**To:** Kallungal, Beatrice  
**Cc:** Jenna.Holm@fresenius-kabi.com; Jeremy.Rybicki@fresenius-kabi.com  
**Subject:** RE: NDA 2010811, Argatroban - Draft package insert with FDA's revisions - 03/19/2015 - PLEASE RESPOND

Hi Beatrice,

As conveyed in our phone conversation a few minutes ago, pursuant to Fresenius Kabi USA's 505(B)2 application, we have not conducted any clinical or non-clinical studies with Argatroban and search of literature in the public domain failed to identify any adequate and well-controlled studies of argatroban use in pregnant women. Additionally, as communicated in Module 2, Section 2.4 of SEQ-0009, no toxicokinetic, genotoxicity, carcinogenicity, or reproductive and developmental toxicity data, or local tolerance data were found in literature. Pregnancy category B reflects the innovator's PI information, and is based on proprietary data submitted to the agency within the innovator's application.

**Consequently, we have no additional data, clinical or non-clinical, to include in the section 8 of the package insert. The final version of the package insert provided in your previous email remains unchanged.**

Best regards,

**Jenna Holm**  
Regulatory Affairs Specialist

Fresenius Kabi USA, LLC  
Three Corporate Drive  
Lake Zurich, Illinois 60047  
T: +1 847-550-2647  
F: +1 847-550-7120  
[jenna.holm@fresenius-kabi.com](mailto:jenna.holm@fresenius-kabi.com)  
[www.fresenius-kabi.us](http://www.fresenius-kabi.us)

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35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
-----

BEATRICE A KALLUNGAL  
03/20/2015

**From:** [Jenna.Holm@fresenius-kabi.com](mailto:Jenna.Holm@fresenius-kabi.com)  
**To:** [Kallungal, Beatrice](mailto:Kallungal, Beatrice)  
**Cc:** [Jenna.Holm@fresenius-kabi.com](mailto:Jenna.Holm@fresenius-kabi.com); [Jeremy.Rybicki@fresenius-kabi.com](mailto:Jeremy.Rybicki@fresenius-kabi.com)  
**Subject:** RE: NDA 2010811, Argatroban - Draft package insert with FDA's revisions - 03/19/2015 - PLEASE RESPOND  
**Date:** Thursday, March 19, 2015 4:22:49 PM  
**Attachments:** [NDA 201811\\_package insert\\_FINAL.doc](#)

---

Hi Beatrice,

As conveyed in our phone conversation a few minutes ago, pursuant to Fresenius Kabi USA's 505(B)2 application, we have not conducted any clinical or non-clinical studies with Argatroban and search of literature in the public domain failed to identify any adequate and well-controlled studies of argatroban use in pregnant women. Additionally, as communicated in Module 2, Section 2.4 of SEQ-0009, no toxicokinetic, genotoxicity, carcinogenicity, or reproductive and developmental toxicity data, or local tolerance data were found in literature. Pregnancy category B reflects the innovator's PI information, and is based on proprietary data submitted to the agency within the innovator's application.

**Consequently, we have no additional data, clinical or non-clinical, to include in the section 8 of the package insert. The final version of the package insert provided in your previous email remains unchanged.**

Best regards,

**Jenna Holm**  
Regulatory Affairs Specialist

Fresenius Kabi USA, LLC  
Three Corporate Drive  
Lake Zurich, Illinois 60047  
T: +1 847-550-2647  
F: +1 847-550-7120  
[jenna.holm@fresenius-kabi.com](mailto:jenna.holm@fresenius-kabi.com)  
[www.fresenius-kabi.us](http://www.fresenius-kabi.us)

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From: "Kallungal, Beatrice" <Beatrice.Kallungal@fda.hhs.gov>  
To: "Jenna.Holm@fresenius-kabi.com" <Jenna.Holm@fresenius-kabi.com>,  
Cc: "Jeremy.Rybicki@fresenius-kabi.com" <Jeremy.Rybicki@fresenius-kabi.com>, "Kallungal, Beatrice" <Beatrice.Kallungal@fda.hhs.gov>  
Date: 03/19/2015 01:55 PM  
Subject: RE: NDA 2010811, Argatroban - Draft package insert with FDA's revisions - 03/19/2015 - PLEASE RESPOND

---

Hi Jenna,  
In comparing the FDA proposed revisions we sent you initially and what you sent

back, it looks like you haven't provided the information we requested in section 8 (I have pasted below and also see attached).

## **8 USE IN SPECIFIC POPULATIONS** [\[A1\]](#)

### **8.1 Pregnancy**

(b) (4) [\[A2\]](#)

Please make the revisions in the most recent version of the label (with file name 'final' in the attached) and send it back to me. I am including the initial draft and the most current version of the label in this e-mail.

Regards,

Beatrice Kallungal  
Senior Regulatory Health Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OHOP  
WO22, Room 2354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-9304 (phone)  
(301) 796-9845 (fax)  
E-Mail: [beatrice.kallungal@fda.hhs.gov](mailto:beatrice.kallungal@fda.hhs.gov)

**From:** Jenna.Holm@fresenius-kabi.com [<mailto:Jenna.Holm@fresenius-kabi.com>]  
**Sent:** Thursday, March 19, 2015 11:28 AM  
**To:** Kallungal, Beatrice  
**Cc:** Jenna.Holm@fresenius-kabi.com; Jeremy.Rybicki@fresenius-kabi.com  
**Subject:** RE: NDA 2010811, Argatroban - Draft package insert with FDA's revisions - 03/18/2015

Good morning Beatrice,

Thank you for the clarification. For you records, we successfully submitted the previously agreed upon revised labels and labeling yesterday afternoon through the gateway. Regrettably, we will not be able to submit the additional, minor revisions within the time frame indicated and, therefore, we thank you for including the required action in the letter on Monday.

Best regards,

**Jenna Holm**  
Regulatory Affairs Specialist

Fresenius Kabi USA, LLC  
Three Corporate Drive  
Lake Zurich, Illinois 60047  
T: +1 847-550-2647  
F: +1 847-550-7120  
[jenna.holm@fresenius-kabi.com](mailto:jenna.holm@fresenius-kabi.com)  
[www.fresenius-kabi.us](http://www.fresenius-kabi.us)

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/s/  
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BEATRICE A KALLUNGAL  
03/20/2015

**From:** [Kallungal, Beatrice](mailto:Kallungal, Beatrice)  
**To:** [Jenna.Holm@fresenius-kabi.com](mailto:Jenna.Holm@fresenius-kabi.com)  
**Cc:** [Kallungal, Beatrice](mailto:Kallungal, Beatrice); [jeremy.rybicki@fresenius-kabi.com](mailto:jeremy.rybicki@fresenius-kabi.com)  
**Subject:** RE: NDA 2010811, Argatroban - Draft package insert with FDA's revisions - 03/18/2015  
**Date:** Wednesday, March 18, 2015 11:47:53 AM  
**Attachments:** [NDA 201811 Revised package insert 03182015.doc](#)

---

Hi Jenna,

As indicated in the enclosed PI, your proposed edits/comments are acceptable to the Agency. Your comment regarding the lot number and expiration date on the carton labeling is also acceptable. In addition, we have added minor edits on pages 1 and 11. Please accept and submit the final version of the USPI to the NDA by **later today or no later than noon tomorrow (3/19/2015)**.

Thanks,

Beatrice

Beatrice Kallungal  
Senior Regulatory Health Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OHOP  
WO22, Room 2354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-9304 (phone)  
(301) 796-9845 (fax)  
E-Mail: [beatrice.kallungal@fda.hhs.gov](mailto:beatrice.kallungal@fda.hhs.gov)

**From:** Jenna.Holm@fresenius-kabi.com [mailto:Jenna.Holm@fresenius-kabi.com]  
**Sent:** Monday, March 16, 2015 1:20 PM  
**To:** Kallungal, Beatrice  
**Cc:** Jenna.Holm@fresenius-kabi.com  
**Subject:** Fw: NDA 2010811, Argatroban - Draft package insert with FDA's revisions  
**Importance:** High

Hello again Beatrice,

My apologies for the delay due to our network crash. I've attached the Word document of the package insert as well as the revised vial and carton labels. As agreed, we will submit everything, including annotated/comparison files for each, electronically, by Wednesday, March 18.

Best regards,

All requested changes have been incorporated into the revised carton label with the exception of the "lot number, expiration date" portion of #6. For all Fresenius Kabi USA, LLC products manufactured, the lot number and expiration date are coded onto the carton label during the labeling and packaging process.

We agree with the labeling revisions and "accept" all the track changes with the exception of comment

A12 which states, [REDACTED] (b) (4)  
Fresenius Kabi USA, LLC does not include the [REDACTED] (b) (4) on the labeling for any of its products.  
Therefore, for the sake of consistency across all Fresenius Kabi USA, LLC labeling, we prefer not to include the [REDACTED] (b) (4).

Additionally, minor editing revisions, such as revising all Table references throughout the text to align with revised Table numbers proposed by the Agency in the information request, were incorporated into revised labeling.

**Jenna Holm**  
Regulatory Affairs Specialist

Fresenius Kabi USA, LLC  
Three Corporate Drive  
Lake Zurich, Illinois 60047  
T: +1 847-550-2647  
F: +1 847-550-7120  
[jenna.holm@fresenius-kabi.com](mailto:jenna.holm@fresenius-kabi.com)  
[www.fresenius-kabi.us](http://www.fresenius-kabi.us)

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----- Forwarded by Jenna Holm/CS/CO/US/HHC/Fresenius on 03/16/2015 11:59 AM -----

From: Jenna Holm/CS/CO/US/HHC/Fresenius  
To: "Kallungal, Beatrice" <[Beatrice.Kallungal@fda.hhs.gov](mailto:Beatrice.Kallungal@fda.hhs.gov)>,  
Cc: Jenna Holm/CS/CO/US/HHC/Fresenius@FRESENIUSINT  
Date: 03/16/2015 11:40 AM  
Subject: Re: FW: NDA 2010811, Argatroban - Draft package insert with FDA's revisions

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as b4 (CCI/TS) immediately following this page

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/s/  
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BEATRICE A KALLUNGAL  
03/18/2015

**From:** [Kallungal, Beatrice](#)  
**To:** [Jenna.Holm@fresenius-kabi.com](mailto:Jenna.Holm@fresenius-kabi.com)  
**Cc:** [Kallungal, Beatrice](#)  
**Subject:** NDA 2010811, Argatroban - Draft package insert with FDA's revisions  
**Date:** Tuesday, March 10, 2015 3:06:27 PM  
**Attachments:** [NDA201811\\_draft-PI\\_03102015.doc](#)

---

Hello,

Attached is the revised draft package insert (PI) for Argatroban, NDA 201811.

Please review the FDA's changes/comments and, using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please address the following comments related to the carton and container labels.

**Immediate Container Label:**

1. Established name needs to be expressed as "Argatroban Injection", which only first letter of each word is capitalized.
2. Administration route should be: for intravenous use
3. Need to add "Rx only"
4. Name of manufacturer/distributor needs to be defined as "marketed by", "distributed by", or "manufactured by" etc.
5. (b) (4) needs to be changed to "see package insert"

**Carton Label:**

1. Established name needs to be expressed as "Argatroban Injection", which only first letter of each word is capitalized.
2. Administration route should be: for intravenous use
3. (b) (4) needs to be changed to "see package insert"
4. Name of manufacturer/distributor needs to be defined as "marketed by", "distributed by", or "manufactured by" etc.
5. Except for preservative free, need to add "sterile and nonpyrogenic" statement as well
6. Need to add "lot number, expiration date, and net content", net content can be listed as "packaged individually."

We request that you respond by **Noon EDT, Friday, March 13, 2015** via e-mail and officially submit to the NDA.

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

Kind regards,

Beatrice

Beatrice Kallungal  
Senior Regulatory Health Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OHOP  
WO22, Room 2354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-9304 (phone)  
(301) 796-9845 (fax)  
E-Mail: [beatrice.kallungal@fda.hhs.gov](mailto:beatrice.kallungal@fda.hhs.gov)

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/s/  
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BEATRICE A KALLUNGAL  
03/10/2015



NDA 201811

**ACKNOWLEDGE -  
CLASS 1 COMPLETE RESPONSE**

Fresenius Kabi USA, LLC  
Attention: Jenna Holm  
Regulatory Specialist  
Three Corporate Drive  
Lake Zurich, IL 60047

Dear Ms. Holm:

We acknowledge receipt of your January 23, 2015 resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban injection, 100 mg/mL.

We consider this resubmission a complete, class 1 response to our February 28, 2014 action letter. Therefore, the user fee goal date is March 23, 2015.

If you have any questions, call me at (301) 796-9304.

Sincerely,

*{See appended electronic signature page}*

Beatrice Kallungal, BS  
Senior Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

-----  
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/s/  
-----

BEATRICE A KALLUNGAL  
02/10/2015

**From:** Laiq, Rabiya  
**Sent:** Friday, February 06, 2015 12:25 PM  
**To:** 'anne.huffman@fresenius-kabi.com'  
**Cc:** Tran-Zwanetz, Catherine  
**Subject:** Resubmission NDA 201811 Clarification Needed

Hi Anne,

My name is Rabiya Laiq, I am the Regulatory and Business Process Manager working on this NDA submission. Please reply to the following request below for clarity as soon as possible.

Please confirm if the following sites that are listed in your NDA resubmission are still applicable since they are not listed on your 356(h).

APP Pharmaceuticals – FEI 3005724920



Fresenius Kabi- FEI 3005742048

Also: These two sites however are on the 356(h) but don't indicate if the facility is ready for inspection. Please clarify.



Thank you,  
Rabiya

**Rabiya Laiq, Pharm.D.**  
**Regulatory Business Process Manager**  
**Office of Program and Regulatory Operations**  
**Office of Pharmaceutical Quality**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
**Phone: (240) 402-6153**  
**Email: [rabiya.laiq@fda.hhs.gov](mailto:rabiya.laiq@fda.hhs.gov)**





NDA 201811

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Fresenius Kabi USA, LLC.  
Attention: Aditi Dron  
Manager, Regulatory Affairs  
Three Corporate Drive  
Lake Zurich, IL 60047

Dear Ms. Dron:

We acknowledge receipt on September 13, 2013 of your September 13, 2013 resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection, 100 mg/mL (2.5 mL in a (b) (4) vial).

We consider this a complete, class 2 response to our April 05, 2013 action letter. Therefore, the user fee goal date is March 13, 2014.

If you have any questions, call me at (301) 796-9304.

Sincerely,

*{See appended electronic signature page}*

Beatrice Kallungal, B.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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BEATRICE A KALLUNGAL  
09/26/2013

## Kallungal, Beatrice

---

**From:** Kallungal, Beatrice  
**Sent:** Monday, January 14, 2013 11:46 AM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Cc:** nicole.cage@fresenius-kabi.com; Kallungal, Beatrice  
**Subject:** RE: Argatroban NDA 201811 - Request for clarification - Labeling request

Hi Aditi,

Please send a red-lined version of the package insert to SEQ-0016 submitted on October 12, 2012. You already submitted a side-by-side comparison of the current and propose labels. We would like to also get the proposed label as a separate word document so that we can work off of that to complete the review.

If you have questions, please call me.

Thanks,

Beatrice

Beatrice Kallungal  
Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OHOP  
WO22, Room 6187  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-9304 (phone)  
(301) 796-9845 (fax)  
E-Mail: [beatrice.kallungal@fda.hhs.gov](mailto:beatrice.kallungal@fda.hhs.gov)

**From:** Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]  
**Sent:** Friday, January 11, 2013 2:05 PM  
**To:** Kallungal, Beatrice  
**Cc:** nicole.cage@fresenius-kabi.com  
**Subject:** RE: Argatroban NDA 201811 - Request for clarification - Labeling request

Hi Beatrice,

We seek clarification for the following aspects of the Agency's request for red-lined package insert, so that we can respond appropriately to the request:

- Where should FK USA start to provide requested separate annotated red line for the PI? Should we start at SEQ-009 dated 11-May-2012? Please note that there have been several correspondences via e-mail and amendments (SEQ-0011, SEQ-012 -vial and carton, only and SEQ-0014) since this submission.
- What exactly do you want see in the separate annotated red line? Is this supposed to be a MS Word document with track changes?

At this time FK USA's understanding is that you want the PI in MS Word format with all changes identified since SEQ-0009 via track changes or other feasible means.

We appreciate your help in facilitating our understanding of the request, so that we can provide the requested red-lined package insert labeling.

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/s/  
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BEATRICE A KALLUNGAL  
03/25/2013



NDA 201811

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Fresenius Kabi USA, LLC.  
Attention: Aditi Dron  
Manager, Regulatory Affairs  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, IL 60173

Dear Mr. Dron:

We acknowledge receipt on October 12, 2012 of your October 12, 2012 resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection, 100 mg/mL (2.5 mL in a (b) (4) vial).

We consider this a complete, class 2 response to our July 23, 2012, action letter. Therefore, the user fee goal date is April 12, 2013.

If you have any questions, call me at (301) 796-9304.

Sincerely,

*{See appended electronic signature page}*

Beatrice Kallungal, B.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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BEATRICE A KALLUNGAL  
10/24/2012



NDA 201811

**ACKNOWLEDGE CORPORATE  
NAME/ADDRESS CHANGE**

Fresenius Kabi USA, LLC.  
Attention: Dale Carlson  
Senior Director, Regulatory Affairs  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, Illinois 60173

Dear Mr. Carlson:

We acknowledge receipt on September 19, 2012, of your September 19, 2012 correspondence notifying the Food and Drug Administration (FDA) that the corporate name and/or address has been changed from

APP Pharmaceuticals, LLC.  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, Illinois 60173

to

Fresenius Kabi USA, LLC.  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, Illinois 60173

for the following new drug application (NDA): NDA 201811 for Argatroban Injection.

We have revised our records to reflect this change.

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their DMFs and send you a copy of the new LOAs.

Please submit these copies of the LOAs to this NDA.

Please cite the NDA number listed above 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

If you have any questions, call me at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Monsurat Lara Akinsanya, M.S.  
Regulatory Health Project Manger  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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MONSURAT O AKINSANYA  
10/16/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Monday, June 04, 2012 2:33 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Cc:** Akinsanya, Lara; Boehmer, Jessica  
**Subject:** Information Request - Microbiology: NDA 201811 (Argatroban) -DUE June 7

Dear Aditi Dron,

Please provide the following information or reference to its location in the subject submission:

- Clarification with regard to when in the drug product manufacturing process the sample is taken for bioburden determination. Figure 3.2.P.3.3-1 depicts that the sample is taken (b) (4). However, Section 1.1 of Module 3.2.P.3.5 provides a limit of NMT (b) (4) CFU/mL for the “(b) (4) test method validation”. Clarify this discrepancy.
- Clarification with regard to the performance of media fill process simulations. Section 4.5 of Module 3.2.P.3.5 states that a (b) (4) units are filled. Further, it is stated in Section 5 (Actions concerning Production when media fills fail) that a (b) (4) vials must be filled and incubated. However, the media fill data reported in the application (batches 7020719, 7020718 and 7020795) demonstrate that (only) (b) (4) vials were filled. Clarify this discrepancy.
- A rationale regarding how the media fill data reported in the application (batches 7020719, 7020718 and 7020795) support the subject drug product manufacturing process. Each of the (b) (4) process simulations utilized (b) (4) mL vials with either a (b) (4) mL or (b) (4) mL fill volume, while the subject drug product is comprised of a (b) (4) vial with a 2.5 mL fill volume.
- The SOP 03-10-08-0017 (*Finished Product/Raw Material BET Validation Procedure Using Kinetic Turbidimetric Analysis*) and the test method used for bacterial endotoxins testing of the finished drug product. The narrative provided in the Microbiological Method Validation Package describes a study that was performed to verify the suitability of use of the bacterial endotoxins test with the subject drug product. The narrative states that the slope of the standard curve, the positive control, the standard curve correlation coefficient, and the negative control all met specification, however the acceptance criteria for each of these are not provided.

Please respond to the above information request by **Thursday, June 7, 2012**.

Thank You

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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/s/  
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MONSURAT O AKINSANYA  
07/23/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Wednesday, June 13, 2012 12:17 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Cc:** Akinsanya, Lara; Boehmer, Jessica  
**Subject:** Labeling - Information Request : NDA 201811 (Argatroban) - DUE June 27, 2012

**Attachments:** Argatroban FDA revised 6-5-12.doc; app-draft-250mg-carton\_FDA Revised\_060412.pdf; app-draft-250mg-vial\_FDA Revised\_060412.pdf

Dear Aditi Dron,

Please see attached revised draft of the PI, carton, and vial labeling for NDA 201811. Please review the changes/comments do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)



Argatroban FDA revised 6-5-12....  
app-draft-250mg-c carton\_FDA Rev...  
app-draft-250mg-vial\_FDA Revis...

Please respond to this information request by **Wednesday, June 27, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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/s/  
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MONSURAT O AKINSANYA  
06/13/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Friday, June 01, 2012 2:48 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Cc:** Akinsanya, Lara; Boehmer, Jessica  
**Subject:** Information Request - DMEPA: NDA 201811 (Argatroban) -DUE June 7

Dear Aditi Dron,

Please respond to the following information request from the Division of Medication Error Prevention and Analysis (DMEPA):

### Label and labeling:

1. Delete the (b) (4) from the statement "(b) (4) Single (b) (4) Vial" and combine the statements "Discard Unused Portion" and Single Use Vial" as follows:

**"Single (b) (4) Vial. Discard Unused Portion"**

We recommend placing these two statements together to emphasize the fact that the vial must not be re-used after a single use.

2. Move the concentration of the product immediately underneath the net quantity as was depicted on your original label and labeling:

**250 mg/2.5 mL**

**(100 mg/mL)**

We recommend this revision because typically most products present their concentration immediately under the net quantity. Thus, we recommend the same revision for ease of identifying the concentration of the product.

3. We continue to recommend expanding the yellow box around the strength of the product to include the concentration as well. We recommend this revision to ensure that the concentration of the product is prominent and visible since there are several Argatroban products on the market that contain different concentration than your product. As a result, it is important that the concentration of your product is emphasized to help prevent dosing errors.

Please respond to the above information request by **Thursday, June 7, 2012**.

Thank You

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)

(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
06/01/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, April 26, 2012 9:57 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Cc:** Akinsanya, Lara  
**Subject:** Information Request - CMC: NDA 201811 (Argatroban) -DUE May 11

Dear Aditi Dron,

Please respond to the following Chemistry, Manufacturing, and Controls information request:

Drug Substance:

1. Provide a response to the following item f from the Complete Response letter (reproduced below for your convenience). Identify and describe the changes made to the method reported in the resubmission as compared to the method submitted in the original NDA.
  - f. The HPLC method for determination of argatroban and impurities and identification of argatroban (10-08-03-6457) and validation report PR-08-00037 contain acceptance criteria for impurities in the raw material and finished product with unjustifiably high values [for example, the percent relative standard deviation (RSD) for precision of NMT  $(b)_{(4)}\%$  at an impurity level of more than  $(b)_{(4)}$  percent, and the percent RSD for precision of NMT  $(b)_{(4)}\%$  at an impurity level of less than  $(b)_{(4)}$  percent]. The same high values are observed in the proposed acceptance criteria for the percent RSD for intermediate precision as well as the percent change in solutions from the initial timepoint. Therefore, revise the acceptance criteria to more accurately match your analytical data.
2. Add the analytical method used for each test to the “Summary of Test Results” issued by APP for argatroban lots. The summary submitted lists test, specification and results.

Reference Standard for stereoisomers of drug substance (21-S Argatroban and 21-R Argatroban):

3. Provide quality control specifications for the individual 21-R and 21-S isomers of argatroban reference standards. The proposed confirmatory testing by NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ) as reported by  $(b)_{(4)}$  for lots op20447-1 (21-R) and lot op20502 (21-S) is not sufficient to distinguish the individual isomers. The purpose of this testing was identified in the  $(b)_{(4)}$  report as “to confirm the NMR spectra provided by  $(b)_{(4)}$  for reference standards 21-S-argatroban and 21-R-argatroban are accurate”. The result reported was “spectra confirmed – see p.38-41”. Since the contents of p. 38-41 were low resolution photocopies of the spectra from the  $(b)_{(4)}$  21-R and 21-S reports entitled “Argatroban Monohydrate Analytical characterization of 21-R Argatroban (op20477-1)”, and there was no comparison of spectra, analysis of the data or demonstration of accuracy, the confirmatory testing is not sufficient. Additionally, the NMR spectra provided in the  $(b)_{(4)}$  analytical report does not distinguish the individual isomers.  $(b)_{(4)}$

$(b)_{(4)}$  The absence of a distinguishing feature in the  $(b)_{(4)}$  spectra makes their NMR method unsuitable for characterization of the 21-R and 21-S isomer reference standards.

Drug Product:

4. Provide the batch analysis and Certificates of Analysis for the lots of drug product manufactured at the new site, Grand Island, NY (Lots R340-032, R340-033 and R340-034). The files submitted (batch-analysis-drug-prod.pdf, etc) were not readable.
5. Revise the stability specifications for the drug product to include testing and acceptance criteria for isomeric ratio.

Please respond to the above information request by **Friday, May 11, 2012**.

Please let me know if you have any questions.

Thank You

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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/s/  
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MONSURAT O AKINSANYA  
04/26/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Monday, April 23, 2012 3:32 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Cc:** Akinsanya, Lara  
**Subject:** Information Request - OSE: NDA 201811 (Argatroban) -DUE May 14

Dear Aditi Dron,

Please respond to the following information request from the office of Surveillance and Epidemiology:

### All Container Labels and Carton Labeling for Argatroban Injection

1. Revise the amount of argatroban per each mL in the statement, "Each mL contains: (b) (4) argatroban and 954 mg propylene glycol" located on the side panel to contain the appropriate amount of argatroban. Each vial contains (b) (4) of Argatroban, not each mL. The revised statement should read, "Each mL contains: 100 mg argatroban and 954 mg propylene glycol."
2. Revise the dangerous abbreviation 'IV' to read "intravenous" that appears on the principle display panels of container and carton labeling. 'IV' is a dangerous abbreviation, which appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because the abbreviation 'IV' has been confused with the abbreviations 'IM' (intramuscular), 'IU' (international units), and 'IN' (intranasal). Revise this statement accordingly.
3. Add the statement "Single Use Vial, Discard Unused Portion" to the principle display panel. If you need more space, delete the product number "512603" from the principle display panel as this number does not carry any pertinent information regarding the product's use and occupies space.
4. Revise the phrase (b) (4) to state "Must be Diluted Prior to Administration" in order to emphasize the necessity of this step prior to administration. The FDA received post marketing cases of the wrong dilution of Argatroban, which resulted in patient harm. Therefore, we request you revise this statement accordingly.
5. Revise the font type of the word "Injection" to be in the same type, size, font and color as the word "Argatroban" to emphasize the dosage form in conjunction with the established name of the product.
6. Expand the yellow box around the strength of the product to include the concentration of the product as well.

Please respond to the above information request by **Monday, May 14, 2012**.

Please let me know if you have any questions.

Thank You

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
04/23/2012



NDA 201811

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

APP Pharmaceuticals, LLC  
Attention: Aditi Dron  
Regulatory Affairs Manager  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, IL 60173

Dear Ms. Dron:

We acknowledge receipt on January 31, 2012, of your January 31, 2012, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection, 100 mg/mL.

We consider this a complete, class 2 response to our February 24, 2011, action letter. Therefore, the user fee goal date is July 31, 2012.

If you have any questions, call me at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Lara Akinsanya, M.S.  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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MONSURAT O AKINSANYA  
02/10/2012

## MEMORANDUM OF TELECON

**MEETING DATE:** November 19, 2010  
**TIME:** 9:30AM – 10: 30AM  
**LOCATION:** CDER WO 2201 conf rm Bldg22  
**APPLICATION:** NDA 201-811  
**SPONSOR:** APP Pharmaceuticals, LLC  
**DRUG NAME:** Argatroban

**MEETING CHAIR:** Sarah Pope Miksinski

**MEETING RECORDER:** Ebla Ali Ibrahim

### **FDA ATTENDEES:**

#### Division of Hematology Products (DHP)

Ann Farrell, M.D., Acting Division Director  
Firoozeh Alvandi, M.D., Medical Officer  
Virginia Kwitkowski, M.D., Medical Officer  
Haleh Saber, Ph.D., Supervisory, Pharmacologist  
Lara Akinsanya, M.S., Regulatory Health Project Manager  
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager

#### Office of New Drug Quality Assessment (ONDQA)

Sarah Pope, Ph.D., Branch Chief  
Janice Brown, Ph.D., Chemistry Team Leader  
Milagros Driver Salazar, Ph.D., Chemist  
Teshara Bouie, Regulatory Project Manager

#### Office of Clinical Pharmacology (OCP)

Julie Bullock, PharmD, Clinical Pharmacology Team Leader  
Lilian Huan Zhang, Ph.D., Clinical Pharmacologist

### **EXTERNAL CONSTITUENT ATTENDEES:**

#### APP Pharmaceuticals, Inc.

Mr. Dale Carlson, Director, Regulatory Affairs  
Ms. Toni A. Glinsey, Manager, Regulatory Affairs  
Ms. Aditi Dron, Regulatory Scientist

**BACKGROUND:**

On September 14, 2010, FDA sent an Information Request, via e-mail, to obtain information regarding a discrepancy in facility information listed in the NDA. On October 15, 2010, APP Pharmaceuticals, LLC provided a response to the 9-14-10 FDA Information Request.

**MEETING OBJECTIVES:**

To understand and discuss the Applicant's rationale for the manufacturing facility site change proposed in the 15-OCT-2010 amendment.

**DISCUSSION POINTS:**

APP Pharmaceuticals, LLC confirmed that the drug product manufacturing site proposed in the NDA had been closed. During the discussion, FDA notified APP Pharmaceuticals, LLC that since there is now no drug manufacturing site currently in this application, the discrepancy in the original NDA manufacturing facility information poses a significant deficiency with regards to moving forward with the CMC review process.

APP Pharmaceuticals, LLC clarified that the decision to close the previously-proposed argatroban manufacturing facility (Barcelona Puerto Rico) was a business decision. APP Pharmaceuticals, LLC also asked if FDA would consider reviewing the application if an amendment proposing a new manufacturing site is submitted. FDA noted that such an amendment would need to include a substantial amount of new CMC information (an updated Module 3) which would not be reviewable within the current review cycle.

APP Pharmaceuticals, LLC asked if it will be feasible to amend the NDA in a stepwise fashion as chemistry, manufacturing and controls (including stability) data becomes available. FDA noted that such a stepwise review was not possible for the current NDA. FDA also confirmed that full term primary stability data of the product from a new site is needed in support of the proposed expiration.

APP Pharmaceuticals, LLC suggested the possibility of bridging product information from the closed site in Puerto Rico to support of the proposed new site.. FDA advised that, since the currently submitted Module 3 applies specifically to the closed manufacturing site in Puerto Rico, and since the newly proposed site (Grand Island, NY) was not submitted in the initial NDA, any attempts to bridge the Barceloneta manufacturing information to the new site would likely be of little to no value at this point in the current review clock.

**DECISIONS (AGREEMENTS) REACHED:**

None

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

None

**ACTION ITEMS:**

- FDA will draft a CR letter and provide to APP Pharmaceuticals, LLC
- APP Pharmaceuticals, LLC will respond to the CR when the new site is ready for manufacturing and complete data is available.

**ATTACHMENTS/HANDOUTS:**

None

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/s/  
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EBLA ALI IBRAHIM  
02/16/2011

**Ali Ibrahim, Ebla**

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Tuesday, October 05, 2010 5:24 PM  
**To:** 'ADron@apppharma.com'  
**Subject:** RE: Information Request - NDA 201-811  
**Follow Up Flag:** Follow up  
**Flag Status:** Red

Hello,

Thank you for your prompt response. The FDA reviewer said that what you submitted on 9/3/10 are the SAS transport files for argatroban concentrations in the stock/spiking solutions and in human plasma samples. You did not submit the raw data for coagulation time measured (PT, aPTT, and TT) in the SAS transport files, so our request (listed below) still remains the same.

Please submit raw data for coagulation time measured as SAS transport files (\*.xpt) for Study AA86231. A description of each data item should be provided in a Define.pdf file. Any concentrations and/or pools that have been excluded from the analysis should be flagged and maintained in the datasets.

In addition,

For the (b) (4) SAS transport file submitted on 9/3/10, please clarify the concentration units used for both Theoretical Conc. and Actual Conc.

Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** ADron@apppharma.com [mailto:ADron@apppharma.com]  
**Sent:** Tuesday, October 05, 2010 11:03 AM  
**To:** Ali Ibrahim, Ebla  
**Subject:** Re: Information Request - NDA 201-811

Hello Ms. Ibrahim,

I have received the request sent by you yesterday evening. This request seems to be similar to that included within the 7-2-10 Filing Letter. APP had provided the SAS transport files and Define.pdf file for the Study

AA86231 within a Minor Amendment (SEQ-0005) submitted to the Agency on 9-3-10.

Can you please check if the Minor Amendment has been received by the Agency?

Thanks,

Aditi Dron  
Regulatory Affairs Scientist  
APP Pharmaceuticals, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: adron@APPpharma.com

From: "Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>  
To: "ADron@apppharma.com" <ADron@apppharma.com>  
Date: 10/04/2010 07:29 PM  
Subject: Information Request - NDA 201-811

---

Hello,

Please see question below and respond as soon as possible:

1. Please submit raw data for coagulation time measured as SAS transport files (\*.xpt) for Study AA86231. A description of each data item should be provided in a Define.pdf file. Any concentrations and/or pools that have been excluded from the analysis should be flagged and maintained in the datasets.

Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

**Ali Ibrahim, Ebla**

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Tuesday, September 14, 2010 10:46 AM  
**To:** 'ADron@apppharma.com'  
**Subject:** Information Request  
**Importance:** High  
**Follow Up Flag:** Follow up  
**Flag Status:** Red

Good Morning,

Please provide the following information and data:

1. Revise the isomeric content method to provide a chromatographic resolution factor of at least (b) (4) with baseline separation of the isomers, since the currently proposed method, document number 10-08-03-6457, does not have such a resolution for argatroban in the Argatroban Injection finished product and in the argatroban raw material.
2. Add acceptance criteria and testing for the identity, including the isomeric ratio, and purity of the argatroban raw material as performed by APP upon its receipt from the supplier.
3. Add acceptance criteria and testing for the identity, including isomeric ratio, of argatroban reference standard as performed by APP upon its receipt from the supplier.
4. Revise the stability specifications for Argatroban Injection, sections 2.3. P.8 and 3.2.P.8 and any other relevant sections, to include sterility testing and the proposed testing schedule.
5. Revise the related substances impurity limits for the Argatroban Injection product to be NMT (b) (4) of NMT (b) (4) % is exceeded. Alternatively, provide qualification data if the qualification threshold of NMT (b) (4) % is exceeded.
6. The acceptance criteria for related substances impurities in the submitted certificates of analysis for the argatroban drug substance do not comply with the ICH Q3A identification threshold of NMT (b) (4) %. Provide updated information to assure the revision of these specifications in the certificates of analysis for the argatroban raw material.

Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research*

Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903

Tel: 301-796-3691  
Fax: 301-796-9849

---

**From:** ADron@apppharma.com [mailto:ADron@apppharma.com]  
**Sent:** Wednesday, July 07, 2010 3:45 PM  
**To:** Ali Ibrahim, Ebla  
**Subject:** RE: Argatroban Injection, NDA 201811 - Filing Date

Hi Ms. Ibrahim,

Thanks for the letter!

Regards,

Aditi Dron  
Regulatory Affairs Scientist  
APP Pharmaceuticals, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: adron@APPpharma.com

From: "Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>  
To: <ADron@apppharma.com>  
Date: 07/07/2010 01:37 PM  
Subject: RE: Argatroban Injection, NDA 201811 - Filing Date

---

Hello,

Please find attached a copy of the filing letter that you should be receiving in the mail. Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159*

Silver Spring, MD 20903

Tel: 301-796-3691

Fax: 301-796-9849

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**From:** ADron@apppharma.com [mailto:ADron@apppharma.com]

**Sent:** Tuesday, July 06, 2010 4:46 PM

**To:** Ali Ibrahim, Ebla

**Subject:** RE: Argatroban Injection, NDA 201811 - Filing Date

Hello Ms. Ibrahim,

Could you please provide the Filing Date for our Argatroban Injection NDA 201811? We are still awaiting the receipt of the letter.

Thanks for your help!

Aditi Dron  
Regulatory Affairs Scientist  
APP Pharmaceuticals, LLC

Phone: 847-330-3898

Fax: 847-413-8570

Email: adron@APPpharma.com

From: "Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>  
To: <ADron@apppharma.com>  
Date: 07/05/2010 05:16 PM  
Subject: RE: Argatroban Injection, NDA 201811 - Filing Status Inquiry

---

Hello,

Your application has been filed. You should be receiving a filing letter in the mail. Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

Tel: 301-796-3691  
Fax: 301-796-9849

---

**From:** ADron@apppharma.com [mailto:ADron@apppharma.com]  
**Sent:** Friday, July 02, 2010 10:59 AM  
**To:** Ali Ibrahim, Ebla  
**Subject:** Argatroban Injection, NDA 201811 - Filing Status Inquiry

Hello Ms. Ibrahim,

I want to inquire about the Filing Status of APP's Argatroban Injection NDA 201811. Has it been found acceptable for filing?

FYI, I had submitted another Telephone Amendment (SEQ-0003) yesterday to address the microbiology comment regarding container closure integrity. The Reviewer has contacted APP and informed that the response provided on July 1, 2010 is insufficient. We have a few months to provide the data requested.

I would appreciate a confirmation of the filing status for this NDA.

Thanks,

Aditi Dron  
Regulatory Affairs Scientist  
APP Pharmaceuticals, LLC

Phone: 847-330-3898

Fax: 847-413-8570

Email: adron@APPpharma.com

[attachment "NDA 201-811 Filing Letter.pdf" deleted by Aditi Dron/RA/SC/US/HHC/Fresenius]



NDA 201-811

**FILING COMMUNICATION**

APP Pharmaceuticals, LLC  
Attention: Aditi Dron  
Regulatory Scientist  
1501 East Woodfield Road  
Suite 300E  
Schaumburg, IL 60173

Dear Ms. Dron:

Please refer to your new drug application (NDA) dated April 5, 2010, received April 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Argatroban 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 February 28, 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 December 28, 2010.

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

Clinical Pharmacology:

1. For Study AA86231, submit the following items:
  - a. Detailed information regarding the assay validation (including raw data) for the methodologies listed below. This information should also include the source and

quality of all reagents and control solutions used as well as the effect of potential confounding factors (e.g., freeze/thaw, hemolysis, hypertriglyceridemia, etc.) on these assays.

- i. Prothrombin time (PT)
  - ii. Activated partial thromboplastin time (aPTT)
  - iii. Thrombin generation assay
- b. Raw data including argatroban concentration in the stock and spiking solutions and in human plasma samples as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

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.

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 note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indications proposed in this application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

If you have any questions, call Ebla Ali Ibrahim, Regulatory Project Manager, at (301) 796-3691.

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, M.D.  
Acting Division Director  
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

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NDA-201811

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ORIG-1

-----  
APP  
PHARMACEUTICA  
LS LLC

-----  
ARGATROBAN INJECTION

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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/  
-----

ANN T FARRELL

07/02/2010

**Ali Ibrahim, Ebla**

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Tuesday, June 29, 2010 1:28 PM  
**To:** 'Aditi Dron'  
**Subject:** Additional Information Request - NDA 201-811  
**Follow Up Flag:** Follow up  
**Flag Status:** Red

Hello,

Here are additional information request:

It is not clear in the NDA if the vials used in the container closure studies consisted of vials from both suppliers.

- Clarify which vials were used in container closure integrity studies.
- Provide container closure integrity study data sets representative of both vials, if not already provided in the NDA.

Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

**Ali Ibrahim, Ebla**

**From:** Ali Ibrahim, Ebla  
**Sent:** Tuesday, June 29, 2010 10:18 AM  
**To:** 'ADron@apppharma.com'  
**Cc:** TGlinsey@apppharma.com  
**Subject:** Additional Information Request - NDA 201-811  
**Follow Up Flag:** Follow up  
**Flag Status:** Red

Hello,

Provide assurance and commitment that the glass formulation from both manufacturers of the vials, (b) (4) will have identical formulation, physical properties and light absorbance characteristic as the Amber (b) (4) composition.

Please respond as soon as possible. Thank you.

*Ebla Ali Ibrahim, MS  
 Regulatory Health Project Manager  
 Division of Hematology Products  
 Office of Oncology Drug Products  
 Center for Drug Evaluation and Research  
 Food and Drug Administration  
 10903 New Hampshire Avenue, Rm 2159  
 Silver Spring, MD 20903*

*Tel: 301-796-3691  
 Fax: 301-796-9849*

---

**From:** ADron@apppharma.com [mailto:ADron@apppharma.com]  
**Sent:** Friday, June 25, 2010 5:13 PM  
**To:** Ali Ibrahim, Ebla  
**Cc:** TGlinsey@apppharma.com  
**Subject:** Re: Information Request - NDA 201-811

Hello Ms. Ibrahim,

APP Pharmaceuticals, LLC (APP) is providing the following response to the CMC information request regarding (b) (4) glass vial communicated on June 22, 2010.

APP Pharmaceuticals, LLC (APP) has specified the following glass vial suppliers for the glass vials to be utilized for the packaging of Argatroban Injection within NDA 201811:

**Vials:** (b) (4) 13 mm finish, amber (b) (4) Type I glass vial supplied from either of the following suppliers:

(b) (4)

(b) (4)

APP acknowledges the Agency's observation that all the three exhibit batches had utilized vials manufactured by (b) (4) (b) (4)

APP is providing the following information in support of the ability to use the vials manufactured by (b) (4) (b) (4) in addition to the vials manufactured by (b) (4) for Argatroban Injection:

- Memorandum from (b) (4) (b) (4) (now called (b) (4) (b) (4) dated June 23, 2010 (**Attachment 1**) which provides certification that the glass (b) (4) utilized in the manufacture of the vials supplied by (b) (4) to APP (vendor lot # 1331325) was obtained from (b) (4) (b) (4) and was identified as (b) (4) amber Type I (b) (4) Glass (b) (4). Please note that this lot of vials was used for the exhibit batches of Argatroban Injection manufactured by APP Pharmaceuticals, LLC in support of NDA 201811. It also certifies that light transmission testing shows compliance with current USP requirements.

- (b) (4) (b) (4) Amber (b) (4) Certification (**Attachment 2**) provides information regarding the amber glass (b) (4) (b) (4) and that it fulfills the requirements of current USP light transmission testing.

- A side by side comparison of the vials manufactured by (b) (4) (b) (4) demonstrating their identical dimensions and specifications is shown in the table below. The detailed drawings (master component specifications) for vials from the two suppliers are provided in **Attachment 3**.

Attributes	Vials from (b) (4)	Packaging	Vials from (b) (4)
APP Part No.	(b) (4)		
Size	(b) (4)		
Color	Amber		Amber
Glass Type	Type I USP		Type I USP
Height (mm)	(b) (4)		
OD (mm)	(b) (4)		
Finish OD (in)	(b) (4)		
Finish ID (in)	(b) (4)		
Bead Height (in)	(b) (4)		
Wall Thickness (mm)	(b) (4)		
Treatment	(b) (4)		

Therefore, even though, APP's exhibit batches utilized vials supplied by (b) (4) the glass (b) (4) utilized by both vial suppliers is the same, (b) (4) (b) (4) which was used during the manufacture of the exhibit batches in support of the subject NDA 201811 for Argatroban Injection. Further, the dimensions and specifications for the vials from both suppliers are identical, which allows APP to designate the same APP part number to these vials, regardless of the supplier.

Hence, it can be reasonably purported that the vials supplied by (b) (4) (b) (4) are identical in every aspect. Therefore, the stability data provided within NDA 201811 is sufficient to support the use of vials from both the suppliers for Argatroban Injection.

Therefore, APP respectfully requests the Agency to allow the use of vials from either of the two aforementioned suppliers for the manufacturing of Argatroban Injection. Furthermore, APP commits to utilizing vials supplied by (b) (4) (b) (4) during the manufacture of validation batches in support of product launch upon NDA approval. Additionally, APP commits to placing those batches on long term stability per the stability regimen included within NDA 201811.

Please inform APP if this response is feasible, as APP intends to provide a response that is sufficient to permit the filing of the subject NDA by the Agency.

Please feel free to contact me in case of questions.

Sincerely,

Aditi Dron  
Regulatory Affairs Scientist  
APP Pharmaceuticals, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: adron@APPpharma.com

From: "Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>  
To: "Aditi Dron" <ADron@apppharma.com>  
Date: 06/22/2010 03:11 PM  
Subject: Information Request - NDA 201-811

---

Hello,

Please see below a CMC information request:

You have not provided 12 month stability and container-closure integrity data in support of for your argatroban product manufactured using the (b) (4) glass vial. As per GRMP's, original submissions of NDAs are to be complete. Twelve months of stability data is the ICH recommended minimum database duration. In addition, 12 months of data are necessary to support a minimal commercially viable expiry period of 12 months. Less than 12 months of stability data does not support a viable drug product expiry and is therefore a refuse to file issue.

If you do not have this data available before the filing date we recommend you remove this container closure system from your application so as to remove this specific filing issue.

Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** Aditi Dron [mailto:ADron@apppharma.com]  
**Sent:** Friday, April 03, 2009 10:15 AM  
**To:** Ali Ibrahim, Ebla  
**Subject:** RE: APP's Argatroban Injection NDA (b) (4)

Hello Ms. Ali Ibrahim,

Thanks for the information. Here is the list of APP attendees:

Lisa McChesney-Harris, Ph.D., Vice President, Regulatory Affairs  
Dale Carlson, Director, Regulatory Affairs  
Toni Glinsey, Manager, Regulatory Affairs,  
Wilberto Robles, Scientist, Regulatory Affairs  
David Bowman, Vice President, Product Development  
Keith Kwok, Ph.D., Senior Manager, Product Development  
Katherine Gregory, Vice President, Business Development  
Tony Wasilewski, Senior Project Manager, Business Development  
Toni Nesnevich, Senior Manager, Business Development  
Sarah DeGuia, Project Manager, Business Development

Regards,

*Aditi Dron*

Regulatory Scientist  
APP Pharmaceuticals, LLC  
Schaumburg, IL

Phone: (847) 330-3898

Fax: (847) 413-8570

---

**From:** Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]  
**Sent:** Thursday, April 02, 2009 2:10 PM  
**To:** Aditi Dron  
**Subject:** RE: APP's Argatroban Injection NDA (b) (4)

Hello,

Here are the FDA attendees:

Rafel (Dwayne) Rieves, M.D., Division Director  
Richard Lostritto, Ph.D., Director  
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead  
Mark Sassaman, Ph.D., Chemist  
Kathy Robie Suh, M.D., Ph.D., Medical Officer - Team Leader  
Kassa Ayalew, M.D, Medical Officer  
Jamali Faranak, M.D., Medical Officer

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Joseph Grillo, Ph.D., Clinical Pharmacologist  
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager

Please email me APP Pharm. attendees. Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** Aditi Dron [mailto:ADron@apppharma.com]  
**Sent:** Wednesday, April 01, 2009 4:00 PM  
**To:** Ali Ibrahim, Ebla  
**Subject:** APP's Argatroban Injection NDA (b) (4)  
Dear Ms. Ali Ibrahim,

I would like to request the names, titles, and departments of the FDA representatives that were present during the teleconference regarding APP Pharmaceuticals' Argatroban Injection NDA (b) (4) earlier this afternoon.

I also want to point out that the 'Refuse to File' letter can be faxed to the fax number (847) 413-8570.

Thank you,

*Aditi Dron*  
Regulatory Scientist  
APP Pharmaceuticals, LLC  
Schaumburg, IL

Phone: (847) 330-3898  
Fax: (847) 413-8570  
Email: adron@apppharma.com

Aditi Dron  
Regulatory Affairs Scientist

APP Pharmaceuticals, LLC

Phone: 847-330-3898

Fax: 847-413-8570

Email: adron@APPpharma.com

From: "Ali Ibrahim, Ebla" <Ebla.Ali-Ibrahim@fda.hhs.gov>  
To: "Aditi Dron" <ADron@apppharma.com>  
Date: 06/22/2010 03:11 PM  
Subject: Information Request - NDA 201-811

---

Hello,

Please see below a CMC information request:

You have not provided 12 month stability and container-closure integrity data in support of for your argatroban product manufactured using the (b) (4) glass vial. As per GRMP's, original submissions of NDAs are to be complete. Twelve months of stability data is the ICH recommended minimum database duration. In addition, 12 months of data are necessary to support a minimal commercially viable expiry period of 12 months. Less than 12 months of stability data does not support a viable drug product expiry and is therefore a refuse to file issue.

If you do not have this data available before the filing date we recommend you remove this container closure system from your application so as to remove this specific filing issue.

Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** Aditi Dron [mailto:ADron@apppharma.com]  
**Sent:** Friday, April 03, 2009 10:15 AM  
**To:** Ali Ibrahim, Ebla  
**Subject:** RE: APP's Argatroban Injection NDA (b) (4)

Hello Ms. Ali Ibrahim,

Thanks for the information. Here is the list of APP attendees:

Lisa McChesney-Harris, Ph.D., Vice President, Regulatory Affairs  
Dale Carlson, Director, Regulatory Affairs  
Toni Glinsey, Manager, Regulatory Affairs,  
Wilberto Robles, Scientist, Regulatory Affairs  
David Bowman, Vice President, Product Development  
Keith Kwok, Ph.D., Senior Manager, Product Development  
Katherine Gregory, Vice President, Business Development  
Tony Wasilewski, Senior Project Manager, Business Development  
Toni Nesnevich, Senior Manager, Business Development  
Sarah DeGuia, Project Manager, Business Development

Regards,

*Aditi Dron*

Regulatory Scientist  
APP Pharmaceuticals, LLC  
Schaumburg, IL

Phone: (847) 330-3898

Fax: (847) 413-8570

---

**From:** Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]

**Sent:** Thursday, April 02, 2009 2:10 PM

**To:** Aditi Dron

**Subject:** RE: APP's Argatroban Injection NDA (b) (4)

Hello,

Here are the FDA attendees:

Rafel (Dwayne) Rieves, M.D., Division Director  
Richard Lostritto, Ph.D., Director  
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead  
Mark Sassaman, Ph.D., Chemist  
Kathy Robie Suh, M.D., Ph.D., Medical Officer - Team Leader  
Kassa Ayalew, M.D, Medical Officer  
Jamali Faranak, M.D., Medical Officer  
  
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Joseph Grillo, Ph.D., Clinical Pharmacologist  
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager

Please email me APP Pharm. attendees. Thank you.

Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903

Tel: 301-796-3691  
Fax: 301-796-9849

---

**From:** Aditi Dron [mailto:ADron@apppharma.com]  
**Sent:** Wednesday, April 01, 2009 4:00 PM  
**To:** Ali Ibrahim, Ebla  
**Subject:** APP's Argatroban Injection NDA (b) (4)

Dear Ms. Ali Ibrahim,

I would like to request the names, titles, and departments of the FDA representatives that were present during the teleconference regarding APP Pharmaceuticals' Argatroban Injection NDA (b) (4) earlier this afternoon.

I also want to point out that the 'Refuse to File' letter can be faxed to the fax number (847) 413-8570.

Thank you,

*Aditi Dron*

Regulatory Scientist  
APP Pharmaceuticals, LLC  
Schaumburg, IL

Phone: (847) 330-3898  
Fax: (847) 413-8570  
Email: adron@apppharma.com

**Ali Ibrahim, Ebla**

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Tuesday, June 22, 2010 4:11 PM  
**To:** 'Aditi Dron'  
**Subject:** Information Request - NDA 201-811  
**Follow Up Flag:** Follow up  
**Flag Status:** Red

Hello,

Please see below a CMC information request:

You have not provided 12 month stability and container-closure integrity data in support of for your argatroban product manufactured using the (b) (4) glass vial. As per GRMP's, original submissions of NDAs are to be complete. Twelve months of stability data is the ICH recommended minimum database duration. In addition, 12 months of data are necessary to support a minimal commercially viable expiry period of 12 months. Less than 12 months of stability data does not support a viable drug product expiry and is therefore a refuse to file issue.

If you do not have this data available before the filing date we recommend you remove this container closure system from your application so as to remove this specific filing issue.

Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** Aditi Dron [mailto:ADron@apppharma.com]  
**Sent:** Friday, April 03, 2009 10:15 AM  
**To:** Ali Ibrahim, Ebla  
**Subject:** RE: APP's Argatroban Injection NDA (b) (4)

Hello Ms. Ali Ibrahim,

Thanks for the information. Here is the list of APP attendees:

Lisa McChesney-Harris, Ph.D., Vice President, Regulatory Affairs  
Dale Carlson, Director, Regulatory Affairs  
Toni Glinsey, Manager, Regulatory Affairs,

Wilberto Robles, Scientist, Regulatory Affairs  
David Bowman, Vice President, Product Development  
Keith Kwok, Ph.D., Senior Manager, Product Development  
Katherine Gregory, Vice President, Business Development  
Tony Wasilewski, Senior Project Manager, Business Development  
Toni Nesnevich, Senior Manager, Business Development  
Sarah DeGuia, Project Manager, Business Development

Regards,

*Aditi Dron*

Regulatory Scientist  
APP Pharmaceuticals, LLC  
Schaumburg, IL

Phone: (847) 330-3898  
Fax: (847) 413-8570

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**From:** Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]  
**Sent:** Thursday, April 02, 2009 2:10 PM  
**To:** Aditi Dron  
**Subject:** RE: APP's Argatroban Injection NDA (b) (4)

Hello,

Here are the FDA attendees:

Rafel (Dwayne) Rieves, M.D., Division Director  
Richard Lostritto, Ph.D., Director  
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead  
Mark Sassaman, Ph.D., Chemist  
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Jamali Faranak, M.D., Medical Officer

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Joseph Grillo, Ph.D., Clinical Pharmacologist  
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager

Please email me APP Pharm. attendees. Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
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**From:** Aditi Dron [mailto:ADron@apppharma.com]  
**Sent:** Wednesday, April 01, 2009 4:00 PM  
**To:** Ali Ibrahim, Ebla  
**Subject:** APP's Argatroban Injection NDA (b) (4)

Dear Ms. Ali Ibrahim,

I would like to request the names, titles, and departments of the FDA representatives that were present during the teleconference regarding APP Pharmaceuticals' Argatroban Injection NDA (b) (4) earlier this afternoon.

I also want to point out that the 'Refuse to File' letter can be faxed to the fax number (847) 413-8570.

Thank you,

*Aditi Dron*

Regulatory Scientist  
APP Pharmaceuticals, LLC  
Schaumburg, IL

Phone: (847) 330-3898  
Fax: (847) 413-8570  
Email: adron@apppharma.com



NDA 201-811

**RECEIPT OF USER FEES**

APP Pharmaceuticals, LLC  
Attention: Aditi Dron  
Regulatory Scientist  
1501 East Woodfield Road  
Suite 300E  
Schaumburg, IL 60173

Dear Ms. Dron:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Argatroban Injection.

You were notified in our letter dated April 29, 2010, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of April 30, 2010.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 29, 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 content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please cite the NDA number listed above 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 Ebla Ali Ibrahim, Regulatory Project Manager, at (301) 796-3691.

Sincerely,

*{See appended electronic signature page}*

Janet Jamison, R.N., C.C.R.P  
Acting Chief Project Management Staff  
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

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NDA-201811

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ORIG-1

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APP  
PHARMACEUTICA  
LS LLC

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ARGATROBAN INJECTION

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/s/  
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JANET K JAMISON

05/04/2010



NDA 201-811

**UNACCEPTABLE FOR FILING**

APP Pharmaceuticals, LLC  
Attention: Aditi Dron  
Regulatory Scientist  
1501 East Woodfield Road  
Suite 300E  
Schaumburg, IL 60173

Dear Ms. Dron:

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

Name of Drug Product: Argatroban Injection

Date of Application: April 2, 2010

Date of Receipt: April 5, 2010

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration  
P.O. Box 70963  
Charlotte, NC 28272-0963

Checks sent by a courier should be addressed to:

Wachovia QLP Lockbox – D1113-022  
Food and Drug Administration, Lockbox 70963  
1525 West WT Harris Blvd  
Charlotte, NC 28262

**NOTE: Please include the User Fee I.D. Number, the Application number, and the FDA P.O. Box number (P.O. Box 70963) on the enclosed check. It would be helpful if you included the user fee cover sheet (Form FDA 3397) with your payment.**

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above 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  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you wish to send payment by wire transfer, or if you have any other questions, please call Bev Friedman or Mike Jones at 301-796-3602.

If you have any questions, call Ebla Ali Ibrahim, Regulatory Project Manager, at (301) 796-3691.

Sincerely,

*{See appended electronic signature page}*

Janet Jamison, R.N., C.C.R.P  
Acting Chief Project Management Staff  
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

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NDA-201811

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ARGATROBAN INJECTION

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/s/  
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JANET K JAMISON  
04/29/2010



NDA 201-811

**NDA ACKNOWLEDGMENT**

APP Pharmaceuticals, LLC  
Attention: Aditi Dron  
Regulatory Scientist  
1501 East Woodfield Road  
Suite 300E  
Schaumburg, IL 60173

Dear Ms. Dron:

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: Argatroban Injection

Date of Application: April 2, 2010

Date of Receipt: April 5, 2010

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 June 4, 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 content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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) 796-3691.

Sincerely,

*{See appended electronic signature page}*

Ebla Ali Ibrahim, M.S.  
Regulatory Health 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

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NDA-201811

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EBLA ALI IBRAHIM  
04/19/2010