CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022434Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # NDA 22434 SUPPL # HFD #

Trade Name Argatroban

Generic Name

Applicant Name Eagle Pharmaceuticals, Inc.

Approval Date, If Known July 12, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

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

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

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?

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Lara Akinsanya, M.S.
Title: Regulatory Project Manager
Date:

Name of Office/Division Director signing form:
Title:

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

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

/s/

LARA M AKINSANYA
06/28/2011

ANN T FARRELL
06/29/2011

DEBARMENT CERTIFICATION [Argatroban Injection RTU]

The following companies listed in the table below with their function have provided debarment certifications that are included in this section.

Company	Function
Eagle Pharmaceuticals	NDA holder
(b) (4)	Drug Substance Manufacturer
Cipla Limited	Drug Product Manufacturer
(b) (4)	In Vitro Study
	USP <660> & USP <387>
	USP <87>

EAGLE PHARMACEUTICALS, INC.

470 Chestnut Ridge Road
Woodcliff Lake, N J 07677
201.326.5300
fax 201.391.2430
www.eagleus.com

CERTIFICATION MADE PURSUANT TO THE GENERIC DRUG ENFORCEMENT ACT OF 1992

On behalf of Eagle Pharmaceuticals, Inc., the applicant, I hereby certify, pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 335a (k)), as amended by the Generic Drug Enforcement Act of 1992, that applicant has not used, is not using, and will not in the future use in any capacity the services of any person who has been debarred pursuant to Section 306(a) and/or Section 306(b), in connection with this application.

Applicant further certifies that there have been no convictions of applicant for any of the types of crimes set forth in Section 306(a) of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a (a) and (b), nor has any person affiliated with applicant, who is responsible in whole or in part for the development or submission of this application, been convicted of any crime of the types listed in Section 306(a) and Section 306(b) of the Generic Drug Enforcement Act of 1992, 21U.S.C. § 3a (a) and (b).

N. J. Cappuccino

Nicholas Cappuccino, Ph.D.
Chief Scientific Officer, Eagle Pharmaceuticals, Inc.

28 July 2008
Date

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Cipla
Cipla Ltd.
Mumbai Central
Mumbai 400 008 India

GENERIC DRUG ENFORCEMENT ACT OF 1992 CERTIFICATION

Section 306 (k) (1) Requirement

In accordance with section 306 (a) or (b) of the Generic drug Enforcement Act of 1992, Cipla Ltd. will not use, in any capacity, the services of any person debarred under subsections 306 (a) or (b), in connection with this application of Argatroban Injection 50 mg/ 50 ml (b) (4)

Section 306 (k) (2) Requirement

Cipla Ltd. has no relevant convictions to report under 306 (a) and (b) for any persons (including contracted affiliations) responsible for the development of data or other information used to support this application of Argatroban Injection 50 mg/ 50 ml (b) (4)

12.07.2008

Mr. Savio Dourado
Head-Corporate Quality Assurance

Date

Phone : (9122) 23082891, 23095521 Fax : (9122) 23070013, 23070393, 23070385, 23020297
E-mail : prc@cipla.com

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22-434 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: Argatroban Injection Dosage Form: Injection		Applicant: Eagle Pharmaceutical Inc. Agent for Applicant (if applicable):
RPM: Lara Akinsanya		Division: Division of Hematology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 20-883

Provide a brief explanation of how this product is different from the listed drug.

This application provides for a change in dosage form and product formulation. The applicant's proposed formulation is a ready to use premixed solution for injection and referenced product needs further dilution for injection. The composition of inactive ingredients is modified.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: June 29, 2011

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.

❖ Actions	
• Proposed action • User Fee Goal Date is July 12, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Refuse To File - November 21, 2008; Complete Response - January 29, 2010

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

❖ 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 http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

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

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

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval, June 29, 2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	June 16, 2011
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	May 16, 2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA May 3, 2011 ☐ DRISK ☐ DDMAC ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	None ☐ Not a (b)(2) June 16, 2011 ☐ Not a (b)(2) June 28, 2011
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: This is a 505(b) 2 Application • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	June 16, 2011; June 1, 2011; May 31, 2011; May 5, 2011; April 7,

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	2011; April 6, 2011; January 26, 2011; March 22, 2010; March 3, 2010.
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg May 3, 2010
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None June 28, 2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None June 28, 2011
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	June 16, 2011
• Clinical review(s) *(indicate date for each review)*	June 16, 2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Reviewer's Review dated January 27, 2010
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None June 16, 2011
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None June 15, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None June 22, 2011
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None June 22, 2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None June 27, 2011
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None June 27, 2011-CMC May 31, 2011- BioPharm
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed June 10, 2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: June 27, 2011 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/

LARA M AKINSANYA
06/29/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # **22-434**	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: **Argatroban Injection** Established/Proper Name: **Argatroban Injection** Dosage Form: **Injection** Strengths: **1 mg/mL**		
Applicant: **Eagle Pharmaceuticals, Inc**		
Date of Receipt: **January 12, 2011**		
PDUFA Goal Date: **July 12, 2011**	Action Goal Date (if different):	
Proposed Indication(s): **Anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. Anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary interventions (PCI)**		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Product label for reference listed drug (Argatroban Injection [Pfizer Inc.]	**Clinical findings of safety and efficacy; findings from animal studies for reproductive toxicity and mutagenesis**
Published literature	**Safety findings**

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

In support of a waiver of in vivo BA/BE data the applicant conducted a bridging study to assess in vitro equivalence of the anticoagulant activities between the applicant's and referenced product. The anticoagulant activities were measured by determining aPTT, PT and TT in pooled human plasma spiked with clinically relevant concentrations of the applicant's formulation or referenced product.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

Argatroban Injection NDA 20-883

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Argatroban Injection	**20-883**	**Y**

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form and product formulation. The applicant's proposed formulation is a ready to use premixed solution for injection and referenced product needs further dilution for injection. The composition of inactive ingredients is modified.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

The listed product is presented as a concentrate that must be diluted prior to use. The 505(b)(2) product is a ready to infuse solution that does not require dilution. Because the two are *not* identical dosage forms, they would not be pharmaceutical equivalents even though the active pharmaceutical ingredient is the same.

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **Argatroban/5,214,052**

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): **5,214,052**
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): ***5/22/09 (Pfizer) and 5/29/09 (Mitsubishi)***

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

LARA M AKINSANYA
06/28/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, June 16, 2011 3:40 PM
To: 'Isabel Lamela'
Cc: 'Brenda Marczi'; Akinsanya, Lara
Subject: Information Request - P/T: NDA 22-434 -DUE June 21

Hi Isabel,

Please respond to the following information request from the Pharmacology/Toxicology reviewers:

You used the following human dose and schedule to justify the dose and schedule in your toxicology study (Study #1773-001):

(b) (4)

We could not locate this dosing regimen in the label. Please indicate where in the label this information is found and how this proposed regimen corresponds to those described in Tables 2 and 3 of the label.

Please respond to the above information request by **Tuesday, June 21**, 2011.

Please let me know if you have any questions.

Thank You

Lara

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

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LARA M AKINSANYA
06/16/2011

Lambert, Tu-Van

From: Lambert, Tu-Van
Sent: Wednesday, June 01, 2011 3:01 PM
To: 'bmarczi@eagleus.com'; 'ilamela@eagleus.com'
Cc: Akinsanya, Lara
Subject: Information Request - CMC review of NDA 22-434 (Argatroban) resubmission

Dear Ms. Marczi,

We are reviewing the Chemistry, Manufacturing, and Control sections of your NDA and have the following information request. Please review and provide a response as promptly as possible. We are available for a teleconference to discuss these items, so let me know when you would like to set up a time.

1. NDA section 3.2.S.4.1 indicates that Cipla performs final release testing of the drug substance lot and generates a certificate of analysis (CoA). Specify whether any test results are accepted from the (b) (4) CoA for use on the Cipla CoA. If yes, then describe how the use of these test results are justified.

2. Regarding the validation studies for the drug substance testing performed by (b) (4):
   (a) Provide complete validation studies for the Identity C, Assay, and R and S Content tests; for the Chromatographic Purity test; and for the Content of (b) (4) These studies are not present in either the application or in the referenced drug master file.
   (b) The two GC methods for Residual Organic Solvents (ROS) were validated to support proposed criteria which are (b) (4) the currently proposed criteria, therefore the submitted studies are not acceptable. Provided complete validation studies for the current versions of these two methods and the currently proposed criteria.

3. Regarding the validation studies for the drug substance testing performed by Cipla, revise the studies for both GC methods for ROS testing performed at (b) (4) to address accuracy, robustness, solution stability and limit of detection.

4. Provide a study establishing the compatibility of the proposed vial solution with appropriate diluents, IV containers and IV administration sets.

5. Regarding the proposed drug product manufacture and control procedures:
   (a) Identify the equipment used for the manufacture of bulk solution and vial filling.
   (b) Provide data to justify the proposed (b) (4) maximum hold time for (b) (4) bulk solution and (b) (4) maximum hold time for (b) (4) bulk solution.
   (c) Describe the expected range of values for density of (b) (4) bulk solution.
   (d) Provide a justification as to how the frequency of fill volume check ((b) (4) for a (b) (4) is sufficient to assure that a consistent product is obtained.

6. Regarding the proposed drug product specification:
   (a) Revise the specification to use a single criterion for assay and related substances at release and on stability.
   (b) Revise the specification for Single Maximum Unknown Impurity to report each unspecified impurity at or above the proposed limit.

7. As to the method descriptions and validation studies for the tests performed by Cipla:
   (a) For the Identity B, Assay, and R and S Isomer Content tests in drug substance and in drug product, provide the following:
      (i) An explanation as to why the system suitability criteria do not address peak shape (tailing or peak asymmetry) or plate count; and
      (ii) Data establishing the effect of variations in column temperature, mobile phase flow rate

and detector wavelength on the chromatograms and on the system suitability test results.

(b) For the Related Substances test in drug substance and in drug product, provide the following:

(i) An explanation as to why the system suitability criteria do not address peak shape (tailing or peak asymmetry) or plate count;

(ii) Data establishing the effect of variations in mobile phase flow rate, detector wavelength, (b) (4) in the mobile phase, and gradient profile on the chromatograms and on the system suitability test results;

(iii) Data establishing accuracy for the measurement of unknown impurities at the proposed limit;

(iv) A justification for the proposed acceptance criterion of (b) (4) used in the validation study for solution stability; and

(v) The observed assay values for each analyte in the validation study for solution stability.

8. Provide environmental assessment information which meets requirements under 21 CFR part 25.

Please confirm that you have received this request, and let me know when you have an idea of when you can provide your responses.

Kindly,

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

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/s/

TU-VAN L LAMBERT
06/01/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, May 31, 2011 2:40 PM
To: 'Isabel Lamela'
Cc: Akinsanya, Lara
Subject: Information Request - Product Quality Microbiology: NDA 22-434

Dear Isabel Lamela,

A review of NDA 22-434 is in progress. Please provide the following information or a reference to its location in the New Drug Application:

1. Provide the acceptance criteria for (b) (4) processing simulations and a list of actions taken following a simulation failure.

2. Provide the following information with regard to personnel monitoring:

    a. The type of microbiological media used

    b. The specific locations monitored

3. Provide the following information with regard to the monitoring of the water for injection:
    a. The type of media used
    b. The incubation conditions for the media
    c. A justification for the water for injection action level of (b) (4) you provided in section 3.2.P.3.3.4.4 of the application. USP<1231> suggests that WFI contain no more than 10 CFU/mL.

Please respond by **Tuesday, June 7,** 2011.

Thanks
Lara

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

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/s/

LARA M AKINSANYA
05/31/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, May 05, 2011 11:55 AM
To: 'Isabel Lamela'
Cc: Brenda Marczi; Akinsanya, Lara
Subject: Information Request - OSE: NDA 22-434 -DUE May 19

Hi Isabel,

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

1. All Container Labels and Carton Labeling for Argatroban Injection"

- Center or left align the name, dosage form, and strength.

- 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.

  **Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.*

- Remove the color box that is used for the name, total drug content, and concentration and instead only box or highlight the total drug content, 50 mg per 50 mL.

- Remove the redundan (b) (4) statement that appears before the 'Single Use Only' statement. Additionally, add the statement 'Discard Unused Portion' so that it appears in conjunction with the 'Single Use Vial', on the principle display panel.

- Remove the box that surrounds the 'Ready to Use' statement and revise the ambiguous statement so that it reads, 'Do not dilute prior to administration' as this better communicates the proper preparation, or lack thereof.

- Include a statement on the side panel that instructs to protect from light.

2. Container Label (50 mg/50 mL)

Invert the name, total drug content, and all statements which pertain to proper administration of Argatroban which appear at the bottom of the label so that they can read while the drug is hanging upside down during infusion.

3. Carton Labeling (50 mg/50 mL)

Remove the redundant statement 'Each mL contains 1 mg of Argatroban', as this is stated in the concentration statement (1 mg/mL) which follows the total drug content statement.

Please respond to the above information request by **Thursday, May 19**, 2011.

Please let me know if you have any questions.

Thank You

Lara

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

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/s/

LARA M AKINSANYA
05/06/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, April 07, 2011 2:59 PM
To: 'Isabel Lamela'
Cc: 'Brenda Marczi'; Akinsanya, Lara
Subject: Information Request - Product Quality Microbiology: NDA 22-434

Hi Isabel,

Please provide the following product quality microbiology information or a reference to its location in the January 10, 2011 submission:

1. A summary of the environmental monitoring procedures used for air, surface, personnel, bulk solution bioburden, and water. Include the sampling frequencies, media used, incubation conditions, and alert and action levels.
2. Diagrams of the flow of product, component, personnel, and air within the manufacturing area.
3. A diagram of the air classification for each of the rooms within the manufacturing area.
4. Be advised that if the product label states that the diluted drug product can be held for more than (b) (4) (b) (4) at room temperature or more than (b) (4) if refrigerated, additional validation studies will be required to show that the diluted drug product does not support microbial growth.

Please let me know if you have any questions.
Thank You
Lara

Lara Akinsanya, M.S.

Regulatory Project Manager

Division of Hematology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

(301) 796-9634 (phone)

(301) 796-9849 (fax)

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/s/

LARA M AKINSANYA
04/07/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, April 06, 2011 4:31 PM
To: 'Isabel Lamela'
Cc: Brenda Marczi
Subject: Information Request - Sample of Bottle: NDA 22-434 (labeling)

Hi Isabel,

We are about to begin the label review of NDA 22-434 application. Would you please send me a sample of the bottle for Argatroban for review?

Thank You
Lara

Lara Akinsanya, M.S.

Regulatory Project Manager

Division of Hematology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

(301) 796-9634 (phone)

(301) 796-9849 (fax)

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/s/

LARA M AKINSANYA
04/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric and Maternal Health Staff	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Lara Akinsanya, RPM, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 8, 2011		22-434	NDA - 505(b)(2)	January 12, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Argatroban	Standard	Antithromibin	March 30, 2011

NAME OF FIRM: Eagles Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☒ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is a Class 2 505(b)(2) NDA resubmission from Eagles Pharmaceuticals, Inc. submitted for Argatroban used as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. Please find attached the packet insert (PI). Please review.
This consult is for both Peds and MHT.

SIGNATURE OF REQUESTOR Lara Akinsanya	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☒ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

LARA M AKINSANYA
02/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric and Maternal Health Staff	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Lara Akinsanya, RPM, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 8, 2011		22-434	NDA - 505(b)(2)	January 12, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Argatroban	Standard	Antithromibin	March 30, 2011

NAME OF FIRM: Eagles Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☒ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

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- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
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IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is a Class 2 505(b)(2) NDA resubmission from Eagles Pharmaceuticals, Inc. submitted for Argatroban used as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. Please find attached the packet insert (PI). Please review.
This consult is for both Peds and MHT.

SIGNATURE OF REQUESTOR Lara Akinsanya	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☒ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

LARA M AKINSANYA
02/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:
Mail: OSE			**Lara Akinsanya, Division of Hematology Products**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 8, 2011		**22-434**	**NDA - 505(b)(2)**	**January 12, 2011**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Argatroban	**Standard**	**Antithrombin**	**March 30, 2011**

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☑ RESUBMISSION
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a Class 2 505(b)(2) NDA resubmission from Eagles Pharmaceuticals, Inc. submitted for Argatroban used as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. Please find attached the packet insert (PI). Please review.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Lara Akinsanya	☑ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

LARA M AKINSANYA
02/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-434

ACKNOWLEDGE – CLASS 2 RESPONSE

Eagle Pharmaceuticals, Inc.
Attention: Brenda Marczi, PharmD
Vice President, Regulatory Affairs
470 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Dr. Marczi:

We acknowledge receipt on January 12, 2011, of your January 10, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection.

We consider this a complete, class 2 response to our January 29, 2010, action letter. Therefore, the user fee goal date is July 12, 2011.

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 Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

LARA M AKINSANYA
01/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-434

MEETING MINUTES

Eagle Pharmaceuticals, Inc.
Attention: Brenda Marczi, Pharm.D.
Vice President, Regulatory Affairs
Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Ms. Marczi:

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

We also refer to the meeting between representatives of your firm and the FDA on March 23, 2010. The purpose of the meeting was to discuss the CMC deficiencies stated in the CR letter.

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

If you have any questions, call me at (301) 796-3691.

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

Enclosure

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	End of Review
Meeting Date and Time:	March 23, 2010
Meeting Location:	White Oak Campus, Building 22
Application Number:	NDA 22-434
Product Name:	Argatroban
Indication:	For prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia and with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary interventions (PCI)
Sponsor/Applicant Name:	Eagle Pharmaceuticals, Inc.
Meeting Chair:	Richard Lostritto, Ph.D.
Meeting Recorder:	Ebla Ali Ibrahim, M.S.

FDA ATTENDEES

Division of Hematology Products

Edvardas Kaminskas, M.D., Acting Deputy Director
Kathy Robie Suh, M.D., Ph.D., Medical Team Leader, Hematology
Firoozeh Alvandi, M.D., Medical Officer
Haleh Saber, Ph.D., Pharmacology Supervisor
Ebla Ali Ibrahim, M.S., Regulatory Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V

Richard Lostritto, Ph.D., Division Director, ONDQA, DPAMS
Mark Sassaman, Ph.D., Chemist, ONDQA, DPAMS

Office of Pharmaceutical Science, New Drug Microbiology Staff

Stephen Langille, M.S., Microbiologist

SPONSOR ATTENDEES

Gregg Stetsko, PhD, Chief Scientific Officer
Sri Sundaram, PhD, Vice President, Pharmaceutical Development
Pui-Ho Yuen, PhD, Sr Director, Pharmaceutical Development
Brenda Marczi, PharmD, Vice President, Regulatory Affairs
Isabel Lamela, Manager, Regulatory Affairs

BACKGROUND:

The proposed indication for Argatroban is as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin induced thrombocytopenia. Eagle Pharmaceuticals, Inc. requested a Type A meeting with the Division to discuss the Chemistry, Manufacturing and Control (CMC) deficiencies stated in the Complete Response (CR) letter dated January 29, 2010. On March 22, 2010, Division of Hematology Product (DHP) sent Eagle Pharmaceuticals, Inc. the preliminary responses to the questions contained in the background package dated March 8, 2010.

MEETING OBJECTIVE:

The meeting objectives are as follows:

- Reach agreement with the Agency on the contents of the CMC portions of the Eagle "Complete Response" amendment to the New Drug Application (NDA).

- Gain an understanding of all outstanding issues and requirements to be fulfilled to enable FDA approval of the NDA.

DISCUSSION:

Eagle informed DHP that they have developed the method for obtaining high purity 21-*R* and 21-*S* isomers. Isomeric purity was assessed as (b) (4) Eagle asked DHP if the method would be suitable. DHP explained that it would be a review issue and that they would have to see the method. DHP also explained that Eagle had previously been provided with a reference in which the authors were able to obtain individual isomers with purity of greater than (b) (4). This would be the standard to which isomeric purity would be compared. Eagle was advised to develop a method to obtain reference standards for individual isomers with purities equal to or greater than those reported in the literature. Eagle responded that it was difficult to get the ideal percentage.

Eagle informed DHP that they are working on LOD and LOQ and that the LOQ would be below the International Conference on Harmonization (ICH) threshold for the daily dose. DHP advised that a side-by-side comparison of the impurities found in the RLD with Eagle's product should be submitted. DHP also advised that any non-clinical information that would be submitted should be included in Module 2 as well as Module 4. Study reports of non-clinical (e.g. qualification) studies should be in Module 4. It would also be appropriate to include summaries of CMC information in Module 2.

(b) (4)

Eagle informed DHP that they have 24 month stability data from the old facility, (b) (4) and that they would like to bridge it with the new method to have a longer dataset. Eagle also informed DHP that the products made in the two facilities are the same but differ in the stopper size/ bottle neck. DHP advised that if a presentation is different, then Eagle would need different stability data. DHP also advised Eagle to submit the data with a comparative summary of the facilities and the bottle size.

Regarding question 4 and DHP response (see attachment below), Eagle explained that the batch records are large and would not like to submit them. DHP explained that they would like the bioequivalence study to be associated with the batches.

Regarding question 2 and DHP response, Eagle stated that the manufacturing sites were previously inspected and passed, and that they would include the inspection date in their response to the CR letter. DHP advised that as stated in the GRMP guidance, all manufacturing sites should be ready for inspection when the application is submitted and that a facility inspected previously can be inspected again.

Regarding question 1 and DHP response, Eagle stated that their submission would be reviewed by a consultant (ex-FDA employee) before submitting. DHP advised Eagle to use the 21st Century Review for their submission to guide them in responding to the CR letter.

Eagle asked DHP for advice on what to do about using lactobionic acid prepared from USP grade (b) (4) DHP advised Eagle to submit a certificate of analysis from the manufacturer (b) (4) and/or to ask the company to submit a DMF in the US.

DHP advised Eagle to submit a complete, stand-alone Module 3 and to send duplicate copies as necessary. DHP also advised Eagle to not throw away any data especially data from (b) (4) which can be considered to be supporting data.

DECISIONS (AGREEMENTS) REACHED:

- Eagle agreed to develop the method for obtaining 21-R and 21-S isomers such that purity would be (b) (4)
- Eagle agreed to submit a side-by-side comparison of the impurities in the RLD with those found in their product
- Eagle agreed to submit a comparative summary of the facilities and the bottle size.

ACTION ITEMS:

- Eagle will submit their response to the CR letter in three months, after a consultant review.

ATTACHMENTS AND HANDOUTS:

See attached FDA's final Comments/Responses to the specific questions asked by Eagle Pharmaceuticals, Inc.

Specific Questions and FDA Responses:

1. *Does the Agency agree with Eagle's plan to provide an updated complete standalone version of Modules 3 in the Complete Response amendment?*

   FDA Response:

   Yes. Submission of a complete, stand-alone version of Module 3 is necessary to begin a new review cycle.

   a. *Does the Agency agree with Eagle's proposed Modules 3 Table of Contents for the new complete version of Module 3 that will be submitted with our Complete Response?*

      FDA Response:

      The table is appropriate (*i.e.*, in CTD format). The contents of each section (including proposed revisions) will be evaluated during the next review cycle.

2. *Does the Agency agree that the information planned for submission in Eagle's upcoming NDA amendment (Complete Response) will address the issue raised by FDA in their January 29, 2010 letter about site inspection readiness of the drug product manufacturer?*

   FDA Response:

   This is a review issue. Information will be evaluated during the next review cycle. However, all sites must be ready for inspection at the time of submission.

3. *Should Eagle provide supportive stability data generated from batches that were manufactured in* (b) (4) *in the proposed new version of Module 3, in addition to the primary stability batch information for product manufactures in* (b) (4)

   FDA Response:

   The value of supporting stability batches (i.e. different from proposed commercial) in establishing approvability and expiry is highly dependent on the degree to which formulation, manufacturing process, manufacturing site, and packaging correspond to the proposed commercial case. This is a review issue. However, supportive stability batches manufactured at a non-commercial site will have diminished impact on approvability and expiry.

4. *Does the Agency agree with Eagle's plan to not submit executed batch records for batches made in* (b) (4) *that were used in the bridging/clotting studies in the new version of Module 3?*

FDA Response:

No. Batch records for drug product used in bridging/clotting studies are planned to be reviewed.

5. *Does the Agency agree with Eagle's plan to provide an updated complete standalone version of Section 2.3S and 2.3P of Module 2 in the Complete Response amendment?*

FDA Response:

Inclusion of summaries in Module 2 per ICH M4Q is appropriate.

6. *Are there any other suggestions FDA would like to make that would help to make FDA's review of the Eagles NDA Module 3 sections easier or does FDA have suggestions or comments that would help to ensure that Module 3 is complete and comprehensive?*

FDA Response:

Stability data for drug product made in (b) (4) **may be used as support but will not be considered as primary stability data. As noted during the telephone conference of October 20, 2009, the current HPLC method has an unacceptable limit of quantitation and is incapable of resolving impurities found by forced degradation. Consequently, all batch analytical data and stability data relying on that method are unusable to establish approvability and expiry. It is therefore necessary that a new method be developed and validated. As part of this effort determine and tabulate the structures of potential and actual impurities (including degradants) with appropriate chemical flowcharts depicting the degradation pattern(s) you ascertain.**

7. *Does the Agency have any final suggestions or comments?*

FDA Response:

Include in Module 3, a complete sterility assurance validation package for all manufacturing equipment to be used in (b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	GI-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

EBLA ALI IBRAHIM
05/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-434 **MEETING REQUEST GRANTED**

Eagle Pharmaceuticals, Inc.
Attention: Brenda Marczi, Pharm.D.
Vice President, Regulatory Affairs
Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Ms. Marczi:

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

We also refer to your April 8, 2010, correspondence requesting a meeting to discuss and gain understanding of all clinical, non-clinical and pharmacology issues and/or requirements to be fulfilled by Eagle for FDA approval. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The teleconference is scheduled as follows:

Date: June 8, 2010
Time: 2:00 PM – 3:00 PM
Phone Arrangements: CALL-IN NUMBER - (b) (4)
PASSCODE – (b) (4)

CDER Participants:

Division of Medical Imaging and Hematology Products (DHP)

Ann Farrell, M.D., Acting Division Director
Edvardas Kaminskas, M.D., Acting Deputy Director
Robert Kane, M.D., Acting Safety Deputy
Kathy Robie Suh, M.D., Ph.D., Medical Team Leader, Hematology
Firoozeh Alvandi, M.D., Medical Officer
Haleh Saber, Ph.D., Pharmacology/Toxicology Supervisor
Shwu-Luan Lee, Ph.D., Pharmacologist
Ebla Ali Ibrahim, M.S., Regulatory Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V

Richard Lostritto, Ph.D., Division Director, ONDQA, DPAMS
Sarah Pope, Ph.D., Branch Chief, ONDQA, DPAMS
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, ONDQA, DPAMS
Mark Sassaman, Ph.D., Chemist, ONDQA, DPAMS

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacologist

Office of Biostatistics, Division of Biometrics V

Satish Misra, Ph.D., Statistician

Submit background information for the meeting (three copies to the application and 10 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by May 8, 2010, we may cancel or reschedule the meeting.

Submit the 10 desk copies to the following address:

Ebla Ail Ibrahim
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2159
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

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
NDA-22434	GI-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

EBLA ALI IBRAHIM
04/20/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 25 March 2010

TO: Ebla Ali Ibrahim
Regulatory Project Manager
OND/OODP/DHP

FROM: Stephen E. Langille, Ph.D. –
Senior Microbiology Reviewer
New Drug Microbiology Staff
Office of Pharmaceutical Science

THROUGH: James McVey
Microbiology Team Leader
New Drug Microbiology Staff
Office of Pharmaceutical Science

SUBJECT: NDA 22-434 - Argatroban Injection

On 8 March 2010, Eagle Pharmaceuticals Inc. submitted a Type A meeting package to the FDA to discuss CMC issues in the complete response letter for NDA 22-434. A meeting was held with Eagle Pharmaceuticals on 23 March 2010 to discuss the re-submission strategy and proposed content for the upcoming submission. During the meeting, it was noted that the initial submission did not contain sterility assurance information for the drug product manufacturing site proposed for the manufacture of Argatroban Injection in (b) (4) of Cipla Limited in Goa, India. The applicant was advised that the NDA re-submission should contain a complete sterility assurance validation package for all manufacturing equipment to be used in (b) (4) Written comments reflecting this request were provided to Eagle Pharmaceuticals.

END

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	GI-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

STEPHEN E LANGILLE
03/29/2010

JAMES L MCVEY
03/29/2010
I concur.

Meeting Date:	**March 23, 2010 Time: 1:00 PM –2:30 PM**
Sponsor:	**Eagles Pharmaceuticals, Inc**
Product:	**Argatroban**
Type:	**Type A**
Proposed Use:	**Used as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia and with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary interventions (PCI)**
Purpose:	**To discuss the CMC deficiencies stated in the CR letter**

Introductory Comment:

This material consists of the reviewers' preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 23, 2010 1:00 PM – 2:30 PM EST between Eagle Pharmaceuticals, Inc. and the Division of Hematology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan or to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. These FDA draft comments were emailed to Brenda Marczi contact on March 21, 2010.

Specific Questions and FDA Responses:

1. *Does the Agency agree with Eagle's plan to provide an updated complete standalone version of Modules 3 in the Complete Response amendment?*

   FDA Response:

   Yes. Submission of a complete, stand-alone version of Module 3 is necessary to begin a new review cycle.

   a. *Does the Agency agree with Eagle's proposed Modules 3 Table of Contents for the new complete version of Module 3 that will be submitted with our Complete Response?*

      FDA Response:

      The table is appropriate (*i.e.*, in CTD format). The contents of each section (including proposed revisions) will be evaluated during the next review cycle.

2. *Does the Agency agree that the information planned for submission in Eagle's upcoming NDA amendment (Complete Response) will address the issue raised by FDA in their January 29, 2010 letter about site inspection readiness of the drug product manufacturer?*

   FDA Response:

   This is a review issue. Information will be evaluated during the next review cycle. However, all sites must be ready for inspection at the time of submission.

3. *Should Eagle provide supportive stability data generated from batches that were manufactured in* (b) (4) *in the proposed new version of Module 3, in addition to the primary stability batch information for product manufactures in* (b) (4)

   FDA Response:

   The value of supporting stability batches (i.e. different from proposed commercial) in establishing approvability and expiry is highly dependent on the degree to which formulation, manufacturing process, manufacturing site, and packaging correspond to the proposed commercial case. This is a review issue. However, supportive stability batches manufactured at a non-commercial site will have diminished impact on approvability and expiry.

4. *Does the Agency agree with Eagle's plan to not submit executed batch records for batches made in* (b) (4) *that were used in the bridging/clotting studies in the new version of Module 3?*

   FDA Response:

   No. Batch records for drug product used in bridging/clotting studies are planned to be reviewed.

5. *Does the Agency agree with Eagle's plan to provide an updated complete standalone version of Section 2.3S and 2.3P of Module 2 in the Complete Response amendment?*

   FDA Response:

   Inclusion of summaries in Module 2 per ICH M4Q is appropriate.

6. *Are there any other suggestions FDA would like to make that would help to make FDA's review of the Eagles NDA Module 3 sections easier or does FDA have suggestions or comments that would help to ensure that Module 3 is complete and comprehensive?*

   FDA Response:

   Stability data for drug product made in (b) (4) **(Lot N^{o} V80615, V80617, and V80620) may be used as support but will not be considered as primary stability data. As noted during the telephone conference of October 20, 2009, the current HPLC method has an unacceptable limit of quantitation and is incapable of resolving impurities found by forced degradation. Consequently, all batch analytical data and stability data relying on that method are unusable to establish approvability and expiry. It is therefore necessary that a new method be developed and validated. As part of this effort determine and tabulate the structures of potential and actual impurities (including degradants) with appropriate chemical flowcharts depicting the degradation pattern(s) you ascertain.**

7. *Does the Agency have any final suggestions or comments?*

   FDA Response:

   Include in Module 3, a complete sterility assurance validation package for all manufacturing equipment to be used in (b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	GI-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

EBLA ALI IBRAHIM
03/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-434 **MEETING GRANTED**

Eagle Pharmaceuticals, Inc.
Attention: Brenda Marczi, Pharm.D.
Vice President, Regulatory Affairs
Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Ms. Marczi:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection.

We also refer to your February 19, 2010, correspondence requesting a meeting to discuss the required steps before NDA 22-434 may be approved. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: March 23, 2010
Time: 1 PM – 2:30 PM

Phone Arrangements: CALL-IN NUMBER - (b) (4)
PASSCODE - (b) (4)

CDER Participants:

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel (Dwaine) Rieves, M.D., Division Director
Kathy Robie Suh, M.D., Ph.D., Medical Team Leader, Hematology
Firoozeh Alvandi, M.D., Medical Officer
Ronald Honchel, Ph.D., Toxicologist
Ebla Ali Ibrahim, M.S., Regulatory Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V

Richard Lostritto, Ph.D., Division Director, ONDQA, DPAMS
Sarah Pope, Ph.D., Branch Chief, ONDQA, DPAMS
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, ONDQA, DPAMS
Mark Sassaman, Ph.D., Chemist, ONDQA, DPAMS

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacologist

Office of Biostatistics, Division of Biometrics V

Satish Misra, Ph.D., Statistician

Provide the background information for the meeting (three copies to the application and 14 desk copies to me FDA, White Oak Campus, Building 22, Room 2159, 10903 New Hampshire Avenue, Silver Spring, MD 20903) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by March 9, 2010, we may cancel or reschedule the meeting.

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 Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	GI-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

EBLA ALI IBRAHIM
03/03/2010

MEMORANDUM OF TELECON

MEETING DATE: October 20, 2009
TIME: 10 AM – 11 AM
APPLICATION: NDA 22-434
DRUG NAME: Argatroban

FDA ATTENDEES:

Rafel Rieves, M.D., Director
Ann Farrell, M.D., Acting Deputy Director
Firoozeh Alvandi, M.D., Medical Officer
Sarah Pope, Ph.D., Branch Chief, ONDQA, DPAMS
Richard Lostritto, Ph.D., Division Director, ONDQA, DPAMS
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, ONDQA, DPAMS
Mark Sassaman, Ph.D., Chemist, ONDQA, DPAMS
Young Moon Choi, Ph.D., Clinical Pharmacologist Team Lead, OCP
Ronald Honchel, Ph.D., Pharmacologist
Stephan Langille, Ph.D., Microbiologist
Ebla Ali Ibrahim, M.S., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Eagle Pharmaceuticals, Inc.

Brenda Marczi, PharmD, VP Regulatory Affairs
Gregg Stetsko, Ph.D., CSO
Sri Sundaram, Ph.D., Sr. Director, Pharmaceutical Development
Pui-Yo Yuen, Ph.D., Sr. Director, Pharmaceutical Development
Isabel Lamela, Manager, Regulatory Affairs

SUBJECT: Chemistry, Manufacturing and Control (CMC) Review Issues

FDA requested a teleconference with Eagle to discuss some of the CMC issues which affect approvability and reviewability of their New Drug Application (NDA).

FDA again recommended that Eagle withdraw their NDA because (1) as previously discussed, the drug product will not be approved at the end of the current review cycle and (2) the application is no longer reviewable due to numerous CMC deficiencies and submission of unsolicited and conflicting information. FDA recognized that the Agency's suggestion to withdraw the NDA is done in consideration of the particular adverse circumstances posed by this NDA. FDA advised Eagle that a viable path forward would be to make appropriate corrections and to submit revised information in a new NDA.

FDA noted that any resubmission to the same NDA would be made much more complex because the resubmission would be reviewed against the totality of information in the NDA, including the original NDA. Conversely, a new NDA submitted subsequent to a withdrawal (of the current NDA) would be a stand-alone document and would not be reviewed against this original submission.

FDA assured Eagle that guidance would be available in a Pre-NDA meeting and that every effort would be made to stream-line the scheduling process on their behalf.

FDA outlined the following areas of concern:

- At the time of submission the drug product had not yet been made in the designated commercial facility (b) (4) new manufacturing equipment had not yet been qualified; and stability data were, therefore, unavailable. This problem came to FDA's attention during a TCON held 20 MAY 2009 and was the subject of subsequent discussions with the applicant.
- In an unsolicited amendment received 25 SEP 2009 Eagle announced a change in the container-closure system and proposed changes to labeling. In effect, the change defined a new presentation for the drug product and, as a consequence, a new NDA would be required.
- The unsolicited amendment of 25 SEP 2009 also contained a Letter of Authorization to a new DMF (glass vials) and listed a new facility involved in manufacturing (b) (4) testing). This information would not be reviewed in the current cycle.
- The HPLC method used for testing purity (as shown in tables of stability data), having a limit of quantitation of (b) (4) was incapable of meeting ICH requirements for reporting (0.05%).
- Forced degradation studies showed the HPLC method to be incapable of detecting anticipated degradants. Specifically, hydrolysis under basic conditions ((b) (4) produced an impurity ((b) (4)) which was hidden in the leading edge of the 21-R isomer (b) (4)). Problems with peak resolution in chromatograms from acid hydrolysis and oxidation studies were also mentioned.
- Since the HPLC method used for impurity analysis was unsatisfactory, stability data relying on that method would be unusable.
- Structures of potential and actual impurities and degradants had not yet been determined and tabulated.
- Reference standards used for determining isomeric content were impure and could not be used for determining accuracy; therefore, the HPLC method (for quantifying 21-R and 21-S isomers) had not been properly validated.
- Deficiencies in the DMF for the drug substance have not yet been resolved.

FDA advised Eagle to request a CMC meeting to obtain guidance before submitting a new NDA.

Eagle stated that their September 24, 2009 amendment is the core submission for CMC and that they would like to respond to the CMC deficiencies in writing.

_____

Ebla Ali Ibrahim
Regulatory Health Project Manager

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	ORIG-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

EBLA ALI IBRAHIM
01/19/2010

MEMORANDUM OF TELECON

MEETING DATE: October 13, 2009
TIME: 11 AM – 11: 30 AM
APPLICATION: NDA 22-434
DRUG NAME: Argatroban

FDA ATTENDEES:

Rafel Rieves, M.D., Director
Kathy Robie Suh, Ph.D., M.D., Medical Officer, Team Leader
Young Moon Choi, Ph.D., Clinical Pharmacology, Team Leader
Joseph Grillo, PharmD., Clinical Pharmacologist
Richard Lostritto, Ph.D., Division Director, DPAMS
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead
Mark Sassaman, Ph.D., Chemist
Ebla Ali Ibrahim, M.S., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Eagle Pharmaceuticals, Inc.

Brenda Marczi, PharmD, VP Regulatory
Gregg Stetsko, Ph.D., CSO
Sri Sundaram, Ph.D., Sr. Director, Pharmaceutical Development
Pui-Yo Yuen, Ph.D., Sr. Director, Pharmaceutical Development

SUBJECT: Clinical Pharmacology Issues

FDA requested a teleconference with Eagle to discuss the clinical pharmacology issues.

FDA expressed the importance of providing timely and comprehensive responses to its information requests.

FDA stated that Eagle's 6/3/09 amendment to its application highlighted fourteen transcription errors in its dataset for study 0409, however; a revised electronic dataset of the coagulation test results was not provided making it difficult to verify the revised analysis. FDA noted that several other datasets related to stock concentrations were available through the electronic document room. Eagle stated that it did not have the resources to submit the data via the electronic gateway and stated the data was submitted via CD's attached to the application. FDA suggested that Eagle consult appropriate guidance regarding the submission of electronic datasets and resubmit the information. Eagle agreed.

FDA expressed concern about the technical error in the concentration of stock, spiking and sample concentration used in study 0409. FDA stated that the magnitude of this error was more than routinely seen in this type of analytical study and that the sponsor should address this issue in detail in a written response. In addition, FDA expressed concern that in an inadvertent labeling error in stock solutions resulting in erroneous results in one sample pool (#10) was not clearly identified and addressed in the application until FDA contacted Eagle with an information request. FDA requested additional clarification regarding Eagle's Quality Assurance Program for this application.

FDA noted that the use of adjusted data in Eagle's analysis was still a review issue. Eagle stated that it provided an analysis of 90% confidence intervals for the coagulation parameters for both adjusted and unadjusted data in the 6/3/09 amendment but would resubmit the information. [addendum: following the meeting FDA verified that this information was in the 6/3/09 amendment; however, the information was presented in summary and the applicant's entire analysis of the unadjusted data (including potential confounding effects) should be provided]

Action Items:

Eagle will provide

- Its procedure or process for quality control in its *in vitro* studies
- Revised electronic datasets for studies where transcription errors were identified and communicated to FDA in the 6/3/09 amendment.
- A comprehensive analysis of unadjusted data from the 0409 study

_____
Ebla Ali Ibrahim
Regulatory Health Project Manager

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	ORIG-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

EBLA ALI IBRAHIM
01/13/2010

MEMORANDUM OF TELECON

DATE: June 3, 2009

APPLICATION NUMBER: NDA 22-434

BETWEEN:
Name: Eagle Pharmaceuticals, Inc.

Representing: Pui-Ho Yuen Ph.D., Development
David Rohrbach, Quality
Wanda Williams, Ph.D., Portfolio and Project Management
Brenda Marczi, Regulatory

AND
Name: DIVISION of Medical Imaging and Hematology Products

Rafel Rieves, M.D., Division Director
Kassa Ayalew, M.D, Medical Officer
Minh Ha Tran, D.O., Medical Officer
Sarah Pope, Ph.D., Branch Chief, ONDQA, DPAMS
Richard Lostritto, Ph.D., Division Director, ONDQA, DPAMS
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, ONDQA, DPAMS
Mark Sassaman, Ph.D., Chemist, ONDQA, DPAMS
Joseph Grillo, PharmD, Clinical Pharmacologist
Stephen Langille, Ph.D., Microbiologist
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager

SUBJECT: Review Impact

On June 3, 2009, the FDA requested a meeting with Eagle Pharmaceuticals to discuss certain manufacturing deficiencies.

FDA explained that not having a facility ready for inspection constitutes a major Chemistry, Manufacturing and Control (CMC) deficiency. Similarly, FDA explained that comprehensive manufacturing information should be submitted with the original NDA application, not submitted as an amendment. Failure to supply this information and the inability to inspect the manufacturing facility in a timely manner may result in the need to issue a Complete Response Letter that cites the deficiencies. FDA also explained that information submitted to the application after the NDA is filed is generally for clarification purposes only.

In light of the substantial manufacturing deficiencies within the original application, FDA noted that the company may wish to withdraw their application and resubmit for another cycle after the manufacturing facility is ready for inspection and all facility supportive information submitted to the NDA. FDA explained that, if Eagle withdraws their application then they would be assigned a new NDA number.

Eagle informed the FDA that they had data for the new facility and would like to amend the application. The FDA explained to Eagle that all NDAs are expected to contain sufficient data for review at the time of submission, and that information submitted as an amendment may not be reviewed in this review cycle, due to time and resource limitations.

FDA advised Eagle that, for future submissions, Investigational New Drug (IND) meetings during development are highly useful for addressing such issues earlier in the process.

Ebla Ali Ibrahim, M.S.
Regulatory Health Project Manger

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	ORIG-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

EBLA ALI IBRAHIM
09/14/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-434

Eagle Pharmaceuticals, Inc
Attention: Brenda Marczi
Vice President Regulatory Affairs
470 Chestnut Ridge Road
Woodcliff Lake, New Jersey 07677

Dear Ms. Marczi:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection.

We also refer to your July 10, 2009, correspondence requesting a meeting to discuss the pending NDA for Argatroban Injection. We are denying the meeting. Instead, you have the option of submitting an amendment with more CMC information. Whether that information will be reviewed will be determined after it is received/along with any impact upon review timelines.

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 Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22434	GI 1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

EBLA ALI IBRAHIM
07/28/2009

MEMORANDUM OF TELECON

DATE: May 14, 2009

APPLICATION NUMBER: NDA 22-434

BETWEEN:
Name: Eagle Pharmaceuticals, Inc.

Representing: Pui-Ho Yuen PhD, Sr Director, Pharmaceutical Development
David Rohrbach, VP, Quality Affairs
Wanda Williams, PhD VP, Portfolio and Project Management
Brenda Marczi, PharmD VP, Regulatory Affairs
Jack Lipman, PhD VP, Preclinical Development
(b) (4)

AND
Name: DIVISION of Medical Imaging and Hematology Products

Rafel Rieves, M.D., Director
Kassa Ayalew, M.D, Medical Officer
Minh Ha Tran, D.O., Medical Officer
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead
Mark Sassaman, Ph.D., Chemist
Young Moon Choi, Ph.D., Clinical Pharmacologist Team Lead
Joseph Grillo, PharmD, Clinical Pharmacologist
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager

SUBJECT: Clarification of the Data Associated with the Refusal To File (RTF) Letter Response and Communicating Filing Deficiencies

On May 14, 2009, FDA requested a meeting with Eagle Pharmaceuticals, Inc. to get clarity of the data associated with the RTF response and to inform Eagle about the filing deficiencies.

FDA explained to Eagle that after reviewing their application resubmission dated March 27, 2009, the application was filed. However, certain deficiencies have been identified and these items will be described in the filing letter.

FDA explained the deficiencies as follows (these citations also include requests):

Clinical Pharmacology:

Clinical Pharmacology comments pertain to the *in vitro* studies that assessed various coagulation parameters.

1. The FDA was unable to locate adequate information regarding validation of the methods used to assess PT, aPTT, and TT in the studies identified as 02-09, 12150801, 0309, and 0409. The supplied validation reference for these studies refers the reviewer to a standard operating procedure (SOP) document (Module 5 p270), not a report from a validation study. Regarding the study by (b) (4) validation information appears to have been supplied in Module 5 (p 558).

   Please identify the location of validation information for Studies 02-09, 12150801, 0309, and 0409 and confirm the location of the validation information for the (b) (4) Supply this information if it was not submitted.

2. Eagle apparently did not address the validity of "adjustment" of observed data if actual concentrations of test solutions did not meet the study acceptance criteria. The use of a proportional adjustment method assumes that a linear relationship exists between the concentration and response; Eagle apparently failed to justify this assumption and data adjustment method. Provide this justification. Alternatively, submit revised analyses that use the actual test solution concentrations, even if these solutions failed meet the study acceptance criteria.

3. Please clarify why the TT was omitted from study 12150801.

4. It appears the CI_{90} for ratios of geometric means (Eagle/GSK) are considerably wider in Study 12150801 (Table 15.10) compared to Study 04-09 (table 15.17). Eagle appears to cite the same methodology and laboratory for both studies. However, the source of the variability between these studies is not described. Please provide clarification of these observations.

5. Provide electronic data sets (SAS transfer files) for test solution concentration data (summarized in tables 15.1 &15.2) for all five studies.

6. Provide electronic data sets (SAS transfer files) for data used to create figure #2 in the (b) (4)

7. Provide a master table of contents that includes page numbers for the various appendices in each study. The supplied table of contents is not conducive to navigation through the supplied study information.

Chemistry, Manufacturing and Controls:

8. Type II DMF (b) (4), Argatroban Hydrate (Non-Sterile Bulk) Drug Substance as Manufactured by (b) (4) was determined to be inadequate to support the new drug application. The DMF holder has been advised of the nature of deficiencies. Contact (b) (4) for additional information.

9. Add a test for residual (b) (4) to the acceptance criteria. Propose limits. Submit revised specifications and batch analysis for Lot N^{o} CC-1877.0-7

10. Prepare or purchase high purity, fully characterized reference standards for argatroban R and S isomers. Revise and validate analytical methods such that the resolution is (b) (4) Submit these revisions.

FDA explained to Eagle that a justification is needed in sections where data are not available.

Eagle stated that they have communicated the issue of the DMF deficiency to the applicable company and that they are working on resolving the issue.

Ebla Ali Ibrahim, M.S.
Regulatory Health Project Manger

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/s/

Ebla Ali Ibrahim

6/17/2009 12:42:20 PM

MEMORANDUM OF TELECON

DATE: May 20, 2009

APPLICATION NUMBER: NDA 22-434

BETWEEN:
Name: Eagle Pharmaceuticals, Inc.

Representing: Pui-Ho Yuen Ph.D., Development
David Rohrbach, Quality
Wanda Williams, Ph.D., Portfolio and Project Management
Brenda Marczi, Regulatory

AND
Name: Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V

Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead
Mark Sassaman, Ph.D., Chemist

SUBJECT: Manufacturing Commercial Supplies in (b) (4)

On May 20, 2009, Eagle Pharmaceuticals, Inc. requested a teleconference with the FDA to discuss Eagle's desire to manufacture commercial supplies in (b) (4) of the Cipla, Goa, India facility) and the best way to accomplish it.

Eagle informed FDA that they plan to manufacture commercial supplies in (b) (4) of Cipla's facility and that they have made several batches and plan to submit data demonstrating the quality of drug product manufactured in (b) (4) to be comparable to that manufactured in (b) (4) (b) (4) Data would also include qualification of new manufacturing equipment and process validation. Eagle asked FDA if the information for (b) (4) can be submitted during the current review cycle for their New Drug Application, NDA 22-434 (which already includes validation data for the (b) (4) manufacturing site). Eagle explained that they have produced one batch each of the two presentations (50 mg/50 mL and (b) (4) in (b) (4) and have three months of stability data available. FDA reminded Eagle of their responsibility to submit complete applications at the time of filing (citing the Guidance: *Good Review Management Principles and Practices for PDUFA Products*) and stated that it was unlikely the Agency would accept these data per Eagle's request. A final decision, however, would be made *only* after internal discussion with the CMC review team and, possibly, the Office of Compliance.

FDA made clear that all manufacturing facilities are expected to be ready for inspection at the time applications are submitted; Eagle had confirmed readiness in response to an information request as part of their amendment dated 29 OCT 2009. Additionally, FDA explained that Prior Approval Supplements are, as a rule, required for facility changes. These supplements are submitted after marketing approval has been granted, not during the review of original applications. FDA then recapitulated the policy pointed out during the formal on-site meeting of 29 JAN 2009: new stability data are not normally accepted during the application review cycle (*i.e.* after an application has been submitted).

FDA informed Eagle that they need to file an Environmental Assessment or Claim for Categorical Exclusion under a specific subsection of 21 CFR 25.31. FDA also informed Eagle about the need for instructions on how the drug is administered. Eagle agreed to provide an Environmental Assessment or Claim and the instructions on how the drug is administered.

Eagle asked if the method validation needed as stated in the Filing Letter was to be done within 10 days. FDA replied that a response was needed within 10 days, but it was understood that validation would require additional time. Eagle informed the FDA that they did not have single isomers for use as reference standards to perform the validation and asked if they could use the reference listed drug (RLD) as their reference standard. FDA replied that the RLD could not be used as a reference standard for individual isomers, and directed Eagle to an article describing separation and purification of argatroban 21-*R* and 21-*S* isomers, published by Rawson, et al. in the Journal of Pharmaceutical Sciences, during the 1990s. Highly purified, well-characterized material would be suitable for use as reference standards.

Ebla Ali Ibrahim, M.S.
Regulatory Health Project Manger

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/s/

Ebla Ali Ibrahim

6/17/2009 12:36:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-434

Eagle Pharmaceuticals, Inc.
Attention: Hindy Schiff
Vice President, Regulatory Affairs
470 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Ms. Schiff:

Please refer to your new drug application (NDA) dated September 26, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Argatroban Injection.

We also refer to your Refusal To File (RTF) response submission dated March 27, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 27, 2010.

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, mid-cycle, 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 27, 2009.

During our filing review of your application, we identified the potential review issues identified below. We also supply certain requests. Please supply the requested information within 10 business days following receipt of this letter.

Clinical Pharmacology:

The following Clinical Pharmacology comments pertain to your *in vitro* studies that assessed various coagulation parameters.

1. We are unable to locate adequate information regarding validation of the methods used to assess PT, aPTT, and TT in the studies identified as 02-09, 12150801, 0309, and 0409. The supplied validation reference for these studies refers the reviewer to a standard operating procedure (SOP) document (Module 5 p270), not a report from a validation study. Regarding the study by (b) (4) validation information appears to have been supplied in Module 5 (p 558).

   Please identify the location of validation information for Studies 02-09, 12150801, 0309, and 0409 and confirm the location of the validation information for the (b) (4) Supply this information if it was not submitted.

2. You apparently did not address the validity of "adjustment" of observed data if actual concentrations of test solutions did not meet the study acceptance criteria. The use of a proportional adjustment method assumes that a linear relationship exists between the concentration and response; you apparently failed to justify this assumption and data adjustment method. Provide this justification. Alternatively, submit revised analyses that use the actual test solution concentrations, even if these solutions failed meet the study acceptance criteria.

3. Please clarify why the TT was omitted from study 12150801.

4. It appears your CI_{90} for ratios of geometric means (Eagle/GSK) are considerably wider in Study 12150801 (Table 15.10) compared to Study 04-09 (table 15.17). You appear to cite the same methodology and laboratory for both studies. However, the source of the variability between these studies is not described. Please provide clarification of these observations.

5. Provide electronic data sets (SAS transfer files) for test solution concentration data (summarized in tables 15.1 &15.2) for all five studies.

6. Provide electronic data sets (SAS transfer files) for data used to create figure #2 in the (b) (4)

7. Provide a master table of contents that includes page numbers for the various appendices in each study. The supplied table of contents is not conducive to navigation through the supplied study information.

Chemistry, Manufacturing and Controls:

8. Type II DMF (b) (4), Argatroban Hydrate (Non-Sterile Bulk) Drug Substance as Manufactured by (b) (4), was determined to be inadequate to support your new drug application. The DMF holder has been advised of the nature of deficiencies. Contact (b) (4) for additional information.

9. Add a test for residual (b) (4) to the acceptance criteria. Propose limits. Submit revised specifications and batch analysis for Lot N^{o} CC-1877.0-7

10. Prepare or purchase high purity, fully characterized reference standards for argatroban R and S isomers. Revise and validate analytical methods such that the resolution is (b) (4) Submit these revisions.

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/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

Sincerely,
{See appended electronic signature page}

Rafel Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

5/19/2009 02:49:19 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-434

Eagle Pharmaceuticals, Inc
Attention: Brenda Marczi, PharmD
Vice President, Regulatory Affairs
470 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Ms. Marczi:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our November 21, 2008 refusal to file letter for the following:

Name of Drug Product:	Argatroban Injection
Review Priority Classification:	Standard (S)
Date of Application:	March 27, 2009
Date of Receipt:	March 30, 2009
Our Reference Number:	NDA 22-434

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 30, 2010.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

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 Medical Imaging and Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Ebla Ali Ibrahim

4/16/2009 02:06:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-434

Eagle Pharmaceuticals, Inc
Attention: Hindy Schiff
Vice President Regulatory Affairs
470 Chestnit Ridge Road
Woodcliff Lake, New Jersey 07677

Dear Mrs. Schiff:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection.

We also refer to your December 15, 2008, correspondence, received December 16, 2008, requesting a meeting to discuss the Refusal to File letter and present data related to the Agency's concerns regarding the *in vitro* studies filed in the 505 (b)(2) and determine a path forward for acceptance and review of the application.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date:	January 29, 2009
Time:	3:00 PM – 4:30 PM
Location:	White Oak Campus, Building 22, Conf. Room 1315 10903 New Hampshire Ave., Silver Spring, MD 20903

CDER Participants:

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel (Dwaine) Rieves, M.D., Division Director
Kathy Robie Suh, M.D., Ph.D., Medical Team Leader, Hematology
Kassa Ayalew, M.D., Medical Team Leader
Minh Ha Tran, D.O., Medical Officer
Laniyonu Adebayo, Ph.D., Supervisory - Pharmacologist
Ronald Honchel, Ph.D., Toxicologist
Florence Moore, M.S., Regulatory Project Manager Acting Team Leader
Diane Leaman, Safety Project Manager
Ebla Ali Ibrahim, M.S., Regulatory Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V

Eldon Leutzinger, Ph.D., Pre-Marketing Assessment Leader
Mark Sassaman, Ph.D., Chemist

Office of Pharmaceutical Science, New Drug Microbiology Team (NDMS)

Stephen Langille, Ph.D., Microbiologist

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacologist

Office of Biostatistics, Division of Biometrics V

Jyoti Zalkikar, Ph.D., Statistical Team Leader

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Ebla.Ali-Ibrahim@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Ebla Ali Ibrahim at 301-796-3691 or Dia Hairston at 301-796-2050.

Provide the background information for this meeting (three copies to the NDA and 14 desk copies to me at FDA, White Oak Campus, Building 22, Room 2159, 10903 New Hampshire Avenue, Silver Spring, MD 20903) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by December 29, 2008, we may cancel or reschedule the meeting.

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 Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Ebla Ali Ibrahim

12/18/2008 10:20:26 AM

RECORD OF TELEPHONE CONVERSATION

NDA: 22-434/Eagle Pharmaceutics/Argatroban/505b2

Today's date: December 16, 2008

Speakers: Dwaine Rieves for FDA and Hindy Schiff for Eagle

Ms. Schiff clarified that Eagle has reanalyzed and reassessed all their available data and now believe they have sufficient information (even without a "new" bridging study) to support an NDA. Hence, Ms. Schiff indicated that the meeting request was for a preNDA meeting. I stated we would work to set up a preNDA meeting.

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/s/

Rafel Rieves

12/16/2008 09:49:04 AM

MEDICAL OFFICER

MEMORANDUM OF TELECON

MEETING DATE: November 21, 2008
TIME: 10:00 AM – 11:00 AM
LOCATION: White Oak Building 22
APPLICATION: NDA 22-434
DRUG NAME: Argatroban Injection

MEETING CHAIR: Rafel Rieves, M.D.

MEETING RECORDER: Ebla Ali Ibrahim, M.S.

FDA ATTENDEES:

Rafel (Dwaine) Rieves, M.D., Division Director
Kassa Ayalew, M.D., Medical Team Leader, Hematology
Minh Ha Tran, D.O.. Medical Officer
Florence Moore, M.S., Regulatory Project Manager Acting Team Leader
Diane Leaman, Acting, Safety Regulatory Health Project Manager
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager
Eldon Leutzinger, Ph.D., Team Lead, Chemistry Reviewer
Mark Sassaman, Ph.D., Chemistry Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D. Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Eagle Pharmaceuticals, Inc.

Nicholas Cappuccino, Ph.D., Chief Scientific Officer
Hindy Schiff, Vice President Regulatory Affairs
(b) (4)

SUBJECT: Refusal To File

FDA requested a teleconference to inform Eagle Pharmaceuticals, Inc. of FDA concerns after a preliminary review of their NDA application, 22-434 received September 29, 2008.

FDA stated that the application was missing information that was importantly related to the bridging study, an important aspect of the application. FDA explained that if the error was clerical and the missing information can be submitted by Monday, November 24, 2008 then the issue may be addressed. FDA continued to state the deficiencies in the application as follows:

1. Data sets that identify the actual Argatroban concentrations in stock and spiked solutions. These data are the only means of verification of the reported concentrations of Argatroban used in this study and drawing reasonable inferences about the study variables. Without these data, the study results are unverifiable and the conclusions unsubstantiated. We note your November 13, 2008, communication states you will repeat the bridging study in order to collect the requisite verification data.

2. Detailed information regarding the assay procedure and 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. Without this information and data, the study results are unverifiable and the conclusions unsubstantiated. We note your November 13, 2008, communication states that you will not have this information and data available until mid December 2008.

    a. Argatroban concentrations in the stock and spiked solutions

    b. Prothrombin time (PT)

    c. Activated partial thromboplastin time (aPTT)

    d. Thrombin generation assay

3. Data sets that contained the data used to support analyses. Please be aware that these data sets must be sufficient to allow us to duplicate your analyses. Apparently, data points were based upon "duplicate runs." However, the specific data points for each run were not supplied in your application.

4. Data sets that allow us to verify the information contained in Figure 2, entitled, “Thrombin generation in Platelet Poor Plasma spiked with GSK- and Eagle-Argatroban.” Without these data, the study results are unverifiable and the conclusions unsubstantiated.

5. Data definition and supportive information for your datasets (electronic). These datasets must contain data definitions for variables and data dictionaries. We suggest you refer to “Guidance for Industry Providing Regulatory Submissions in Electronic Format — General Considerations.”

The sponsor stated that the deficiencies were not clerical and that their study would not be complete until January 2009. FDA informed the sponsor that these deficiencies prohibit a substantive review and the FDA anticipated that they may prompt a refusal to file (RTF) determination for the NDA. FDA explained that a RTF determination would stop the PDUFA clock and that a new 10 month PDUFA clock would start once the missing information is submitted.

The sponsor promised to submit the protocol under the IND for the FDA to review and also promised to redo the assay.

Ebla Ali Ibrahim, M.S.
Regulatory Health Project Manger

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/s/

Ebla Ali Ibrahim

12/2/2008 03:37:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-434

Eagle Pharmaceuticals, Inc.
Attention: Hindy Schiff
Vice President, Regulatory Affairs
470 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Ms Schiff:

Please refer to your September 26, 2008, New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) due to the omission of critical data and supportive information needed to evaluate effectiveness and safety. Specifically, we cite data omissions related to the *in vitro* studies essential to assess your drug's similarity to the reference listed drug. These omissions render your application materially incomplete.

In your application, you proposed to rely upon the clinical data of the reference listed drug to support the marketing of your drug. To verify the similarity of your drug and the reference listed drug, you proposed to rely importantly upon *in vitro* studies. We cite omission of the following items pertaining to the study found in section 4.1.2 (the "bridging" study) of the application:

1. Data sets that identify the actual Argatroban concentrations in stock and spiked solutions. These data are the only means of verification of the reported concentrations of Argatroban used in this study and drawing reasonable inferences about the study variables. Without these data, the study results are unverifiable and the conclusions unsubstantiated. We note your November 13, 2008, communication states you will repeat the bridging study in order to collect the requisite verification data.

2. Detailed information regarding the assay procedure and 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. Without this information and data, the study results are unverifiable and the conclusions unsubstantiated. We note your November 13, 2008, communication states that you will not have this information and data available until mid December 2008.

a. Argatroban concentrations in the stock and spiked solutions

b. Prothrombin time (PT)

c. Activated partial thromboplastin time (aPTT)

d. Thrombin generation assay

3. Data sets that contained the data used to support analyses. Please be aware that these data sets must be sufficient to allow us to duplicate your analyses. Apparently, data points were based upon "duplicate runs." However, the specific data points for each run were not supplied in your application.

4. Data sets that allow us to verify the information contained in Figure 2, entitled, “Thrombin generation in Platelet Poor Plasma spiked with GSK- and Eagle-Argatroban.” Without these data, the study results are unverifiable and the conclusions unsubstantiated.

5. Data definition and supportive information for your datasets (electronic). These datasets must contain data definitions for variables and data dictionaries. We suggest you refer to “Guidance for Industry Providing Regulatory Submissions in Electronic Format — General Considerations.”

While not a basis for our decision to not file your application, please be aware that our initial examination of your submission indicates that your *in vitro* data do not provide persuasive evidence of sufficient similarity between your drug and the reference listed drug. You may wish to consider additional *in vitro* studies. If so, we suggest you submit protocols for these studies in order to obtain our comments upon the study designs.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager, at 301-796-3691.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

11/21/2008 02:30:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-434

INFORMATION REQUEST LETTER

Eagle Pharmaceuticals, Inc.
Attention: Hindy Schiff
Vice President, Regulatory Affairs
470 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Ms Schiff:

Please refer to your September 26, 2008 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban.

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

1. A table showing all facilities involved in manufacturing, testing, and release of the drug substance and drug product, including addresses, contact information, establishment number, and functions performed. Note that Section 3.2.P.3.1 identifies Cipla Ltd, India as performing manufacturing, packaging, labeling, QA, stability and analytical testing, receiving of raw materials, etc, for the drug product, but then lists five cGMP compliant establishments with no specified function.

2. A statement that all of the (apropos) listed facilities are ready for inspection.

3. A schematic or engineer's drawing of the rubber stopper showing which areas are (b) (4) (b) (4).

4. Verify that references in (b) (4) Letter of Authorization are for reformulated (b) (4) (b) (4)

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

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

10/22/2008 08:38:35 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-434

NDA ACKNOWLEDGMENT

Eagles Pharmaceuticals, Inc.
Attention: Hindy Schiff
Vice President, Regulatory Affairs
Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Ms. Schiff:

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: September 26, 2008

Date of Receipt: September 29, 2008

Our Reference Number: NDA 22-434

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 November 28, 2008 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/oc/datacouncil/spl.html. 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 note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial

(NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,* to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

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 Medical Imaging and 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/cder/ddms/binders.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 Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Ebla Ali Ibrahim

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