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APPLICATION NUMBER:

022434Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	**22-434**
Submission Type	Class 2 Resubmission, 505(b)(2) / SDN 27
Submission Date	10 January 2011
Brand Name	Argatroban Injection
Generic Name	Argatroban
Indication	An anticoagulant 1) for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS); 2) in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)
Formulation	An intravenous solution containing 1 mg/mL of argatroban (50 mg of argatroban in 50 mL vial)
Dosing Regimen	1) HIT/HITTS: 2 μg/kg/min as a continuous infusion then adjusted to steady-state aPTT being 1.5 - 3 times baseline 2) PCI: 25 μg/kg/min and a bolus of 350 μg/kg administered over 3 to 5 minutes then adjusted based on activated clotting time
Sponsor	Eagle Pharmaceuticals
OCP Reviewer	Lillian Hua Zhang, Ph.D.
OCP Team Leader	Julie Bullock, Pharm.D.
OCP Division	Division of Clinical Pharmacology 5
OND Division	Division of Hematology Products

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1 EXECUTIVE SUMMARY

This 505(b)(2) application is a Class 2 resubmission by Eagle Pharmaceuticals for Argatroban Injection, 1 mg/mL in single-use vials. The application was previously submitted on February 27, 2009 using Pfizer's ARGATROBAN Injection approved by the FDA as the reference listed drug (RLD). In the previous submission, Eagle submitted an *in vitro* "bridge" study report (0409) to assess the equivalence of the anticoagulant activity between Eagle's product and Pfizer's product to support a waiver of *in vivo* bioequivalence (BE). PD effects were measured by determining the activated partial thromboplastin time (aPTT), the prothrombin time (PT), and the thrombin time (TT) in pooled donor human plasma spiked with clinically relevant concentrations of Eagle's or Pfizer's argatroban product. Clinical pharmacology review concluded that Eagle's product met the predefined criteria for equivalence to Pfizer's RLD and the application was acceptable from a clinical pharmacology perspective. However, due to major deficiencies identified with respect to product quality and facility inspections, a Complete Response (CR) letter was issued by the FDA on January 29, 2010. This re-submission is intended to address the deficiencies as outlined in the CR letter.

In this re-submission, Eagle submitted another *in vitro* "bridge" study report (EAG-ARG-10-CLOT) to compare the anticoagulant activity between Eagle's product and the RLD - Pfizer's ARGATROBAN Injection in support of a waiver of *in vivo* bioequivalence (BE). The study design and conduct of the study are similar to those indicated in the study report (0409) submitted on February 27, 2009, except that the formulation batch used in the current study was from the commercial site rather than that from the non-commercial site used in Study 0409. The results of the data analyses of the current study indicate that an acceptable *in vitro* bridge between Eagle's product and Pfizer's product was established.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 considers this NDA acceptable from a clinical pharmacology perspective.

For labeling recommendations, please refer to Section 3.

1.2 PHASE 4 REQUIREMENT

None.

1.3 SIGNATURES

Lillian Hua Zhang, Ph.D. Reviewer Division of Clinical Pharmacology 5	Julie Bullock, Pharm.D. Team Leader Division of Clinical Pharmacology 5

Cc: DDOP: CSO - L Akinsanya; MTL - V Kwitkowski; MO - R Alvandi
DCP-5: Reviewers - L Zhang; TL - J Bullock; DDD - B Booth
DD - A Rahman

1.4 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Argatroban is a synthetic small molecule direct thrombin inhibitor. ARGATROBAN Injection, the reference listing drug (RLD) for this 505(b)(2) application, was approved by the FDA under NDA 20-883 (Encysive Pharmaceuticals, Inc., now Pfizer) for the following indications:

- as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS);
- as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)

The RLD is a sterile solution and available in 250 mg in 2.5 mL (100 mg/mL) single-use vials. The injection solution (100 mg/mL) needs to be diluted in 0.9% Sodium Chloride for Injection, 5% Dextrose for Injection, or Lactated Ringer's for Injection to a final concentration of 1 mg/mL prior to infusion.

Eagle's proposed argatroban product is a ready-to-use solution at a concentration of 1 mg/mL (50 mg of argatroban in 50 mL single-use vials) in 0.8% sodium chloride. Formulation differences between Eagle's product and the RLD include: 1) absence of the inactive ingredients of the RLD (D-Sorbitol and dehydrated alcohol) in Eagle's product as these inactive ingredients are not required to dissolve argatroban in the Eagle's ready-to-use solution and 2) addition of L-Methionine USP ((b) (4)), Lactobionic Acid (b) (4), and Sodium Hydroxide NF (pH adjusting agent) to Eagle's product. See Table 1 for the formulation comparison between Eagle's product and Pfizer's RLD product.

The Applicant is seeking approval for all the RLD indications.

Table 1. Formulation Comparison Between Eagle's Argatroban Injection and RLD ARGATROBAN Injection

Ingredients	Eagle	RLD	
	Argatroban Injection in Sodium Chloride, 1 mg/mL (amount per mL)	Argatroban Injection diluted in Sodium Chloride, 1 mg/mL (amount per mL)	Argatroban Injection as Supplied, 100 mg/mL (amount per mL)
Argatroban	1 mg	1 mg	100 mg
Sodium Chloride	8 mg	9 mg	--
Dehydrated Alcohol	--	4 mg	400 mg
Sorbitol	--	3 mg	300 mg
Lactobionic Acid	2 mg	--	--
L-Methionine	2 mg	--	--
Water for Injection	(b) (4) (b) (4)		--

*The RLD is supplied in 2.5 mL solution in single-use vials at a concentration of 100 mg/mL.

In support of a waiver of *in vivo* BE, the applicant conducted an *in vitro* "bridge" study (Study EAG-ARG-10-CLOT) to assess the equivalence of the anticoagulant (PD) activity between Eagle's Argatroban Injection and the RLD. The PD effects were measured by determining PT, aPTT, and TT in pooled donor human plasma spiked with clinically relevant concentrations of argatroban from either Eagle or RLD product. Results of the study indicate that equivalence of Eagle's product *versus* the RLD was demonstrated as for the three observed PD parameters, the 90% confidence intervals (CI_{90}) of the ratios of geometric means between Eagle's product and the RLD were within the acceptance criteria of 90 – 110% as defined by the applicant.

2 QUESTION BASED REVIEW

Refer to ARGATROBAN Inject original NDA 20-883 (Approval Date: 30-June-2000) and the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette for the Clinical Pharmacology related issues. For brevity only QBR questions related to the current NDA submission are addressed below.

2.1 GENERAL ATTRIBUTITES

2.1.1 What are the proposed dosage and route of administration?

Eagle's Argatroban Injection is a sterile solution containing 1 mg/mL of argatroban which is intended for intravenous administration.

2.2 GENEARL BIOPHARMACEUTICS

2.5.1 What is the composition of the to-be-marketed formulation?

Eagle's Argatroban Injection is available in 50 mg (in 50 mL) single-use vial. Each mL of sterile, nonpyrogenic solution contains 1 mg Argatroban, 2 mg lactobionic acid, 2 mg L-Methionine, and 8 mg sodium chloride. The composition of the formulation and the function of each component are presented in Table 2.

Table 2. Argatroban Injection (b) (4)

Ingredients	Quantity per unit (or per mL)	Function
Argatroban	1 mg	Active ingredient
Lactobionic Acid	2 mg	(b) (4)
L-Methionine	2 mg	
Sodium Chloride	8 mg	
Sodium Hydroxide	(b) (4)	pH Adjusting agent
Water for Injection	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Eagle's Argatroban Injection has the same active ingredient, dose strength, dosage form, and route of administration as the RLD product. The difference between the two products is the composition of the inactive ingredients. Refer to Section 1.4 for the quantitative and qualitative comparisons between Eagle's to-be-marketed product and the RLD.

2.5.2 What data support or do not support a waiver of in vivo BE data?

In support of the waiver of *in vivo* BE, Eagle conducted an *in vitro* "bridge" study (Study EGL-ARG-10-CLOT) to assess the equivalence of the anticoagulant activity between Eagle's product (the test product, 1 mg/mL) and the RLD (the reference product, 100 mg/mL as supplied).

Briefly, blood samples were collected from 160 healthy subjects (76 males and 84 females) and were pooled for a total of 40 plasma pools (19 male pools and 21 female pools). The spiking solution of the test product at 0.2 mg/mL and the stock and spiking solutions of the reference product at 1 mg/mL and 0.2 mg/mL, respectively, were prepared daily using 0.9% Sodium Chloride for Injection. Aliquots of pooled human plasma were spiked with spiking solutions of

each product or the sodium chloride vehicle. Plasma concentrations of argatroban at 1.0, 3.0, 5.0, and 8.0 μg/mL were prepared and tested for PT and concentrations at 0.25, 0.5, 1.0, 2.0, 3.0, 5.0, and 8.0 μg/mL were evaluated for aPTT. Concentrations of argatroban up to 0.75 μg/mL were tested for TT. Concentrations of argatroban in stock and spiking solutions were measured by a high performance liquid chromatography (HPLC)/UV method and concentrations of argatroban in plasma were determined by a validated LC/MS/MS method (see Section 2.3).

Equivalence of Eagle's product to the RLD was to be demonstrated if the $CI_{90\%}$ of the ratio of their geometric means for PT, aPTT, and TT fell within the acceptance criteria of 90-110%.

Results

In vitro comparison of the anticoagulation effect of Eagle's Product to RLD

Results of equivalence analysis using observed data from all samples are presented in Table 3.

Table 3. Comparison of the PD Effect of Eagle's Product to RLD Based on *In Vitro* Coagulation Parameters

Conc (μg/mL)	Product		Ratio (CI_{90})
	Eagle	RLD	
	aPTT (sec)*		
0.25	51.3 (10.7)	51.1 (10.3)	100.4 (99.6 -101.2)
0.5	61.6 (11.2)	60.8 (10.9)	101.3 (100.6 – 101.9)
1.0	75.6 (12.4)	75.5 (12.0)	100.2 (99.5 – 100.9)
2.0	96.9 (12.2)	95.6 (12.3)	101.4 (101.0 – 101.8)
3.0	110.4 (12.4)	109.1 (12.4)	101.2 (100.6 – 101.7)
5.0	133.9 (12.6)	132.6 (12.8)	101.0 (100.4 – 101.6)
8.0	160.7 (12.5)	159.1 (12.8)	101.0 (100.5 – 101.5)
	PT (sec)*		
1.0	17.7 (7.9)	17.4 (8.4)	101.7 (100.4 – 103.0)
3.0	30.9 (10.2)	30.3 (9.8)	101.7 (99.9 – 103.4)
5.0	42.0 (7.0)	41.0 (7.3)	102.4 (101.3 – 103.5)
8.0	54.4 (7.0)	53.6 (6.5)	101.5 (100.3 – 102.6)
	TT (sec)*		
0.1	58.3 (12.1)	56.7 (12.0)	102.8 (101.6 – 104.0)
0.25	114.6 (15.7)	113.9 (13.5)	100.6 (98.4 – 102.9)
0.5	196.1 (15.6)	192.3 (15.3)	102.0 (99.8 – 104.3)
0.75	270.2 (14.7)	264.7 (15.9)	102.1 (100.4 – 103.8)

*Geo-mean (CV%)

The statistical analyses demonstrate that the CI_{90} of the ratios of geometric means for the PD parameters between Eagle's product and the RLD fell within the acceptance criteria of 90% - 110% for equivalence as defined by the applicant.

The effect of dilution vehicle and excipients on aPTT, PT, & TT

The statistical comparisons of plasma argatroban PD parameters for the dilution vehicle (0.9% saline) *versus* the blank (plasma only) are summarized in Table 4. The results indicate that the dilution vehicle had no effect on the coagulation tests.

Table 4. Effect of Vehicle on PT, aPTT, & TT

	aPTT (sec)*	Ratio (CI_{90}) Vehicle/Blank
Blank (plasma only)	31.1 (7.9)	
Vehicle	31.9 (7.6)	102.6 (101.8 -103.4)
	PT (sec)*	
Blank (plasma only)	10.4 (4.6)	
Vehicle	10.9 (4.7)	102.4 (101.7 - 103.1)
	TT (sec)*	
Blank (plasma only)	18.4 (6.3)	
Vehicle	18.6 (7.7)	98.5 (97.0 – 100.1)

*Geo-mean (CV%)

Although the effect of excipients on the PD parameters was not evaluated in the current *in vitro* bridging study, specificity studies were conducted with placebo formulations of both products during the clotting assay validation process to confirm the absence of clotting effects from excipients. Compared to the observed aPTT, PT, and TT values obtained from plasma alone or dilution vehicle samples, the excipients of each placebo formulation corresponding to argatroban concentrations at 0.1, 1.0, 4.0 and 8.0 μg/mL had no effect on the coagulation tests.

2.3 ANALYTICAL SECTION

2.3.1 How are the active moieties identified and measured in the *in vitro* bridging study?

For argatroban in stock and spiking solutions, a final solution diluted by 0.9% saline at an argatroban concentration of 0.2 mg/mL was measured by a Waters Alliance HPLC System with a PDA or UV detector at a wavelength of 330 nm.

Concentrations of argatroban in plasma were determined by a validated LC/MS/MS method. Argatroban in plasma was extracted using acetonitrile with a precipitation procedure. $^{13}C_6$ Argatroban was used as an internal standard (IS). The extracted samples were analyzed using reverse-phase HPLC and the analytes were detected using tandem MS detection. Argatroban was monitored by the *m/z* 509.4→ *m/z* 384.4 transition and $^{13}C_6$-Argatroban was monitored by the *m/z* 515.4 → *m/z* 390.1 transition.

The aPTT, PT, and TT tests were photo-optical measurements of the time to clot after addition of reagents to the plasma samples using a BCS® Coagulation Analyzer. Assessment of PT was performed by adding tissue extract and calcium to a plasma sample. Thromborel S PT Reagent was used. Assessment of aPTT was accomplished using Pathromtin SL aPTT Reagent to obtain a the time to clot after addition of calcium, activator and phospholipids to a plasma sample. TT was measured after addition of thrombin (BC Thrombin reagent) to a plasma sample.

2.3.2 Were the analytical procedures used to determine the drug concentration and assays used to measure the clotting time acceptable in this NDA?

With respect to the HPLC/UV assay used to measure the concentration of argatroban in stock and spiking solutions, a summary of the method validation is presented in Table 5.

Table 5. Validation Summary

Analyte	Argatroban
Reference standard	Argatroban hydrate
Method description	Dilution procedure with analysis by HPLC/UV
Limit of quantization (mg/mL)	0.1
Standard curve concentrations (mg/mL)	0.1, 0.15, 0.2, 0.25, and 0.3
Regression Type	Linear analysis with 1/x weighting
Intra-assay precision range (% CV)	0.1 – 1.4
Intra-assay accuracy range (% of the nominal concentration)	99.5 – 100.6
Inter-assay precision range (% CV)	0.3 – 0.8
Inter-assay accuracy range (% of the nominal concentration)	99.8 – 100.5
Bench-top stability	10 days @ ambient temperature
Long-term storage stability in Refrigerator	23 days
Freeze-thaw stability	2 cycles freeze – thaw cycles

The analytical method and validation parameters for the LC/MS/MS assay used to determine the concentration of argatroban in plasma are given in Table 6.

Table 6. Validation Summary

Analyte	Argatroban
Internal standard (IS)	$^{13}C_6$-Argatroban
Method description	Dilution procedure with analysis/detection by LC-MS/MS
Limit of quantization (μg/mL)	0.077
Standard curve concentrations (μg/mL)	0.077 to 9.798
Regression Type	Linear analysis with $1/x^2$ weighting
QC concentrations (μg/mL)	0.077, 0.205, 3.413, and 6.825
Average recovery of Argatroban (%) (Low , Med, High QC)	94.5%, 94.7%, 92.6%
Average Recovery of IS (% Mean)	100.5%
QC intra-assay precision range (% CV)	1.0 – 4.3
QC intra-assay accuracy range (% of the nominal concentration)	93.3 – 97.1
QC inter-assay precision range (% CV)	0.4 – 1.3
QC inter-assay accuracy range (% of the nominal concentration)	94.3 – 95.7
Bench-top stability	6 hours @ ambient temperature
Processed stability	93 hours @ 4°C
Freeze-thaw stability (freeze-thaw cycles)	4 freeze-thaw cycles
Long-term storage stability in Refrigerator	47 days
Long-term storage stability at -80°C	47 days
Dilution integrity	up to 34.127 μg/mL diluted 5 fold

The assay appears to be validated in a manner consistent with the "Bioanalytical Method Validation" guidance.

Regarding the coagulation assays, the accuracy, precision, and stability of the quality control samples are summarized in Table 7.

Table 7. Validation Parameters for Coagulation Assays

	PT	aPTT	TT
Accuracy (% of the nominal concentrations range)			
Intra-Assay	80.0 – 100.0	99.3 – 103.9	100.0 – 100.02
Inter-Assay	81.8 – 96.2	99.9 – 102.6	100.0 – 100.01
Precision range (% CV)			
Intra-Assay	0.8 – 4.7	0.3 – 2.1	1.0 – 6.0
Inter-Assay	1.3 – 5.1	0.9 – 3.3	0.6 – 6.0
Bench-top stability (ambient temperature)	6 hours	6 hours	4 hours
Freeze-thaw stability (freeze-thaw cycles)	2	2	1
Long-term storage stability (@ - 70° C)	14 days	14 days	7 days

3 DETAILED LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology sections of the applicant's proposed PLR format package insert are reproduced. The changes made by the reviewer are in Red.

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/s/

LILLIAN H ZHANG
06/15/2011

JULIE M BULLOCK
06/16/2011

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 22-434	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	January 12, 2011	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	OODP/DHP	**Date of Review:**	May 31, 2011
Sponsor:	Eagle Pharmaceuticals, Inc.		
Trade Name:	Argatroban Injection	**Type of Submission:** 505 (b)(2) NDA Re-Submission	
Generic Name:	Argatroban Injection		
Indication:	• 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 intervention (PCI).		
Formulation/strengths	Inject able IV Solution/1 mg/mL premix (50 mg/50 mL (b) (4)		
Route of Administration	Intravenous		
Type of Review:	**BIOWAIVER REQUEST**		

SUBMISSION:

On January 12, 2011, Eagle Pharmaceuticals submitted their responses to the FDA's Complete Response Letter dated January 29, 2010 for their NDA 22-434 for Argatroban Premix Injection 1 mg/ml ("Eagle's RTU") under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) application relies for approval on the FDA's findings of safety and effectiveness for the Reference Listed Drug. The proposed Argatroban Injection has the same active ingredient, same dosage form (i.e., injectable solution), and route of administration as the Reference Listed Drug (RLD), ARGATROBAN Injection, 100 mg/ml concentrate. The reference drug product was approved by the FDA under NDA 20-883 on June 30, 2000, for the following indications:

- As an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS);
- As an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

The Reference Listed Drug was approved under Encysive Pharmaceuticals, Inc, but it is currently marketed by Pfizer.

BIOPHARMACEUTICS:

Formulation: Eagle's Argatroban Injection, 1 mg/mL is an isotonic solution of argatroban that is ready for administration without further dilution. Each single use 50-mL vial contains 50-mg of argatroban plus the following inactive ingredients: Lactobionic acid, EP, L-methionine, USP, Sodium

chloride, USP, Sodium hydroxide, NF and Water for Injection, USP.
The excipients are different for the Eagle and RLD Argatroban products. Formulation differences between the Eagles and RLD include: 1) Absence of sorbitol and ethanol in the Eagle's formulation, and 2) Addition of L-Methionine USP, Lactobionic Acid, and Sodium Hydroxide NF to the Eagle's formulation.

The comparative description of the proposed Eagle's formulation and the RLD formulation is given in the table below.

PRODUCT	**RLD Argatroban Injection** (Admixed)	**Eagle Argatroban Injection RTU** (Premixed)
Argatroban Concentration:	100 mg/mL	1 mg/mL
(b) (4)	N/A	Sodium Chloride 8 mg/mL
	Ethanol 1000 mg/mL	Water for injection, USP QS (b) (4)
	D-Sorbitol 750 mg/mL	N/A
	N/A	L-Methionine, USP 2 mg/mL
	N/A	Lactobionic Acid 2 mg/mL
pH Adjuster:	N/A	Sodium Hydroxide, NF QS (b) (4)
Total Vial volume	2.5 mL	50 (b) (4) (b) (4)

All excipients fall below the FDA Inactive Ingredient Guide (IIG) limits for intravenous administration, with the exception of lactobionic acid (for which no limit is given)

Inactive Ingredients

Ingredient	**Amount per unit volume of Argatroban Injection**		**Maximum IIG levels from FDA Website**
	mg/mL	**% (w/v)**	
Lactobionic Acid	2.0 mg	0.2	Not available
L-Methionine, USP	2.0 mg	0.2	49.2%
Sodium Chloride, NF	8.0 mg	0.8	90.0%

BIOWAIVER REQUEST:

In the Original NDA submission dated March 27, 2009, Eagle Pharmaceuticals requested a waiver for the CFR's requirement to provide in vivo Bioavailability or Bioequivalence (BA/BE) data for their product. To support the BA/BE waiver request, Eagle Pharmaceuticals provided information showing that the proposed Argatroban Injection will be administered at the same dosage level, for the same duration, and for the same indications as the RLD product, Argatroban Injection from Pfizer.

Also, to support the biowaiver request, Eagle conducted bridging study No. 04-09 assessing the in vitro equivalence of the anticoagulant (PD) activity between the Eagle and RLD formulation. In this study, the pharmacodynamic effects were measured by determining aPTT, PT, and TT in pooled donor human plasma spiked with clinically relevant concentrations of Eagle's RTU or RLD products. The data from this in vitro bridging study were evaluated by Dr. Joseph Grillo from the Office of Clinical Pharmacology. In his review, Dr. Grillo concluded that the in vitro study bridging the

proposed Eagle's Argatroban product and Pfizer's Argatroban RLD product was acceptable (*for details refer to Dr. Grillo's review dated 1/20/2010 in DARRTS*).

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed the information included in NDA 22-434 for Argatroban Injection 1 mg/ml. Based on the information showing that;

- The in vitro pharmacodynamic activity (aPTT, PT, and TT) of the proposed Argatroban Injection is similar to the activity of the RLD product,
- The difference in the inactive ingredients will not have an impact on the bioavailability of the product,
- The inclusion of (b) (4) L-Methionine USP, Lactobionic Acid in the formulation did not raise a safety concern,
- The proposed product will be administered at the same dosage level for the same duration, and,
- The route of administration, dosage form and indications of the proposed product are the same as the RLD product,

ONDQA-Biopharmaceutics is of the opinion that the provided information supports the biowaiver request, therefore, a waiver for the CFR's requirement to provide in vivo bioavailability or bioequivalence data to support the approval of the proposed Argatroban Premix Injection (50 mg/50 mL (b) (4) manufactured by Eagle Pharmaceuticals is granted.

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drug Quality Assessment

cc: NDA 22-434

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/s/

ANGELICA DORANTES
05/31/2011

PATRICK J MARROUM
05/31/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: **22-434**	Submission Date(s): **12/16/08, 3/27/09, & 6/3/09**
Brand Name	**Argatroban Injection RTU**
Generic Name	**Argatroban hydrate**
Reviewer	**Joseph A. Grillo, Pharm.D.**
Team Leader	**Young Moon Choi, Ph.D.**
OCPB Division	**5**
ORM division	**OND/OODP/DMIHP**
Applicant	**Eagle Pharmaceuticals, Inc. (Eagle)**
Relevant IND(s)	**102,622**
Submission Type; Code	**505(b)(2), Standard Review**
Formulation; Strength(s)	**1 mg/mL premix (50 mg/50 mL &** (b) (4)
Indication	• **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 intervention (PCI).**

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1 Executive Summary

Argatroban Injection is approved in the United States under NDA 20-883 (Encysive Pharmaceuticals, Inc.) and manufactured & distributed by GlaxoSmithKline (GSK). Eagle is submitting the current application for Argatroban injection premix ("Eagle's RTU") under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("The Act") . Argatroban injection is indicated as 1) An anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS) and 2) An anticoagulant in patients with or at risk for heparin-induced thrombocytopenia (HIT/HITTS) undergoing percutaneous coronary intervention (PCI).

Eagle's proposed formulation is a ready to use premix solution (50 mg/50 mL & (b) (4) in 0.8% sodium chloride and Encysive Reference Listed Drug (Encysive's RLD) is a 250-mg (in 2.5-mL) single-use vials that requires further dilution. The type of excipients used are also different between Eagle's RTU and Encysive's Reference Listed Drug (Encysive's RLD).

In support of a waiver of in vivo BE data the applicant conducted a bridging study (04-09) to assess in vitro equivalence of the anticoagulant (PD) activity between Eagle's RTU and Encysive's RLD formulation. PD effects were measured by determining aPTT, PT, and TT in pooled donor human plasma spiked with clinically relevant concentrations of Eagle's RTU or Encysive's RLD formulation.

The reviewer finds the applicants "adjustment" of observed aPTT, PT, and TT using an unsubstantiated linear or polynomial equation in its statistical analysis of the difference between observed and expected levels when the concentration of Argatroban exceeds 5% (negatively or positively) for a particular plasma sample inappropriate. However, a reviewer generated analysis of the applicant's raw unadjusted data revealed that 90% confidence intervals (CI_{90}) of the ratios of geometric means between Encysive's RLD and Eagle's RTU for unadjusted observed aPTT, PT, and TT at clinically relevant argatroban concentrations showed that all of the CI_{90}'s were within the equivalence range between 0.9 and 1.11 that was defined by the applicant. These results are consistent with an analysis CI_{90}'s of unadjusted data submitted, in summary, by the applicant as part of a 6/3/09 amendment. This conclusion was confirmed by examining the apparent relationship between these coagulation parameters for both formulations. No obvious clinically relevant confounding effects were noted. This analysis is acceptable, however, was limited by technical error in the accurate and precise preparation of stock and spiking solutions.

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is ACCEPTABLE provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Deficiencies

1.2.1 None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

ARGATROBAN Injection is approved in the United States under NDA 20-883 (Encysive Pharmaceuticals, Inc.) and manufactured & distributed by GlaxoSmithKline (GSK). Eagle is submitting the current application for Argatroban injection premix solution under section 505(b)(2) of the Act.

Eagle's proposed formulation is a ready to use premix solution (50 mg/50 mL (b) (4) (b) (4) in 0.8% sodium chloride. Formulation differences between the Eagles RTU and Encysive's RLD include: 1) Absence of sorbitol in Eagle's RTU, 2) Absence of ethanol in the Eagle's RTU, and 3) Addition of L-Methionine USP, Lactobionic Acid, and Sodium

Hydroxide NF to Eagle's RTU. The absence of sorbitol & ethanol may have a minor effect on biliary and renal elimination, but clinically relevant changes not anticipated.

In support of a waiver of *in vivo* BE data the applicant conducted a bridging study (04-09) to assess in vitro equivalence of the anticoagulant (PD) activity between Eagle's RTU and Encysive's RLD formulation. PD effects were measured by determining aPTT, PT, and TT in pooled donor human plasma spiked with clinically relevant concentrations of Eagle's RTU or Encysive's RLD formulation.

The reviewer finds the applicants "adjustment" of observed aPTT, PT, and TT using an unsubstantiated linear or polynomial equation in its statistical analysis of the difference between observed and expected levels when the concentration of Argatroban exceeds 5% (negatively or positively) for a particular plasma sample inappropriate. Since this adjustment of data significantly confounded the analysis, the applicant's conclusions, as reported, are not sufficient to adequately demonstrate an *in vitro* bridge between Eagle's RTU and the innovator using comparative effect on aPTT, PT, and TT.

However, a reviewer generated analysis of the applicant's raw unadjusted data. The 90% confidence intervals (CI_{90}) of the ratios of geometric means between Encysive's RLD and Eagle's RTU for unadjusted observed aPTT, PT, and TT at clinically relevant argatroban concentrations showed that all of the CI_{90}'s were within the equivalence range between 0.9 and 1.11 that was defined by the applicant. These results are consistent with an analysis CI_{90}'s of unadjusted data submitted, in summary, by the applicant as part of a 6/3/09 amendment. This conclusion was confirmed by examining the apparent relationship between these coagulation parameters for both formulations. No obvious clinically relevant confounding effects were noted from a reviewer analysis of gender or comparing blank, vehicle alone, or excipient alone to argatroban containing samples for both Encysive's RLD and Eagle's RTU at the argatroban concentrations studied. Therefore, Eagle's RTU met the predefined criteria for equivalence to the Encysive's RLD.

This analysis was limited by technical error. A lofty, yet acceptable, degree of consistent technical error in the accurate and precise preparation of stock and spiking solutions was noted by the reviewer.

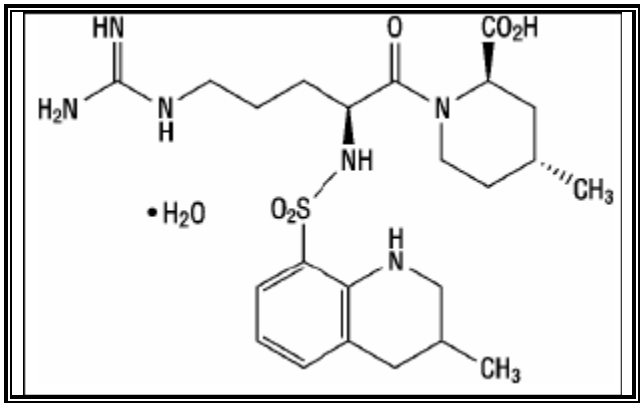
Signatures

Joseph A. Grillo, Pharm.D Clinical Pharmacology Reviewer Division of Clinical Pharmacology 5	Young Moon Choi, Ph.D. Team Leader DMIHP Division of Clinical Pharmacology 5

2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?



Established name: Argatroban

Molecular Weight: 526.66

Molecular Formula: $C_{23}H_{36}N_6O_5S•H_2O$

Chemical Name: 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate.

Description: white, odorless crystalline powder

Solubility: Freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ethyl acetate, and ether.

Eagle's Argatroban Injection RTU is a sterile clear, colorless to pale yellow, aqueous solution. It is available in 50 mg (in 50 mL) (b) (4) single-use vials, with white flip-top caps. Each mL of sterile, nonpyrogenic solution contains 1 mg Argatroban. Inert ingredients: 2 mg lactobionic acid, 2 mg L-Methioine, 8 mg sodium chloride.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Argatroban is a direct thrombin inhibitor that reversibly binds to the thrombin active site. Argatroban does not require the co-factor antithrombin III for antithrombotic activity. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or –induced reactions, including fibrin formation; activation of coagulation factors V, VIII, and XIII; activation of protein C; and platelet aggregation.

Argatroban is highly selective for thrombin with an inhibitory constant (Ki) of 0.04 μM. At therapeutic concentrations, Argatroban has little or no effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein).

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin. Argatroban does not interact with heparin-induced antibodies. Evaluation of sera in 12 healthy subjects and 8 patients who received multiple doses of Argatroban did not reveal antibody formation to Argatroban

Argatroban is indicated as:

- An anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS).
- An anticoagulant in patients with or at risk for heparin-induced thrombocytopenia (HIT/HITTS) undergoing percutaneous coronary intervention (PCI).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Adult Heparin-Induced Thrombocytopenia (HIT/HITTS)

The recommended initial dose of Argatroban for adult patients without hepatic impairment is 2 mcg/kg/min, administered as a continuous infusion. After the initial dose of Argatroban, the dose can be adjusted as clinically indicated (not to exceed 10 mcg/kg/min), until the steady-state aPTT is 1.5 to 3 times the initial baseline value (not to exceed 100 seconds).

Adult Percutaneous Coronary Interventions (PCI) in HIT/HITTS Patients

An infusion of Argatroban should be started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous (IV) line over 3 to 5 minutes. Activated clotting time (ACT) should be checked 5 to 10 minutes after the bolus dose is completed. The procedure may proceed if the ACT is greater than 300 seconds. If the ACT is less than 300 seconds, an additional IV bolus dose of 150 mcg/kg should be administered, the infusion dose increased to 30 mcg/kg/min, and the ACT checked 5 to 10 minutes later. If the ACT is greater than 450 seconds, the infusion rate should be decreased to 15 mcg/kg/min, and the ACT checked 5 to 10 minutes later. Once a therapeutic ACT (between 300 and 450 seconds) has been achieved, this infusion dose should be continued for the duration of the procedure. In case of dissection, impending abrupt closure, thrombus formation during the procedure, or inability to achieve or maintain an ACT over 300 seconds, additional bolus doses of 150 mcg/kg may be administered and the infusion dose increased to 40 mcg/kg/min. The ACT should be checked after each additional bolus or change in the rate of infusion. If a patient requires anticoagulation after the procedure, Argatroban may be continued, but at a lower infusion dose.

Hepatic Impairment

For adult patients with heparin-induced thrombocytopenia with hepatic impairment, the initial dose of Argatroban should be reduced. For adult patients with moderate hepatic impairment, an initial dose of 0.5 mcg/kg/min is recommended, based on the approximate 4-fold decrease in Argatroban clearance relative to those with normal hepatic function. The aPTT should be monitored closely, and the dosage should be adjusted as clinically indicated.

For hepatic Impairment in HIT/HITTS Patients Undergoing PCI carefully titrate Argatroban until the desired level of anticoagulation is achieved.

Renal Impairment

No dosage adjustment is necessary in patients with renal impairment.

Pediatric HIT/HITTS Patients

Initial Argatroban infusion doses are lower for seriously ill pediatric patients compared to adults with normal hepatic function.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.4.3 Does this drug prolong the QT or QTc interval?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

Given this is a RTU formulation (50 mg/50 mL [redacted] (b) (4) and Encysive's RLD is a vial concentrate, how the required bolus doses will be administered is an important issue. However, this is not clear from the applicant's submission. In clinical practice with other drugs that are available in premix only formulation, yet a bolus dose is required, can

overcome this using an IV pump capable of administering an IV bolus, adjusting the rate of infusion to allow the bolus dose to be administered, or drawing the bolus dose via the access port of the premixed bag and administering the bolus using a separate syringe. This should be addressed in the labeling for this drug.

2.2.5 PK characteristics of the drug and its major metabolite

2.2.5.1 What are the single dose and multiple dose PK parameters?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.5.3 What are the characteristics of drug absorption?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

Since this is an intravenously administered product, it would be reasonable to expect 100% absorption.

2.2.5.4 What are the characteristics of drug distribution?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, June 5, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.5.6 What are the characteristics of drug metabolism?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.5.7 What are the characteristics of drug excretion?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.5.8 How do the PK parameters change with time following chronic dosing?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.2.5.9 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.3.2.2 Pediatric patients

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.3.2.3 Gender

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.3.2.4 Race

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.3.2.5 Renal impairment

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.3.2.6 Hepatic impairment

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.3.2.7 What pregnancy and lactation use information is there in the application?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette, January 7, 2000, OCP review by David Udo, and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

Given this is a RTU formulation (50 mg/50 mL (b) (4)) and Encysive's RLD is a vial concentrate, how the required bolus doses will be administered is an important issue. However, this is not clear from the applicant's submission. In clinical practice with other drugs that are available in premix only formulation, yet a bolus dose is required, can overcome this using an IV pump capable of administering an IV bolus, adjusting the rate of infusion to allow the bolus dose to be administered, or drawing the bolus dose via the access port of the premixed bag and administering the bolus using a separate syringe. This should be addressed in the labeling for this drug.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Not applicable.

2.5.2.1 What data support or do not support a waiver of *in vivo* BE data?

The formulations of Eagle's RTU and Encysive's RLD are similar with the following exceptions noted in Table 1 below. Eagle's proposed formulation is a ready to use premix solution (50 mg/50 mL (b) (4) in 0.8% sodium chloride. Formulation differences between the Eagles RTU and Encysive's RLD include: 1) Absence of sorbitol in Eagle's RTU, 2) Absence of ethanol in the Eagle's RTU, and 3) Addition of L-Methionine USP, Lactobionic Acid, and Sodium Hydroxide NF to Eagle's RTU. The absence of sorbitol & ethanol may have a minor effect on biliary and renal elimination, but clinically relevant changes not anticipated.

Table 1: Comparison Between Encysive's Argatroban and Eagle's Argatroban Formulations

Product:	Encysive's RLD Argatroban Injection (Admixed)	Eagle Argatroban Injection RTU (Premixed)
Argatroban Concentration:	100 mg/mL	1 mg/mL
(b) (4)	N/A	Sodium Chloride 8 mg/mL
	Ethanol 1000 mg/mL	Water for injection, USP QS (b) (4)
	D-Sorbitol 750 mg/mL	N/A
	N/A	L-Methionine, USP 2 mg/mL
	N/A	Lactobionic Acid 2 mg/mL
pH Adjuster:	N/A	Sodium Hydroxide, NF QS pH (b) (4)
Total Vial volume	2.5 mL	50 (b) (4)

In support of a waiver of *in vivo* BE data the applicant conducted a bridging study (04-09) to assess *in vitro* equivalence of the anticoagulant (PD) activity between Eagle's RTU and Encysive's RLD formulation. PD effects were measured by determining aPTT, PT, and TT in pooled donor human plasma spiked with clinically relevant concentrations of Eagle's RTU or Encysive's RLD formulation. Please see section 4.2 (Individual Study Reviews) for an overview of the materials and methods used in this study. Briefly, Pooled human plasma (11 pools for each gender, 22 pools total) were spiked with different levels of Test Drug, Reference Drug, their respective placebo formulations or vehicle (saline). Spiked plasma samples (0.6 mL) were transferred to labeled assay tubes for aPTT, PT, and TT analysis (assayed in triplicate). In addition, 0.5 mL of the plasma sample was removed from each tube and transferred to a labeled tube for argatroban quantitation.

The reviewer finds the applicants "adjustment" of observed aPTT, PT, and TT using an unsubstantiated linear or polynomial equation in its statistical analysis of the difference between observed and expected levels when the concentration of Argatroban exceeds 5% (negatively or positively) for a particular plasma sample inappropriate. The reviewer believes this method evolved out of a misinterpretation of a comment by FDA in a 1/29/09 meeting where it stated "we recommend that theoretical target values should be adjusted for the purposes of data evaluation if the mean measured spiking solution value deviated from its target concentration by +/- 5%." Spiking solutions refer to bulk solutions of drug that are introduced into the sample not the samples themselves. Unfortunately, since this adjustment of data significantly confounded the analysis, the applicant's conclusions, as reported, are not sufficient to adequately demonstrate an *in vitro* bridge between Eagle's RTU and the innovator using comparative effect on aPTT, PT, and TT.

However, a reviewer generated analysis of the applicant's raw unadjusted data was attempted to adequately demonstrate an *in vitro* bridge between Eagle's RTU and the innovator using comparative effect on aPTT, PT, and TT. An analysis of the applicant's stock and spiking solutions are shown in Table 2. The within day precision was less than eight percent and

consistent for both formulations. Accuracy was between 89.4 and 111% which, while not ideal, is acceptable since an obvious trend suggesting a difference between the two formulations was not apparent. This was most likely the result of technical error on the part of those preparing the solutions.

Table 2: Comparison of Argatroban Concentrations in stock and spiking solutions for the Encysive's RLD and Eagles RTU

Date Prepared	Concentration (µg/mL)				
	Encysive			Eagle	
	1000	100	20	1000	20
2/23/2009		97.1	16.2	1112.1	18.8
2/27/2009	893.1		19.9	1134.6	21.3
2/27/2009				1069.2	18.7
3/3/2009	965.4		17.8		
3/6/2009*	934.7		17.2		
3/9/2009	1023.1		18.3		
Mean	**954.1**	**N/A**	**17.9**	**1105.3**	**19.6**
CV (%)	**5.7**	**N/A**	**7.6**	**3.0**	**7.6**
Accuracy (%)	**95.4**	**97.1**	**89.4**	**111**	**98.1**

*These data were transposed in the applicant's data set, but communication with the applicant and an analysis of plasma samples suggests that the labels of these bulk solutions were likely switched.

Despite this technical error in preparing the bulk and spiking solutions, an analysis of argatroban concentrations in the actual spiked pooled plasma samples showed a percent difference of +/- 5% (Table 3) which is acceptable for assuming theoretical concentrations for purposes of the subsequent coagulation analysis. In addition, the relationship between theoretical and observed argatroban concentrations in these samples is similar for both Encysive's RLD and Eagles RTU (Figure 1) suggesting the variability is likely a result of technical error in the preparation of these samples. It is important to note that plasma pool #10 was omitted from this and other analyses due to erroneous results based on the probable spiking of these samples with a bulk spiking solution that was incorrectly labeled and contained a 50-fold higher argatroban concentration than was labeled (Table 2).

Table 3: Comparison of Argatroban Concentrations in plasma pool samples (n=21) for the Encysive's RLD and Eagles RTU

Theoretical Concentration	N*	Eagle RTU		Encysive's RLD	
		Mean (SD)	%diff	Mean (SD)	%diff
100 ng/mL	21	104.39 (5.13)	4.39	98.67 (6.46)	-1.33
250 ng/mL	21	251.84 (13.69)	0.73	238.49 (10.89)	-4.6
400 ng/mL	21	417.79 (24.72)	4.45	400.67 (23.68)	0.17
500 ng/mL	21	502.55 (25.09)	0.51	480.49 (24.72)	-3.9
1000 ng/mL	21	1034.33 (48.72)	3.43	974.44 (59.57)	-2.56
1500 ng/mL	21	1542.74 (52.95)	2.85	1451.3 (83.16)	-3.25

** Pool # 10 omitted (see text for additional information)*

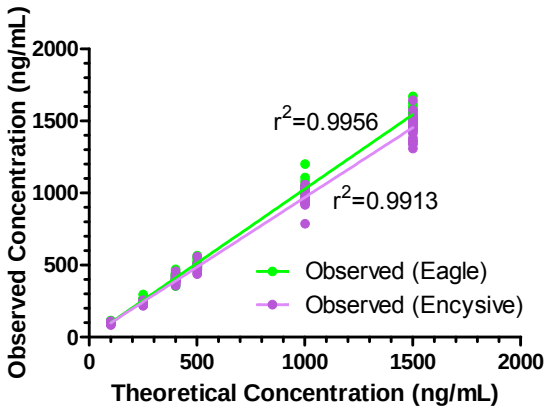


Figure 1: Relationship between theoretical and observed argatroban concentrations for Encysive's RLD and Eagles RTU
Pool # 10 omitted (see text for additional information)

A reviewer generated analysis of the 90% confidence intervals (CI_{90}) of the ratios of geometric means between Encysive's RLD and Eagles RTU for unadjusted observed aPTT, PT, and TT at clinically relevant argatroban concentrations showed that all of the CI_{90}'s were within the equivalence range between 0.9 and 1.11 that was defined by the applicant (Table 4). Again, data from plasma pool # 10 were omitted from these analyses for reasons stated above. These results are consistent with an analysis CI_{90}'s of unadjusted data submitted, in summary, by the applicant as part of a 6/3/09 amendment.

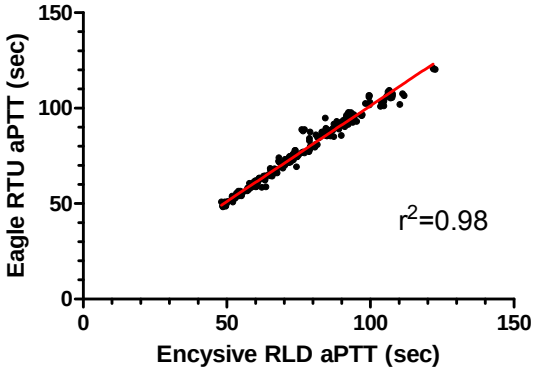
Table 4: Reviewer analysis of CI_{90} of the ratios of geometric means between Encysive's RLD (n=21*)and Eagles RTU (n=21*) for unadjusted observed aPTT, PT, and TT at clinically relevant argatroban concentrations

Argatroban Conc. (µg/mL)	Product	Mean (CV)	Ratio	CI_{90}
aPTT (sec)				
0.25	Eagle RTU	56.7 (9.7)	1.011	1.005,1.016
	Encysive's RLD	56.1 (9.7)		
0.5	Eagle RTU	68.7 (10.3)	1.009	1,1.018
	Encysive's RLD	68.1 (9.6)		
1	Eagle RTU	86.2 (9.9)	1.016	1.006,1.025
	Encysive's RLD	84.9 (10.5)		
1.5	Eagle RTU	98.5 (9.3)	1.023	1.008,1.039
	Encysive's RLD	96.4 (11.5)		
PT (sec)				
0.25	Eagle RTU	14.7 (5.4)	1.008	1.003,1.013
	Encysive's RLD	14.6 (5.6)		
0.5	Eagle RTU	16.8 (6.8)	1.005	0.999,1.012
	Encysive's RLD	16.7 (6.8)		
1	Eagle RTU	21.6 (7.8)	1.026	1.018,1.035
	Encysive's RLD	21.0 (8.4)		
1.5	Eagle RTU	25.9 (8.6)	1.021	1.013,1.03
	Encysive's RLD	25.4 (9.2)		
TT (sec)				
0.1	Eagle RTU	59.1 (6.9)	1.032	1.013,1.051
	Encysive's RLD	57.3 (7.8)		
0.25	Eagle RTU	109.8 (8.3)	1.052	1.038,1.066
	Encysive's RLD	104.3 (7.1)		

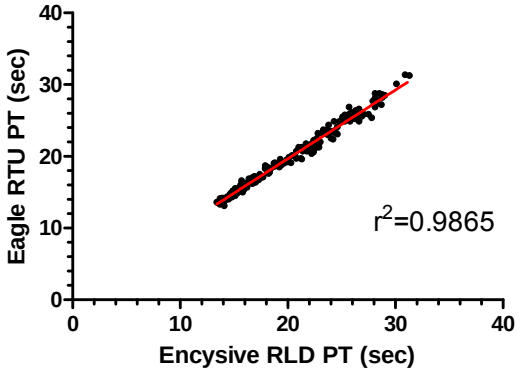
0.4	Eagle RTU	159.5 (9.1)	1.048	1.027,1.069
	Encysive's RLD	151.9 (6.8)		
0.5	Eagle RTU	181.4 (8.9)	1.044	1.024,1.065
	Encysive's RLD	173.6 (7.6)		
**Pool # 10 omitted (see text for additional information)*				

This conclusion was confirmed by examining the apparent relationship between these coagulation parameters for both formulations (Figure 2). This relationship was also consistent for the individual pools with the exception of pool #22 (aPTT, r^2=.90401). This discrepancy appears to result from divergence between the formulations at the three highest aPTT values. However, since the individual #22 pool relationship between both formulations for both PT & TT and the remaining aPTT values were consistent with the overall assessment, the reviewer deems this to be likely the result of technical error and not clinically relevant.

A



B



C

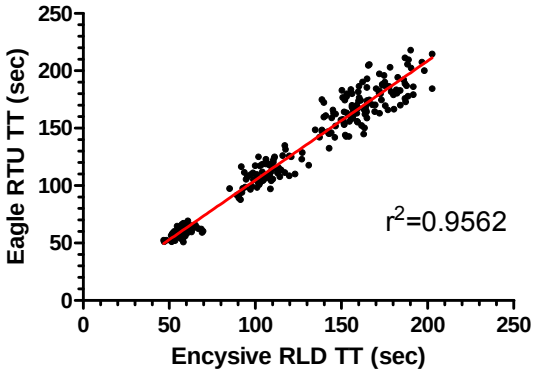
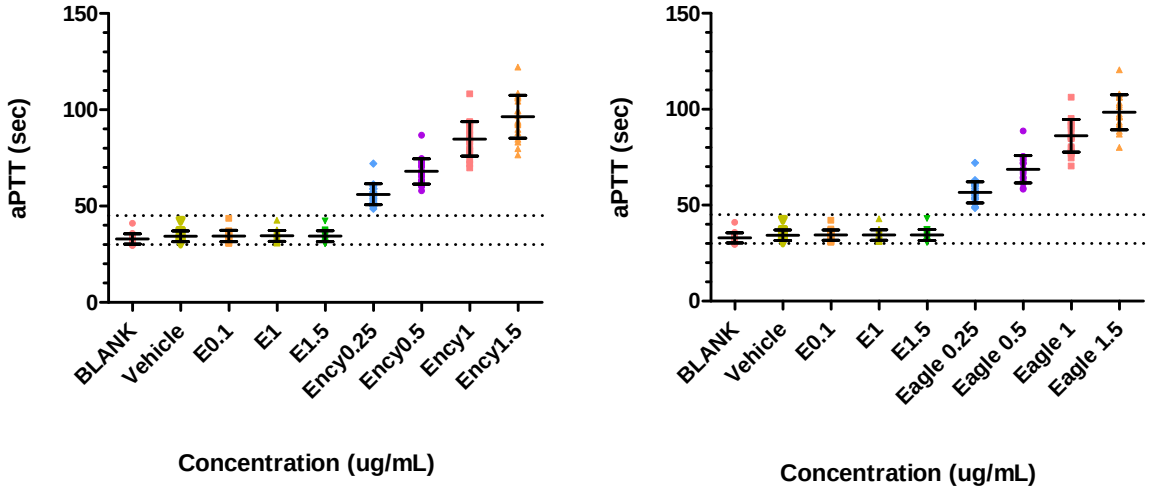


Figure 2: Relationship between Encysive's RLD and Eagle's RTU for aPTT (A), PT (B), and TT (C)

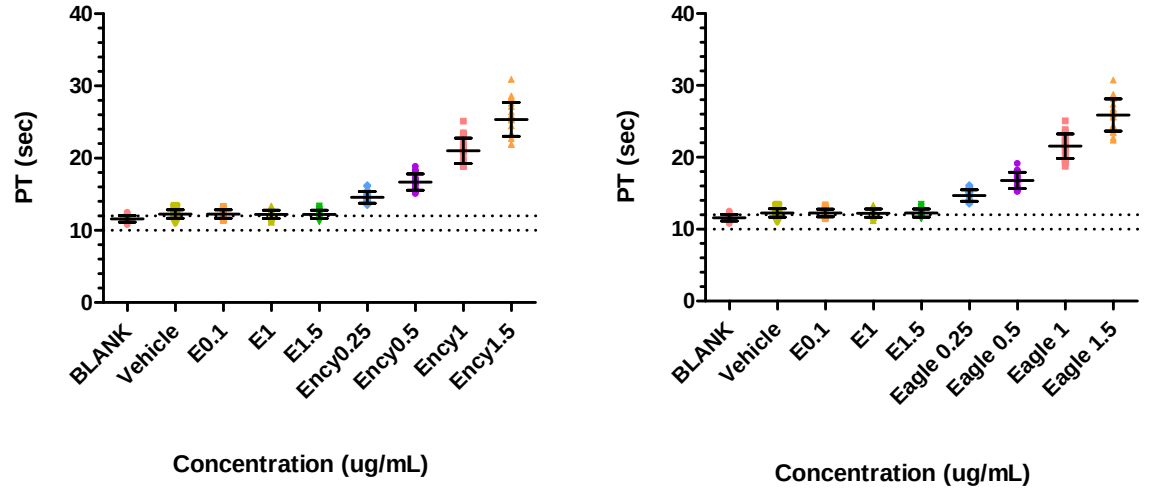
Pool # 10 omitted (see text for additional information)

No obvious clinically relevant confounding effects were noted from a reviewer analysis of blank, vehicle alone, or excipient alone when compared to argatroban containing samples for both Encysive's RLD and Eagle's RTU at the argatroban concentrations studied (Figure 3).

A



B



C

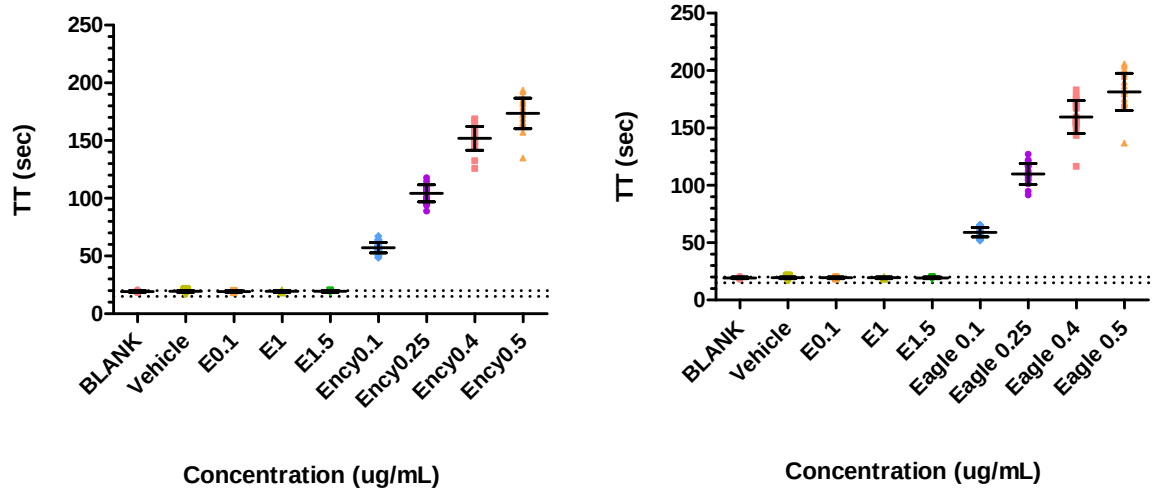


Figure 3: Comparison of mean ± SD aPTT (A), PT (B), and TT (C) for blank, vehicle alone, excipient alone, and argatroban containing samples for both Encysive's RLD and Eagle's RTU at clinically relevant concentrations

1. *Legend: E0.1=excipient alone 0.1 µg/mL; E1= excipient alone 1 µg/mL; E1.5= excipient alone 1.5 µg/mL*
2. *Horizontal lines represent the generally accepted normal range for the respective coagulation parameter*
3. *Pool # 10 omitted (see text for additional information)*

In addition, no obvious clinically relevant confounding effects were noted from a reviewer analysis of gender for both Encysive's RLD and Eagle's RTU at the argatroban concentrations studied. The percent difference between females and males was within ±10% (Table 5). Variability is likely attributed to technical error given the variability is relatively consistent between the formulations. There was a trend suggesting higher TT in males for both formulations, but this difference is not likely to be clinically relevant.

Table 5: Comparison of mean aPTT , PT, and TT by gender for both Encysive's RLD and Eagle's RTU at clinically relevant concentrations

Dose (ug/mL)	Product	Mean APTT (sec)		%diff	Mean PT (sec)		%diff	Mean TT (sec)		%diff
		Female	Male		Female	Male		Female	Male	
0.1	Eagle							56.6	61.3	-7.7
0.1	Encysive							56	58.4	-4.1
0.25	Eagle	56.6	56.7	-0.2	14.7	14.7	0.5	103.9	115.3	-9.9
0.25	Encysive	56	56.2	-0.3	14.7	14.5	1.6	100.7	107.6	-6.4
0.4	Eagle							152.1	166.2	-8.5
0.4	Encysive							148.8	154.7	-3.8
0.5	Eagle	68.3	69.1	-1.1	17	16.6	2.2	173	189.2	-8.6
0.5	Encysive	68.4	67.7	1	16.8	16.5	1.8	169.6	177.2	-4.3
1	Eagle	85	87.2	-2.4	21.7	21.4	1.7			
1	Encysive	85	84.7	0.3	21.4	20.6	3.7			
1.5	Eagle	97.5	99.3	-1.8	26.3	25.5	3.2			
1.5	Encysive	95.5	97.3	-1.9	25.9	24.9	4			

Pool # 10 omitted (see text for additional information)

Therefore, a reviewer analysis of the applicant's raw data has provided sufficient evidence to adequately demonstrate an *in vitro* bridge between Eagle's RTU and the innovator using comparative effect on aPTT, PT, and TT.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Not applicable.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Concentration of Eagle RTU and prepared Encysive's RLD admixture were determined by validated high performance liquid chromatography – tandem mass spectrometry (HPLC/MS/MS) assay (Table 6).

Table 6: Assay methodology

Equipment	LC/MS/MS	API 4000 with Shimadzu Prominence HPLC
	Chromatography	Reverse phase
	Column	XBridge Shield RP 18
Standards and Reagents	Argatroban (b) (4)	Overall Purity: 97.1%
	Diclofenac Sodium USP (Internal Standard)	Overall Purity: ~ 100%
	Blank Human Plasma (sodium citrate)	(b) (4)
HPLC conditions:	Mobile phase:	10mM Ammonium acetate pH 4.0 : Acetonitrile (40:60)
	Column Temperature	40°C
	Flow rate:	0.4 mL/min
	Run Time	4 minutes
	Injection volume:	10 µL

Source: Adapted from Applicant report SAI-VR08121

Argatroban was extracted from human plasma using precipitation extraction procedure. Diclofenac Sodium was used as an Internal Standard (IS). The extracted samples were analyzed using reverse-phase liquid chromatography and the analytes were detected using tandem MS detection. Validation results are provided in Table 7. Twelve independent blank lots were screened for possible interference of matrix with the analyte and internal standard. No interference was observed at the retention time of analyte and internal standard. Recovery was outside of the ± 15% range for the MedQC sample (984.6 ng/mL), but the overall validation is acceptable given the results of the other parameters. Therefore, this assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."

Table 7: Validation parameters for the Argatroban LC/MS/MS method

Analytes	Argatroban
Internal standard (IS)	Diclofenac Sodium USP
Method description	Precipitation
Limit of quantitation (nglmL)	19.2 ng/mL (LLOQ)
	2461.5 ng/mL (ULOQ)
Average recovery of Argatroban (%) (Low , Med, High QC)	86.2, 82.4, 86.5
Average recovery of IS (%)	101.7
Standard curve concentrations (ng/mL)	19.2, 38.5, 76.9, 153.8, 307.7, 615.4, 1230.7, 2461.5
QC concentrations (ng/mL)	19.2, 54.2, 984.6, 1969.2
QC Intraday precision range (%)	Day 1: 2.3 to 3.1
	Day 2: 1.7 to 2.6
	Day 3: 1.3 to 3.5
QC Intraday accuracy range (%)	Day 1: 94.8 to 99.1
	Day 2: 100.7 to 102.7
	Day 3: 97.9 104.1
QC Interday precision range (%)	1.6 to 4.1
QC Interday accuracy range (%)	98.3 to 101
Sensitivity (%)	100.3
Intra batch accuracy (%)	1.2 to 1.3
Intra batch precision (%)	99.7 to 101.3
Bench-top stability (hrs)	6 hours @ room temperature
Maximum batch size	No instrument drift evident
Stock stability (days/hours)	6 hours @room temperature Argatroban & IS 14 & 27 days refrigerated for Argatroban & IS, respectively
Processed stability (hrs)	143 hours @ 4^{o}C 7 hours room temperature
Freeze-thaw stability (freeze-thaw cycles)	4 freeze-thaw cycles
Long-term storage stability (days)	-20^{o}C for 14 days
Dilution integrity	3938.4 ng/mL diluted 2 & 10 fold
Selectivity	No interfering peaks noted in blank plasma samples

Source: Adapted from Applicant report SAI-VR08121

Assessment of aPTT was accomplished using the Dade-Behrng BCScl instrument to obtain a photo-optical measurement of the time to clot. Assessment of PT was accomplished using the Dade-Behrng BCScl instrument to obtain a photo-optical measurement of the time to clot after the addition of thromboplastin and calcium chloride. Assessment of TT was accomplished using the Dade-Behrng BCScl instrument to obtain a photo-optical measurement time to clot after human thrombin is mixed with the patient plasma sample.

All assays were validated in the same manner. Validation parameters investigated include: Method Comparability, Instrumental Precision, and Linearity (Table 8). The sponsor also reports Method Precision, but this is based on 04-09 data and is addressed in Section 2.5.2.1.

Table 8: Validation parameters for the Argatroban LC/MS/MS method

Experimental Parameter	Instrument	Validation Result		
		aPTT	PT	TT
Comparability	BCS #1 vs BCS #2	r=0.9727	r=0.9998	r=0.9613
Accuracy	BCS #1	ND	ND	ND
	BCS #2	ND	ND	ND
Instrument precision (CV_{normal} / CV_{high}) - within run	BCS #1	0.5% / 0.7%	1.7% / 3.1%	1.2% / ND
	BCS #2	3.1% / 1.3%	0.8% / 3.1%	1.5% / ND
Instrument precision (CV_{normal} / CV_{high}) - between run	BCS #1	1.2 % / 2.9 %	2.2 % / 6.2 %	2.5 % / NR
	BCS #2	NR/ NR	NR/ NR	NR/ NR
Linearity	Not specified	nonlinear	linear	nonlinear
NR= Not reported; ND=Not determined				

Source: Adapted from Applicant's report for study 04-09 Section 18.8

The reviewer disagreed with the Applicant's position that comparability to a previously used coagulometer/reagent system serves as a substitute for accuracy determination in this bridging study. Demonstrating that the applicants assay is accurate is a key factor in determining the reliability of the data reported in study 04-09 and the conclusion of whether an acceptable bridge to the Encysive's RLD was demonstrated. The reviewer communicated this concern to the applicant in an October 13, 2009, information request. While the applicant did not formally assess accuracy of these assays under study conditions it was able to provide accuracy data from daily quality control (QC) samples of the laboratory for these analyzers for the reported study time period (Table 9). While this is not ideal, the reviewer finds these results adequate to support the findings of study 04-09.

Table 9: Accuracy results based on the Applicant's reported daily laboratory QC results from study days

Test	Days (n) BCS#1/BCS#2	Plasma	Expected (sec)	Mean Observed (sec) BCS#1/BCS#2	Mean Acurracy (%) BCS#1/BCS#2
PT	39/41	NC	11.9	13.0/12.9	109.4/108.6
	39/42	HC	25.3	27.9$/27.7#	110.3/109.3
aPTT	42/41	NC	34.1	34.8/34.8	102.2/102.5
	42/42	HC	94.4	95.5/96.2	101.1/101.9
TT	33/6	NC	21.5	22.5*/21.8	104.4/101.2
	ND	HC	ND	ND	ND

ND=Not determined; $ 10% outside ± 15%; # 7% outside ± 15%; * 3% outside ± 15%;
Source: Adapted from the Applicant's 10/26/09 submission to FDA pursuant to an information request

The reviewer disagrees with the Applicant's position that linearity may be assumed based on difference plots of linear vs. nonlinear estimates over a range of concentrations based on NCCLS guidelines. Forcing an obvious nonlinear relationship into a linear one is inconsistent with the guidance "Bioanalytical Method Validation." Despite this the reviewer does not consider this a deficiency since the purpose of this analysis was to develop a method to created "adjusted" observed data in trial 04-09 which has been deemed inappropriate by the reviewer (see Section 2.5.2.1).

The between run aPTT, PT and TT instrument precision analysis from the BCS Analyzer S/N 261869 (BCS#2) was part of the applicant's reported validation method yet the results are omitted from the final report without justification. Demonstrating that the two instruments used in the study are similar with regard to between day precision and the TT assay is precise at CPP are key factors in determining the reliability of the data reported in study 04-09 and the conclusion of whether an acceptable bridge to the Encysive's RLD was demonstrated. The reviewer communicated this concern to the applicant in an October 13, 2009, information request. In its 10/26/09 response to FDA, the Applicant

reported that these raw data "could not be located." The applicant proposed using precision data from daily QC samples of the laboratory for these analyzers for the reported study time period. The QC between run instrument precision (CV_{normal} / CV_{high}) for BCS #2 was 1.3/4.0 (PT), 1.0/2.1 (aPPT), and 3.8/ND (TT). While this is not ideal, the reviewer finds these results are adequate to support the finding of study 04-09.

Potential confounding factors such as hemolysis or lipemia was addressed by making these exclusion criteria for the 04-09 study.

2.6.2 Which metabolites have been selected for analysis and why?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Please see the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette and the approved product labeling for the Reference Listed Drug NDA 20-883 (See Section 4.5).

2.6.4 What bioanalytical methods are used to assess concentrations?

See Section 2.6.1

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See Section 2.6.1. The calibration curve consists of a control blank, a zero standard and eight non-zero calibration standards covering a concentration range 19.230 to 2461.485 ng/mL. The range is appropriate for the expected concentrations used in the bridging study 04-09.

A linear, weighted regression ($1/x^2$) was chosen to represent the peak area ratio response of Argatroban (analyte) to Diclofenac Sodium (Internal Standard). The correlation coefficient (r) for calibration curves obtained during the validation ranged from calibration curves obtained during validation were 0.9995 to 0.9998. This appears consistent with the guidance "Bioanalytical Method Validation.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Section 2.6.1

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

See Section 2.6.1

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

See Section 2.6.1 regarding the HPLC/MS/MS assay

Regarding the coagulation assays, the applicant conducted a freeze-thaw study where pooled plasma samples spiked with Test Drug or Reference Drug or Vehicle were assayed either within 4 h of spiking or within 4 hours being thawed after freezing for 72 h at -80^{o}C.

The applicant's adjustment of observed data in its analysis was deemed inappropriate for the same reasons stated in Section 2.5.2.1. However, a reviewer generated

analysis of observed values showed a mean percent difference of approximately ±5% for the theoretical compared to the observed aragatroban concentrations for both products at the 0.25 and 0.5 µg/mL concentrations and less than ±9% for the 1.5 µg/mL concentration. While the difference observed in the later concentration is not ideal the reviewer deems it acceptable for this freeze-thaw study.

Therefore, assuming the theoretical concentrations, a reviewer generated analysis of observed values showed a mean percent difference of less than ±10% (in most cases less than ±5%) between the fresh and frozen/thawed aPTT, PT, and TT measurements for both the Eagle RTU and the Encysive's RLD formulations. Based on this analysis the reviewer agrees with the applicants conclusion that the freeze thaw conditions studied did not result in a clinically relevant change in the coagulation measurement for either the Eagle RTU or Encysive's RLD formulations.

2.6.4.5 What is the QC sample plan?

Quality Control (QC) samples at four different concentration levels corresponding to LLOQQC 19.230ng/mL, LQC 54.153ng/mL, MQC 984.594ng/mL and HQC 1969.188 ng/mL were analyzed with every precision and accuracy assay batch. Quality control samples were intermittently spread throughout a batch to monitor instrument drift.

There was no QC plan submitted for the coagulation assays.

3 Detailed Labeling Recommendations

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

4.1.2 Patient Product Labeling

None submitted

4.2 Individual Study Reviews

4.2.1 Study 0409: *In Vitro* Bridging Study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: An *In Vitro* Bridging Study Comparing Argatroban Injection RTU (1 mg/mL, Eagle Pharmaceuticals, Inc.) to Argatroban Injection (100 mg/mL, GlaxoSmithKline), on Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and Thrombin Time (TT) over the possible Therapeutic Ranges in Pooled Male and Pooled Female Human Plasma

Study period: 2/24/09– 3/12/09

Reviewer Comments:

- The reviewer finds the applicant's "adjustment" of observed aPTT, PT, and TT using linear or polynomial equation as unsubstantiated. This adjustment of observed data significantly confounded the analysis making the applicant's conclusions, as reported, not sufficient to adequately demonstrate an in vitro bridge between Eagle's RTU and the innovator using comparative effect on aPTT, PT, and TT.
- A lofty, yet acceptable, degree of consistent technical error in the accurate and precise preparation of stock and spiking solutions was noted by the reviewer and should be further evaluated by the applicant as a quality assurance issue.
- Plasma pool #10 was noted to have erroneous results based on the probable spiking of these samples with a bulk spiking solution that was incorrectly labeled and contained a 50-fold higher argatroban concentration than was labeled. This labeling error was disclosed by the applicant only after an information request from the reviewer regarding the consistency of these data.
- Applicant reported numerous data transcription errors in the original dataset and provided a revised report in June 2009. A revised dataset was not provided by the applicant, but was updated by the reviewer.
- Applicant failed to assess accuracy as part of its validation of the coagulation assays, failed to report instrument precision for one of the two devices used to measure the coagulation parameters, and instrument precision analysis for the "abnormally high plasma" (CPP) samples for the TT assay.

2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Eagle Pharmaceuticals, Inc.</td></tr>
<tr><td colspan="2">Name of Investigational Product: Argatroban Injection RTU (1 mg/mL)</td></tr>
<tr><td colspan="2">Name of Active Ingredient:
Argatroban is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate</td></tr>
<tr><td colspan="2">Title of the Study:
An In Vitro Bridging Study Comparing Argatroban Injection RTU (1 mg/mL, Eagle Pharmaceuticals, Inc.) to Argatroban Injection (100 mg/mL, GlaxoSmithKline), on Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and Thrombin Time (TT) over the possible Therapeutic Ranges in Pooled Male and Pooled Female Human Plasma</td></tr>
<tr><td colspan="2">Objectives:
To conduct an in-vitro bridging study comparing Argatroban Injection RTU (1 mg/mL, Eagle Pharmaceutical, Inc.) to Argatroban Injection (100 mg/mL, Glaxo SmithKline), on Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and Thrombin Time (TT) over the possible therapeutic ranges in Pooled Male and Pooled Female Human Plasma.</td></tr>
<tr><td colspan="2">Methodology:
Pooled human plasma (11 pools for each gender, 22 pools total) were spiked with different levels of Test Drug, Reference Drug, their respective placebo formulations or vehicle (saline). Spiked plasma samples (0.6 mL) were transferred to labeled assay tubes for aPTT, PT, and TT analysis (assayed in triplicate). In addition, 0.5 mL of the plasma sample was removed from each tube and transferred to a labeled tube for argatroban quantitation.</td></tr>
<tr><td colspan="2">Study Center (s):</td></tr>
<tr><td>Clinical Laboratory:
Emory Healthcare Systems</td><td>Analytical Laboratory:
(b) (4)</td></tr>
<tr><td>Study Dates:
Initiated: February 24, 2009
Last Sample Analyzed: March 12, 2009</td><td>Phase of Development:
This is a In Vitro Comparability Study</td></tr>
<tr><td colspan="2">Principal Investigator:
James Ritchie, PhD</td></tr>
<tr><td colspan="2">Test Drug, Manufacturer, and Lot Number:
Argatroban Injection RTU (1 mg/mL)
Eagle Pharmaceuticals, Inc.
Batch # J80091, Date of Manufacture Feb. 2008</td></tr>
</table>

Reference Drug, Manufacturer, and Lot Number:
Argatroban Injection (100 mg/mL)
GlaxoSmithKline
Lot # C366043, Expiration Date May 2010

Vehicle, Manufacturer, and Lot Number:
Sodium Chloride for Injection USP 0.9%
Baxter Healthcare Corp.
Lot # C730283, Expiration Date July 2009

Test Drug Placebo, Manufacturer, and Lot Number
Eagle Pharmaceuticals, Inc.
Batch Number VPL8011, Date of Manufacture September 2008

Statistical Analysis Methods (See Statistical Analysis Plan for details, Appendix 18.1):

Sample Size: The study sample size was chosen based on the assumption that the standard deviation would be 0.20 seconds or less for all 3 parameters. With a total of 18 subjects per group the study would have at least 80% power to reject the null hypothesis of the test and the reference formulations non-equivalence using the two 1-sided t-test at the 0.05 significance level for each test. Therefore, this study required a minimum of 22 evaluable subjects, 11 each from each gender (i.e., 22 evaluable pooled plasma samples). Since each plasma pool contained plasma from 2 volunteers of the same gender, at least 44 volunteers (22 males and 22 females) were recruited in order to obtain 11 evaluable pooled plasma samples per gender.

Analysis Population: It was planned to perform all analysis on both the Intent-to-Treat population (all samples collected, n=22) and the Per Protocol population (samples met all inclusion/exclusion criteria). All subjects met the inclusion/exclusion criteria; thus the ITT and the PP populations were identical, therefore the analyses were performed only once on the ITT population.

Analysis Methods: Primary (aPTT and PT) and secondary (TT) endpoints were summarized using descriptive statistics. Summary statistics, including the formulation-dose specific geometric mean of responses, coefficients of variation, and the ratio of the geometric means of test and reference formulations, were calculated for aPTT, PT and TT and were presented separately for males and females. Because there was a difference between the observed and expected plasma concentration of argatroban in the samples, all analyses used was on an adjusted response where if the difference between the observed and the expected levels of the concentration of Argatroban exceeded 5% (negatively or positively) for a particular plasma sample, the observed response was adjusted (i.e., dose normalized) to the observed concentration of Argatroban. Under the assumption that the observed response for aPTT, PT or TT was proportional to the expected concentration of Argatroban, the following linear regression model of response on the observed dose was fitted for each subject where $Y = a + bX$, and Y was the observed response at given dose, X was the observed dose of the sample. After the intercept and the slope were estimated for each subject for each formulation, and the adjusted response was calculated as: Adjusted response = [(a + b*expDose) / (a + b*obsDose)] x Observed response. Where the expDose was the expected concentration and obsDose was the observed dose of the sample.

The results were evaluated for outlier and influential observations, effect of gender, and the effect of excipients. Equivalence of the two formulations was conducted utilizing a Mixed Model Analysis to carry out the Two One-Sided Test (TOST) and the results reported as the estimated paired differences between the two drug products means and the associated 90% confidence intervals for log-transformed aPTT, PT and TT measures. At a given dose, in vitro equivalence between test and reference

formulations or between the control and placebo doses of the test and reference formulations was declared if the upper and lower bounds of the aPTT, PT and TT ratio's 90% confidence interval ranged from 90% to 110%. Additionally, overall equivalence between the control and placebo doses (excipients) of Argatroban Injection RTU (1 mg/mL, Eagle Pharmaceutical, Inc.) or Argatroban Injection RTU (100 mg/mL, GlaxoSmithKline) was declared if equivalence was demonstrated using activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT), and Thrombin Time (TT) at all 3 excipient concentrations (0.10, 1.0, and 1.5µg/mL). Finally, overall equivalence between Argatroban Injection RTU (1 mg/mL, Eagle Pharmaceutical, Inc.) and Argatroban Injection (100 mg/mL, GlaxoSmithKline), was declared if equivalence was demonstrated using activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT) at all 4 Argatroban concentrations (0.25, 0.5, 1.0, and 1.5 µg/mL); and using Thrombin Time (TT) at all 4 Argatroban concentrations (0.1, 0.25, 0.4 and 0.5 µg/mL).

Results:

There were no observations that met the outlier/influential value criteria. Six samples from 1 subject (subject 10, sample number 15 to 20 treated with GSK argatroban dose 0.10 to 1.5 µg/mL) were excluded from the analysis because the observed concentration of argatroban found in those samples were more than 10 times of calibration ranges.

aPTT: The differences between male and females were not statistically significant in any of the tested groups for the Eagle formulation. For the GSK formulation in the Argatroban 1.5 µg/mL group female aPTT mean value was statistically lower than male (P = 0.0297). The difference between male and female was not statistically significant in all other tested groups.

PT: No gender effect was observed for any dose of the GSK Reference Drug but the female PT mean value was observed to be statistically higher than the male value at the highest dose (1.5 µg/mL) for the Eagle product (P = 0.0330).

TT: For TT parameter the gender effect was highly significant for both formulations and in all tested groups with females having lower TT values than males.

The effects of excipients on the aPTT, PT and TT parameters were small; the mean difference, expressed as the ratios of geometric means, was less than or equal to 2% between the control and the placebo groups for the Eagle formulation and was less than or equal to 6% for the GSK formulation. All 90% confidence intervals of the ratios were within the range of 90% to 110%.

The results of equivalence analysis are provided in Synopsis Table 1. The statistical analyses results indicated that the 2 formulations of argatroban were equivalent using the criteria of 90% to 110% for all 3 parameters (aPTT, PT and TT) in all tested groups.

Results: (Continued)

Synopsis Table 1 Results of the Equivalence Analyses Between the Test (EAGLE) and the Reference (GSK) Formulations for Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT), and Thrombin Time (TT) using Adjusted Data

Group	Ratios of Geometric Means (Eagle / GSK) [90% Confidence Intervals][1]		
	aPTT (%)[2]	PT (%)[2]	TT (%)[2]
Blank/Control	104.65 [103.75 , 105.55]	105.87 [105.25 , 106.49]	100.49 [100.06 , 100.92] #
Excipient 0.10 µg/mL	99.73 [99.39 , 100.07]	99.93 [99.48 , 100.38]	99.59 [98.38 , 100.82] #
Excipient 1.00 µg/mL	99.80 [99.46 , 100.14]	99.96 [99.38 , 100.55]	99.71 [99.23 , 100.18][3] #
Excipient 1.50 µg/mL	100.24 [99.84 , 100.64]	100.10 [99.63 , 100.58]	99.45 [98.82 , 100.08] #
Argatroban 0.10 µg/mL	NA	NA	100.25 [98.16 , 102.38] €
Argatroban 0.25 µg/mL	99.84 [99.16 , 100.52]	100.04 [99.72 , 100.37]	100.88 [98.86 , 102.95] ¥
Argatroban 0.40 µg/mL	NA	NA	101.35 [99.00 , 103.75] €
Argatroban 0.50 µg/mL	99.44 [98.55 , 100.34]	99.51 [98.81 , 100.21]	100.83 [99.31 , 102.38][4] ¥
Argatroban 1.00 µg/mL	99.07 [97.84 , 100.30]	100.70 [99.84 , 101.56]	NA
Argatroban 1.50 µg/mL	99.51 [98.04 , 101.00]	99.85 [98.63 , 101.08]	NA

[1] Estimates and corresponding 90% Confidence Intervals were derived from a mixed effects model on the natural log-transformed parameter for repeated measures. Models included gender as a fixed effect, formulation and subjects within each formulation were specified as random and repeated measures, respectively and the covariance matrix of FAO (2) was used.
[2] Gender effect was not a statistically significant covariate for parameters of aPTT and PT but was a significant covariate for the TT parameter at all dose groups. #: P<0.001, ¥: P<0.01, €: p<0.05.
[3] FA0(2) covariance structure produced an estimated G matrix that was not positive definite. This was fixed by using the UN structure instead of FA0(2).
[4] Fitted model has an estimated G matrix that was not positive definite with either FA0(2), CSH or UN covariance structures. Results shown are for the UN structure.

Conclusion:
The statistical analysis results indicated that the Argatroban Injection RTU (1 mg/mL) manufactured by Eagle Pharmaceuticals was equivalent with the Argatroban Injection manufactured by GSK in this in-vitro bridging study at argatroban concentrations of 0, 0.25, 0.50, 1.0, and 1.50 µg/mL for aPTT and PT and at the argatroban concentrations of 0, 0.10, 0.25, 0.40, and 0.50 µg/mL for TT using equivalence criteria of 90% to 110%. Additionally, there was no difference between the two excipient formulations detected.

4.3 Cover sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-434	Brand Name	Argatroban Injection
OCPB Division (I, II, III)	5	Generic Name	Argatroban Injection
Medical Division	OND/OODP/DMIHP	Drug Class	Direct thrombin inhibitor
OCPB Reviewer	Joseph A. Grillo, Pharm.D.	Indication(s)	
		• As an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. • As an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).	
OCPB Team Leader	Young Moon Choi, Ph.D.	Dosage Form	RTU Solution for intravenous use (50 mg/50 mL & 100 mg/mL)
Clinical MO	Froozeh Alvandi, MD	Dosing Regimen	
		• HIT/HITTS: 2 mcg/kg/min, administered as a continuous infusion then adjust to steady-state aPTT is 1.5 to 3 times baseline. • PCI: 25 mcg/kg/min and a bolus of 350 mcg/kg and adjusted based on ACT monitoring.	
Date of Submission	3/27/2009	Route of Administration	Intravenous
Estimated Due Date of OCPB Review	11/27/2009	Sponsor	Eagle Pharmaceuticals, Inc
PDUFA Due Date	1/27/2010	Priority Classification	Standard Review
Division Due Date	12/27/2009		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			Not sufficient. This issue was communicated to the applicant
Tabular Listing of All Human Studies	N/A			
HPK Summary	N/A			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	4	4	
I. Clinical Pharmacology				
Mass balance:	N/A			
Isozyme characterization:	N/A			
Blood/plasma ratio:	N/A			
Plasma protein binding:	N/A			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	N/A			
multiple dose:	N/A			
Patients-				
single dose:	N/A			
multiple dose:	N/A			
Dose proportionality -				
fasting / non-fasting single dose:	N/A			
fasting / non-fasting multiple dose:	N/A			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	N/A			
In-vivo effects of primary drug:	N/A			
In-vitro:				

Subpopulation studies -				
ethnicity:	N/A			
gender:	N/A			
pediatrics:	N/A			
geriatrics:	N/A			
renal impairment:	N/A			
hepatic impairment:	N/A			
PD:				
Phase 2:	N/A			
Phase 3:	N/A			
PK/PD:				
Phase 1 and/or 2, proof of concept:	N/A			
Phase 3 clinical trial:	N/A			
Population Analyses -				
Data rich:	N/A			
Data sparse:	N/A			
II. Biopharmaceutics				
Absolute bioavailability:	N/A			
Relative bioavailability -				
solution as reference:	N/A			
alternate formulation as reference:	N/A			
Bioequivalence studies -				
traditional design; single / multi dose:	N/A			
replicate design; single / multi dose:	N/A			
Food-drug interaction studies:	N/A			
Dissolution:	N/A			
(IVIVC):	N/A			
Bio-wavier	X			
BCS class	N/A			
III. Other CPB Studies				
Genotype/phenotype studies:	N/A			
Chronopharmacokinetics	N/A			
Pediatric development plan	X			
In vitro PD bridge study	X	4	4	
Literature References	X	33	33	
Total Number of Studies		41	41	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	Yes	
Comments sent to firm ?	X	FDA provided the applicant with an information request on 5/19/09 regarding missing information regarding validation methods for the coagulation assays, missing data sets regarding concentrations of argatroban in sample, spiking and stock solutions, and justification for adjusting observed coagulation data to account for technical error in argatroban sample preparation.
QBR questions (key issues to be considered)	Should the (21CFR§320.22(d)3) waiver be granted thus waving the requirement for the submission of evidence obtained *in vivo* measuring the bioavailability or demonstrating the bioequivalence of the drug product because the data submitted shown the product to meet an *in vitro* test that has been correlated with *in vivo* data. Is the applicant's method adjusting observed coagulation data to account for technical error in argatroban sample preparation adequately justified? How does the loft degree of technical error in the preparation of sample, spiking and stock solutions effect the applicant's conclusions from the bridging study?	
Other comments /info not included above	Submitted under Section 505(b)(2) of the FD&C Act.	
Primary reviewer Signature and Date	/s/ Joseph A. Grillo, Pharm.D.	
Secondary reviewer Signature and Date	/s/ Young Moon Choi, Ph.D.	

4.4 Referenced OCP Reviews

60 pages have been Withheld in Full immediately following this page as Duplicative of another review for NDA 20883 which can be found at www.fda.gov

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

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

/s/

JOSEPH A GRILLO
01/20/2010

YOUNG M CHOI
01/20/2010
I concur.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-434	Brand Name	Argatroban Injection
OCPB Division (I, II, III)	5	Generic Name	Argatroban Injection
Medical Division	OND/OODP/DMIHP	Drug Class	Direct thrombin inhibitor
OCPB Reviewer	Joseph A. Grillo, Pharm.D.	Indication(s)	
		• As an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. • As an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).	
OCPB Team Leader	Young Moon Choi, Ph.D.	Dosage Form	Solution for intravenous use
Clinical MO	Minh Ha Tran, MD	Dosing Regimen	
		• HIT/HITTS: 2 mcg/kg/min, administered as a continuous infusion then adjust to steady-state aPTT is 1.5 to 3 times baseline. • PCI: 25 mcg/kg/min and a bolus of 350 mcg/kg and adjusted based on ACT monitoring.	
Date of Submission	9/26/2008	Route of Administration	Intravenous
Estimated Due Date of OCPB Review	4/21/2009	Sponsor	Eagle Pharmaceuticals, Inc
PDUFA Due Date	7/27/2009	Priority Classification	Standard Review
Division Due Date	"May 2009"		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	N/A			
HPK Summary	N/A			
Labeling	X			• Not properly formatted for PLR
Reference Bioanalytical and Analytical Methods	--			• Not submitted for bridging study
I. Clinical Pharmacology				
Mass balance:	N/A			
Isozyme characterization:	N/A			
Blood/plasma ratio:	N/A			
Plasma protein binding:	N/A			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	N/A			
multiple dose:	N/A			
Patients-				
single dose:	N/A			
multiple dose:	N/A			
Dose proportionality -				
fasting / non-fasting single dose:	N/A			
fasting / non-fasting multiple dose:	N/A			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	N/A			
In-vivo effects of primary drug:	N/A			
In-vitro:				
Subpopulation studies -				
ethnicity:	N/A			
gender:	N/A			

pediatrics:	N/A			
geriatrics:	N/A			
renal impairment:	N/A			
hepatic impairment:	N/A			
PD:				
Phase 2:	N/A			
Phase 3:	N/A			
PK/PD:				
Phase 1 and/or 2, proof of concept:	N/A			
Phase 3 clinical trial:	N/A			
Population Analyses -				
Data rich:	N/A			
Data sparse:	N/A			
II. Biopharmaceutics				
Absolute bioavailability:	N/A			
Relative bioavailability -				
solution as reference:	N/A			
alternate formulation as reference:	N/A			
Bioequivalence studies -				
traditional design; single / multi dose:	N/A			
replicate design; single / multi dose:	N/A			
Food-drug interaction studies:	N/A			
Dissolution:	N/A			
(IVIVC):	N/A			
Bio-wavier	X			
BCS class	N/A			
III. Other CPB Studies				
Genotype/phenotype studies:	N/A			
Chronopharmacokinetics	N/A			
Pediatric development plan	X			• Waiver requested
In vitro PD bridge study	X	1		• Validation not submitted • Raw data not submitted • Data analysis does not test equivalence • Underpowered?
Literature References	X	40		
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	No	Important information regarding the validity of the assays used in the bridging study omitted (communicated to sponsor 10/22/08). In its 11/13/2008 response, the sponsor stated that the validation will be completed retroactively. The sponsor further stated that samples of the stock & spiking solutions of Argatroban were not collected. The sponsor will repeat the bridging study so that the concentrations of the stock & spiking solutions can be collected and reported. We recommend refuse to file until complete data & validation from the bridging study is submitted. The sponsor reported it plan to complete this by 1/6/2009.

Comments sent to firm ?	X	1. FDA requests the sponsor submit the following ASAP or identify where this information is located in the NDA if they believe they submitted it: a. Assay validation report & data for assessment of aragtroban concentration in stock and spiked solutions from the bridging study found in section 4.1.2 of the NDA. b. Assay validation report for PT assay (manufacturer's instructions are not sufficient) from the bridging study found in section 4.1.2 of the NDA. c. Assay validation report for aPTT assay (manufacturer's instructions are not sufficient) from the bridging study found in section 4.1.2 of the NDA. d. Assay validation report for thrombin generation assay (manufacturer's instructions are not sufficient) from the bridging study found in section 4.1.2 of the NDA. e. All raw data from bridging study found in section 4.1.2 of the NDA in SAS file transfer format. 2. Labeling is not in correct PLR format 3. Electronic submission of labeling not properly rendered in adobe acrobat (e.g., can not cut and paste from the file). In addition, a version of the labeling in MSWord should be submitted.
QBR questions (key issues to be considered)	Should the (21CFR§320.22(d)3) waiver be granted thus waving the requirement for the submission of evidence obtained *in vivo* measuring the bioavailability or demonstrating the bioequivalence of the drug product because the data submitted shown the product to meet an *in vitro* test that has been correlated with *in vivo* data.	
Other comments or information not included above	Submitted under Section 505(b)(2) of the FD&C Act.	
Primary reviewer Signature and Date	/s/ Joseph A. Grillo, Pharm.D.	
Secondary reviewer Signature and Date	/s/ Young Moon Choi, Ph.D.	

CC: NDA 22-291, HFD-850(Electronic Entry or Lee), HFD-160(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)

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

/s/

Joseph Grillo
11/18/2008 12:02:18 PM
BIOPHARMACEUTICS

Young-Moon Choi
11/18/2008 12:05:12 PM
BIOPHARMACEUTICS