CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201743Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 201-743	**Reviewer:** Angelica Dorantes, Ph.D.	
Submission Date:	April 13, 2010	**Supervisor:** Patrick J. Marroum, Ph.D.	
Division:	OODP/DHP	**Date of Review:**	January 26, 2011
Sponsor:	Sandoz, Inc.		
Trade Name:	ARGATROBAN INJECTION in 5% Dextrose, for intravenous infusion only	**Type of Submission:** 505 (b)(2) NDA	
Generic Name:	Argatroban Injection		
Indication:	Argatroban is an anticoagulant indicated for: 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/strengths	Injectable Solution/1 mg/ mL (each 125 mL vial contains 125 mg of Argatroban)		
Route of Administration	Intravenous Infusion		
Type of Review:	**BIOWAIVER REQUEST**		

SUBMISSION:

On April 13, 2010, Sandoz submitted NDA 201-743 for Argatroban Injection (in Dextrose) 1 mg/ml 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 innovator 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).

Reviewer Comment:
Please note that the original owner of NDA 20-833 for Argatroban Injection was Encysive Pharmaceuticals, Inc. However in 2008, the ownership was transferred to Pfizer, the current owner of this NDA *(DARRTS document dated 12/17/2008)*

BIOPHARMACEUTICS:

Formulation: The formulation proposed by Sandoz is a ready-to-use Argatroban solution at a concentration of 1 mg/mL (125 mg of Argatroban in 125 mL single-use vials in 5% Dextrose). The composition of the formulation and the function of each component are detailed in the next Table.

Composition of the Formulation for Argatroban Injection Proposed by Sandoz			
Ingredients	**Quantity per unit**	**Percentage**	**Function**
Argatroban	1 mg	(b) (4)	Active ingredient
Dextrose Anhydrous	50 mg		(b) (4)
Sorbitol	3 mg		
Water for Injection	q.s. 1 mL		
(b) (4)			
	1 ml	100%	

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

Comparative Formulations of the Proposed Product and Reference product			
Ingredients	**Sandoz**	**RLD- Pfizer**	
	Argatroban Injection in Dextrose, 1 mg/mL	Argatroban Injection diluted in Dextrose, 1 mg/mL	Argatroban Injection as Supplied, 100 mg/mL**
Argatroban	1 mg	1 mg	100 mg
Dextrose Anhydrous			(b) (4)
Dehydrated Alcohol*			
(b) (4)			
Water for Injection	q.s. 1 mL	q.s. 1 mL	q.s. 1 mL
(b) (4)			

*The Sandoz formulation does not include Dehydrated Alcohol, at the level of 1 mg/mL, alcohol is no required to solubilize the API.
** The RLD is supplied in 2.5 mL solution in single-use vials at a concentration of 100 mg/mL.

The RLD, ARGATROBAN Injection solution (100 mg/mL) needs to be diluted in 0.9% Sodium Chloride for Injection, or Dextrose for Injection, or Lactated Ringer's for Injection to a final concentration of 1 mg/mL prior to infusion. However, the Sandoz's proposed Argatroban product is **a ready-to-use solution** at a concentration of 1 mg/mL (125 mg of Argatroban in 125 mL single-use vials in 5% dextrose). The only difference between Sandoz's product and the RLD is the lack of dehydrated alcohol in the Sandoz formulation.

The absence of alcohol influences the osmolality of the product. Sandoz conducted some physical tests for their proposed Argatroban Injection product and for the RLD product from Pfizer and the results are presented in the next table. Sandoz mentions that their product's osmolality values for each formulation are within the iso-osmotic range.

Comparative Characteristics of the Formulations

Physical Tests	**Sandoz** **Product in 5% Dextrose**	**Pfizer** **RLD diluted in 5% Dextrose Solution**
pH	6.2	6.9
Density at 20°C		(b) (4)
Viscosity at 20°C		
Osmolality		

BIOWAIVER REQUEST:

In this NDA submission, Sandoz is requesting that the Agency waives the CFR's requirement to provide in vivo bioavailability/bioequivalence (BA/BE) data for their product. To support their biowaiver request, Sandoz provided information showing that the proposed Argatroban Injection in Dextrose, 1 mg/ml 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.

Additionally, based on 21 CFR 320.22 (d)(3) and as agreed upon in the PreNDA meeting held on May 27, 2008 (IND 101,957), to demonstrate similarity between their proposed Argatroban Injection product and the listed product, Sandoz conducted an *in vitro* bridging study (**Study No. 286**) designed to evaluate the *in vitro* equivalence of the anticoagulant pharmacodynamic (PD) activity between the Argatroban Sandoz's and Pfizer's products. The pharmacodynamic 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 Sandoz's or Pfizer's Argatroban products. The data from this in vitro equivalence bridging study were evaluated by Dr. Lillian Zhang from the Office of Clinical Pharmacology. In her review, Dr. Zhang concluded that the in vitro equivalence study bridging the proposed Sandoz's Argatroban product and the Argatroban Pfizer's RLD product was acceptable (*for details refer to Dr. Zhang's review dated 1/26/11 in DARRTS*).

Reviewer Comments:

1. ***The proposed product contains the same active ingredient as the reference listed drug product.***
2. ***The proposed Argatroban Injection in Dextrose product contains no additional inactive ingredients. The only difference is the lack of dehydrated alcohol.***
3. ***Argatroban Injection is a dosage form intended solely for IV administration and is a true solution.***
4. ***The route of administration, dosage form and indications of the proposed product are the same as the RLD product.***
5. ***The in vitro pharmacodynamic activity (aPTT, PT, and TT) of the proposed Argatroban Injection is similar to the activity of the RLD product.***
6. ***The results from the in vitro equivalence study (Study No. 286) support the pharmacodynamic similarity of the proposed Argatroban Injection in Dextrose and the RLD product, therefore the 21 CFR 320.22(d)(3) requirements of evidence of BA/BE have been met.***

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.
*Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in §320.21(c), may request FDA to waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application., FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), **(d),** or (e) of this section.*
***(d)** For certain drug products, bioavailability may be measured or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product if the drug product meets one of the following criteria:*
***(3)** The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.*

RECOMMENDATION:

The Office of New Drugs Quality Assessment (ONDQA)-Biopharmaceutics has reviewed the information included in NDA 22-485 for Argatroban Injection in Dextrose, 1 mg/ml. Based on the provided information, ONDQA-Biopharmaceutics considers that Sandoz's request for a waiver of the CFR's requirement to provide in vivo BA/BE data to support the approval of their product is acceptable and the biowaiver for the proposed Argatroban Injection in Dextrose, 1 mg/ml is granted.

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cc: NDA 201-743

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/s/

ANGELICA DORANTES
01/29/2011

PATRICK J MARROUM
01/31/2011

Clinical Pharmacology Review

NDA	**201-743**
Submission Type	Original, 505(b)(2)
Submission Date	13 April 2010, 27 May 2010, 12 October 2010
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 1mg/mL of argatroban (each 125 mL vial contains 125 mg of argatroban)
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	Sandoz
OCP Reviewer	Hua Lillian Zhang, Ph.D.
OCP Team Leader	Julie Bullock, Pharm.D.
OCPB Division	Division of Clinical Pharmacology 5
ORM Division	Division of Drug Oncology Products

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1 EXECUTIVE SUMMARY

This 505(b)(2) application submitted by Sandoz Inc. is for Argatroban Injection, 1 mg/mL in single-dose vials. The Sandoz Argatroban Injection has the same active ingredient, same dosage form, and route of administration as the innovator drug approved by the FDA under NDA 20-883 (Encysive Pharmaceuticals, Inc.). The innovator's ARGATROBAN Injection is the reference listed drug (RLD) for this 505(b)(2) application.

In support of a waiver of *in vivo* bioequivalence (BE), the applicant conducted an *in vitro* bridging study to assess *in vitro* equivalence of the anticoagulant pharmacodynamic (PD) activity between Sandoz's and Encysive's products. 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 Sandoz's or Encysive's argatroban product. The application was limited by variability in the assay runs and the absence of argatroban concentration data in the stock and spiking solutions. Despite these limitations, the results of the data analyses indicate that an acceptable *in vitro* bridge between Sandoz's product and Encysive's RLD 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 Zhang, Ph.D. Reviewer Division of Clinical Pharmacology 5	Julie Bullock, Pharm.D. Team Leader Division of Clinical Pharmacology 5

Cc: DDOP: CSO - E Ali Ibrahim; 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 RLD for this 505(b)(2) application, was approved by the FDA under NDA 20-883 (Encysive Pharmaceuticals, Inc) 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.

Sandoz's proposed Argatroban product is a ready-to-use solution at a concentration of 1 mg/mL (125 mg of argatroban in 125 mL single-use vials) in 5% Dextrose for Injection. See Table 1 for the formulation comparison between Sandoz's product and Encysive's RLD product. The applicant is seeking approval for all the RLD indications.

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

Ingredients	Sandoz	RLD- Encysive	
	Argatroban Injection in Dextrose, 1 mg/mL	Argatroban Injection diluted in Dextrose, 1 mg/mL	Argatroban Injection as Supplied, 100 mg/mL*
Argatroban	1 mg	1 mg	100 mg
Dextrose anhydrous	50 mg	50 mg	N/A
Dehydrated Alcohol	N/A	4 mg	(b) (4)
Sorbitol	3 mg	3 mg	
Water for Injection	q.s. 1 mL	q.s. 1 mL	q.s. 1 mL
(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, Sandoz conducted an *in vitro* "bridge" study (Study No. 286) to assess the equivalence of the anticoagulant (PD) activity between Sandoz's Argatroban Injection to the RLD. The PD effects were measured by determining aPTT, PT, and TT in pooled donor human plasma spiked with clinically relevant concentrations of argatroban from either the Sandoz or RLD product. The results of the data analyses show that all of the 90% confidence intervals (CI_{90}) of the ratios of geometric means between Sandoz and the RLD for observed aPTT, PT, and TT at clinically relevant argatroban concentrations were within the equivalence range between 90 and 111% that was 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?

Sandoz's Argatroban Injection is a ready-to-use solution intended for intravenous administration.

2.2 GENEARL BIOPHARMACEUTICS

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

Sandoz's ready-to-use Argatroban solution is prepared at a concentration of 1 mg/mL (125 mg of argatroban in 125 mL single-use vials) in 5% Dextrose for Injection. The composition of the formulation and the function of each component are detailed in Table 2.

Table 2. Argatroban Injection in Dextrose, 1 mg/mL

Ingredients	Quantity per unit	Percentage	Function
Argatroban	1 mg	(b) (4)	Active ingredient
Dextrose anhydrous	50 mg		(b) (4)
Sorbitol	3 mg		
Water for Injection	q.s. 1 mL		
			(b) (4)

The only difference between Sandoz's product and the RLD is the absence of dehydrated alcohol in Sandoz's. Refer to Section 1.4 for the quantitative and qualitative comparisons between Sandoz's to-be-marketed product and the RLD. The active ingredient, dosage form, and route of administration for Sandoz's product are the same as 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, Sandoz conducted an *in vitro* "bridge" study (Study No. 286) to assess the equivalence of the anticoagulant (PD) activity between the Sandoz's product and the RLD. Briefly, blood samples were collected from 48 healthy subjects (24 males and 24 females) and were pooled for a total of six pools. The spiking solutions of either the RLD or Sandoz's product were prepared at 50 and 20 µg/mL using 5% Dextrose for Injection. An aliquot of each pooled human plasma (5.4 mL) was spiked with spiking solutions of each product, their placebo solutions, or the dextrose vehicle. Five plasma concentrations of argatroban at 0.25, 0.5, 1, 3 and 5 µg/mL were prepared and tested for PT and aPTT. Concentrations up to 1 µg/mL were tested for TT. Concentrations of argatroban in plasma were determined by a validated LC/MS/MS method (see Section 2.3).

Equivalence of the Sandoz's product to the RLD was to be demonstrated if the $CI_{90\%}$ of the ratio of their geometric means for aPTT, PT, and TT fell within the acceptance criteria of 90-111%.

Results

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

The applicant generated results are presented in Table 3.

Table 3. Ratios and 90% Confidence Intervals of PD Parameters Between Sandoz's Product and the RLD

	Ratio (CI_{90})
PT	
Test 1* *vs.* RLD	97.9 (95.0 – 100.9)
Test 2 *vs.* RLD	99.1 (96.1 – 102.1)
Test 3 *vs.* RLD	101.8 (98.8 - 104.9)
aPTT (sec)*	
Test 1 *vs.* RLD	100.5 (97.4 – 103.6)
Test 2 *vs.* RLD	102.1 (99.0 – 105.3)
Test 3 *vs.* RLD	106.5 (103.2– 109.8)
TT (sec)*	
Test 1 *vs.* RLD	98.8 (96.8 - 100.7)
Test 2 *vs.* RLD	102.5 (100.5 - 104.5)
Test 3 *vs.* RLD	101.8 (99.8 – 103.8)

*Test 1: Sandoz's batch no. 1250804
Test 2: Sandoz's batch no. 1260804
Test 3: Sandoz's batch no. 1270804

The results indicate that the CI_{90} of the ratios of geometric means for the PD parameters between the Sandoz's product and the RLD fell within the acceptance criteria of 90% -111% for equivalence as defined by the applicant. However, this analysis was limited by variability in the assay runs as argatroban plasma concentrations were less than 85% of the target concentrations for some of the samples (see Table 4 below).

Table 4. Samples Whose Actual Concentration < 85% of the Target

Formulation	Plasma Pool	Target Conc (µg/mL)	% Target
Test 1	3	3	75%
Test 2	3	3	70%
Test 1	4	3	63%
Test 2	4	3	71%
Test 1	3	5	74%
Test 2	3	5	74%
Test 1	4	5	72%
Test 2	5	5	70%

Test 1: Sandoz's batch 1250804
Test 2: Sandoz's batch 1260804

The exact reason(s) for the lower than targeted concentration for those samples cannot be identified as the argatroban concentrations in the spiking solutions of each product were not determined by the applicant.

The applicant's data analysis represents the comparison of the PD effect of each Sandoz's batch to the RLD. It would be more clinically meaningful to compare the PD effect of the Sandoz's product as a whole to the RLD at clinically relevant concentrations of argatroban. Therefore, by pooling the data from all the three batches, the reviewer re-analyzed the data and compared the PD results between the Sandoz's and the RLD at each argatroban concentration tested.

The reviewer generated analysis confirmed that the CI_{90} of the ratios of geometric means for the PD parameters between the Sandoz's product and the RLD were within the equivalence range between 90% and 111% as defined by the applicant (see Table 5). Although a quality assurance issue was identified for which the plasma concentrations of some samples were less than 85% of the target concentrations, this is unlikely to impact the conclusion that the two products were equivalent in terms of PD effects.

Table 5. Comparison of the PD Effect of Sandoz to RLD Based on *In Vitro* Coagulation Parameters

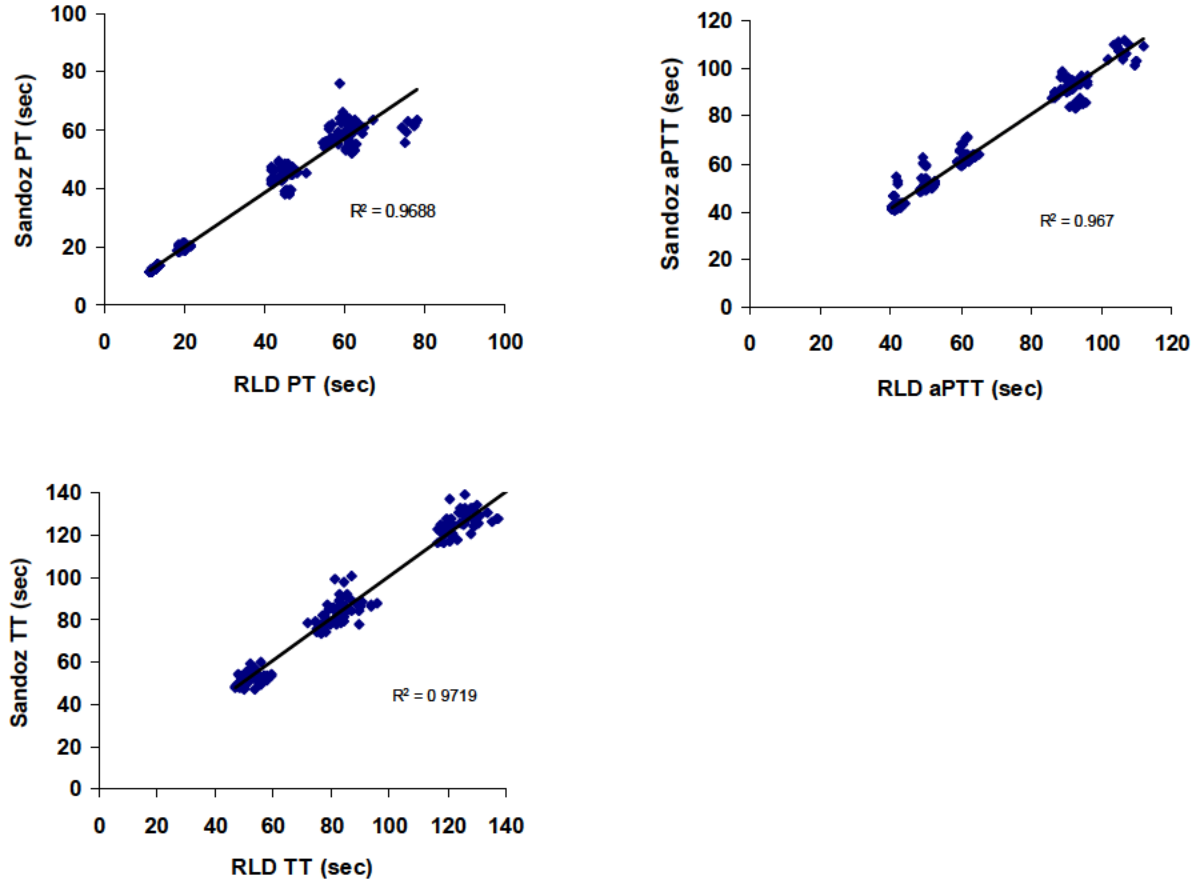
Conc (µg/mL)	Product		
	Sandoz's	RLD	Ratio (CI_{90})
	PT (sec)*		
0.25	11.7 (2.4)	11.6 (1.6)	100.5 (99.8 -101.1)
0.5	13.4 (2.7)	13.3 (2.2)	100.7 (100.0 – 101.5)
1	19.8 (4.4)	19.7 (3.7)	100.2 (98.9 – 101.5)
3	43.9 (7.6)	44.8 (4.2)	98.0 (96.1 – 99.95)
5	59.1 (7.0)	61.9 (9.2)	95.4 (93.0 – 98.0)
	aPTT (sec)*		
0.25	42.9 (6.0)	41.8 (2.4)	102.7 (101.2 – 104.2)
0.5	51.6 (5.7)	50.3 (2.5)	102.6 (101.1 – 104.0
1	62.9 (4.5)	61.6 (2.5)	102.2 (101.0 – 103.4)
3	91.2 (4.5)	91.7 (3.0)	99.5 (98.3 – 100.7)
5	107.0 (5.4)	106.3 (2.5)	100.7 (98.8 – 102.6)
	TT (sec)*		
0.25	52.1 (5.5)	51.9 (6.1)	100.4 (98.5 – 102.3)
0.5	83.5 (7.0)	82.6 (6.1)	101.1 (99.1 – 103.3)
1	126.2 (4.3)	125.1 (4.9)	100.9 (00.4 – 103.4)

*Geo-mean (CV%)

Reviewer Generated Regression of Sandoz versus RLD Data for PT, aPTT, & TT

The individual PD data obtained for all the samples at tested concentrations were used to perform regressions of Sandoz (y) against RLD (x). The data, including the r regression coefficient, are shown in Figure 1.

Figure 1. Regression of Sandoz *versus* RLD Data for PT, aPTT, & TT



In general the data for the three coagulation parameters tested between the Sandoz's product and the RLD were correlated well across the concentration range except that the data seems to be more scattered at the higher concentration tested, especially for PT. For aPTT, a few samples had early detection error at 5 µg/mL.

Reviewer generated analysis of the effect of excipients on PT, aPTT, & TT for Sandoz versus RLD

To evaluate the excipients effect on the PD parameters, the reviewer calculated the $CI_{90\%}$ of the geometric mean ratios between the Sandoz's placebo solution and the blank control sample, and between the Sandoz's placebo solution and the RLD placebo solution, respectively. The results indicate that the anticoagulant effects of the Sandoz's excipients were equivalent to that of the blank control sample and the RLD's excipients.

Table 6. Effect of Excipients on PT, aPTT, & TT

	PT (sec)*	Ratio (CI_{90}) Sandoz/Blank	Ratio (CI_{90}) Sandoz/RLD
Dextrose vehicle only	10.3 (1.4)		
Blank (plasma only)	10.1 (1.2)		
RLD placebo	10.4 (2.0)		
Sandoz placebo	10.4 (1.8)	102.4 (101.4 -103.3)	99.5 (98.6 – 100.4)
	aPTT (sec)*		
Dextrose vehicle only	26.8 (1.3)		
Blank (plasma only)	26.2 (1.5)		
RLD placebo	27.6 (4.5)		
Sandoz placebo	27.2(2.2)	104.1 (100.7 - 103.7)	98.6 (97.2 - 100.1)
	TT (sec)*		
Dextrose vehicle only	18.5 (2.0)		
Blank (plasma only)	18.5 (2.5)		
RLD placebo	17.9 (1.6)		
Sandoz placebo	18.0 (1.9)	97.4 (96.3 – 98.5)	100.6 (99.4 - 101.7)

*Geo-mean (CV%)

Conclusions
Despite variability in the assay runs and the absence of argatroban concentration data in the stock/spiking solutions of each product, Sandoz's product met the predefined criteria for the PD equivalence to the RLD.

2.3 ANALYTICAL SECTION

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

Argatroban concentrations in plasma were determined by validated high performance liquid chromatography - tandem mass spectrometry (HPLC/MS/MS) assay.

The clotting time measurement was conducted based on the principle of light-scattering. Assessment of PT was accomplished using Sysmex CA-1500 Coagulation Analyzer to obtain a photo-optical measurement of the time to clot. Assessment of aPTT was accomplished using Sysmex CA-1500 Coagulation Analyzer to obtain a photo-optical measurement of the time to clot after the addition of calcium chloride. Assessment of TT was accomplished using Sysmex CA-1500 Coagulation Analyzer to obtain a photo-optical measurement time to clot after human thrombin is mixed with the patient plasma sample.

2.3.2 What bioanalytical methods are used to assess concentrations?

Argatroban was extracted from human plasma using methanol with a dilution procedure. $^{13}C_6$ Argatroban was used as an Internal Standard (IS). The extracted samples were analyzed by an HPCL equipped with an AB/MDS Sciex API 400 mass spectrometer. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. Argatroban was monitored by the *m/z* 509.2 → *m/z* 384.3 transition and $^{13}C_6$-Argatroban was monitored by the *m/z* 515.2 → *m/z* 390.3 transition.

2.3.2.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ ULOQ)? What are the accuracy, precision and selectivity at these limits? What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)? What is the QC sample plan?

Regarding the HPLC/MS/MS assay, the range of the standard concentration curve is 25-5000 ng/mL. The calibration curve was established by a weighted (1/x2) linear regression analysis of peak area ratios of the analyte and IS. Validation summary is presented in Table 7.

Table 7. 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)	0.025
Average recovery of Argatroban (%) (Low , Med, High QC)	97%, 91%, 94%
Average Recovery of IS (% Mean)	89%
Standard curve concentrations (µg/mL)	0.025, 0.050, 0.100, 0.200, 0.500, 1.00, 2.00, 4.00, 5.00
QC concentrations (µg/mL)	0.075, 0.375, 3.75
QC intra-assay precision range (% CV)	0.6 to 6.7
QC intra-assay accuracy range (% bias)	1.3 to 13.6
QC inter-assay precision range (% CV)	1.7 to 5.9
QC inter-assay accuracy range (% bias)	2.7 to 10.8
Bench-top stability (hours)	26 hours @ ambient temperature
Processed stability (hours)	125 hours @ 5°C
Freeze-thaw stability (freeze-thaw cycles)	3 freeze-thaw cycles
Long-term storage stability (days)	13 days @ -80°C
Dilution integrity	up to 50.0 µg/mL diluted 25 fold

With respect to the coagulation assays, the accuracy, precision, and stability of the quality control samples are summarized in Table 8.

Table 8. Validation Parameters for Coagulation Assays

	PT	aPTT	TT
Accuracy (% of the nominal concentrations range)			
Intra-Assay	100.0 – 101.7	99.3 – 101.1	100.0 – 100.02
Inter-Assay	100.8 – 101.7	99.9 – 100.3	100.0 – 100.01
Precision range (% CV)			
Intra-Assay	0.0 – 0.5	0.4 – 0.8	2.5 – 5.7
Inter-Assay	0.6 – 1.1	0.7 – 1.6	2.8 – 3.7
Refrigerator stability (@ 2 - 8° C)	24 hours	24 hours	71 hours
Bench-top stability (ambient temperature)	3 hours	3 hours	5 hours
Freeze-thaw stability (freeze-thaw cycles)	4	4	4
Long-term storage stability (@ - 20° C)	46 days	46 days	6 days

3 DETAILED LABELING RECOMMENDATIONS

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Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**201-743**	**Brand Name**	**Argatroban Injection in Dextrose**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Argatroban**
Medical Division	**OND/OODP/DHP**	**Drug Class**	**A synthetic direct thrombin inhibitor**
OCP Reviewer	**Hua Lillian Zhang, Ph.D.**	**Indication(s)**	**As an anticoagulant for** • **prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS)** • **patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)**
OCP Team Leader	**Julie Bullock, Pharm.D.**	**Dosage Form**	**An intravenous solution containing 1mg/mL of argatroban (each 125 mL vial contains 125 mg of argatroben)**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**HIT/HITTS:** 2 µg/kg/min as a continuous infusion then adjusted to steady-state aPTT being 1.5 - 3 times baseline **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
Date of Submission	**13-April-2010**	**Route of Administration**	**IV**
Estimated Due Date of OCP Review		**Sponsor**	**Sandoz**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**14-February-2011**		

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				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

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single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
In vitro PD bridge study		**1**	**1**	
Literature References				
Total Number of Studies				

Comments:

This is a 505 b (2) submission.

Argatroban Injection in Dextrose developed by Sandoz is a ready to use formulation of the Reference Listed Drug (RLD), ARGATROBAN by Pfizer. The Sandoz product does not contain alcohol and is ready to use at a concentration of 1 mg/mL while the RLD is formulated with alcohol at a concentration of 100 mg/ml which requires dilution to 1 mg/mL prior to use. The dosage and administration route for the Sandoz product are the same as the RLD.

Sandoz conducted an *in vitro* "bridge" study (Study No. 286) to assess the equivalence of the anticoagulant (PD) activity between the Sandoz's product and the RLD formulation. Using PT, aPTT, and

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TT assays, the *in vitro* anticoagulant effect of Sandoz's product was compared to the RLD formulation in pooled donor human plasma.

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			x	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			x	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?		x		Hyperlinks are not available. This makes it difficult to search.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			x	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as			x	

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	described in the WR?				
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Hua Lillian Zhang, Ph.D	02-June-10
Reviewing Clinical Pharmacologist	Date
Julie Bullock, Pharm. D.	02-June-10
Team Leader/Supervisor	Date

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

/s/

HUA ZHANG
01/14/2011

JULIE M BULLOCK
01/25/2011