

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022485Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**BIOPHARMACEUTICS REVIEW**  
Office of New Drugs Quality Assessment

<b>Application No.:</b>	NDA 22-485	<b>Reviewer:</b> Angelica Dorantes, Ph.D
<b>Submission Date:</b>	March 16, 2010	<b>Supervisor:</b> Patrick J. Marroum, Ph.D
<b>Division:</b>	OODP/DHP	<b>Date of Review:</b> December 22, 2010
<b>Sponsor:</b>	Sandoz, Inc.	
<b>Trade Name:</b>	Argatroban Injection	<b>Type of Submission:</b> 505 (b)(2) NDA
<b>Generic Name:</b>	Argatroban Injection (in Sodium Chloride)	
<b>Indication:</b>	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)	
<b>Formulation/strengths</b>	Injectable Solution/1 mg/ mL	
<b>Route of Administration</b>	Intravenous	
<b>Type of Review:</b>	<b>BIOWAIVER REQUEST</b>	

**SUBMISSION:**

On March 16, 2010, Sandoz submitted NDA 22-485 for Argatroban Injection (in Sodium Chloride) 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 NDA 20-833 for ARGATROBAN Injection (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 (250 mg of Argatroban in 250 mL single-use vials) in 0.9% sodium chloride. 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
Sodium Chloride	9 mg		
Sorbitol	3 mg		
Water for Injection	q.s. 1 mL		

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 Sodium Chloride, 1 mg/mL	Argatroban Injection diluted in Sodium Chloride, 1 mg/mL	Argatroban Injection as Supplied, 100 mg/mL
Argatroban	1 mg	1 mg	100 mg
Sodium Chloride	9 mg	9 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

\*The Sandoz formulation does not include dehydrated alcohol. The presence of alcohol is no required to solubilize the API.

The RLD, ARGATROBAN 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. However, the Sandoz's proposed Argatroban product is a ready-to-use solution at a concentration of 1 mg/mL (250 mg of Argatroban in 250 mL single-use vials) in 0.9% sodium chloride. The only difference between Sandoz's product and the RLD is the lack of dehydrated alcohol in the Sandoz formulation.

As presented above, the only difference between the two products is the presence of dehydrated alcohol in the RLD product. The presence 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.

Physical Tests	Sandoz Product	Pfizer RLD diluted in 0.9% Sodium Chloride Solution
pH	6.3	6.2
Density at 20oC		(b) (4)
Viscosity at 20oC		
Osmolality		

#### **BIOWAIVER REQUEST:**

In this NDA submission, Sandoz is requesting that the Agency waives the CFR's requirement to provide in vivo bioavailability/bioequivalence data for their product. To support their biowaiver request, Sandoz provided information showing that the proposed Argatroban Injection (in Sodium Chloride), 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, to demonstrate similarity between their proposed Argatroban Injection product and the listed product, Sandoz conducted an *in vitro* bridging study 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* bridging study were evaluated by Dr. Hua 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 12/17/10 in DARRTS*)

**Reviewer Comments:**

- 1. The proposed Argatroban Injection in Sodium Chloride product contains no additional inactive ingredients. The only difference is the lack of dehydrated alcohol.***
- 2. Argatroban Injection is a dosage form intended solely for IV administration and is a true solution.***
- 3. The results from the *in vitro* equivalence study support the pharmacodynamic similarity of the proposed Argatroban Injection 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:**

ONDQA-Biopharmaceutics has reviewed the information included in NDA 22-485 for Argatroban Injection (in Sodium Chloride), 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 proposed product contains the same active ingredient as the reference listed drug product, 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* BA/BE to support the approval of the proposed Argatroban Injection (in Sodium Chloride) 1 mg/ml, manufactured by Sandoz is granted.

**Angelica Dorantes, Ph. D.**

Biopharmaceutics Team Leader  
Office of New Drugs Quality Assessment

**Patrick J. Marroum, Ph. D.**

Biopharmaceutics Supervisor  
Office of New Drugs Quality Assessment

cc: NDA 22-485, J. Brown

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/s/  
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ANGELICA DORANTES  
12/23/2010

PATRICK J MARROUM  
12/23/2010

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA/BLA Number	22-485	Brand Name	Argatroban Injection
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)	<ul style="list-style-type: none"> <li>As an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS)</li> <li>As an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)</li> </ul>
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	<b>HIT/HITTS:</b> 2 µg/kg/min as a continuous infusion then adjusted to steady-state aPTT being 1.5 - 3 times baseline <b>PCI:</b> 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	16-March-2010	Route of Administration	IV
Estimated Due Date of OCP Review		Sponsor	Sandoz
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	17-January-2011		

***Clin. Pharm. and Biopharm. Information***

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

**Comments:**

This is a 505 b (2) submission.

Argatroban Injection 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

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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
<b>Criteria for Refusal to File (RTF)</b>					
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.
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
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	
<b>Studies and Analyses</b>					
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	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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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			
<b>General</b>					
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.

- Please submit raw data in SAS file transfer format for Study 286.

Hua Lillian Zhang, Ph.D	27-April-10
Reviewing Clinical Pharmacologist	Date
Julie Bullock, Pharm. D.	27-April-10
Team Leader/Supervisor	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HUA ZHANG  
12/20/2010

JULIE M BULLOCK  
12/21/2010

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## Clinical Pharmacology Review

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<b>NDA</b>	<b>22-485</b>
<b>Submission Type</b>	Original, 505(b)(2)
<b>Submission Date</b>	16 March 2010, 01 April 2010, 27 May 2010, 12 October 2010
<b>Brand Name</b>	Argatroban Injection
<b>Generic Name</b>	Argatroban
<b>Indication</b>	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)
<b>Formulation</b>	An intravenous solution containing 1mg/mL of argatroban (each 125 mL vial contains 125 mg of argatroban)
<b>Dosing Regimen</b>	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
<b>Sponsor</b>	Sandoz
<b>OCP Reviewer</b>	Hua Lillian Zhang, Ph.D.
<b>OCP Team Leader</b>	Julie Bullock, Pharm.D.
<b>OCPB Division</b>	Division of Clinical Pharmacology 5
<b>ORM Division</b>	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 reviewer's 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

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Lillian Zhang, Ph.D.

Reviewer

Division of Clinical Pharmacology 5

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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 (250 mg of argatroban in 250 mL single-use vials) in 0.9% sodium chloride. 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 Sodium Chloride, 1 mg/mL	Argatroban Injection diluted in Sodium Chloride, 1 mg/mL	Argatroban Injection as Supplied, 100 mg/mL*
Argatroban	1 mg	1 mg	100 mg
Sodium Chloride	9 mg	9 mg	N/A
Dehydrated Alcohol	N/A	4 mg	(b) (4)
Sorbitol	3 mg	3 mg	(b) (4)
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 reviewer's data analyses show that all of the 90% confidence intervals (CI<sub>90</sub>) 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 0.9 and 1.11 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 GENERAL 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 (250 mg of argatroban in 250 mL single-use vials) in 0.9% sodium chloride. The composition of the formulation and the function of each component are detailed in Table 2.

**Table 2. Argatroban Injection in Sodium Chloride, 1 mg/mL**

Ingredients	Quantity per unit	Percentage	Function
Argatroban	1 mg	(b) (4)	Active ingredient
Sodium Chloride	9 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 0.9% sodium chloride. An aliquot of each pooled human plasma (5.4 mL) was spiked with spiking solutions of each product, their placebo solutions, or the saline 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<sub>90%</sub> 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 <sub>90</sub> )
<b>PT</b>	
Test 1* vs. RLD	106.2 (103.8 - 108.7)
Test 2 vs. RLD	105.5 (103.4 - 107.7)
Test 3 vs. RLD	104.9 (102.7 - 107.2)
<b>aPTT (sec)*</b>	
Test 1 vs. RLD	103.4 (101.0 - 105.9)
Test 2 vs. RLD	102.9 (100.7 - 105.2)
Test 3 vs. RLD	104.7 (102.3 - 107.2)
<b>TT (sec)*</b>	
Test 1 vs. RLD	105.6 (102.8 - 107.4)
Test 2 vs. RLD	102.5 (101.6 - 106.1)
Test 3 vs. RLD	104.9 (102.6 - 107.2)

\*Test 1: Sandoz's batch no. 1220804-121;

Test 2: Sandoz's batch no. 1230804-121;

Test 3: Sandoz's batch no. 1240804-121

The reviewer finds the applicant's data analysis is inappropriate as the applicant excluded those samples whose argatroban plasma concentrations were less than 85% of the target concentrations (see Table 4 below). In addition, the applicant's data analysis represents the comparison of the PD effect of each Sandoz's batch to the RLD rather than the PD effect of the Sandoz's product as a whole to the RLD at clinically relevant concentrations of argatroban, which is more clinically meaningful.

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

<b>Formulation</b>	<b>Plasma Pool</b>	<b>Target Conc (µg/mL)</b>	<b>% Target</b>
RLD 3	1	0.5	84%
RLD 3	6	3	84%
Test 1	3	3	74%
Test 3	3	3	77%
Test 1	4	3	67%
Test 3	4	3	77%
Test 1	5	3	73%
Test 1	6	3	71%
Test 1	3	5	73%
Test 3	3	5	81%
Test 1	4	5	71%
Test 3	4	5	77%
Test 1	5	5	70%
Test 1	6	5	72%

RLD 3: Encysive's batch C417960;  
 Test 1: Sandoz's batch 1220804-121;  
 Test 2: Sandoz's batch 1230804-121;  
 Test 3: Sandoz's batch 1240804-121

By including and pooling the data from all the samples including those whose argatroban plasma concentrations were less than 85% of the target and 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. Despite the fact that the plasma concentrations of some samples were less than 85% of the target concentrations, the reviewer generated analysis showed that all of the CI<sub>90</sub> of the ratios of geometric means for the PD parameters between the Sandoz's product and the RLD were within the equivalence range between 0.9 and 1.11 as defined by the applicant (see Table 5).

The exact reason(s) for the lower than targeted concentration for those samples mentioned above cannot be identified as the argatroban concentrations in the spiking solutions of each product were not determined by the applicant. While this is a quality assurance issue for the applicant, it 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**

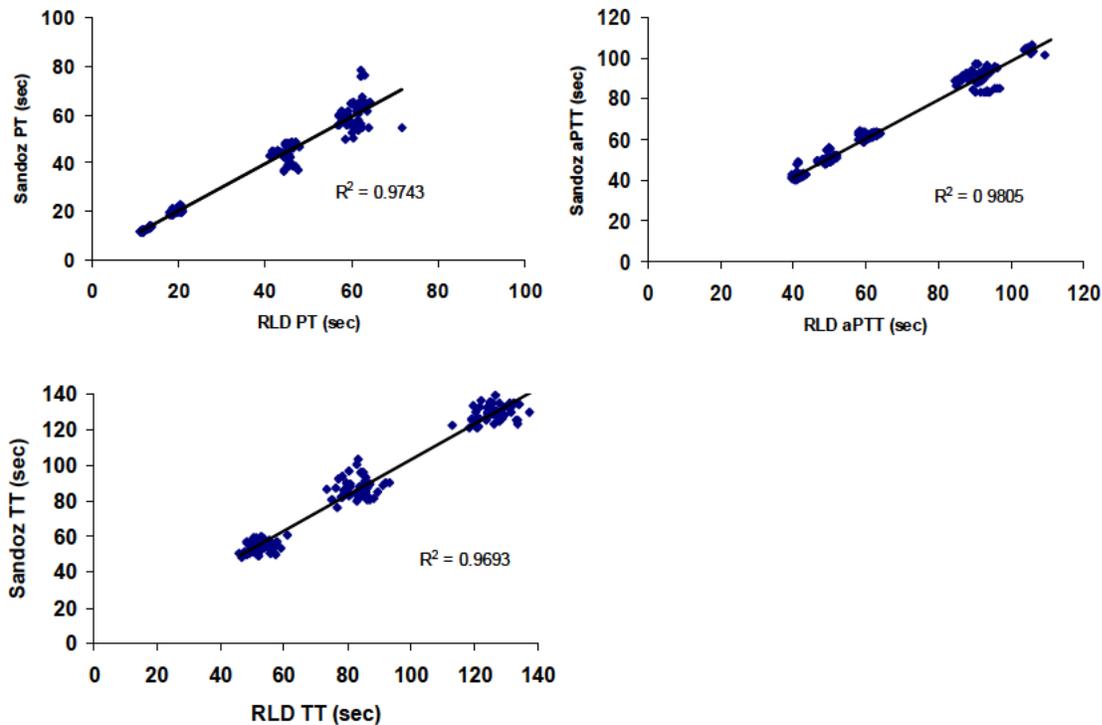
Conc (µg/mL)	Product		Ratio (CI <sub>90</sub> )
	Sandoz's	RLD	
	<b>PT (sec)*</b>		
0.25	11.8 (2.1)	11.7 (1.9)	100.9 (100.3 -101.6)
0.5	13.3 (2.5)	13.4 (2.3)	101.2 (100.4 – 101.9)
1	19.5 (4.6)	20.1 (4.2)	103.3 (101.9 – 104.8)
3	44.9 (7.9)	43.9 (3.9)	97.87 (95.95 – 99.84)
5	60.7 (9.3)	59.8 (4.1)	98.52 (96.29 – 100.8)
	<b>aPTT (sec)*</b>		
0.25	42.5 (3.9)	41.4 (2.3)	102.6 (101.6 – 103.6)
0.5	50.6 (3.0)	49.8 (2.5)	101.6 (100.7 – 102.5)
1	62.1 (2.5)	61.0 (2.8)	101.8 (101.0 – 102.6)
3	90.1 (4.6)	91.2 (3.5)	98.8 (97.5 – 100.1)
5	104.9 (3.1)	107.0 (2.2)	98.1 (96.7 – 99.6)
	<b>TT (sec)*</b>		
0.25	54.1 (5.5)	52.2 (6.1)	103.7 (101.8 – 105.6)
0.5	87.1 (6.0)	83.2 (5.1)	104.7 (102.8 – 106.6)
1	129.6 (3.7)	126.7 (4.3)	102.4 (101.1 – 103.7)

\*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<sub>90%</sub> 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 reviewer generated analysis indicates 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 <sub>90</sub> ) Sandoz/Blank	Ratio (CI <sub>90</sub> ) Sandoz/RLD
Saline vehicle only	10.4 (1.7)		
Blank (plasma only)	10.1 (1.2)		
RLD placebo	10.4 (1.9)		
Sandoz placebo	10.4 (1.6)		
	aPTT (sec)*		
Saline vehicle only	26.6 (1.2)	102.5 (101.5 - 103.6)	99.6 (98.6 - 100.6)
Blank (plasma only)	26.2 (1.5)		
RLD placebo	26.9 (3.0)		
Sandoz placebo	26.9 (1.1)		
	TT (sec)*		
Saline vehicle only	18.6 (2.2)	98.3 (97.2 - 99.40)	100.3 (99.2 - 101.40)
Blank (plasma only)	18.5 (2.4)		
RLD placebo	18.1 (1.3)		
Sandoz placebo	18.2 (1.9)		

\*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. <sup>13</sup>C<sub>6</sub> 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 <sup>13</sup>C<sub>6</sub>-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/x<sup>2</sup>) 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)	<sup>13</sup> C <sub>6</sub> -Argatroban
Method description	Dilution procedure with analysis/detection by LC-MS/MS
Limit of quantization (µg/mL)	0.025 µg/mL (LLOQ); 5000 µg/mL ULOQ
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
Dilution integrity	No significant interference at the retention time and mass transition of argatroban in any of the 10 plasma samples

With respect to the coagulation assays, the accuracy, precision, and stability of the quality control (QC) 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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/s/  
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HUA ZHANG  
12/14/2010

JULIE M BULLOCK  
12/17/2010