

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201743Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 201743/000	Sponsor:	SANDOZ
Org Je:	161		2555 WEST MIDWAY BLVD
Priority:	5		BROOMFIELD, CO 80038
Stamp Date:	14-APR-2010	Brand Name:	ARGATROBAN INJECTION 1 MG/ML
PDUFA Date:	14-FEB-2011	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	16-DEC-2010	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION, INJECTION; ARGATROBAN; 1MG/125ML

FDA Contacts:	T. LAMBERT	Project Manager	301-796-4246
	R. KASLIWAL	Review Chemist	301-796-1386
	J. BROWN	Team Leader	301-796-1652

Overall Recommendation:	ACCEPTABLE	on 09-SEP-2010	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD	on 01-JUN-2010	by M. STOCK	(HFD-320)	301-796-4753

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-JUN-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9615155 FEI: 3000280957
SANDOZ CANADA INC
145 JULES-LEGER STREET
BOUCHERVILLE, QC, CANADA

DMF No: (b) (4) **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-MAY-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-JUL-2010

Decision: ACCEPTABLE

Reason: BASED ON FILE REVIEW

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/s/

NIKOO N MANOCHEHRI-KALANTARI
05/18/2011

NDA 201743

**Argatroban Injection
In 5% Dextrose
1 mg/mL**

**Sandoz Canada Inc.,
Alison Sherwood, c/o Sandoz Inc.,
2555 W. Midway Blvd.,
P.O. Box 446,
Broomfield, CO 80038**

**Ravindra K. Kasliwal, Ph.D.
Division of New Drug Quality Assessment –III
Division of Hematology Products**

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Chemistry Review Data Sheet

1. NDA 201743
2. REVIEW #: 1
3. REVIEW DATE: 13-Jan-2011
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	13-Apr-2010
Amendment (QR)	30-Apr-2010
Amendment (BD)	12-Jul-2010
Amendment (QR)	19-Nov-2010
Amendments (QR and LC)	12-Jan-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Sandoz Canada Inc.
2555 W. Midway Blvd.,
Address: P.O. Box 446
Broomfield, CO 80038

Representative: Alison Sherwood, c/o Sandoz Inc.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Argatroban Injection
- c) Code Name/# (ONDC only): +AGT (b)(4); 1006435 (Sandoz)
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission Priority: S

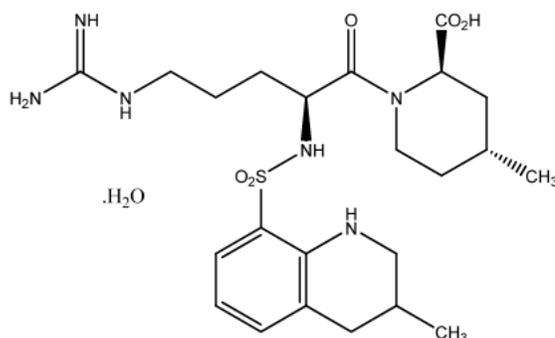
9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Anticoagulant
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 1 mg/mL
13. ROUTE OF ADMINISTRATION:
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(1) 2-Piperidinecarboxylic acid, 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[[(1,2,3,4-tetrahydro-3-methyl-8-quinoliny)lsulfonyl]amino]pentyl]-4-methyl-, monohydrate; (2) (2*R*,4*R*)-4-Methyl-1-[*N*²-[(1,2,3,4-tetrahydro-3-methyl-8-quinolyl)sulfonyl]-*L*-arginyl] pipercolic acid, monohydrate.



Chemical Formula: C₂₃H₃₆N₆O₅S

Molecular Weight: 508.63

Elemental Analysis: C, 54.31; H, 7.13; N, 16.52; O, 15.73; S, 6.30

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Argatroban	3	Adequate	19-Nov-2008	DMF was reviewed by Dr. Mark Sassaman and was found to be adequate.
	III	(b) (4)	(b) (4)	4	NA	NA	NA
	III	(b) (4)	(b) (4)	7, 3	See Micro	See Micro	The DMF describes (b) (4)

Chemistry Review Data Sheet

		(b) (4)		Review	Review	(b) (4) See micro Review for validation assessment.
(b) (4)	III		3	Adequate	19-May-2004	DMF was reviewed by Dr. Rapti Madhurawe for injectable solution and was found to be adequate.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None.

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		Injectable product.
EES	Acceptable	09-Sep-2010	M. Stock, Office of Compliance.
Pharm/Tox	Pending	Pending	Shwu Luan Lee, Ph.D.
Biopharm	Not Applicable		
LNC	Not applicable		Argatroban is an established name not an NME.
Methods Validation	Not Applicable		The analytical methods used are well established methods and a methods validation by FDA labs was not requested.
ODS / DMEPA	There is no trademark proposed. DEMEPA labeling comments were sent to the applicant.	See DMEPA review 13-Dec-2010	Yelena L Maslov
EA	Categorical claim for exemption is justified under 21CFR25.31 (a).	21-Dec-2010	Ravindra K. Kasliwal, Ph.D.
Microbiology	Pending	Pending	Stephen E. Langille, Ph.D.

The Chemistry Review for NDA 201743

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action, provided the microbiology review finds the microbiology related information to be acceptable, for chemistry, manufacturing and controls (CMC) under section 505 of the Act.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The formulation of Argatroban Injection, 1 mg / mL, in 5% Dextrose is based on the information obtained from the outer label and package insert of the Reference Listed Drug (RLD), Argatroban Injection, manufactured by GlaxoSmithKline for Encysive Pharmaceuticals Inc. The qualitative difference between the two formulations is that Dehydrated Alcohol was removed from the Sandoz product to create a ready to use formulation. In the RLD, alcohol was needed to dissolve Argatroban, as the supplied solution contained 100 mg/ml of Argatroban in the supplied solution which was diluted to a 1 mg/ml solution at the site of use. The proposed formulation contains 1 mg/ml of Argatroban and does not need any further dilution.

(b) (4)

The finished Argatroban Injection is a sterile, non-pyrogenic, clear, and colorless to pale yellow isotonic solution. It is supplied in a single-use clear glass vial containing 125 mg of argatroban in 125 mL sodium chloride solution. Each mL contains 1 mg argatroban, 50 mg dextrose, USP, 3 mg sorbitol, NF in water for injection, USP. The pH of the solution is between 3.2 – 7.5

The applicant has submitted 18 months data and has requested a ^(b)₍₄₎-month expiration dating period. However, the data only supports an acceptable expiration dating period of 12-months. Therefore, an **expiration dating period of 12-months is may be approved, when the product is stored between 20°C and 25°C (See USP Controlled Room Temperature) in original container. The approved expiration dating period should be clearly indicated in the action letter.** The solution needs to be protected from light during storage and should not be kept in refrigerator or freezer, as at lower temperature argatroban may precipitate from solution. The labeling submitted on 12-Jan-2011, addresses these issues.

(b) (4)

Argatroban has 4 asymmetric carbons. One of the asymmetric

Executive Summary Section

carbons has an *R* configuration (stereoisomer Type I) and an *S* configuration (stereoisomer Type II). Argatroban consists of a mixture of *R* and *S* stereoisomers in a ratio of approximately 65:35.

The solubility of the API is an important in the manufacturing process as the finished dosage form is a true solution. Argatroban is very slightly soluble in water. Studies performed at Sandoz Canada Inc. (b) (4)

A retest period of (b) (4) months was established by the drug substance manufacturer (b) (4). The Argatroban drug substance is re-tested by Sandoz Canada Inc. at (b) (4) months in line with the manufacturers until the expiration date of the drug substance.

B. Description of How the Drug Product is Intended to be Used

Argatroban Injection has been indicated to be used under two situations. One, it is indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). Second, it is indicated as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

Argatroban is supplied as a ready to use solution for intravenous administration and no further dilutions are required or recommended. For HIT, a maximum of 3 doses are recommend during the procedure (75 mg within one surgery / day of 10 hours). For PCI use, a maximum of 3 doses are recommended during the procedure (560 mg within one surgery / day of 3hours).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for an approval action (provided microbiology finds the product / process to be acceptable for sterilization and endotoxin controls) for chemistry, manufacturing and controls (CMC) based on the following:

- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the Argatroban drug substance. Further the drug Master File (DMF) (b) (4), referencing the drug substance manufacturing and controls, has been assessed to be adequate.
- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
- The referenced drug master files (DMF) are adequate to support the product application.
- The Office of Compliance has recommended that the drug substance and drug product manufacturing facilities are acceptable as of 09-Sep-2009 (see appendix 1).
- There are no outstanding issues with impurities.
- Issues related to carton and container labels have been adequately resolved (submission dated 12-Jan-2011)

III. Administrative

A. Reviewer's Signature

Ravindra K Kasliwal, Ph.D.

B. Endorsement Block

Chemist Name / Date: Ravindra K. Kasliwal, Ph.D.

Chemistry Team Leader Name / Date: Sarah Pope-Miksinski, Ph.D.

Project Manager Name / Date: Tu-Van Lee Lambert

C. CC Block: See DARRTS

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/s/

RAVINDRA K KASLIWAL
01/14/2011

SARAH P MIKSINSKI
01/14/2011

NDA 201743

Argatroban Injection in 5% dextrose

Request for CMC information:

1. Provide updated labels for container and carton that have been updated in a manner similar to “Argatroban Injection in 0.9% Sodium Chloride”, except for the following”
 - Label product as “Argatroban Injection in 5% Dextrose”, and
 - Use a color scheme for the “Argatroban Injection in 5% Dextrose” that is different than the color scheme for the “Argatroban Injection in 0.9% Sodium Chloride”.
2. Provide amended drug product specifications with following changes:
 - Change impurity (b) (4) limits to “<” from “≤”.
 - Report all impurities above 0.1%.
3. Be advised that linear regression analysis of your submitted 18 month long term storage data suggest that the level of impurity (b) (4) may exceed the specification limit of (b) (4) at (b) (4) months (at one sided 95% confidence level) for all three batches. Hence a proposed (b) (4) months expiration dating period for Argatroban Injection in 5% Dextrose does not appear to be supported by the submitted data. The data will, however, support a 12 month expiration dating period.

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/s/

EBLA ALI IBRAHIM
01/03/2011

Initial Quality Assessment (IQA)
Branch II

Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

OND Division: Division of Hematology Products

NDA: **201743**

Applicant: Sandoz Inc., Alison Sherwood, c/o Sandoz Inc., 2555 W. Midway Blvd., P.O. Box 446, Broomfield, CO 80038

Stamp Date: 13-Apr-2010

PDUFA Date: 17-Jan-2010

Trademark: None

Established Name: Argatroban Injection (in Dextrose)

Laboratory Code: +AGT (b)(4); 1006435 (Sandoz)

Dosage Form: Injection solution

Route of Administration: Intravenous Injection

Strength: 1 mg/ mL (125 mL)

Indication: Argatroban is an anticoagulant indicated for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). It is also approved for use during percutaneous coronary interventions in patients who have HIT or are at risk for developing it.

CMC Reviewer: Ravindra K. Kasliwal, Ph.D.

	YES	NO
ONDQA Fileability:	X	
Comments for 74-Day Letter		X

Summary and Critical Issues:

A. Summary

Background Summary

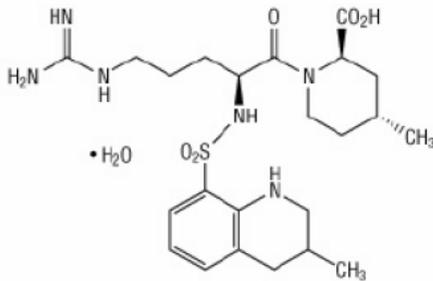
The company has identified a reference listed drug (RLD) for Argatroban Injection, manufactured by GlaxoSmithKline for Encysive Pharmaceuticals Inc. The RLD is supplied as a 2.5 mL solution in single-use vials at a concentration of 100 mg/mL, and contains dehydrated alcohol ((b)(4)), Sorbitol ((b)(4)) in water for injection. This product is diluted with Dextrose solution to a concentration of 1 mg/ mL Argatroban prior to administration. Each milliliters of the diluted RLD contains 50 mg dextrose, (b)(4) dehydrated alcohol, (b)(4) sorbitol in water for injection.

Sandoz has developed and proposed a ready to use formulation of the RLD which reduces the manipulations performed by physicians and nurses. The proposed Sandoz formulation contains Argatroban at a concentration of 1 mg/mL, and contains 50 mg dextrose, 3 mg sorbitol in water for injection. A ready to use formulation allowed the removal of dehydrated alcohol from the formulation (relative to RLD); since it is solely required to increase the solubility of Argatroban in the concentrated form of the RLD (the API is very slightly soluble in water, but sparingly soluble in ethanol).

As the proposed Sandoz formulation is different from the cited RLD in respects that are not allowed in 505(j) applications, a 505(b)(2) application has been submitted.

Drug Substance Summary:

Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine. The chemical name for Argatroban is: 2-Piperidine carboxylic acid, 1-[5-(aminoiminomethyl)amino]-1-oxo-2[[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-, monohydrate Argatroban has 4 asymmetric carbons; three are fixed asymmetry and one has an R configuration (stereoisomer Type I) and an S configuration (stereoisomer type II). Argatroban consists of a mixture of R and S stereoisomers at a ratio of approximately 65:35.



The molecular formula of Argatroban is C₂₃H₃₆N₆O₅S.H₂O. The molecular weight is 526.66. Argatroban is a white, odorless crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ethyl acetate, and ether.

The drug substance is manufactured at (by):

(b) (4)

FEI number: (b) (4); last FDA inspection was held in March, 2009.

The drug substance information has been referenced to (b) (4). A Letter of Authorization (dated 19-Jan-2010) from (b) (4) is provided in Module 1 of the NDA.

The NDA contains detailed impurity characterization data, which should be reviewed for safety and conformance to ICH requirements.

A retest period of (b) (4) months has been proposed by the drug substance manufacturer (b) (4) Sandoz, Inc.

Drug Product Summary: The composition of Argatroban Injection in Dextrose, 1 mg/mL is:

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

The maximum daily dose for Argatroban is 560 mg. This is a 505(b)(2) application and its safety and efficacy are related to the RLD. The reviewer should verify that the differences between this formulation and the RLD do not present potential concerns with respect to therapeutic equivalence.

The solubility of the API is an important characteristic to consider in the manufacturing process as the finished dosage form is a true solution. Argatroban is very slightly soluble in water. Studies performed at Sandoz Canada Inc. demonstrated a solubility of (b) (4)

(b) (4)

(b) (4)

The following facilities are involved in drug product manufacture and testing:

Name and address	Responsibilities	D-U-N-S	Facility Establishment Identifier	cGMP Certification and Debarment certification
Sandoz Canada Inc. 145 Jules-Léger Street Boucherville Canada QC J4B 7K8 <u>US Agent:</u> Alison Sherwood Ph# (303) 438-4513 e-mail : alison.sherwood@sandoz.com	<ul style="list-style-type: none"> • Drug product manufacturer • Drug substance testing • Drug product testing • Stability Testing 	24-406-2071	3000280957	Provided on page # 8

(b) (4)

Based on the data obtained, Sandoz Canada Inc. has proposed a shelf life of (b) (4) months. The labeling will indicate that the product must be stored between 20°C and 25°C, protected from light. The company has provided 18-month long term and 6 month accelerated data to support the proposed expiration dating period.

B. Critical Issues for Review

Following are preliminary CMC aspects that have been noted and the primary reviewer should review the NDA in detail for CMC acceptability. The following steps are critical steps and particular attention should be paid to these during the review.

- The controls for the input materials in the drug product are adequate.
- Argatroban is very slightly soluble in water. Studies performed at Sandoz Canada Inc. demonstrate a solubility of (b) (4).
The reviewer should make sure that the manufacturing hold times are fully delineated and justified with respect to stability of the product solution and that the active does not precipitate in the final product on storage.
- Reviewer should evaluate the thermal stress stability studies, an important characteristic for the finished dosage form.
- Argatroban consists of a mixture of R and S stereoisomers at a ratio of approximately 65:35. The reviewer should make sure that the analytical method is capable of assaying this ratio and that the manufacturing conditions and drug product storage do not affect this ratio.
- Critical process parameters and product specifications should be evaluated.
- Product's stability as well as in-use stability should be evaluated.
- Container closure system that maintains product sterility. This is an aseptically filled product.

C. Comments for 74-Day Letter

None.

Fileability Summary

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		
5.	Is a statement provided that all the facilities are ready for cGMP / PAI inspection?	X		
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		
7.	Does the section contain controls for drug substance?	X		
8.	Does the section contain controls for drug product?	X		
9.	Has the stability data and analysis been provided to support the proposed expiry?	X		
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	X		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	X		
13.	Has the applicant provided a method validation package?	X		
14.	Is a separate microbiological section included?		X	Microbiology information is provided in module 3 of the NDA.

Drug Master Files Referenced					
DMF Number	Holder	Item Referenced	LOA Included		Comments
			Yes	No	
	(b) (4)	Argatroban	X		Type II; LOA is located in M1, Section 1.4.1.
	(b) (4)	(b) (4)	X		Type III; LOA is located in M1, Section 1.4.1.
	(b) (4)	(b) (4)	X		Type III; LOA is located in M1, Section 1.4.1.

(b) (4)		
	X	Type III; LOA is located in M1, Section 1.4.1.

Consults To Be Initiated:	
Item	Consult To
1. Trademark: There is no proposed Trademark.	N/A
2. Microbiology	OPS Microbiology Staff

IQA Performed By: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer

Date: 28-May2010

Branch Chief: Sarah Pope Miksinski, Ph.D.

Date: 28-May-2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201743	ORIG-1	SANDOZ INC	ARGATROBAN INJECTION 1 MG/ML

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/s/

RAVINDRA K KASLIWAL
06/01/2010

WILLIAM M ADAMS
06/01/2010
William Adams, acting for Sarah Pope Miksinski