

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203049Orig1s000

CHEMISTRY REVIEW(S)

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

Establishment: CFN: 1123053 FEI: 1000123236
AFTON SCIENTIFIC CORPORATION
2020-2030 AVON CT
CHARLOTTESVILLE, VA 229028735

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: MANUFACTURING SITE, RELEASE TESTING OF DRUG SUBSTANCE, DRUG PRODUCT, EXCIPIENT TESTING (on 31-MAR-2011 by T. LAMBERT () 301-796-4246)
Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-APR-2011				BROWNJA
SUBMITTED TO DO	06-APR-2011	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	11-APR-2011	Product Specific			BSEEMAN
INSPECTION SCHEDULED	08-JUN-2011		30-SEP-2011		BSEEMAN
INSPECTION PERFORMED	26-SEP-2011		26-SEP-2011		BSEEMAN

THIS DIRECTED, COMPREHENSIVE PRE-APPROVAL & GMP INSPECTION OF A STERILE PHARMACEUTICAL MANUFACTURER WAS CONDUCTED AS PER BLT-DO FY10 WORKPLAN & AS PER CDER EES REQUEST UNDER FACTS ASSIGNMENT NUMBER 6883821, OPERATION IDENTIFICATION NUMBER 5389012. THE INSPECTION WAS CONDUCTED IN ACCORDANCE WITH CP 7346.832, PRE-APPROVAL INSPECTIONS/ INVESTIGATIONS, CP 7356.002, DRUG PROCESS INSPECTION, & CP 7371.001, 5ANIMAL DRUG MANUFACTURING. ASSIGNMENT COVERED OPERATIONS FOR NDA 203-049, ARGATROBAN INJECTION.

CURRENT INSPECTION REVEALED FIRM TO CONTINUE MANUFACTURING STERILE SMALL VOLUME PARENTERALS IN ADDITION TO COMPONENTS. INSPECTION COVERED 4 SYSTEMS, INCLUDING QUALITY, PRODUCTION, FACILITIES & EQUIPMENT, & MATERIALS. PROFILE CLASS SVS WAS COVERED. 2 ITEM FDA-483 WAS ISSUED CITING: WRITTEN PROCEDURES NOT ESTABLISHED FOR CLEANING/ MAINTENANCE OF EQUIPMENT, & FAILURE TO USE (b) (4) SAMPLING TECHNIQUES IN COLLECTING A SAMPLE. DISCUSSION ITEMS BROUGHT TO FIRM'S ATTENTION: LACK OF VALIDATION FOR 5ML GLASS VIAL DEPYROGENATION CYCLE; ENSURING INVESTIGATIONS ARE CLEAR & COMPLETE; ARGATROBAN MASTER BATCH RECORD LACKS SPACE TO DOCUMENT TIMES & MIXING PARAMETERS & DOES NOT LIST CORRECT FILTER & (b) (4) INSTRUCTIONS; FLOOR MATS OBSERVED HANGING ON EQUIPMENT & ROOM IS NOT EXHAUSTED PROPERLY SO HUMIDITY MAY BE PROBLEM; ALCOHOL CONTAINERS IN CLEAN ROOM APPEAR TO BE EXPIRED; & MICRO GROWTH MEDIA LABELED FOR STORAGE AT 15-25°C OBSERVED STORED IN WAREHOUSE WHICH IS NOT TEMPERATURE CONTROLLED OR MONITORED. MR. THOMAS THORPE, PRESIDENT, ACKNOWLEDGED EACH OBSERVATION; MS. JESSICA KAHLE, MANGER QUALITY ASSURANCE, STATED HER FIRM WOULD REPLY IN WRITING.

NO REFUSALS WERE ENCOUNTERED. NO SAMPLES WERE COLLECTED.

DO RECOMMENDATION 26-SEP-2011 ACCEPTABLE BSEEMAN

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

COMPLETE; ARGATROBAN MASTER BATCH RECORD LACKS SPACE TO DOCUMENT TIMES & MIXING PARAMETERS & DOES NOT LIST CORRECT FILTER (b) (4) INSTRUCTIONS; FLOOR MATS OBSERVED HANGING ON EQUIPMENT & ROOM IS NOT EXHAUSTED PROPERLY SO HUMIDITY MAY BE PROBLEM; ALCOHOL CONTAINERS IN CLEAN ROOM APPEAR TO BE EXPIRED; & MICRO GROWTH MEDIA LABELED FOR STORAGE AT 15-25°C OBSERVED STORED IN WAREHOUSE WHICH IS NOT TEMPERATURE CONTROLLED OR MONITORED. MR. THOMAS THORPE, PRESIDENT, ACKNOWLEDGED EACH OBSERVATION; MS. JESSICA KAHLE, MANGER QUALITY ASSURANCE, STATED HER FIRM WOULD REPLY IN WRITING.

NO REFUSALS WERE ENCOUNTERED. NO SAMPLES WERE COLLECTED.

OC RECOMMENDATION

03-OCT-2011

ACCEPTABLE

TOULOUSEM

DISTRICT RECOMMENDATION

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

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE (on 31-MAR-2011 by (b) (4))

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-APR-2011				(b) (4)
OC RECOMMENDATION	06-APR-2011			ACCEPTABLE BASED ON PROFILE	(b) (4)

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Establishment Comment: DRUG SUBSTANCE MANUFACTURE AND CONTROL: (b) (4)
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE (b) (4)

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-APR-2011				(b) (4)
OC RECOMMENDATION	06-APR-2011			ACCEPTABLE BASED ON PROFILE	

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

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

(b) (4)

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

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE, DRUG PRODUCT, EXCIPIENT TESTING, STABILITY TESTING (on 31-MAR-2011 (b) (4))
PLEASE CONDUCT PAI AND GMP INSPECTION OF THIS CONTRACT TESTING LABORATORY. LAST PAI/GMP OF THIS FIRM WAS CONDUCTED ON 6/26-28/07 AND WAS CLASSIFIED VAI.

PLEASE COMPLETE PAGE 2 OF THE EES INSPECTION REPORT AND SUBMIT TO PAI MANAGER ALONG WITH A COPY OF ANY FDA 483 ISSUED, WITHIN ONE DAY OF COMPLETION OF THE EI. (on 11-APR-2011 by (b) (4))

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

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-APR-2011				(b) (4)
SUBMITTED TO DO	07-APR-2011	GMP Inspection			(b) (4)
ASSIGNED INSPECTION TO (b) (4)	11-APR-2011	Product Specific			(b) (4)
INSPECTION PERFORMED	(b) (4)				(b) (4)
DO RECOMMENDATION	13-MAY-2011 (b) (4)			ACCEPTABLE INSPECTION	(b) (4)
PAI/GMP INSPECTION DATED (b) (4) IS CLASSIFIED VAI. DEFICIENCY REGARDING ADEQUATE LABORATORY PRACTICES WAS DOCUMENTED ON THE FORM FDA-483. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.					
OC RECOMMENDATION	16-MAY-2011			ACCEPTABLE	(b) (4)
10-MAY-2011				DISTRICT RECOMMENDATION	

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

/s/

NIKOO N MANOCHEHRI KALANTARI
01/10/2012

NDA 203049

Argatroban® (argatroban) Injection

Hikma Pharmaceuticals Co. Ltd.

Li-Shan Hsieh, Ph. D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I/Branch II**

**CMC REVIEW OF NDA 203049
For the Office of Hematology and Oncology Drug Products
Division of Hematology Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 203049
2. REVIEW #: 1
3. REVIEW DATE: 01-Dec-2011
4. REVIEWER: Li-Shan Hsieh, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND (b)(4) submission	20-Oct-2008
Original IND (b)(4) CMC review	N/A
Pre-IND meeting for advise on 5050(b)(2)	03-Dec-2008
CMC end-of-phase-2 meeting	N/A
MC only pre-NDA meeting	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	03/18/2011	03/21/2011
Amendment (BC) (Clarification of the manufacturer functions and addresses)	N/A		
Amendment (BC) (Response to FDA mm/dd/yy CMC IR)	N/A		
Amendment (Response to 10/05/11 CMC IR)	11	10/21/2011	10/24/2011
Amendment (container and carton labeling)	7	09/26/2011	09/26/2011
Amendment (Response to mm/dd/yy telecon)	N/A		
Amendment (Updated post-approval stability protocols for DS and DP --response to mm/dd/yy CMC request)	N/A		
Amendment (Revised container and carton labeling)	e-mail	11/14/2011	11/14/2011
Amendment (Revised container and carton labeling)	N/A		

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Hikma Pharmaceuticals Co. Ltd.
Address: Industrial Area, Bayader Wadu El Seer, Armman, Jordan Exela
US Agent: Pharma Sciences, LLC.
Address: 1325 William White Place NE, Lenoir, NC 28645
Representative: Jonathan Sterling, Director of Quality, regulatory & Product
Telephone: 828-448-8744, Fax: 828-757-7888

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Argatroban Injection (Pfizer's generic name)
b) Non-Proprietary Name: Argatroban Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5 (New Formulation)
 - Submission Priority: S (Standard)

9. LEGAL BASIS FOR SUBMISSION: 314.54(a)(1)(iii) and under Section 505(b)(2)

10. PHARMACOL. CATEGORY: An anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia or in patients with or at risk for heparin induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

11. DOSAGE FORM: Solution
12. STRENGTH/POTENCY: 100 mg/mL
13. ROUTE OF ADMINISTRATION: Intravenous administration
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

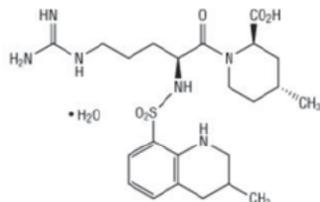
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CMC Review Data Sheet

IUPAC Name: (2*R*,4*R*)-1-[(2*S*)-5-(diaminomethylideneamino)-2-[[*(3R)*-3-methyl-1,2,3,4-tetrahydroquinolin-8-yl]sulfonylamino]pentanoyl]-4-methyl-piperidine-2-carboxylic acid

1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[*(1,2,3,4-tetrahydro-3-methyl-8-quinoliny]*l)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate

CAS name : Argatroban monohydrate

Structure:

C₂₃H₃₆N₆O₅ S. H₂O
526.65 g/mol
Salt/base ratio: 1.258

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	1	Adequate	14-Oct-2011 Li-Shan Hsieh	Drug substance
	III		(b) (4)	3	Adequate	Dr. Bart Ho, 24-Nov-2008	
	III			3	Adequate	Josephine Jee 24-May-2011	(b) (4)
	III			3	Adequate	Dr. Marla K Stevens-Riley, 21-Jun-2011	(b) (4)

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")

CMC Review Data Sheet

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	pIND meeting request
NDA	20883	Pfizer's Argatroban Injection, the Reference Listed Product

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	03-Oct-2011	Office of Compliance
Pharm/Tox	Approval	01-Dec-2011	Shwu-Luan Lee, Ph.D.
Biopharm	Acceptable	21-Nov-2011	Deepika Laklani, Ph.D.
LNC	N/A		
Methods Validation	Acceptable	N/A	Methods are standard.
DMEPA*	Pending		
EA	Categorical exclusion (see review)		Li-Shan Hsieh, Ph.D.
Microbiology	Approval	29-Nov-2011	Denise Miller, Ph.D.

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 203049

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This New Drug Application for Argatroban Injection, 100mg/mL, is recommended for approval from the Chemistry, Manufacturing and Controls perspective, pending the receipt of acceptable final labeling.

The following language needs to be inserted into the action letter:

A **24-month expiration dating period** is granted for the drug product when stored at room temperature [20°C - 25°C (68°C - 77°F); excursions permitted to 15° to 30°C (59° to 86°F)]. Do not freeze.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

Argatroban is not a new molecular entity. The complete manufacturing process of drug substance is described in Type II DMF No. (b)(4) for the argatroban drug substance.

Argatroban contains (b)(4)

(b)(4) Argatroban (b)(4) consists of a mixture of *R* and *S* stereoisomers at a ratio of approximately 65:35.

Argatroban is relatively stable, and no extraordinary storage precautions are required other than standard protection from moisture and light. A retest period of (b)(4) at (b)(4) storage condition is supported by the drug substance stability data. This is what was proposed by the DMF holder (DMF (b)(4)) so no further action is needed with regard to the retest period.

Executive Summary Section

(b) (4) argatroban manufacturing process and process controls, materials control, critical steps and intermediates, process evaluation studies, controls; and manufacturing process development have been reviewed and found adequate.

(2) Drug Product

Exela's proposed drug product has the same active ingredient, dosage form, strength, route of administration, and conditions of use as Pfizer's Argatroban Injection (under NDA 20883). However, Exela's proposed drug product contains a different quality and quantity of excipients than the previously approved drug. The formulation change has been made to the (b) (4) In Exela's formulation, USP grade propylene glycol replaces D-sorbitol (b) (4) and the quantity of (b) (4) dehydrated alcohol, is different.

Argatroban Injection, 100 mg/mL, has the same active ingredient, dosage form, strength, route of administration, and conditions of use as Pfizer Inc.'s listed drug product. Argatroban Injection is supplied as a sterile, clear, and colorless to pale yellow solution in (b) (4) single-use, clean amber glass vials. Each mL contains 100 mg Argatroban, (b) (4) mg dehydrated alcohol, and (b) (4) mg propylene glycol in Water for Injection, USP.

Argatroban Injection is formulated to be further diluted with either in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL. The compatibility evaluation indicated that Argatroban Injection is compatible with all diluents as described in the package insert at the concentration of 1.0 mg/mL (b) (4)

The quality of Argatroban Injection has been assessed based on its manufacturing process, process controls, analytical procedures for identification, purity, and strength, and stability. Argatroban Injection contains an amount (b) (4) of the labeled amount of argatroban ($C_{23}H_{36}N_6O_5S \cdot H_2O$).

Based on the provided stability data, a 24 month expiration dating period is granted for the drug product when stored at 20° to 25°C (68° to 77°F), (b) (4) protected from light by an amber vial and shelf carton.

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

Argatroban Injection is supplied as a sterile, clear, yellow viscous solution with a concentration of 100 mg/mL in 2.5 mL as a solution in single-use vials at the concentration of 100 mg/mL. Each vial contains 250 mg of Argatroban. Argatroban Injection is intended for intravenous use after dilution with a compatible intravenous fluid. Argatroban Injection will be packaged in amber, (b) (4) USP glass vials, sealed with stoppers from (b) (4) stopper, in a single unit carton, and oversealed.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant. All drug substance and drug product manufacturing, packaging and control facilities were submitted to EES. An overall recommendation was Acceptable and was issued from the Office of Compliance, dated 03-Oct-2011.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Li-Shan Hsieh, Ph. D. Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Janice Brown, CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (ONDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

39 Pages has been
Withheld in Full as b4
(CCI/TS)
immediately
following this page

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/s/

LI SHAN HSIEH
12/05/2011

SARAH P MIKSINSKI
12/05/2011

**Initial Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

OND Division: Division of Hematology Products
 NDA: 203049
 Applicant: Hikma Pharmaceuticals Co. Ltd., Amman,
 Jordan
 Authorized U.S. Agent: Exela Pharma Sciences
 Stamp Date: 28-Mar-2011
 PDUFA Date: 28-Jan-2012
 Proprietary (Brand) Name of Drug Product: N.A.
 Established Name: Argatroban Injection
 Dosage Form(s): Solution
 Strength(s): 100 mg/mL
 Route of Administration: Intravenous infusion
 Proposed Indication(s): Prophylaxis or treatment of thrombosis in patients
 with heparin-induced thrombocytopenia; for
 heparin-induced thrombocytopenia undergoing
 percutaneous coronary intervention (PCI)
 Pharmacologic Class: Direct thrombin inhibitor
 CMC Lead: Janice Brown, Branch II/DNDQA1/ONDQA
 Chief, Branch II: Sarah Pope Miksinski, Ph.D., DNDQA1/ONDQA
 Review team recommendation: Single reviewer

	Yes	No
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	X

CONSULTS/ CMC RELATED REVIEWS

Consult	Comment
Biopharm/ClinPharm	Reviewer requested
CDRH	Not Applicable
EA	Categorical exclusion requested
EES	Refer to attachment 1 for a list of manufacturing sites submitted in EES
DMETS	Labeling consult request will be sent as part of DHP request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Denise Miller assigned reviewer
Pharm/Tox	To be determined by Primary Reviewer.

Initial Quality Assessment

SUMMARY

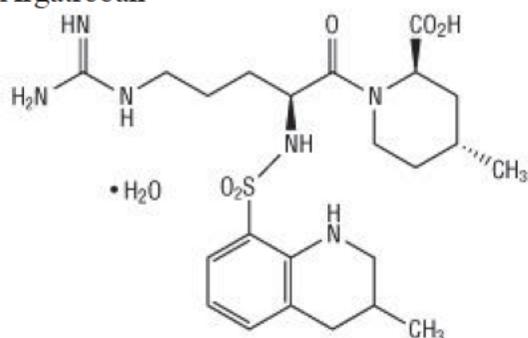
This 505(b)(2) application relies on the FDA's finding of safety and effectiveness for the reference listed drug, Argatroban Injection marketed by Pfizer under the approved NDA # 20-883. A comparison table of Exela's and Pfizer's Argatroban is summarized in table 1.12-1 below.

Table 1.12-1: Comparison of Exela's Argatroban Injection to Pfizer's Argatroban Injection

Item	Exela's Argatroban Injection	Pfizer's Argatroban Injection
Active Ingredient	Argatroban	Argatroban
Dosage Form	Injectable	Injectable
Total Drug Content	250 mg/vial	250 mg/vial
Route of Administration	Intravenous Infusion	Intravenous Infusion
Indication(s)	(b) (4)	(b) (4)

Argatroban is a direct thrombin inhibitor derived from L-arginine that reversibly binds to the thrombin active site. Argatroban has 4 chiral carbons. Three of the chiral carbons are from the starting materials. One of the asymmetric 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 at a ratio of approximately 65:35. The structural formula is shown below:

Argatroban



DRUG SUBSTANCE

1. The applicant provided a letter of authorization from (b) (4) allowing the agency to review the confidential information in DMF No. (b) (4)

Initial Quality Assessment

2. Argatroban drug substance is manufactured and controlled by:



3. There is a (b) (4) step manufacturing process for Argatroban drug substance. A manufacturing flow diagram is reproduced in Attachment 2.
4. The applicant submitted the COA for three batches (batch no. 71070AA004, 71070AA005, 71070AA006) of Argatroban drug substance. All batches met the proposed acceptance criteria.
5. A comparative drug substance specification for (b) (4) and Exela is reproduced in Table 3.2.S.4-1, Attachment 3. The specifications for Argatroban drug substance (b) (4)

DRUG PRODUCT

6. The applicant has identified a listed drug (LD) for Argatroban Injection, manufactured by Pfizer, Inc., NDA No. 20-883. The LD is supplied as a 2.5-mL solution in a single-use amber vial, with a gray flip-top cap. Each mL contains 100 mg Argatroban, 750 mg D-sorbitol, and 1,000 mg dehydrated alcohol. Exela's drug product has the same active ingredient, dosage form, strength, route of administration, and conditions of use as Pfizer's Argatroban Injection. The difference is Exela's proposed drug product contains a different excipient than Pfizer's approved Argatroban injection drug. In Exela's formulation propylene glycol replaces D-sorbitol (b) (4). Another change to Exela's drug product is the quantity of dehydrated alcohol used in the product. Exela's product contains (b) (4) of dehydrated alcohol and where as the Listed Product (Pfizer's Argatroban Injection) contains (b) (4). A comparison of the ingredients in Exela's Argatroban Injection, 250 mg/vial and with Pfizer's Argatroban Injection is presented in the following table.

Table 1: Comparison of Exela's and Pfizer's Argatroban Injection Formulation

Ingredients	Exela's Formulation	Pfizer's Formulation
Each vial contains: (in mg)		
Argatroban	250	250
Dehydrated Alcohol, USP	800	1000
D-Sorbitol USP	--	750
Propylene Glycol, USP	1300	--
Water for Injection, USP	q.s.	q.s.

7. Exela Pharma Sciences, Inc. has requested a biowaiver that will be reviewed by ONDQA biopharmaceutics group.

Initial Quality Assessment

8. Argatroban injection is available in 2.5 mL solution in single-use vials at the concentration of 100 mg/mL. Each vial contains 250 mg of Argatroban. Argatroban Injection is intended for intravenous use after dilution with a compatible intravenous fluid. Argatroban injection should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL. The composition is reproduced in table 2.3.P.1-1.

Table 2.3.P.1-1 Unit Composition for Argatroban Injection

Ingredients	Function of Components	Concentration (mg/mL)	Content per vial (mg/Vial)
Argatroban	Active Pharmaceutical Ingredient	100	250
Propylene Glycol, USP	(b) (4)	520	1300
Dehydrated Alcohol, USP	(b) (4)	320	800
Water for Injection, USP	Solvent	q.s.	q.s.

9. The drug product flow diagram is reproduced in Attachment 4. Argatroban Injection is a (b) (4) product.

10. Container/Closure System - The proposed container/closure system is as follows:

Component	Specifications	Suppliers
Vial	5 mL, 20 mm Amber Finish (b) (4) Glass Tubing	(b) (4)
Stopper	(b) (4)	
Overseal	(b) (4)	

11. The product should be stored at 20° to 25°C (68° to 77°F). It is protected from light by an amber vial and shelf carton.

12. Exela Pharma Sciences, LLC (b) (4)

13. STABILITY

a. Exela is requesting a 24-month expiration dating period when stored at 25±2°C for Argatroban Injection. The applicant submitted 24 months of long term stability (25 ± 2°C) and six month data at the accelerated condition of (40 ± 2°C at 75 ± 5% RH) for three batches of Argatroban Injection. The product appears to be temperature sensitive. Long term stability results shows that at 24 months, the product is at the NMT (b) (4) w/w limit for total unspecified impurities and impurity (b) (4) for two lots (lots 821-08 and/or 820-08) and fails total unspecified impurities for lot 812-08. Consider granting a (b) (4) shelf life instead of the requested 24 months.

b. Results at accelerated conditions (40°C ± 2°C/75% ± 5% RH) shows that lot 820-08 fail the total impurity limit (result (b) (4)).

Initial Quality Assessment

- c. Results at the intermediate conditions met the proposed acceptance criteria.
- d. The applicant also performed thermal cycling study. The study evaluated Assay values and did not include impurity testing so the validity of this study is questionable.
- e. A photostability study was performed and surprisingly there was no significant difference in the assay and impurities of Argatroban, in the light-exposed samples. Photo-degradants are known to form on exposure of Argatroban drug substance to light.
- f. The applicant performed an in-use study to simulate the compatibility of Exela's Argatroban Injection with Sodium Chloride (0.9%) Injection USP, Lactated Ringer's Injection USP, Dextrose (5%) Injection, USP. The study protocol lists the Argatroban injection manufacturer as (b) (4). Consider obtaining clarification on the manufacturer of Argatroban Injection used in this and most of the other stability studies. The in-use stability should be performed with the applicant's product.

14. The formulation is relatively simple and there are no QbD aspects to the submission.

DMFs

Supporting DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	II	(b) (4)	Argatroban Drug Substance	<u>DMF review needed</u>
	III		(b) (4)	<u>DMF review needed</u>
	III			<u>DMF review needed</u>
	III			<u>DMF review needed</u>

Critical issues for review

1. Starting Materials
 - a. The purity and quality of the starting materials and drug substance needs to be examined critically. Verify appropriate specifications for carry-over impurities present in the starting materials to the final drug substance have been established.
 - b. Verify that there is a change control strategy for any potential revisions to the manufacture of the proposed starting materials, including procedures for the vendor's reporting of any changes in starting material manufacture to the applicant.
 - c. Verify that there are validated analytical methods capable of resolving and quantifying impurities in the drug substance that are carried over from the proposed starting materials and process related impurities.

Initial Quality Assessment

2. It is known that Argatroban drug substance is sensitive to light and (b) (4) degradants are formed (b) (4). Consider requesting that the applicant provide an explanation why their studies showed that their product is not light sensitive.
3. Consider requesting a combined drug product release/stability specification.
4. The applicant's proposed 24-month shelf life should be denied. Consider granting a (b) (4) month shelf life instead of the requested 24 months.

Additional issues

Administrative: The applicant has submitted a claim for categorical exclusion under 25.31(d) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment. The ONDQA reviewer will evaluate the categorical exclusion request.

Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of argatroban injection is reproduced in attachment 1.

Comments for 74-Day Letter: None

Initial Quality Assessment

Attachment 1: Manufacturing Sites

Company Name	Contact Name Phone Number	Address	FEI	Operation
(b) (4)				
Exela Pharma Sciences	Tel.: (828) 758-5474 Fax: (828) 757-7888	1325 William White Place Lenior, NC 28645	No FEI no.	(b) (4)
Afton scientific Corporation	Tel.: (434) 979-3737 Fax: (434) 979-3738	2030 Avon Court Charlottesville, VA 22902	(b) (4)	Manufacturing Site. (b) (4)
(b) (4)				

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/s/

JANICE T BROWN
05/09/2011

SARAH P MIKSINSKI
05/09/2011

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number:	Supplement Number and Type:	Established/Proper Name:
203049		Argatroban Injection
Applicant:	Letter Date:	Stamp Date:
Hikma Pharmaceuticals Co. Ltd.	18-Mar-2011	18-Mar-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	Agency requested comparative stability data of the reference listed product and your product in the final injectable dosage form after dilution. Comparative studies were not performed.

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			N.A.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		Will be reviewed by ONDQA Biopharmaceutics Group
	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Argatroban Drug Substance	11-Feb-2011	<u>DMF review needed</u>
	III		(b) (4)	10-Sep-2010	<u>DMF review needed</u>
	III			16-Mar-2011	<u>DMF review needed</u>
	III			16-Mar-2011	<u>DMF review needed</u>

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
33.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?			
34.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		
35.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}

Janice Brown, Branch II/DNDQA1/ONDQA

27-Apr-2011

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D., DNDQA1/ONDQA

27-Apr-2011

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

/s/

JANICE T BROWN

05/09/2011

No filing issues

SARAH P MIKSINSKI

05/09/2011