CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201811Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

›plication:	NDA 201811/000	**Sponsor:**	FRESENIUS KABI USA
Org. Code:	161		1501 EAST WOODFIELD RD STE 300E
Priority:	5		SCHAUMBURG, IL 60173
Stamp Date:	05-APR-2010	**Brand Name:**	ARGATROBAN INJECTION
PDUFA Date:	12-APR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	11-FEB-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; (b) (4)	INJECTION; ARGATROBAN; 100MG/1ML

FDA Contacts:	A. RUSSELL	Prod Qual Reviewer	(HFD-530)	3017962014
	J. METCALFE	Micro Reviewer	(HFD-805)	3017961576
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	J. BROWN	Team Leader		3017961652

Overall Recommendation:	WITHHOLD	on 18-JAN-2013	by EES_PROD
	WITHHOLD	on 15-AUG-2012	by EES_PROD
	WITHHOLD	on 22-FEB-2012	by EES_PROD
	WITHHOLD	on 07-OCT-2010	by EES_PROD

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

(b) (4)

DMF No: **AADA:**

Responsibilities:	DRUG SUBSTANCE RELEASE TESTER
	FINISHED DOSAGE RELEASE TESTER
Profile:	CONTROL TESTING LABORATORY
Last Milestone:	OC RECOMMENDATION
Milestone Date:	11-MAY-2010
Decision:	ACCEPTABLE
Reason:	DISTRICT RECOMMENDATION

OAI Status: NONE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 1450022 **FEI:** 1450022		
	APP PHARMACEUTICALS LLC A CO OF THE FRESENIUS KABI GROUP		
	MELROSE PARK, , UNITED STATES 601601112		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE STERILITY TESTER		
	FINISHED DOSAGE STERILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-OCT-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** **FEI:** 3008604776		
	APP PHARMACEUTICALS LLC A CO OF THE FRESENIUS KABI GROUP		
	SKOKIE, , UNITED STATES 600775318		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-OCT-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 1321116 **FEI:** 3001833549

APP PHARMACEUTICALS, LLC.

GRAND ISLAND, , UNITED STATES 140722028

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: (b) (4) **OAI Status:** OAI ALERT

Last Milestone: EIR RECEIVED BY OC

Milestone Date: 19-MAR-2013

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: 15-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STERILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-OCT-2012

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 OTHER TESTER		
	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-OCT-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

pplication:	NDA 201811/000	**Sponsor:**	APP PHARMS
rg. Code:	161		1501 EAST WOODFIELD RD STE 300E
riority:	5		SCHAUMBURG, IL 60173
tamp Date:	05-APR-2010	**Brand Name:**	ARGATROBAN INJECTION
DUFA Date:	31-JUL-2012	**Estab. Name:**	
ction Goal:		**Generic Name:**	
istrict Goal:	01-JUN-2012	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; (b) (4)	INJECTION; ARGATROBAN; 100MG/1ML

DA Contacts:	S. GOLDIE	Project Manager	(HFD-800)	3017962055
	M. SALAZAR DRIVER	Review Chemist		3017961451
	J. BROWN	Team Leader		3017961652

verall Recommendation: WITHHOLD on 22-FEB-2012 by EES_PROD

WITHHOLD on 07-OCT-2010 by EES_PROD

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

(b) (4)

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE RELEASE TESTER

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

ast Milestone: OC RECOMMENDATION

ilestone Date: 11-MAY-2010

ecision: ACCEPTABLE

eason: DISTRICT RECOMMENDATION

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stablishment: **CFN:** 1450022 **FEI:** 1450022

APP PHARMACEUTICALS LLC A CO OF THE FRESENIUS KABI GROUP

MELROSE PARK, , UNITED STATES 601601112

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE STERILITY TESTER

FINISHED DOSAGE STERILITY TESTER

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

ast Milestone: OC RECOMMENDATION

ilestone Date: 06-FEB-2012

ecision: ACCEPTABLE

eason: DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

stablishment: **CFN:** **FEI:** 3008604776

APP PHARMACEUTICALS LLC A CO OF THE FRESENIUS KABI GROUP

SKOKIE, , UNITED STATES 600775318

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

rofile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

ast Milestone: OC RECOMMENDATION

ilestone Date: 03-FEB-2012

ecision: ACCEPTABLE

eason: BASED ON PROFILE

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stablishment: **CFN:** 1321116 **FEI:** 3001833549

APP PHARMACEUTICALS, LLC.

GRAND ISLAND, , UNITED STATES 140722028

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

rofile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** OAI ALERT

ast Milestone: OC RECOMMENDATION

ilestone Date: 24-FEB-2012

ecision: WITHHOLD

eason: DISTRICT RECOMMENDATION
WARNING LETTER ISSUED

rofile: (b) (4) **OAI Status:** OAI ALERT

ast Milestone: OC RECOMMENDATION

ilestone Date: 24-FEB-2012

ecision: WITHHOLD

eason: DISTRICT RECOMMENDATION
WARNING LETTER ISSUED

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

stablishment: **CFN:** **FEI:** 3005724920

APP PHARMACEUTICALS, LLC.

BARCELONETA, , UNITED STATES 00617

MF No: 10095 **AADA:**

1546

9543

esponsibilities: FINISHED DOSAGE MANUFACTURER

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

ast Milestone: OC RECOMMENDATION

ilestone Date: 07-OCT-2010

ecision: WITHHOLD

eason: DISTRICT RECOMMENDATION
FACILITY OUT OF BUSINESS

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

(b) (4)

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE MANUFACTURER

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

ast M tone: OC RECOMMENDATION

ilestone Date: 04-MAY-2010

ecision: ACCEPTABLE

eason: BASED ON PROFILE

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

(b) (4)

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE STERILITY TESTER

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

ast Milestone: OC RECOMMENDATION

ilestone Date: 03-FEB-2012

ecision: ACCEPTABLE

eason: BASED ON PROFILE

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

stablishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
MF No:		**AADA:**	
esponsibilities:	DRUG SUBSTANCE OTHER TESTER		
	FINISHED DOSAGE OTHER TESTER		
rofile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
ast Milestone:	OC RECOMMENDATION		
ilestone Date:	03-FEB-2012		
ecision:	ACCEPTABLE		
eason:	BASED ON PROFILE		

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

/s/

MARY GRACE LUBAO
04/01/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 17, 2015
FROM: Nina Ni, Ph. D., Review Chemist, Branch II, DNDP I/ONDP
THROUGH: Janice Brown, M.S., QAL, Branch II, DNDP I/ONDP
SUBJECT: Addendum to CMC Review #5 for NDA 201811
TO: NDA 201811

Nina Ni -S
Digitally signed by Nina Ni -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nina Ni -S, 0.9.2342.19200300.100.1.1=20003722205
Date: 2015.03.18 07:23:49 -04'00'

Janice T. Brown -A
Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001016855, cn=Janice T. Brown -A
Date: 2015.03.18 07:41:09 -04'00'

In my CMC review #5, dated 03/09/2015, this NDA was recommended for approval pending on the final acceptance of label/labeling by the applicant. As of today, the following deficiencies pertinent to the label/labeling have been satisfactorily resolved as described below:

(a) "Highlights" Section (21CFR 201.57(a))

- Administration route expresses as: for intravenous use
- Strength expresses as: 250 mg per 2.5 mL (100 mg per mL)

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

- Strength expresses as: 250 mg per 2.5 mL (100 mg per mL)

#11: Description (21CFR 201.57(c)(12))

- Dosage form and administration route are added

Following Section #17, at the end of PI: Manufacturer/distributor name listed at the end of PI

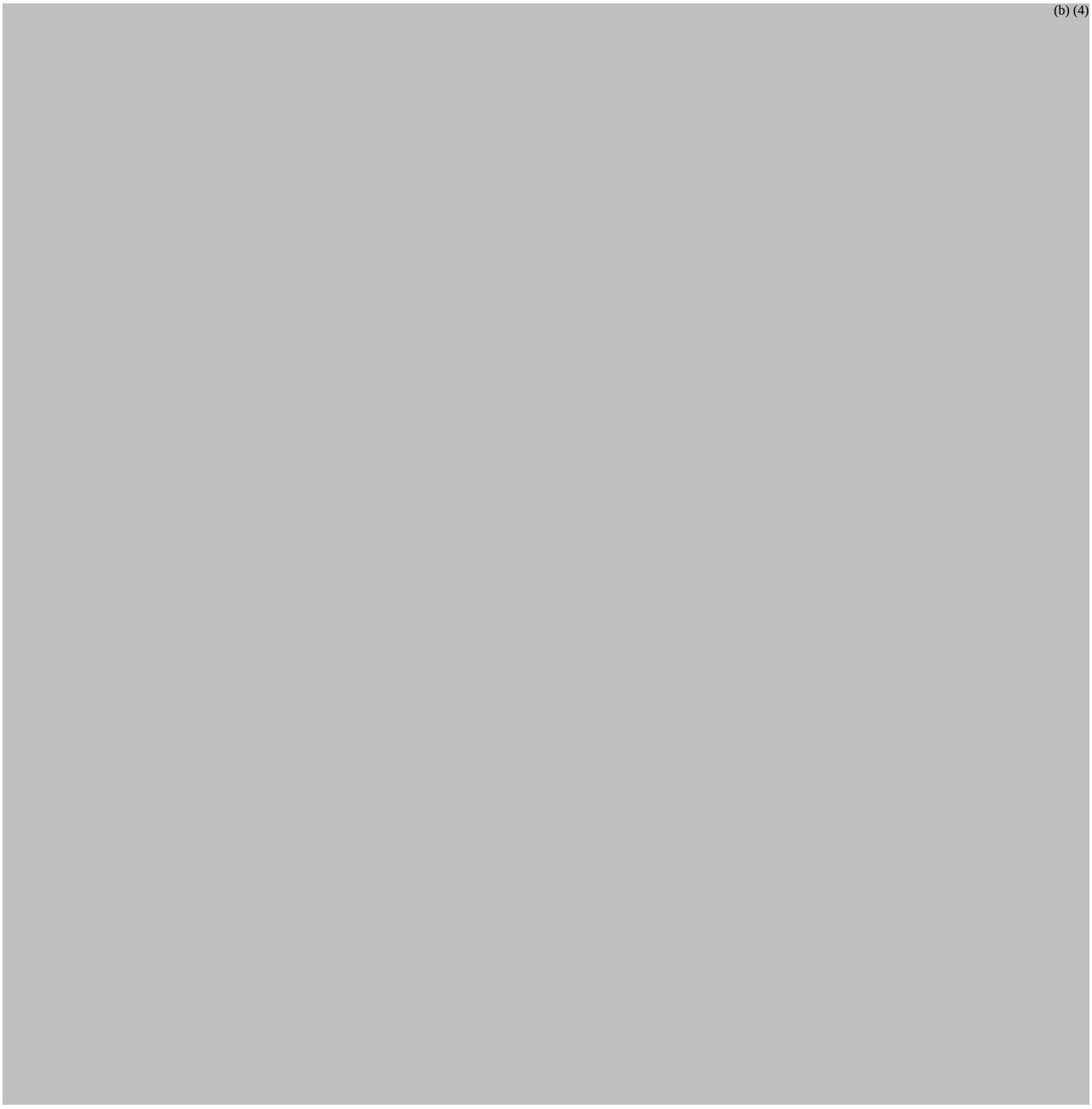
- "Manufactured by" is added

Updated carton and container labels are provided in the Attachment.

Thus, this NDA is recommended for approval from a CMC perspective.

Attachment - Carton and Container Labels

(b) (4)



Resubmission

Recommendation:
NDA: Approval

NDA 201811
Review # 5
Review Date: 03/09/2015

Drug Name/Dosage Form	Argatroban Injection/Injection
Strength	250 mg per 2.5 mL vial (100 mg per mL)
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi USA, LLC
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment 0022	01/23/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	NA	NA
Drug Product	Nina Ni	II/ONDP
Process	NA	NA
Microbiology	Denise Miller	OPF
Facility	Steven Fong	OPF
Biopharmaceutics	NA	NA
Project/Business Process Manager	Rabiya Laiq	OPRO
Application Technical Lead	Janice Brown	II/ONDP
Laboratory (OTR)	NA	NA
ORA Lead	NA	NA
Environmental Assessment (EA)	NA	NA

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has satisfactorily resolved all the issues listed on the CR letter. It is recommended for approval pending on the final acceptance of label/labeling by the applicant.

A "Complete Response" action was issued for this NDA based on the withhold recommendation from the Office of Compliance on February 28, 2014 in the previous cycle due to the Fresenius drug product manufacturing and testing site located in Grand Island, NY which was found unacceptable. The Applicant submitted a Class 1 Resubmission on 01/23/2015 to address complete response issues with the 505(b)(2) application.

In this resubmission, there is no new CMC information provided.

The Office of Compliance has issued an overall "Acceptable" recommendation (date: 02/25/2015), see the attachment 1.

Currently, label/labeling is under review and comments were communicated to the applicant.

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

None

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARGATROBAN INJECTION safely and effectively. See full prescribing information for ARGATROBAN INJECTION.

Argatroban Injection, for intravenous (b) (4) only

Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Argatroban is a direct thrombin inhibitor indicated:

- For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) (1.1).
- As an anticoagulant in adult patients with or at risk for (HIT) undergoing percutaneous coronary intervention (PCI) (1.2).

DOSAGE AND ADMINISTRATION

Argatroban injection must be diluted 100-fold by mixing with 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection to a final concentration of 1 mg/mL (2.1). Argatroban injection dosage may be adjusted for pediatric use (8.4).

Heparin-Induced Thrombocytopenia (2.1)

The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min administered as a continuous infusion (2.1).

Percutaneous Coronary Intervention (2.2)

The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes (2.2).

DOSAGE FORMS AND STRENGTHS

- 250 mg/2.5 mL (100 mg/mL) single (b) (4) vial. (b) (4) (b) (4) (3).

CONTRAINDICATIONS

- Major bleeding (4).
- History of hypersensitivity to this product (4).

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: None Established Name: Argatroban	Adequate.
Dosage form, route of administration	Dosage: injection Route: for intravenous (b) (4) only	Inadequate. It is for intravenous use
Controlled drug substance symbol (if applicable)	NA	Adequate.
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Argatroban injection, (b) (4) (b) (4)	Inadequate. Strength needs to be expressed as: 250 mg per 2.5 mL (100 mg per mL)

Conclusion: Inadequate.

i. Administration route needs to be expressed as : for intravenous use
ii. Strength needs to be expressed as: 250 mg per 2.5 mL (100 mg per mL)

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4) vial. (b) (4)
(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Single use injection vial	Adequate.
Strengths: in metric system	(b) (4)	Inadequate. Strength needs to be expressed as: 250 mg per 2.5 mL (100 mg per mL)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4)	Adequate.

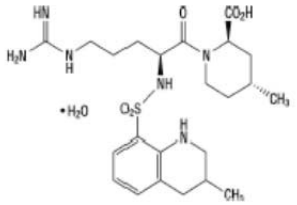
Conclusion: Inadequate.

i. Strength needs to be expressed as: 250 mg per 2.5 mL (100 mg per mL)

#11: Description (21CFR 201.57(c)(12))

Argatroban is a synthetic direct thrombin inhibitor and the chemical name is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate. Argatroban has 4 asymmetric carbons. 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 molecular formula of argatroban is $C_{23}H_{36}N_6O_5S \cdot H_2O$. Its molecular weight is 526.66 g/mol. The structural formula is:



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.

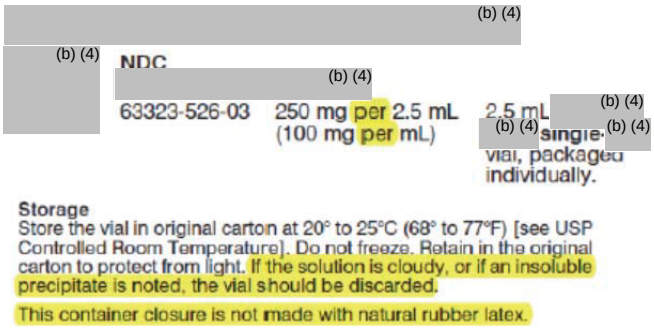
Argatroban injection is a sterile clear, colorless to pale yellow, slightly viscous solution in a single-use amber vial containing 250 mg/2.5 mL of argatroban. Each mL of sterile, nonpyrogenic solution contains 100 mg argatroban. Inert ingredients: 954 mg propylene glycol.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Only established name, argatroban is provided.	Adequate.
Dosage form and route of administration	Argatroban injection	Inadequate. Argatroban injection for intravenous use
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	Adequate.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	954 mg propylene glycol	Adequate.
Statement of being sterile (if applicable)	Provided.	Adequate.
Pharmacological/ therapeutic class	Direct thrombin inhibitor	Adequate.
Chemical name, structural formula, molecular weight	Provided.	Adequate.
If radioactive, statement of important nuclear characteristics.	NA	Adequate.
Other important chemical or physical properties (such as pKa, solubility, or pH)	Argatroban injection is a sterile clear, colorless to pale yellow, slightly viscous solution	Adequate.

Conclusion: Inadequate.

i. Dosage form and administration route are needed.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))


(b) (4)

(b) (4) NDC (b) (4)

63323-526-03 250 mg per 2.5 mL (100 mg per mL) 2.5 mL (b) (4) (b) (4) single (b) (4) vial, packaged individually.

Storage
Store the vial in original carton at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not freeze. Retain in the original carton to protect from light. If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

This container closure is not made with natural rubber latex.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	250 mg per 2.5 mL	Adequate.
Available units (e.g., bottles of 100 tablets)	Packaged individually	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number provided.	Adequate.
Special handling (e.g., protect from light, do not freeze)	Do not freeze. Retain in the original carton to protect from light.	Adequate.
Storage conditions	Store the vail in original carton at 20 to 25°C (68 to 77°F) [see USP controlled room temperature]	Adequate.

Conclusion: Adequate.

Manufacturer/distributor name listed at the end of PI, following Section #17

The brand names mentioned in this document are the trademarks of their respective owners.

451160 (b) (4) (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	The company needs to be qualified.	Inadequate. Marketed and distributed by Fresenius Kabi

Conclusion: Inadequate.

i. The company needs to be qualified as "marketed by", "manufactured by", or "distributed by" etc.

2. Labels

1) Immediate Container Label

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ARGATROBAN INJECTION	Inadequate. Established name needs to be expressed as Argatroban Injection.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	250 mg per 2.5 mL, 100 mg per mL For intravenous (b) (4) only	Inadequate. For intravenous administration
Net contents (21 CFR 201.51(a))	NA	Adequate.
Lot number per 21 CFR 201.18	Provided	Adequate.
Expiration date per 21 CFR 201.17	Provided	Adequate.
"Rx only" statement per 21 CFR 201.100(b)(1)	Not provided	Inadequate.
Storage (not required)	Provided	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Not provided	Adequate. NDC number is provided in the carton label.
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adquate.
Name of manufacturer/distributor	Not defined	Inadequate.
Others	Usual dosage: (b) (4)	Inadequate. See package insert.

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Inadequate.

i. Established name needs to be expressed as "Argatroban Injection"
ii. Administration route should be: for intravenous use
iii. Need to add "Rx only"
iv. Name of manufacturer/distributor needs to be defined as "marketed by", "distributed by", or "manufactured by" etc.
v. (b) (4) needs to be changed to "see package insert".

2) Cartons

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Provided inaccurately	Inadequate. Need to be expressed as "Argatroban Injection"
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided	Adequate.
Net contents (21 CFR 201.51(a))	Not provided	Inadequate.
Lot number per 21 CFR 201.18	Not provided	Inadequate.
Expiration date per 21 CFR 201.17	Not provided	Inadequate.
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Provided	Adequate.
Sterility Information (if applicable)	Provided inaccurately	Inadequate. Need to add sterile, and nonpyrogenic.
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	Adequate.
Storage Conditions	Provided	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate.
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate.
Name of manufacturer/distributor		Inadequate. Need to be defined.
"See package insert for dosage information" (21 CFR 201.55)	Provided inaccurately	Inadequate. Need to written as "see package insert"
"Keep out of reach of children" (optional for Rx, required for OTC)	Not provided	Adequate since it is Rx drug.
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Provided inaccurately	Inadequate. Needs to be changed to for intravenous use.

Conclusion: Inadequate.

i. Established name needs to be expressed as “Argatroban Injection”
ii. Administration route should be: for intravenous use
iii. (b) (4) needs to be changed to "see package insert".
iv. Name of manufacturer/distributor needs to be defined as “marketed by”, “distributed by”, or “manufactured by” etc.
v. Need to add sterile and nonpyrogenic.
vi. Need to add “lot number, expiration date, and net content”

III. List of Deficiencies To Be Communicated:

CMC Comments for label/labeling, including container labels:

(a) “Highlights” Section (21CFR 201.57(a))

- Administration route needs to be expressed as : for intravenous use
- Strength needs to be expressed as: 250 mg per 2.5 mL (100 mg per mL)

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

- Strength needs to be expressed as: 250 mg per 2.5 mL (100 mg per mL)

#11: Description (21CFR 201.57(c)(12))

- Dosage form and administration route are needed

Following Section #17, at the end of PI: Manufacturer/distributor name listed at the end of PI

- The company needs to be qualified as “marketed by”, “manufactured by”, or “distributed by” etc.

Immediate Container Label:

1. Established name needs to be expressed as “Argatroban Injection”, which only first letter of each word is capitalized.
2. Administration route should be: for intravenous use
3. Need to add “Rx only”
4. Name of manufacturer/distributor needs to be defined as “marketed by”, “distributed by”, or “manufactured by” etc.
5. (b) (4) needs to be changed to “see package insert”

Carton Label:

1. Established name needs to be expressed as “Argatroban Injection”, which only first letter of each word is capitalized.
2. Administration route should be: for intravenous use

3. (b) (4) needs to be changed to "see package insert"
4. Name of manufacturer/distributor needs to be defined as “marketed by”, “distributed by”, or “manufactured by” etc.
5. Need to add sterile and nonpyrogenic
6. Need to add “lot number, expiration date, and net content”

IV. Administrative

A. Reviewer’s Signature

Nina Ni, Ph. D., 03/09/2015

Nina Ni -S Digitally signed by Nina Ni -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nina Ni -S, 0.9.2342.19200300.100.1.1=2000372205
Date: 2015.03.09 10:07:44 -04'00'

Janice Brown, M.S., 03/09/2015

Janice T. Brown -A Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
Date: 2015.03.09 12:53:37 -04'00'

B. Endorsement Block

Primary Reviewer: Nina Ni, Ph. D., Date: 03/09/2015
Secondary Reviewer: Janice Brown, M.S., Date: 03/09/2015
Project Manager: Rabiya Laiq, Date: 03/09/2015

Attachment 1: Acceptable Facility Recommendation

From: Fong, Steven
Sent: Wednesday, February 25, 2015 5:06 PM
To: Kallungal, Beatrice; Brown, Janice; Laiq, Rabiya
Subject: Facility Approval Recommendation for NDA201811, Argatroban - Class 1 Resubmission

Dear Beatrice and Janice—

I just spoke with the Panorama help desk regarding the "Inspection View" component for NDA 201811. It seems there's a bug in the Mercado platform that does now allow one to submit a final "Overall Manufacturing Inspection Recommendation" for this application into the Panorama database. This bug may take some time to resolve. In the meantime, the help desk informed me that sufficient justification exists for my issuing an approve recommendation for this NDA since all facilities listed in Panorama are officially checked off as being approved. Based on this, I formally recommend approval of NDA 201811 from a compliance standpoint.

Steven E. Fong, M.S., Ph.D.
Microbiologist, Office of Process and Facilities
Division of Inspectional Assessment, Branch 1
Center for Drug Evaluation & Research
US Food and Drug Administration
10903 New Hampshire Avenue
Bldg 51, Room 4210
Silver Spring, MD 20993-0002
(301) 796-1501

NDA 201-811
Complete Response

Argatroban Injection
100 mg/mL (250 mg/2.5 mL vial)

Fresenius Kabi USA, LLC
(formerly APP Pharmaceuticals, LLC)

Anne Marie Russell, Ph.D.
CMC Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II
for
Division of Hematology Products (DHP)

Table of Contents

CMC Review Data Sheet

1. NDA 201-811

2. REVIEW #: 4 (Complete Response)

3. REVIEW DATE: 09-JAN-2014

4. REVIEWER: Anne Marie Russell, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA submission	02-APR-2010
02	28-JUN-2010
03	1-JUL-2010
04	5-AUG-2010
05	3-Sep-2010
06	15-OCT-2010
07	22-NOV-2010
09 Complete response	31-JAN-2012
10	14-MAY-2012
12	7-JUN-2012
Complete Response NDA Submission	12-OCT-2012
Amendment CMC – DMFs' LOAs	14-NOV-2012
Amendment Labeling –Vial, Carton and package insert	11-FEB-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Stamp Date
Complete Response NDA Submission	0021	13-SEPT-2013
Amendment – facility information and revised DS specifications	0022	27-SEPT-2013

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Fresenius Kabi USA, LLC
Address:	Three Corporate Drive Lake Zurich, IL 60047
Representative:	Aditi Dron, Manager, Regulatory Affairs
Telephone:	(847) 550-2298

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Argatroban
b) Non-Proprietary Name: Argatroban
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5 (new manufacturer)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
FDC Act: 505(b)(2)
RLD: Argatroban Injection (Pfizer NDA 020883)
Dosage Form: injection, (b) (4)

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 100 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

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

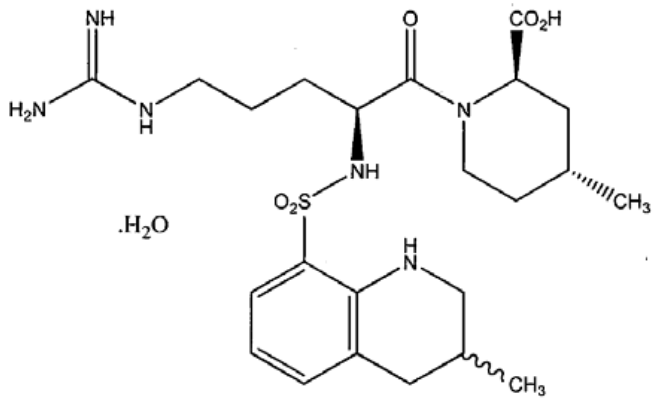
_____ SPOTS product – Form Completed

__√__ Not a SPOTS product

CMC Review Data Sheet

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

Chemical name: (2*R*,4*R*)-4-Methyl-1-N^2-[[(*R*,*S*)-1,2,3,4-tetrahydro-3-methyl-8-quinolonyl]sulfonyl]-L-arginyl]pipecolic acid monohydrate



Empirical Formula	$C_{23}H_{36}N_6O_5S.H_2O$
Molecular Weight	526.65
CAS Registry Number	(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)		3	Adequate	19-NOV-2008
	III			3	Adequate	2-FEB-2011 Milagros Salazar, CMC review #1 N201-811
	III			1	Adequate	28-Dec-2012 George Lunn
	III			1	Adequate	19-Sept-2012 Donald Klein
	III			1	Adequate	25-Jun-2012 Marla Steven Riley

CMC Review Data Sheet

[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
IND		
NDA		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES	Withhold	06-DEC-2013	OC Overall Recommendation
Pharm/Tox	Approval	11-JAN-2013	Shwu Luan Lee
Biopharm	Approval	24-APR-2012	Angelica Dorantes, Ph.D
EA	Adequate	30-JUN-2012	Anne Marie Russell, Ph.D.
Microbiology	Approval	25-FEB-2013	John W. Metcalfe, Ph.D.

Chemistry Review of NDA 201-811

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA received an Overall Recommendation of Withhold from the Office of Compliance on 06-DEC-2013. Until the facility inspection issues are resolved, a recommendation for approvability cannot be made.

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

None

II. Summary of CMC Assessments

A. Responses to Complete Response (Summary)

The drug product manufacturing site; Grand Island, NY failed inspection. The NDA received an Overall Recommendation of Withhold from the Office of Compliance on 06-DEC-2013.

The two CMC deficiencies identified in the Complete Response letter were resolved in this review cycle. See review for more detailed information.

B. Basis for Approvability or Not-Approval Recommendation

The NDA received an Overall Recommendation of Withhold from the Office of Compliance on 06-DEC-2013. This is the basis for the not-approval recommendation.

III. Administrative

A. Reviewer's Signature:
Anne Marie Russell, Ph.D.
(See appended electronic signature page)

C. Endorsement Block:
Ali Al-Hakim, Ph.D. – Branch Chief
(See appended electronic signature page)

C. CC Block: entered electronically in DARRTS

CMC Assessment

I. Introduction

Original Submission: The Chemistry, Manufacturing and Controls review of APP's original submission was completed on 16-FEB-2011 (Milagros Salazar-Driver, Ph.D.). The application was found to be deficient in several areas, including no manufacturing site for Drug Product. A Complete Response Letter was issued to APP on 24-Feb-2011 (Review Cycle #1).

1st Complete Response JAN 2012: APP submitted a Complete Response (31-JAN-2012). The CMC review of this CR was completed on 06-JUL-2012 (Anne Marie Russell, Ph.D.). The application was found to be deficient in several areas, including an overall WITHHOLD recommendation from the Office of Compliance for the new manufacturing site in Grand Island, NY. A Complete Response Letter was issued to APP on 23-JUL-2012 (Review Cycle #2).

2nd Complete Response OCT 2012: Fresenius, formerly APP, submitted a Complete Response (12-OCT-2012). The application was found to be deficient in several areas, including an overall WITHHOLD recommendation from the Office of Compliance for the new manufacturing site in Grand Island, NY. A Complete Response Letter was issued to APP on 05-APR-2013 (Review Cycle #3).

3rd Complete Response SEPT 2013: Fresenius submitted a Complete Response (13-SEPT-2013). This CMC review #4 is an assessment of that Complete Response (Review Cycle #4).

II. New Information submitted in the Complete Response:

- Certificates of Analysis for Reference Standards
- Updated stability data (24 months) on the three Grand Island Drug Product lots submitted in Complete Response 2012 (Review Cycle #2).
- No additional Drug Product lots manufactured since Complete Response 2012
- Revised Drug Substance Specifications (added bacterial endotoxin test and removed (b) (4) test).

III. Review of Responses to Complete Response Letter :

The Complete Response letter included two CMC deficiencies. Below, each deficiency is evaluated individually. The **deficiencies are in bold font**, followed by the *Applicant's responses which are in italics* and then the review/comments/evaluation which are in normal font. The deficiency numbering matches that used in the Complete Response letter dated 05-APR-2013.

1. **Provide the Analytical Procedure and Validation of Analytical Procedure for the method used in the Identification Test cited in "Table 3.2.S.5-1 Specification for Individual Isomers Argatroban 21-S and 21-R" and demonstrated adequacy of the method to distinguish the individual isomers.**

Applicant Response:
Certificates of Analysis from (b) (4) *for Argatroban 21-S and 21-R reference standards were provided in the submission. See Appendix. The acceptance criteria includes NMR spectra consistent* (b) (4) *The* (b) (4) *spectra provided for 21-R-Argatroban Reference Standard lot 20447 and 21-S-Argagtroban Reference Standard lot 20502 reports the same peak positions as:*

- *21R Argatroban Reference Standard,* (b) (4)
- *21S Argatroban Reference Standard,* (b) (4)

Evaluation: Acceptable. The analytical method for the reference standards is capable of distinguishing the individual isomers. The difference in (b) (4) peak position for (b) (4) This is minor since the (b) (4) NMR method adequately resolves the R and S isomers.

2. **Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.**

Applicant Response:
Updated stability data (24 months, 25ºC) for drug product argatroban injection lots R340032, 33 and 34 were submitted for (b) (4)*. All attributes were within specification. Assay declined, Impurity* (b) (4) *increased. Isomeric ratio was provided for the first time at 24 months timepoint.*

Evaluation: Acceptable.

CMC Assessment Section

Other changes to the application submitted in the Complete Response:

Fresenius revised the drug substance specifications to include a bacterial endotoxin test and remove the (b) (4) test. See revised specifications below. No other changes were made to the specifications.

The Microbiology Reviewer, John Metcalfe, was consulted and advised that this change is acceptable. See email below.

From: Metcalfe, John
Sent: Wednesday, January 29, 2014 7:52 AM
To: Russell, Anne Marie
Subject: RE: N201811 add bacterial endotoxin test and remove (b) (4) test

Hi Anne Marie,

The use of LAL (bacterial endotoxins testing) in lieu of (b) (4) testing is acceptable. I do not intend to write an additional review, so please use this email as my concurrence.

Thank you,
John

John W. Metcalfe, Ph.D.
Senior Review Microbiologist
Center for Drug Evaluation and Research
Food and Drug Administration

CMC Assessment Section

Table 3.2.S.4.1- 1 Regulatory Specifications for Argatroban

Tests	Acceptance Criteria	Test Method[1]
Description	White, crystalline powder	Visual Examination
Identification:	(b) (4)	
A. Infrared Absorption		A. USP <197K>
B. HPLC		B. 10-08-01-6397
Water		USP <921>, Method IA
Heavy Metals		USP <231>, Method II
Residue on Ignition		USP <281>
		10-08-01-6386
		USP <467>
Isomeric Ratio		0-08-03-6689
Assay		0-08-01-6397
Related Substances		0-08-01-6399
(b) (4		
		0-08-01-6397
G. Total Impurities		
Microbial Bioburden		SP <61> and <1111>
Bacterial Endotoxin		SP <85>

1 (b) (4)

III. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert:

Label and PI review not conducted due to Complete Response action.

B. Environmental Assessment Or Claim Of Categorical Exclusion

N/A

C. Establishment Evaluation Report

A recommendation to withhold was issued by the Office of Compliance on 06-DEC-2013 for the NDA (Grand Island facility failed inspection). See email below.

-----Original Message-----
From: ees_admin@fda.gov [mailto:ees_admin@fda.gov]
Sent: Friday, December 06, 2013 3:09 PM
Subject: Withhold DO Recommendation - NYK NDA 201811/000 CFN: 1321116 FEI: 3001833549 Profile: (b) (4)

This is a system generated email message to notify you that there
is a District Recommendation of 'Withhold' for the above EER.

IV. List Of Deficiencies Communicated and Resolved:

All CMC deficiencies have been resolved. A Complete Response is recommended due to the withhold issued by the Office of Compliance for the Grand Island, New York facility.

V. List Of Deficiencies to be Communicated in the Complete Response letter:

No CMC deficiencies.
The language regarding facilities from the previous CR letter would be appropriate for this CR letter (FACILITY INSPECTIONS: During a recent inspection of the APP Pharmaceuticals, LLC, Grand Island, NY manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application maybe approved.)

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ANNE M RUSSELL
01/30/2014

ALI H AL HAKIM
01/30/2014

NDA 201-811
Complete Response

Argatroban Injection
100 mg/mL (250 mg/2.5 mL vial)

Fresenius Kabi USA, LLC
(formerly APP Pharmaceuticals, LLC)

Anne Marie Russell, Ph.D.
CMC Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II
for
Division of Hematology Products (DHP)

Table of Contents

CMC Review Data Sheet

1. NDA 201-811

2. REVIEW #: 3 (Complete Response)

3. REVIEW DATE: 13-FEB-2012

4. REVIEWER: Anne Marie Russell, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA submission	02-APR-2010
02	28-JUN-2010
03	1-JUL-2010
04	5-AUG-2010
05	3-Sep-2010
06	15-OCT-2010
07	22-NOV-2010
09 Complete response	31-JAN-2012
10	14-MAY-2012
12	7-JUN-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Stamp Date
Complete Response NDA Submission	0016	12-OCT-2012
Amendment CMC – DMFs' LOAs	0017	14-NOV-2012
Amendment Labeling –Vial, Carton and package insert	0018	11-FEB-2013

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Fresenius Kabi USA, LLC
Address:	1501 East Woodfield Road Suite 300 East Schaumburg, Il 60173
Representative:	Aditi Dron, Manager, Regulatory Affairs
Telephone:	(847) 330-3898

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Argatroban
b) Non-Proprietary Name: Argatroban
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
FDC Act: 505(b)(2)
RLD: Argatroban Injection (Pfizer NDA 020883)
Dosage Form: injection, (b) (4)

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 100 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: √ Rx ___OTC

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

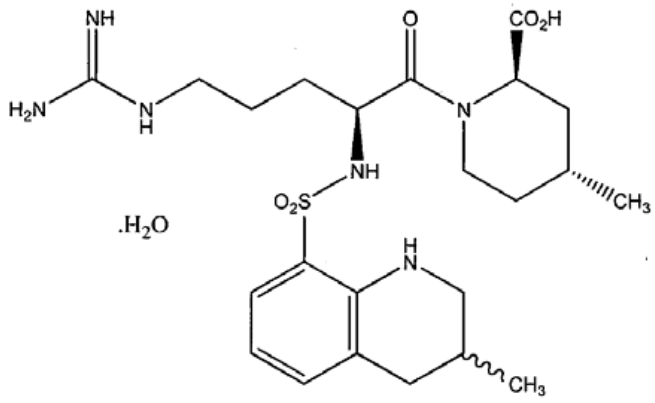
_____SPOTS product – Form Completed

√ Not a SPOTS product

CMC Review Data Sheet

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

Chemical name: (2*R*,4*R*)-4-Methyl-1-N^2-[[(*R*,*S*)-1,2,3,4-tetrahydro-3-methyl-8-quinolonyl]sulfonyl]-L-arginyl]pipecolic acid monohydrate



Empirical Formula	$C_{23}H_{36}N_6O_5S.H_2O$
Molecular Weight	526.65
CAS Registry Number	(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)		3	Adequate	19-NOV-2008
	III			3	Adequate	2-FEB-2011 Milagros Salazar, CMC review #1 N201-811
	III			1	Adequate	28-Dec-2012 George Lunn
	III			1	Adequate	19-Sept-2012 Donald Klein
	III			1	Adequate	25-Jun-2012 Marla Steven Riley

CMC Review Data Sheet

[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
IND		
NDA		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES	Withhold	18-JAN-2013	OC Overall Recommendation
Pharm/Tox	Approval	11-JAN-2013	Shwu Luan Lee
Biopharm	Approval	24-APR-2012	Angelica Dorantes, Ph.D
EA	Adequate	30-JUN-2012	Anne Marie Russell, Ph.D.
Microbiology	Approval	25-FEB-2013	John W. Metcalfe, Ph.D.

Chemistry Review of NDA 201-811

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

APP has not yet provided acceptable responses to the deficiencies identified in the Complete Response letter dated 23-JUL-2012. As a result, the application cannot be recommended for approval at this time. In addition, the NDA received an Overall Recommendation of Withhold from the Office of Compliance on 18-JAN-2013.

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

None

II. Summary of CMC Assessments

A. Responses to Complete Response (Summary)

The drug product manufacturing site; Grand Island, NY failed inspection. The NDA received an Overall Recommendation of Withhold from the Office of Compliance on 18-JAN-2013.

Some of the additional deficiencies identified in the Complete Response letter were resolved in this review cycle, but some remain unresolved. See review for more detailed information.

B. Basis for Approvability or Not-Approval Recommendation

The NDA received an Overall Recommendation of Withhold from the Office of Compliance on 18-JAN-2013. This is the basis for the not-approval recommendation. Additionally, there are outstanding CMC issues need to be addressed adequately by the applicant.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

B. Endorsement Block:
(See appended electronic signature page)

C. CC Block: entered electronically in DARRTS

CMC Assessment

I. Introduction

Original Submission: The Chemistry, Manufacturing and Controls review of APP's original submission was completed on 16-FEB-2011 (Milagros Salazar-Driver, Ph.D.). The application was found to be deficient in several areas, including no manufacturing site for Drug Product. A Complete Response Letter was issued to APP on 24-Feb-2011 (Review Cycle #1).

Complete Response 2012: APP submitted a Complete Response (31-JAN-2012). The CMC review of this CR was completed on 06-JUL-2012 (Anne Marie Russell, Ph.D.). The application was found to be deficient in several areas, including an overall WITHHOLD recommendation from the Office of Compliance for the new manufacturing site in Grand Island, NY. A Complete Response Letter was issued to APP on 23-JUL-2012 (Review Cycle #2).

Complete Response 2013: Fresenius, formerly APP, submitted a Complete Response (12-OCT-2012). This CMC review #3 is an assessment of that Complete Response (Review Cycle #3).

II. New Information submitted in the Complete Response:

- Corporate name change from APP to Fresenius
- Updated Letters of Authorization with the Fresenius corporate name
- Updated stability data (18 months) on Grand Island Drug Product lots submitted in Complete Response 2012 (Review Cycle #2).
- No additional Drug Product lots manufactured since Complete Response 2012
- Additional DMFs for vials and stoppers (b) (4)
    - LOA for (b) (4) submitted to DMF on 15-Oct-2013, receipt date in DARRTS 23-Oct-2012
    - LOA for (b) (4) submitted to DMF on 15-Oct-2013, receipt date in DARRTS 23-Oct-2012
    - LOA for (b) (4) submitted to DMF 6-Nov-2012, receipt date in DARRTS 3-Dec-2012.

III. Review of Responses to Complete Response Letter :

Each deficiency is evaluated individually. The **deficiencies are in bold font**, followed by the *Applicant's responses which are in italics* and then the review/comments/evaluation which are in normal font. The deficiency numbering matches that used in the Complete Response letter dated 23-JUL-2012.

1. **The HPLC method for determination of argatroban and impurities and identification of argatroban (10-08-03-6457) and validation report PR-08-00037 contain acceptance criteria for impurities in the raw material and finished product with unjustifiably high values [for example, the percent relative standard deviation (RSD) for precision of NMT (b) (4) % at an impurity level of more than (b) (4), and the percent RSD for precision of NMT (b) (4) % at an impurity level of less than (b) (4)]. The same high values are observed in the proposed acceptance criteria for the percent RSD for intermediate precision as well as the percent change in solutions from the initial timepoint. Therefore, revise the acceptance criteria to more accurately match your analytical data ((b) (4) %) and conduct the proposed future validation utilizing the revised criteria prior to future testing.**

Applicant Response:
Fresenius provided updated criteria for future validation and data from current validation to demonstrate conformity to the updated criteria. See Table 1 and Table 2.

Table 1: Raw Material Precision Results for Argatroban Impurities and Future Validation Criteria

Table 2: Finished Product Precision Results for Argatroban Impurities and Future Validation Criteria

Evaluation: Acceptable.

2. Provide the certificates of analysis and control testing data for all argatroban, API lots used in the preparation of the drug product for any proposed manufacturing site(s), utilizing the proposed NDA test methods. Note that the Summary of Test Results (SOTR) submitted for lots of drug substance (1002935, 1009636 and 1002937) used to manufacture the exhibit lots of drug product (R340-032, R340-033 and R340-034), reported test results using the defunct isomeric ratio test method (10-08-03-6457) instead of the current method (10-08-03-6689).

Applicant Response:
Fresenius provided revised summary of test results (SOTR) for API lots (1002935, 1002936 and 1002937) used in the preparation of the drug product (exhibit lots: R340-032, R340-033, and R340-034) manufactured at FK USA's Grand Island, NY facility using the current isomeric ratio test method (10-08-03-6689). Lot 1002935 reproduced below. Lots 1002936 and 1002937 very similar.

SUMMARY OF TEST RESULTS
INNOVATION AND DEVELOPMENT

ARGATROBAN

(Version 6.0, Page 1 of 2)

Fresenius Kabi USA, LLC

8045 Lamon Avenue
Suite 300
Skokie, Illinois 60077
T 847-983-7100
F 847-983-7054
www.fresenius-kabi.us

Manufacturer: (b) (4)

Manufacturer's Lot Number: AGT09L006

Expiration /Retest Date: (b) (4)

Date of Manufacture:: 06/23/2009

APP SAP Lot #: 1002935

APP Specification Version: 8.0

TEST	METHOD, VERSION, AND DATE TESTED	SPECIFICATION	RESULTS
Description	Visual Examination Tested: 05/06/2010	White, crystalline powder	White, crystalline powder
Identification A. Infrared Absorption B. HPLC	(b) (4)		A. Meets requirements B. Meets requirements
Water			(b) (4)
Heavy Metals			
Residue on Ignition			
Residual Solvents			
Isomeric Ratio / HPLC			
Assay / HPLC			

[1] Per Option 1

Evaluation: Acceptable.

3. **Include full quality control specifications for the individual 21-R and 21-S isomers of argatroban as part of the methodology proposed for isomeric ratio. The proposal to submit manufacture's Certificate of Analysis and to confirm the structure of using proton NMR is does not provide sufficient quality control for these reference standards. Provide specifications, including attribute, test method and acceptance criteria.**

Applicant Response:
Proposed specifications submitted:

Table 3.2.S.5- 1 Specification for Individual Isomers Argatroban 21-S and 21-R

(b) (4)

Comment:
The above specifications, first proposed in this resubmission, are for the R and S reference standards used in the new isomeric ratio method (#10-08-03-6689) previously submitted to the NDA in review cycle #2 in response to deficiency 3h in the original Complete Response Letter. The information submitted at that time in support of this new method did not include adequate characterization of the reference standards. Of most concern were the absence of any specifications for acceptance testing of the reference standards and inadequacy of the proposed method for confirmation of the isomer structure by NMR testing at (b) (4)

In review cycle #2, the applicant referenced isomer identification by proton NMR spectra collected (b) (4)

(b) (4)

Evaluation: Not Acceptable

Comment for the CR letter:

Provide the Analytical Procedure and Validation of Analytical Procedure for the method used in the Identification Test cited in "Table 3.2.S.5-1 Specification for Individual Isomers Argatroban 21-S and 21-R" and demonstrated adequacy of the method to distinguish the individual isomers.

4. **Provide comparative purity profile data for the RLD and the proposed product. The file of the referenced Report #PD11-NPA-018 in the Complete Response was not included in the submission.**

Applicant Response:
Fresenius provided reports PD11-NPA-018 and PD11-NPA-018 Amendment 1 which reported data for Reference listed drug lot C511442 (RLD) and APP finished product lot R340-032 (FP) - analyzed by APP's finished product method. See Table 1 below.

TABLE I
Impurity Data Comparison

RLD Versus APP Finish Product

Sample	(%)					
	Impurity (b) (4)	Impurity	Impurity	Impurity	Impurity	Total Impurities (%)
APP FP R340-032	(b) (4)					
RLD C511442						
	(b) (4)					

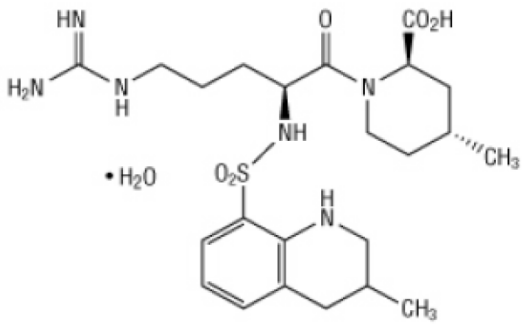
Comment: RLD lot C511442 and APP/Fresenius lot R340-032 similar impurity profile. Further, the impurity profile of RLD (N20883), as evaluated in CMC review (dated 29-JUL-2005, author Ali Al-Hakim, retrieved from DARRTS) for lots C111559, 653803A, 653853A and 865303A is very similar as that reported in Table 1 above for lot C511442.

Evaluation: Acceptable

5. **Provide specifications at release and during stability for impurities** (b) (4) **Refer to ICH Q3B(R2) - Impurities in New Drug Products. The file of the referenced Report #PD11-NPA-018 in the Complete Response, submitted to support the proposal to omit impurities, was not included in the submission.**

Applicant Response:
Fresenius provided report PD11-NPA-018 which includes data to support the proposed omission of API process impurities (b) (4)

Argatroban structure



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CMC Assessment Section

Table 3.2.P.5.1- 1 Regulatory Specifications for Argatroban Injection

Test	Acceptance Criteria	Test Method[1]
Description	Liquid in an amber glass vial	Visual Inspection
Visual Inspection:		
A. Clarity	A. Clear	A. USP <1>
B. Particulate Matter	B. Essentially free of visible particulates	B. USP <1>
C. Visual Color	C. Colorless to slightly yellow	C. 10-08-05-6005
Volume Check[2]	NLT (b) (4)	USP <1>
Instrumental Color (b) (4)	NMT	99-08-00-6016 (I & D)[4] 03-08-07-0057 (site)[4]
Identification:[2]		
A. UV spectra using photodiode array detector	A. The extracted spectra collected between 200 nm and 350 nm at the apex of the argatroban peak in the *Standard Preparation* and *Finished Product Assay Preparation* exhibit maxima at the same wavelength (± 2 nm).	A. 10-08-03-6457
B. HPLC	B. The chromatogram of the *Finished Product Sample Preparation* exhibits a major peak for (R) -argatroban and (S) -argatroban, for which the retention times correspond to those exhibited in the chromatogram of the *Standard* (b) (4)	B. 10-08-03-6457

Impurities:		
A. Known Impurity (b) (4)	A. NMT (b) (4)%	10-08-03-6457
B. Any Other Impurity	B. NMT %	
C. Total Impurities	C. NMT %	
Isomeric Ratio	Isomer R (b) (4) % Isomer S: %	10-08-03-6689
Argatroban Assay Label Claim: 100 mg/mL	(b) (4) % of label claim	10-08-03-6457
Container/Closure Integrity[3] (b) (4)	(b) (4)	A. 10-08-03-6458 (specific) 10-08-00-6015 (general) B. 10-08-00-6031 (general) 10-08-00-6032 (specific)
Particulate Matter in Injections	(b) (4) particles/container articles/container	USP <788>
Bacterial Endotoxin	NMT (b) (4)	USP <85>
Sterility[2]	Sterile	USP <71>
Other Requirements[2]	Meets the requirements under Injections USP <1>	USP <1>
(b) (4)		

Evaluation: Acceptable

7. Report the test method (including version) and indicate the date testing was conducted on all submitted data – including Summary of Test Result (SOTR), certificates of analysis, batch analysis reports and stability reports.

Applicant Response:
Documentation were revised to include the test method (including version)and the date test was conducted for the following:

• Section 3.2.S.4.4 - Summary of Test Results (SOTR) for API lots API lots (1002935, 1002936 and 1002937) used in the preparation of the drug product (exhibit lots: R340-032, R340-033, and R340-034) manufactured at FK USA's Grand Island, NY facility. (See deficiency 2).

• *Section 3.2.P.5.4 - Certificate of Analysis (CoA) for drug product (exhibit lots: R340-032, R340-033, and R340-034).* See below.

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(b) (4)

Evaluation: Not Acceptable

Comment for the CR letter:

Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.

III. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Labeling for carton and container, revised to include the new corporate name, were submitted in this Complete Response. The current carton and container (vial) labeling adequately addresses the six deficiencies cited by DMEPA review (13-DEC-2010) as recorded in CMC review #1 (dated 16-FEB-2011, author Milagros Salazar Driver).

Per the recent draft guidance, Draft Guidance for Industry *"Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex"* (March 11, 2013) the proposed carton statement "This carton closure is not made with natural rubber latex" is consistent with recommended language.

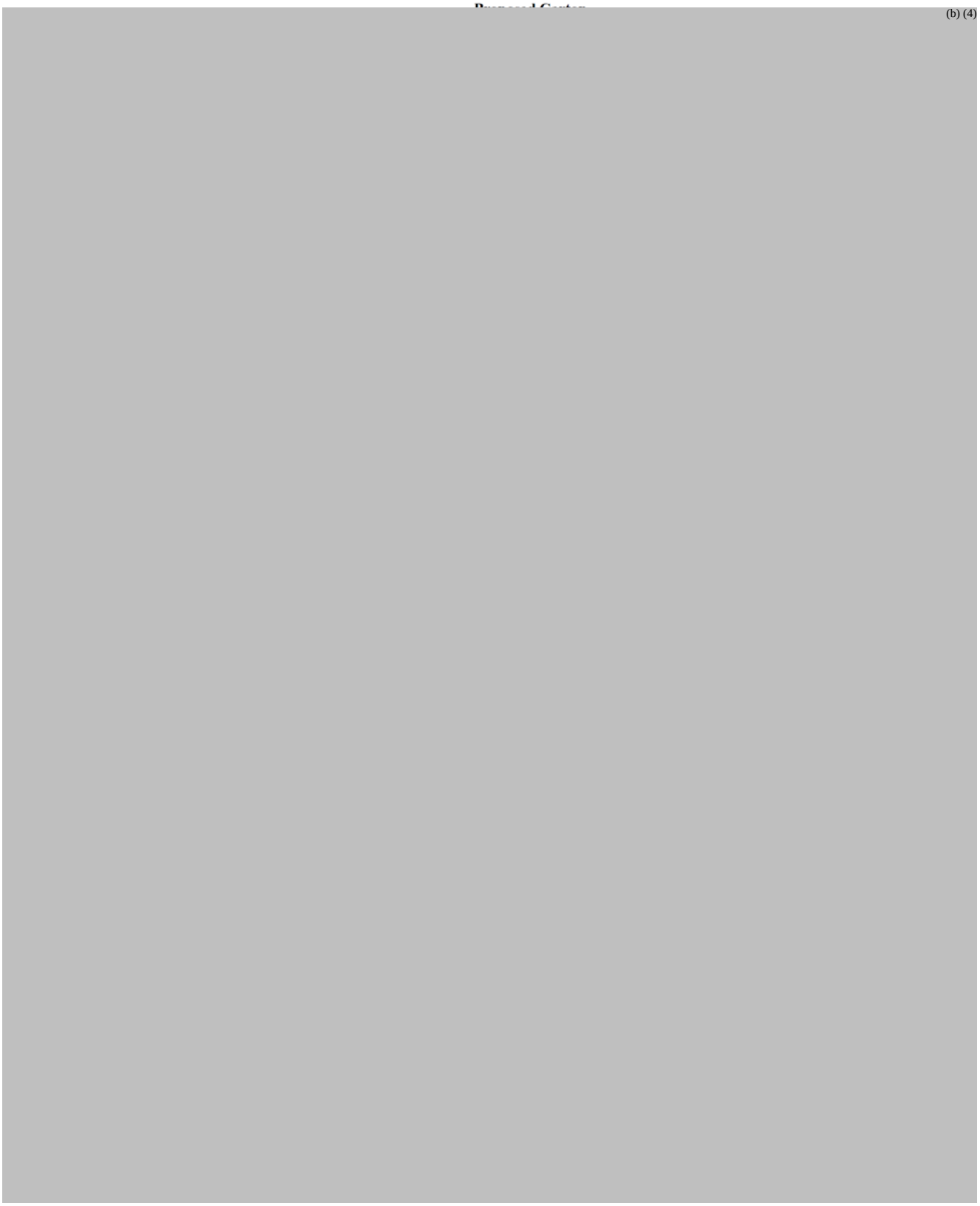
However, the statement "(b) (4)" in section 11 description of the drug product in product labeling is not covered in the guidance and should be evaluated in the next review cycle.

Evaluation: Acceptable except for latex statement (see comment above). See labels below.

CMC Assessment Section

Proposed Center

(b) (4)



B. Environmental Assessment Or Claim Of Categorical Exclusion

N/A

C. Establishment Evaluation Report

A recommendation to withhold was issued by the Office of Compliance on 18-JAN-2013 for the NDA (Grand Island facility failed inspection).

-----Original Message-----
From: ees_admin@fda.gov [mailto:ees_admin@fda.gov]
Sent: Friday, January 18, 2013 3:07 PM
To: Russell, Anne Marie; Olagbaju, Bose*; Godwin, Francis; Brown, Janice; Martin, Jewell; Salganik, Maria*; Kyada, Yogesh*
Subject: Overall OC Recommendation NDA 201811/000 Decision: WITHHOLD, Decision Date: 01/18/2013, Re-evaluation Date:

This is a system generated email message to notify you that the
Overall Compliance Recommendation has been made for the above Application.

IV. List Of Deficiencies Communicated and Resolved

This Complete Response resolved some deficiencies, but several remain unresolved in this review cycle. These remaining deficiencies are identified in the review. See the next section of the review for deficiencies to be communicated in the Complete Response letter for this review cycle.

V. List Of Deficiencies to be Communicated in the Complete Response letter:

1. Provide the Analytical Procedure and Validation of Analytical Procedure for the method used in the Identification Test cited in “Table 3.2.S.5-1 Specification for Individual Isomers Argatroban 21-S and 21-R” and demonstrated adequacy of the method to distinguish the individual isomers.

2. Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.

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

/s/

ANNE M RUSSELL
03/19/2013

ALI H AL HAKIM
03/19/2013

NDA 201-811
Complete Response

Argatroban Injection
100 mg/mL (250 mg/2.5 mL vial)

APP Pharmaceuticals, LLC

Anne Marie Russell, Ph.D.
CMC Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II
for
Division of Hematology Products (DHP)

Table of Contents

CMC Review Data Sheet

1. NDA 201-811

2. REVIEW #: 2 (Complete Response)

3. REVIEW DATE: 30-JUN-2012

4. REVIEWER: Anne Marie Russell, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA submission	02-APR-2010
Amendments	
02……	28-JUN-2010
03……	1-JUL-2010
04……	5-AUG-2010
05……	3-Sep-2010
06……	15-OCT-2010
07……	22-NOV-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Stamp Date
Complete Response NDA Submission	0009	31-JAN-2012
Amendment CMC	0010	14-MAY-2012
Amendment Container and Carton	0012	7-JUN-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	APP Pharmaceuticals, LLC
Address:	1501 East Woodfield Rd – Suite 300E Chaumburg, IL 60173
Representative:	
Telephone:	(847) 969-2700

8. DRUG PRODUCT NAME/CODE/TYPE:

CMC Review Data Sheet

a) Proprietary Name: Argatroban
b) Non-Proprietary Name: Argatroban
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
   FDC Act: 505(b)(2)
   RLD: Argatroban Injection
   Dosage Form: injection, (b) (4)

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 100 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

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

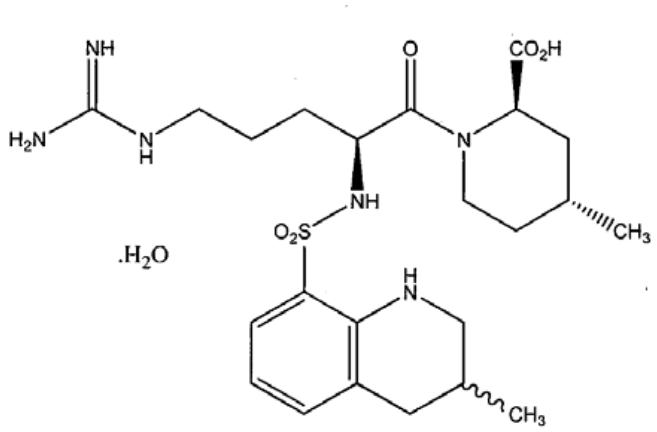
_____ SPOTS product – Form Completed

__√__ Not a SPOTS product

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

Chemical name: (2*R*,4*R*)-4-Methyl-1-N^2-[[(*R*,*S*)-1,2,3,4-tetrahydro-3-methyl-8-quinolonyl]sulfonyl]-L-arginyl]pipecolic acid monohydrate

CMC Review Data Sheet



Empirical Formula	$C_{23}H_{36}N_6O_5S.H_2O$
Molecular Weight	526.65
CAS Registry Number	(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	19-NOV-2008	LOA
	III			3	Adequate	2-FEB-2011 Milagros Salazar, CMC review #1 N201-811	LOA

[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
IND		
NDA		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES	Withhold	22-FEB-2012	OC Overall Recommendation
Pharm/Tox	Approval	04-JUN-2012	Shwu Luan Lee
Biopharm	Approval	24-APR-2012	Angelica Dorantes, Ph.D
LNC	Not applicable		
Methods Validation	Not applicable, according to the current ONDQA policy		
ODS/DMEPA*	Pending at time of review	30-JUN-2012	
EA	Adequate	30-JUN-2012	Anne Marie Russell, Ph.D.
Microbiology	Approval	29-JUN-2012	John W. Metcalfe, Ph.D.

*DMEPA: Division of Medication Error Prevention and Analysis

Chemistry Review of NDA 201-811

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

APP has not yet provided acceptable responses to the deficiencies identified in the Complete Response letter dated 24-FEB-2011. As a result, the application cannot be recommended for approval at this time.

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

None

II. Summary of CMC Assessments

A. Responses to Complete Response (Summary)

In response to the first deficiency regarding the closed drug product manufacturing site, APP manufactured new lots of drug product at a new manufacturing site; Grand Island, NY. This site failed inspection. The NDA received an Overall Recommendation of Withhold from the Office of Compliance on 22-FEB-2012.

Some of the additional deficiencies identified in the Complete Response letter were resolved in this review cycle, but many remain unresolved. See review for more detailed information.

B. Basis for Approvability or Not-Approval Recommendation

The NDA received an Overall Recommendation of Withhold from the Office of Compliance on 22-FEB-2012. Consequently, the response to Deficiency #2 is not adequate. This is the basis for the not-approval recommendation.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

B. Endorsement Block:
(See appended electronic signature page)

C. CC Block: entered electronically in DARRTS

CMC Assessment

I. Introduction

The Chemistry, Manufacturing and Controls review of APP's original submission was completed on 16-FEB-2011. The application was found to be deficient in several areas. Marketing approval would, therefore be contingent on submission of complete and acceptable responses to deficiencies.

II. Review of Responses to Complete Response Letter :

Each deficiency is evaluated individually. The **deficiencies are in bold font**, followed by the *Applicant's responses which are in italics* and then the review/comments/evaluation which are in normal font. The deficiency numbering matches that used in the Complete Response letter dated 24-FEB-2011.

1. **N/A (non-clinical deficiency regarding specification for Impurity (b) (4). See non-clinical review.**

2. **As you confirmed in the 19-Nov-2010 teleconference, all information in the submitted Module 3 applies to a manufacturing site that is no longer manufacturing the proposed drug product. Therefore, the submitted information does not support a commercially viable product.**

   The new manufacturing site for drug product is APP Pharmaceuticals, LLC at 3159 Stanley Road Grand Island, New York 14072. The most recent FDA inspection at APP's Grand Island, NY manufacturing facility took place during 13 June 2011 to 08 July 201. Three lots (exhibit batches: R340-032, R340-033 and R340-034) were manufactured in October 2010.

   Evaluation
   This site received a withhold recommendation from the Office of Compliance on 22-Feb-2012. This is cause for CMC recommending a Complete Response action in this review cycle.

   Unsatisfactory. See List of Deficiencies to be Communicated (#1)

3. **Although the submitted information applies to a commercially non-viable product, the following deficiencies were identified during this review cycle and are provided for your reference. While these deficiencies are not comprehensive, consider these deficiencies, as applicable, in your development of a complete and updated Module 3:**

Drug Substance:

a. For Related Compounds (b) (4) revise the acceptance limits to conform with ICH Q3A Impurities in New Drug Substances, or provide appropriate qualification data.

Revised specifications submitted(below) reduce the acceptance limit to NMT (b) (4) %.

Table 1. Regulatory Specifications for Argatroban

Tests	Acceptance Criteria	Test Method[1]
Description	White, crystalline powder	Visual Examination
Identification: A. Infrared Absorption B. HPLC	(b) (	(b) (4)
Water		
Heavy Metals		
Residue on Ignition		
Residual Solvents		
Residual Solvents		
Isomeric Ratio		
Assay		
Related Substances		
(b) (4)		
Microbial Bioburden		
Bacterial Endotoxin		
(b) (4		
		(b) (4)

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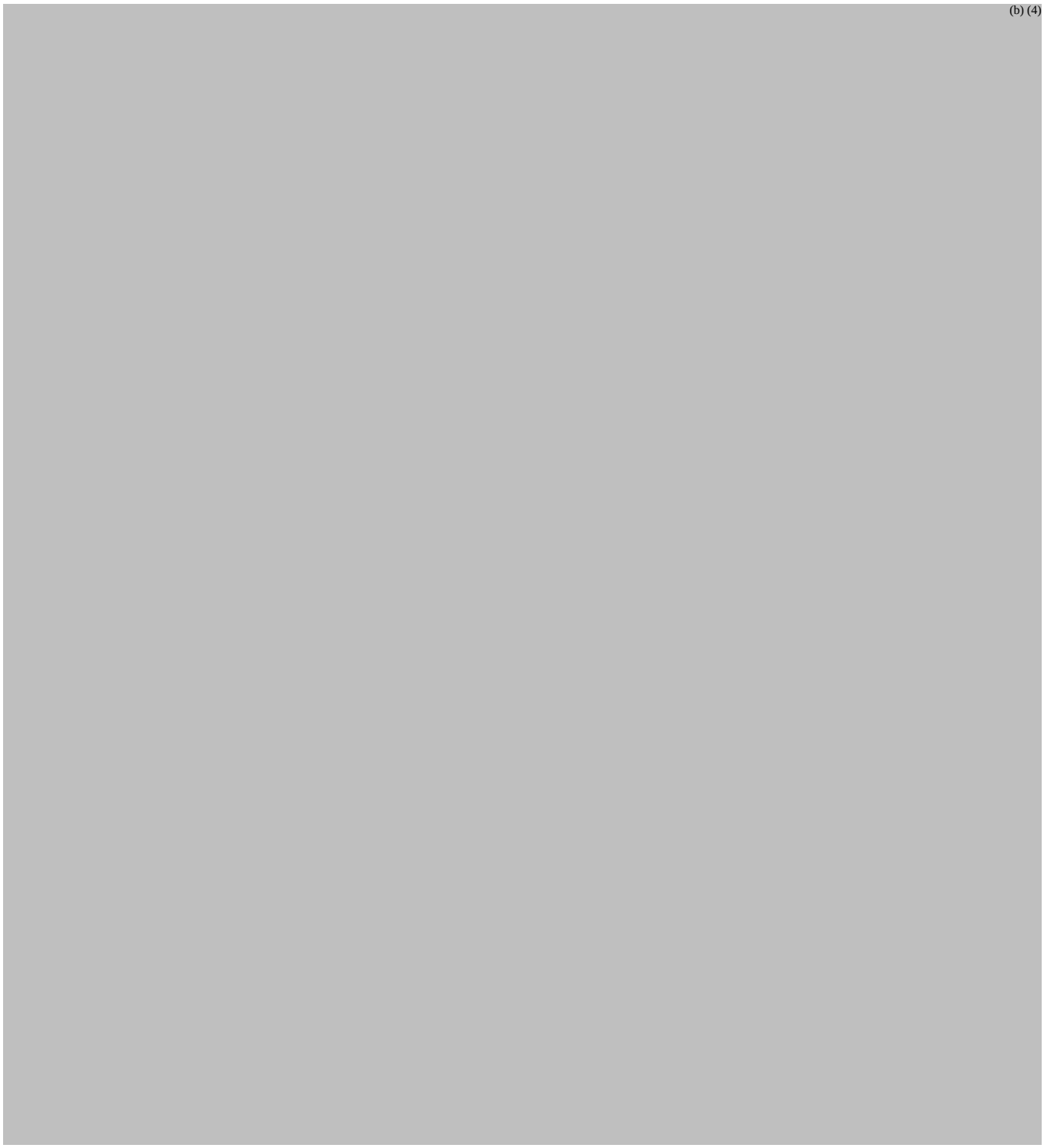
(b) (4)



Drug Product:

j. Revise the drug product specifications by adding testing and acceptance criteria for isomeric ratio at release and during stability studies.

Provided for release test specifications, but not for stability testing.

Table 3.2.P.5.1- 1 Regulatory Specifications for Argatroban Injection

Test	Acceptance Criteria	Test Method[1]
Description	Liquid in an amber glass vial	Visual Inspection
Visual Inspection:		
A. Clarity	A. Clear	A. USP <1>
B. Particulate Matter	B. Essentially free of visible particulates	B. USP <1>
C. Visual Color	C. Colorless to slightly yellow	C. 10-08-05-6005
Volume Check[2]	NLT (b) (4)	USP <1>
Instrumental Color (b) (4)	NMT	99-08-00-6016 (I & D)[4] 03-08-07-0057 (site)[4]
Identification:[2]		
A. UV spectra using photodiode array detector	A. The extracted spectra collected between 200 nm and 350 nm at the apex of the argatroban peak in the *Standard Preparation* and *Finished Product Assay Preparation* exhibit maxima at the same wavelength (± 2 nm).	A. 10-08-03-6457
B. HPLC	B. The chromatogram of the *Finished Product Sample Preparation* exhibits a major peak for (R) -argatroban and (S) -argatroban, for which the retention times correspond to those exhibited in the chromatogram of the *Standard* (b) (4)	B. 10-08-03-6457
Impurities:		
A. Known Impurity (b) (4)	A. NMT (b) (4) %	10-08-03-6457
B. Any Other Impurity	B. NMT %	
C. Total Impurities	C. NMT (b) (4) %	
Isomeric Ratio	Isomer R: (b) (4) Isomer S:	10-08-03-6689
Argatroban Assay Label Claim: 100 mg/mL	(b) (4) of label claim	10-08-03-6457
Container/Closure Integrity[3] (b) (4)	(b) (4)	A. 10-08-03-6458 (specific) 10-08-00-6015 (general) B. 10-08-00-6031 (general) 10-08-00-6032 (specific)
Particulate Matter in Injections	(b) (4) articles/container rticles/container	USP <788>
Bacterial Endotoxin	NMT (b) (4)	USP <85>
Sterility[2]	Sterile	USP <71>
Other Requirements[2]	Meets the requirements under Injections USP <1>	USP <1>
(b) (4)		

CMC Assessment Section

Comment sent to the Applicant in IR#1 26-April-2012:

Revise the stability specifications for the drug product to include testing and acceptance criteria for isomeric ratio.

Response to comment received 14-MAY-2012:

Provided.

Comment:

The specifications for stability testing were updated to include the isomeric ratio.

Table 3.2.P.8.1- 1 Regulatory Specifications for Argatroban Injection

Test	Acceptance Criteria	Test Method[1]
Description	Liquid in an amber glass vial	Visual Inspection
Visual Inspection:		
A. Clarity	A. Clear	A. USP <1>
B. Particulate Matter	B. Essentially free of visible particulates	B. USP <1>
C. Visual Color	C. Colorless to slightly yellow	C. 10-08-05-6005
Instrumental Color (b) (4)	NMT (b) (4)	99-08-00-6016 (SEQ-0000) 03-08-07-0057 (SEQ-0000)
Impurities:		
A. Known Impurity (b) (4)	A. NMT (b) (4) %	10-08-03-6457 (SEQ-0000)
B. Any Other Impurity	B. NMT %	
C. Total Impurities	C. NMT %	
Isomeric Ratio	Isomer R (b) (4) Isomer S	10-08-03-6689 (SEQ-0010)
Argatroban Assay (b) (4) Label Claim: 100 mg/mL	of label claim	10-08-03-6457 (SEQ-0000)
Container/Closure Integrity: (b) (4) (b) (4)		A. 10-08-03-6458 (SEQ-0000) 10-08-00-6015 (SEQ-0000) B. 10-08-00-6031 (general) 10-08-00-6032 (specific)
Particulate Matter in Injections (b) (4)	particles/container articles/container	USP <788>
Bacterial Endotoxin	NMT (b) (4)	USP <85>
(b) (4)		

CMC Assessment Section

The drug product stability test schedule for commercial stability batches was updated to include isomeric ratio at all time points.

Table 3.2.P.8.2 - 1 Stability Test Schedule for Commercial Stability Batches for Argatroban Injection; Controlled Room Temperature (25±2°C/60 ± 5% RH)

Test Name	Test Point (months)							
	0	3[3]	6	9[3]	12[1]	18	24[1]	36[2]
Description	(b) (4)							
Visual Inspection								
Instrumental Color								
Impurities								
Isomeric Ratio								
Argatroban Assay								
Container/Closure Integrity[4]								
Particulate Matter in Injections								
Bacterial Endotoxin								
	(b) (4)							

:

Evaluation:

Satisfactory

k. Provide comparative purity profile data for the RLD and the proposed product.

The Applicant stated that this information was submitted in Section 3.2.P.2.4.1 "Determination of Process-Related Impurities (b) (4) *in Argatroban Injection by HPLC" in Report #PD11-NP/A-018. The file was not found in the submission.*

Also, the file for Report #PD11-NP/A-019, described in Section3.2.P.2.4.2 "Identification of Impurity (b) (4) *in Argatroban Injection by Liquid Chromatography Mass Spectrometry (LCMS)" was not found in the submission.*

Evaluation:

Unsatisfactory. See List of Deficiencies to be Communicated (#5).

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(b) (4)

III. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Review completed for PI, carton and container. No further action due to Complete Response.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Pursuant to 21 CFR § 25.31(a), APP Pharmaceuticals, LLC claimed a categorical exclusion from the requirements of an environmental impact analysis statement. Under 21 CFR § 25.31(a), a categorical exclusion exists for Action on a 505(b)(2) NDA if the action does not increase the use of the active moiety. Further, APP Pharmaceuticals, LLC certified that, to the best of its knowledge and in its opinion, its Grand Island, New York manufacturing facility is in compliance with all federal, state and local environmental protection requirements and that it has a certified waste disposal program, as provided in the submitted EPA COMPLIANCE STATEMENT.

Evaluation: Satisfactory.

C. Establishment Evaluation Report

A recommendation to withhold was issued by the Office of Compliance on 22-FEB-2012 for the NDA (Grand Island facility failed inspection).

> From: ees_admin@fda.gov [mailto:ees_admin@fda.gov]
> Sent: Wednesday, February 22, 2012 8:04 AM
> Subject: Overall OC Recommendation NDA 201811/000 Decision: WITHHOLD, Decision Date: 02/22/2012, Re-evaluation Date:
>
> This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

IV. List Of Deficiencies Communicated and Resolved

This Complete Response resolved some deficiencies, but several outstanding deficiencies remain. These remaining deficiencies are identified in the review above as **Unsatisfactory**. See the next section of the review for deficiencies to be communicated in the Complete Response letter for this review cycle.

One CMC information request (IR) letter was conveyed to the applicant on 26-APR-2012. Refer to pertinent sections of this review for the comments and an evaluation of the applicant's response received 14-MAY-2012.

V. List Of Deficiencies to be Communicated

1. During a recent inspection of the APP Pharmaceuticals manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved

2. The HPLC method for determination of argatroban and impurities and identification of argatroban (10-08-03-6457) and validation report PR-08-00037 contain acceptance criteria for impurities in the raw material and finished product with unjustifiably high values [for example, the percent relative standard deviation (RSD) for precision of NMT (b) (4) % at an impurity level of more than (b) (4), and the percent RSD for precision of NMT (b) (4)% at an impurity level of less than (b) (4)]. The same high values are observed in the proposed acceptance criteria for the percent RSD for intermediate precision as well as the percent change in solutions from the initial timepoint. Therefore, revise the acceptance criteria to more accurately match your analytical data ((b) (4)%) and conduct the proposed future validation utilizing the revised criteria prior to future testing.

3. Provide the certificates of analysis and control testing data for all argatroban, API lots used in the preparation of the drug product for any proposed manufacturing site(s), utilizing the proposed NDA test methods. Note that the Summary of Test Results (SOTR) submitted for lots of drug substance (1002935, 1009636 and 1002937) used to manufacture the exhibit lots of drug product (R340-032, R340-033 and R340-034), reported test results using the defunct isomeric ratio test method (10-08-03-6457) instead of the current method (10-08-03-6689).

4. Include full quality control specifications for the individual 21-R and 21-S isomers of argatroban as part of the methodology proposed for isomeric ratio. The proposal to submit manufacture's Certificate of Analysis and to confirm the structure of using proton NMR is does not provide sufficient quality control for these reference standards. Provide specifications, including attribute, test method and acceptance criteria.

5. Provide comparative purity profile data for the RLD and the proposed product. The file of the referenced Report #PD11-NPA-018 in the Complete Response was not included in the submission

.

6. Provide specifications at release and during stability for impurities (b) (4). Refer to ICH Q3B(R2) - Impurities in New Drug Products. The file of the referenced Report #PD11-NPA-018 in the Complete Response, submitted to support the proposal to omit impurities, was not included in the submission.

7. In the drug product stability protocol, revise the specifications to include other individual impurities. The proposal to omit the impurities was not supported due to the absence of Report #PD11-NPA-018 from the submission.

8. Report the test method (including version) and indicate the date testing was conducted on all submitted data – including Summary of Test Result (SOTR), certificates of analysis, batch analysis reports and stability reports.

9. Provide acceptance, release and stability test data conducted using the current submitted methods for all lots of drug substance and drug product. Identify any test data conducted using outdated test methods.

10. Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.

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/s/

ANNE M RUSSELL
07/06/2012

JANICE T BROWN
07/06/2012

NDA 201-811

Argatroban Injection
100 mg/mL (250 mg/2.5 mL vial)

APP Pharmaceuticals, LLC

Milagros Salazar, Ph.D.
CMC Review Chemist

Office of New Drug Quality Assessment
Division I, Premarketing Branch II
for
The Division of Hematology Products (DHP)

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-811

2. REVIEW #: 1

3. REVIEW DATE: 15-Feb-2011

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N (b) (4)	RTF 4/1/2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	2-Apr-2010
Amendment-0002	28-Jun-2010
Amendment-0003	1-Jul-2010
Email with responses to AIR	6-Oct-2010
Email on DP manufacturing facility	14-Oct-2010
Amendment-0004	5-Aug-2010
Amendment-0005	3-Sep-2010
Amendment-0006	15-Oct-2010
Amendment-0007	22-Nov-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	APP Pharmaceuticals, LLC
Address:	1501 East Woodfield Road - Suite 300E Schaumburg, IL 60173
Representative:	N/A
Telephone:	(847) 969-2700

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Argatroban
b) Non-Proprietary Name (USAN): Argatroban
c) Code Name/# (ONDC only): 512603

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3, 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 100 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

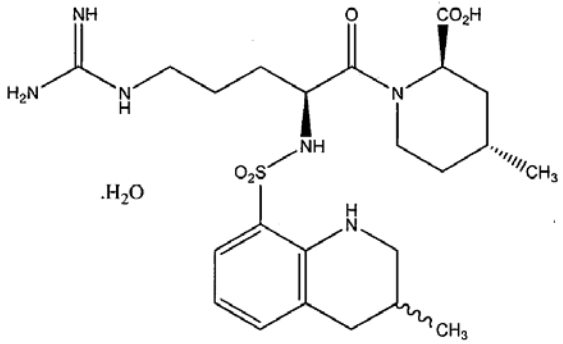
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical name: (2*R*,4*R*)-4-Methyl-1-N^2-[[(*R*,*S*)-1,2,3,4-tetrahydro-3-methyl-8-quinolonyl]sulfonyl]-L-arginyl]pipecolic acid monohydrate



Empirical Formula	$C_{23}H_{36}N_6O_5S.H_2O$
Molecular Weight	526.65
CAS Registry Number	(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW	COMMENTS

						COMPLETED	
(b) (4)	II		(b) (4)	3	Adequate	19-Nov-2008	LoA 27-Jun-2008
	III			4	Adequate	2-Feb-2011	LoA 20-Jun-2008
	III			4	Adequate	2-Feb-2011	LoA 13-Feb-2008
	III			4	Adequate	2-Feb-2011	LoA 1-Apr-2008

[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 (location) 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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Withhold	7-Oct-2010	OC Overall Recommendation

Pharm/Tox	Not Approval	2-Feb-2011	Shwu Luan Lee, Ph.D.
Clinpharm	In review		Hua Zhang, Ph.D.
LNC	N/A		
Methods Validation	N/A	2-Feb-2011	Milagros Salazar, Ph.D.
DMEPA	Changes recommended	13-Dec-2010	Yelena Maslov, Pharm.D.
EA	Inadequate	2-Feb-2011	Milagros Salazar. Ph.D.
Microbiology	Not Approval	13-Jan-2011	John Metcalfe, Ph.D.

N/A = Not Applicable

Review Team:

PM-OND: Ebla Ali Ibrahim
PM-ONDQA: Don Henry
Clinical: Foroozeh Alvandi
Clin Pharm: Hua Zhang
Pharm/Tox: Shwu Luan Lee
CMC: Milagros Salazar
Micro: John Metcalfe
Marketing & Adv consumer reviewer: Juwon Lee
Marketing & Adv professional reviewer: James Dvorsky
Marketing & Adv Reg PM: Michael Wade
DMEPA: Yelena Maslov

The Chemistry Review for NDA 201-811

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This is a recommendation not to approve this product from the Chemistry, Manufacturing and Controls (including Microbiology) standpoint. The original application provided CMC information for argatroban injection as manufactured by APP Pharmaceuticals, LLC at the Barceloneta, PR site. Although the Barceloneta site was proposed in the NDA as the drug product manufacturing site, the company actually closed the site on 30-Aug-2010, which was discovered during the FDA's pre-approval inspection process. Accordingly, there is an overall recommendation of withhold from the Office of Compliance as of 7-Oct-2010. In addition, there are outstanding CMC and Microbiology deficiencies. Therefore, this application cannot be recommended for approval.

The CMC section for the drug produced at the Barceloneta site is covered in this review. While the information applies to a site no longer producing this product, major deficiencies related to the identification and quantitation of the 21-*(R)* and 21-*(S)* stereoisomeric ratio and inadequate specifications for the drug substance and the final drug product were noted. These identified deficiencies are listed below and at the end of this review and should be referenced in future review cycles. However, the following deficiencies are not comprehensive, and additional CMC deficiencies may be identified when reviewing updated information for a new site.

The following language should be inserted in the CR action letter:

1. As you confirmed in the 10-Nov-2010 teleconference, all information in the submitted Module 3 applies to a manufacturing site that is no longer manufacturing the proposed drug product. Therefore, the submitted information does not support a commercially viable product.

2. Although the submitted information applies to a commercially non-viable product, the following deficiencies were identified during this review cycle and are provided for your reference. While these deficiencies are not comprehensive, consider these deficiencies, as applicable, in your development of a complete and updated Module 3.

a. Argatroban, API

1.- For Related Compound (b) (4) revise the acceptance limits to conform with ICH Q3A-Impurities in New Drug Substances, or provide appropriate qualification data.

2.- Report all individual impurities/related compounds present at levels at or above (b) (4) % .

3.- Include a test and propose criteria for (b) (4) content in the proposed specification.

4.- Establish a base line resolution for the isomeric ratio in the proposed quantitation method (10-08-03-6457),. Confirm that the acceptance limit for resolution between the individual *R*- and *S*-isomers of argatroban is at least (b) (4).

5.- For the method of determination of the isomeric ratio of argatroban (10-08-03-6457), provide for the use of the individual *R*- and *S*- isomers reference standards of argatroban, and utilize them to adequately evaluate the accuracy, precision, linearity, intermediate precision and quantitation limit of this test.

6.- The HPLC method for determination of argatroban and impurities and identification of argatroban (10-08-03-6457) and validation report PR-08-00037 contain acceptance criteria for impurities in the raw material and finished product with unjustifiably high values [for example, the percent relative standard deviation (RSD) for precision of NMT (b) (4)% at an impurity level of more than (b) (4) and the percent RSD for precision of NMT (b) (4)% at an impurity level of less than (b) (4). The same high values are observed in the proposed acceptance criteria for the percent RSD for intermediate precision as well as the percent change in solutions from the initial timepoint. Therefore, revise the acceptance criteria to more accurately match your analytical data.

7.- Provide the certificates of analysis and control testing data for all argatroban, API lots used in the preparation of the drug product for any proposed manufacturing site(s).

b. Argatroban, Reference Standards

8.- Include full quality control specifications for the individual 21-*R* and 21-*S* isomers of argatroban as part of the methodology proposed for testing identification, assay and isomeric ratio.

9.- Provide certificates of analysis for the individual 21-*R* and 21-*S* isomers of argatroban, as generated by the reference standard supplier.

c. Argatroban, 100 mg/mL, Injection

10.- Revise the drug product specifications by adding testing and acceptance criteria for isomeric ratio at release and during stability studies.

11.- Provide comparative purity profile data for the RLD and the proposed product.

12.- Provide specifications at release and during stability for impurities (b) (4). Refer to ICH Q3B(R2)- Impurities in New Drug Products.

13.- In addition to the testing proposed, include the following in the stability protocol:

- A test for individual 21-*(R)* and 21-*(S)* argatroban diastereomers at specified time intervals consistent with ICH Guidance Q1A(R2) –Stability Testing of New Drug Substance and Products.

- Revise specifications for Impurity (b) (4) and other individual impurities as described above.

14.- Submit validation for the analytical method for isomeric ratio determination in argatroban injection using the individual 21-*R* and 21-*S* argatroban diastereomers as reference standards.

15.- Provide the specific location in DMF (b) (4), including volume, page numbers and date, in which the appropriate cross-referenced information on the stopper is located.

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

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine. The chemical name for argatroban is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate. Argatroban has 4 asymmetric carbons. 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. 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. In solution, argatroban is a zwitter ion. The drug substance is manufactured by (b) (4) (b) (4) and supported by an acceptable Type II DMF (b) (4). The control specification for the impurities was found not acceptable based on the innovators proposed levels, ICH Q3B recommendations and the lack of qualification studies, which was assessed by the pharmacology review team in their review dated 2-Feb-2011.

Argatroban Injection is a sterile clear, colorless to pale yellow, slightly viscous solution. Argatroban Injection is available in 250 mg (in 2.5 mL) single-use amber vials. Each mL of sterile, nonpyrogenic solution contains 100 mg argatroban. Inert ingredients: 954 mg propylene glycol. Each 2.5 mL vial contains 250 mg of argatroban; and, as supplied, is a concentrated drug (100 mg/mL), which must be diluted 100-fold prior to infusion. The Product number is 5126601 with NDC number 63323-526-03. The storage of the vials in original cartons is recommended to be at room temperature [25°C (77°F), (b) (4)]. Do not freeze and to retain in the original carton to protect from light are additional caution statements. (b) (4) The expiration dating proposed is (b) (4) months.

The drug product specifications were found deficient in the full identification and quantification of the R-S-stereoisomers and their ratio in the drug product. This was evident based on the lack of adequate reference standards for separate isomers and the lack of resolution of the se isomers in the analytical HPLC method proposed for their identification

and quantitation. According to the original submission, the drug product was to be manufactured at the APP Barceloneta, Puerto Rico plant. However, the company decided to close up that plant in August of 2010 based on a business decision which was discovered upon the FDA inspection. As a result, the Office of Compliance issued an overall recommendation of withhold for the application on 7-Oct-2010. During the T-con of 19-Nov-2010 between the company and the review team (clinical, non/clinical, clin/pharm/, CMC and PM), the FDA explained that approvability was not possible at this time because if the application did not provide a viable manufacturing site and drug product. A determination to issue an action letter with a complete response letter was communicated to the applicant.

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

It is intended as single-dose sterile, (b) (4), manufactured (b) (4). The product is a concentrate drug of 100 mg/mL and must be diluted 1:100 fold prior to infusion. 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 product is a direct thrombin inhibitor indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia, and as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI). It is a narrow therapeutic drug. The recommended initial dose of argatroban is 2 micrograms/kg/min (not to exceed (b) (4) micrograms/kg/min). The intended maximum daily dose (MDD) is (b) (4).

C. Basis for Approvability or Not-Approval Recommendation

This application is filed under 505 (b)(2) regulatory status. The RLD is approved under NDA 20-883. Based on the lack of a manufacturing site to produce the drug product, as per 21 CRF 211 and mayor CMC deficiencies found under 21 CFR 314.50, this application is not recommended for approval.

III. Administrative

A. Reviewer's Signature

Review Chemist, Milagros Salazar, Ph.D./Date:

B. Endorsement Block

Branch Chief/ Sarah Pope, Ph.D./Date

C. CC Block

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/s/

MILAGROS SALAZAR DRIVER
02/15/2011
CMC recommendation: Not Approval.

SARAH P MIKSINSKI
02/16/2011

Initial Quality Assessment (IQA)
For
Division of New Drug Quality Assessment I, Branch II
Office of New Drug Quality Assessment

OND Division: DHP
NDA: 201-811
Applicant: APP Pharmaceuticals, LLC. 1501 East Woodfield Road, Suite 300 East, Schaumburg, IL 60173
Stamp Date: 04/05/2010
PDUFA Date: TBD, pending whether priority or standard
Trademark: Argatroban Injection
Established Name: Argatroban
Dosage Form: Sterile solution
Route of Administration: IV
Indication: "An anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia." It is indicated for "patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)."

CMC Lead: Eldon E. Leutzinger, Ph.D.

ONDQA Fileability YES NO

Comments for 74-Day Letter (Not at this time, and awaits start of formal review)

Summary and Critical Issues:

A. Summary

Drug Product

The Chemical Type is 5 (New Formulation – New Manufacturer), and is determined by DHP for a standard review.
Argatroban drug product is a clear, colorless to pale yellow, slightly viscous solution. Each milliliter of drug product contains the following:

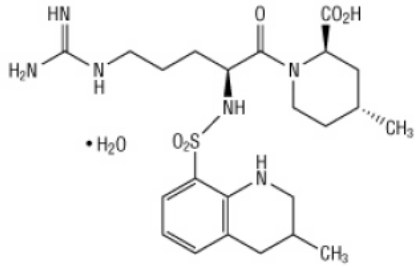
100 mg Argatroban
Approx. (b) (4) mL of Propylene glycol (or (b) (4)% v/v)

The drug product is packaged (primary) as a 2.5 mL solution in (b) (4) amber (b) (4) glass vials (Type I), with 13 mm, and a 13 mm stopper (b) (4), and a 13 mm Flip-cap, (b) (4) aluminum crimp seal. The glass (b) (4) vial is obtained from (b) (4) or (b) (4). Stoppers and Fli-Cap aluminum crimp seals are obtained from (b) (4). Secondary

packaging consists of individual cartons, made of (b) (4) paperboard.

COMMENTS:
Since the level of propylene glycol is (b) (4) in APP's Argatroban drug product, than what has commonly been used in FDA-approved IV products (30% - 82%), the safety of this level should be determined by P/T and the clinical reviewers.

Argatroban drug substance is 2-Piperidinecarboxylic acid, 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-, monohydrate, $C_{23}H_{36}N_6O_5S \cdot H_2O$; CAS No: [141396-28-3]. It has a MW of 526.65, and has the following structure:



Argatroban drug substance is a white crystalline powder with melting point of 179 ± 3^0C (Merck Index). It has a specific optical rotation of $[\alpha]_D^{27}$ of $+ 76.1^0$; APP indicates that typical values in 0.2 N HCl conform to this value. Argatroban is very slightly soluble in water, sparingly soluble in ethanol, and is insoluble in acetone, ethyl acetate, chloroform and diethylether.

The CMC section is in CTD format, and a brief look-through of the sections appear to be complete, accounting for all of the expected parts of the standard CTD format for CMC.

B. Critical Issues for Review

Drug Substance

A reference standard for argatroban is used to determine whether the ratio of isomers (R and S) conforms to the specification (3.2.S.4.1). Yet, it is not clear from the certificate of analysis (b) (4) how they know which isomer is which. This bears on the issue of authenticity of the standard, and bears on the issue of accuracy of the isomeric composition, an issue that has been existent for other argatroban applications. Although this may turn out to be a non-issue for this application, it is noted here as a potential issue and the primary reviewer should be aware of these considerations – that this issue has been existent with the other argatroban applications. This is Issue #1. I have spoken to the reviewer (Milagros Salazar, Ph.D.) about this already, so she is aware of the potential issue. Also, I have advised her to talk with the CMC reviewer of the previous NDA's on argatroban, since the same issue of isomeric ratio was part of an extensive exchange with the applicants of those NDA's. Some of the issues surrounding the isomeric ratio have been resolved in the previous applications, but

it is not clear at this point how it will relate to NDA 201-811. I have not identified any other specific issues regards the drug substance, based on this very preliminary review.

Drug product

The main issue for drug product is its proposed packaging - in either of two container systems – both amber, (b) (4) Type I USP glass vials (b) (4) . Both vials are closed with (b) (4) -2 faced stoppers by (b) (4) and capped with aluminum flip-cap seals (provided by either (b) (4)). References to DMF's are made for each of these component parts. Only one glass vial supplier (b) (4) was used for the exhibit stability batches. On the face of what is provided, one might consider there not to be any concerns for not including vials from the other supplier in the stability studies – on the assumption that Type 1 glass is the same from any source. However, it is well-known that glass is not all the same (even that in Type 1), due to the ingredients going into the manufacture of the glass. There could be effects on the chemical stability of product packaged in the two different vials. That is well-known to be the case for radiopharmaceuticals. Whether this will be an issue for argatroban is to be determined – may be theoretical, but needs to be considered. There could also be effects on microbiological stability. This is Issue #2 and is of concern because of its impact from a stability standpoint as the data is not completely representative of the entire line of container closure expected to be used in the marketed drug.

C. Comments for 74-Day Letter

No comments are being recommended for the 74-day letter, based on the initial review of the application, and will defer to a more in-depth analysis by the reviewer.

The reviewer has determined the status of fileability, and I fully agree on the basis of a cursory independent examination of the application. The following was provided by the reviewer, and I am reproducing it accordingly:

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		Ready for CGMP inspection statement provided.
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	only data for one of the two proposed vials has been provided
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			N/A-no pre-NDA meeting, previous submission as NDA (b) (4), with a RTF on 4/1/2009
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has an investigational formulations section been provided?	√		
14	Is there a Methods Validation package?		√	eCTD contains DP analytical procedures and their validation in Sections 3.2.P.5.2 & P.5.3; Specs in Section 3.2.P.5.1 and Batch analysis in Section 3.2.P.5.4.
15	Is a separate Microbiological section included?			N/A –eCTD format
16	Have all consults been identified and initiated?		√ √	DMEPA Microbiology Biopharm Statistics LNC DMETS/ODS

Drug Master Files
Reproduced from information provided by Milagros Salazar (CMC Reviewer of this applkication)

DMF Number	Holder	Description	LOA Included	Status
(b) (4) Type II	(b) (4)		27-Jun-2008	Adequate
(b) (4) Type III			20-Jun-2008	Adequate
(b) (4) Type III			13-Feb-2008	Adequate
(b) (4) Type III			1-Apr-2008	Adequate

Inspections for this application have been entered into EES. There is one manufacturing site, indicated as follows:

Address: APP Pharmaceuticals, LLC **(FINAL DOSAGE MANUFACTURER)**
Road 140 Km 64.4
Barceloneta, Puerto Rico 00617 **FEI: 3005724920**

The following are listed othersites envolved in this application (list provided by the reviewer). See the next page.

Facility Name	Address	Contact Information	CFN / EIN	Responsibilities
(b) (4)				

Facility Name	Address	Contact Information	CFN / EIN	Responsibilities
(b) (4)				
APP Pharmaceuticals, LLC	Call Box 7070 Road 140 Km. 64.4 Barceloneta, Puerto Rico 00617	Rosaura Ortiz, Director of QA/QC Phone: (787) 621-5000 Fax: (787) 621-5193 Email: rortiz@APPpharma.com	3005724920	FP manufacturing, release/stability testing, and packaging; API release testing
APP Pharmaceuticals, LLC	2045 North Cornell Avenue Melrose Park, IL 60160	David Bowman, VP of Product Development Phone: (708) 343-6100 Fax: (708) 486-2095 Email: dbowman@APPpharma.com	1421790	Product development, and alternate API release, and FP release/stability testing
APP Pharmaceuticals, LLC	2020 Ruby Street Melrose Park, IL 60160	Anne Huffman, Director of QA/QC Phone: (708) 345-6170 Fax: (708) 450-7563 Email: ahuffman@APPpharma.com	1450022	Alternate API release, and FP release/stability testing
APP Pharmaceuticals, LLC	3159 Staley Road Grand Island, NY 14072	Anne Huffman, Director of QA/QC Phone: (708) 345-6170 Fax: (716) 773-0846 Email: ahuffman@APPpharma.com	1321116	Alternate API release, and FP release/stability testing
(b) (4)				

All the facilities listed are ready for cGMP inspection. For complete details, refer to SECTIONS 3.2.S.2 and 3.2.P.3.1.

COMMENTS:
I have checked the NDA submission for accuracy in this information, and concur with the reviewer. All sites have been entered into EES.

CMC Lead: Eldon E. Leutzinger, Ph.D. Date: 05/25/2010
Division of New Drug Quality Assessment III
Branch VII

Branch Chief (Acting): William Adams, Ph.D.
Division of New Drug Quality Assessment I
Branch II

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201811	ORIG-1	APP PHARMACEUTICALS LLC	ARGATROBAN INJECTION

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/s/

ELDON E LEUTZINGER
05/26/2010

WILLIAM M ADAMS
05/26/2010
William Adams, acting for Sarah Pope Miksinski