

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206769Orig1s000**

**CHEMISTRY REVIEW(S)**

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

**Application:** NDA 206769/000  
**Org. Code:** 161  
**Priority:** 5  
**Stamp Date:** 28-FEB-2014  
**PDUFA Date:** 28-DEC-2014  
**Action Goal:**  
**District Goal:** 29-OCT-2014

**Sponsor:** TEVA PHARMS USA  
425 PRIVET RD  
HORSHAM, PA 19044  
**Brand Name:** ARGATROBAN INJECTION  
**Estab. Name:**  
**Generic Name:** ARGATROBAN INJECTION  
**Product Number; Dosage Form; Ingredient; Strengths**  
001; INJECTION; ARGATROBAN; 250MG

<b>FDA Contacts:</b>	W. ADAMS	Prod Qual Reviewer	3017961321
	J. COLE	Micro Reviewer	3017965148
	T. AGOSTO	Product Quality PM	2404023777
	N. KORMANIK	Regulatory Project Mgr	2404024227
	J. BROWN	Team Leader	3017961652

---

**Overall Recommendation:** ACCEPTABLE on 24-SEP-2014 by T. SHARP ( ) 3017963208  
PENDING on 18-MAR-2014 by EES\_PROD

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

**DMF No:** **AADA:**  
**Responsibilities:** FINISHED DOSAGE LABELER  
**Profile:** (b) (4) **OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 20-MAR-2014  
**Decision:** ACCEPTABLE  
**Reason:** BASED ON PROFILE

---

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

**DMF No:** **AADA:**  
**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 20-MAR-2014  
**Decision:** ACCEPTABLE  
**Reason:** BASED ON PROFILE

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**NDA 206769**

**Argatroban Injection  
250 mg/250 mL**

**Teva Pharmaceuticals USA**

**William M. Adams**

**Review Branch II**

**Division of New Drug Quality Assessment I**

**Office of New Drug Quality Assessment**

**For the Division of Hematology Products  
Office of Hematology and Oncology Products**



# CMC Review Data Sheet

1. **NDA 206,769**
2. **REVIEW #2**
3. **REVIEW DATE:** 23 Nov 2014
4. **REVIEWER:** William Adams
5. **PREVIOUS DOCUMENTS:** None
6. **SUBMISSION(S) BEING REVIEWED:** See CMC Review 01 dated 13 Nov 2014
7. **NAME & ADDRESS OF APPLICANT:** See CMC Review 01 dated 13 Nov 2014
8. **DRUG PRODUCT NAME/CODE/TYPE:** See CMC Review 01 dated 13 Nov 2014
9. **LEGAL BASIS FOR SUBMISSION:** 505(b)(2)
10. **PHARMACOL. CATEGORY:** See CMC Review 01 dated 13 Nov 2014
11. **DOSAGE FORM:** Injection
12. **STRENGTH/POTENCY:** 50 mg/250 mL (large volume parenteral)
13. **ROUTE OF ADMINISTRATION:** IV infusion
14. **Rx/OTC DISPENSED:**  Rx  OTC
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** No
16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:** See CMC Review 01 dated 13 Nov 2014
17. **RELATED/SUPPORTING DOCUMENTS:** Se CMC Review 01 dated 13 Nov 2014
18. **CONSULTS/CMC-RELATED REVIEWS:** See CMC Review 01 dated 13 Nov 2014



## The CMC Review for NDA 206769

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

The proposed application is recommended for APPROVAL from the CMC perspective in that complete and acceptable supporting information has been provided.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None**

#### II. Summary of CMC Assessments

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

###### DRUG PRODUCT

Biopharmaceutics (review dated 14 Nov 2014) concluded that the request for waiver of *in vivo* BA/BE requirements is justified based on the evaluation of *in vitro* study 6000133 by Clinical Pharmacology (review dated 19 Nov 2014).

See also CMC Review 01.

DRUG SUBSTANCE: See CMC Review 01 dated 13 Nov 2014

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

The product is intended to be administered in adults by IV infusion without further dilution.

##### C. Basis for Approvability or Not-Approval Recommendation

The original CMC recommendation for this NDA was approvable pending satisfactory Clinical Biopharmaceutics review and conclusion. (see CMC Review 01 dated 13 Nov 2014). Clinical Biopharmaceutics has completed their review and recommended approval for this NDA. Therefore, the NDA is recommended for APPROVAL from the CMC perspective in that complete and acceptable supporting information has been provided regarding the drug substance, drug product and labeling; the manufacturing and controls sites have been shown to meet cGMP requirements; and the request for biowaive has been granted.



CMC Assessment Section

**III. Administrative**

**A. Reviewer's Signature:**

William M. Adams

CMC Reviewer/Branch II/DNDQA I/ONDQA

Digitally signed by William M. Adams -A

DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300006782, cn=William M. Adams -A

Date: 2014.11.24 07:11:44 -05'00'

**B. Endorsement Block:**

Ali al Hakim, Ph.D.

Chief/Branch II/DNDQA I/ONDQA

**Ali H. Al-**

Digitally signed by Ali H. Al- Hakim

-S

DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=13000

93815, cn=Ali H. Al- Hakim -S

Date: 2014.11.24 10:49:31 -05'00'

**Hakim -S**

**C. CC Block: entered electronically in DFS**

DHP/RPM/N.Kormanik

DNDQA I/PMQ/J.Martin

DNDQA I/CMC Lead/J.Brown



**CMC REVIEW**



**NDA 206769**

**Argatroban Injection  
250 mg/250 mL**

**Teva Pharmaceuticals USA**

**William M. Adams**

**Review Branch II**

**Division of New Drug Quality Assessment I**

**Office of New Drug Quality Assessment**

**For the Division of Hematology Products  
Office of Hematology and Oncology Products**

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CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 206,769
2. REVIEW #1
3. REVIEW DATE: 13 Nov 2014
4. REVIEWER: William Adams
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<i>eCTD Sequence</i>	<i>Submission</i>	<i>Submission Date</i>
S-000/SD-001	Initial NDA	02/28/14
	Quality filing review	04/12/14
	NDA filing review issues letter	05/02/14
S-002/SD-003	Revised package insert and labels	06/07/14
S-003/SD-004	Withdraw alternate labeling site	07/02/14
S-005/SD-006	Response to NDA filing letter	07/22/14
	IR letter for CMC	09/23/14
	Email labeling comments	09/25/14
	Email labeling comments	10/03/14
S-006/SD-007	Response to CMC IR letter	09/29/14
S-007/SD-008	Updated labels & labeling per 09/25/14 & 10/03/14	10/08/14
	IR letter for CMC labeling	10/30/14
S-008/SD-009	Updated CMC documents for S-006	11/05/14
S-009/SD-010	Response to IR letter for CMC labeling	11/04/14

7. NAME & ADDRESS OF APPLICANT:

Name           Teva Pharmaceuticals USA  
 Address       425 Privet Road, Horsham, PA 19044  
 Representative   [REDACTED] (b) (4)  
 Telephone     [REDACTED]  
 E-mail         [REDACTED]

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:                   None
- b) Non-Proprietary Name (USAN):   Argatroban Injection
- c) Code Name/# (ONDQA only):       None
- d) Chem. Type/Submission Priority (ONDQA only):

CMC Review Data Sheet

- **Chem. Type:** 5
- **Submission Priority:** Standard

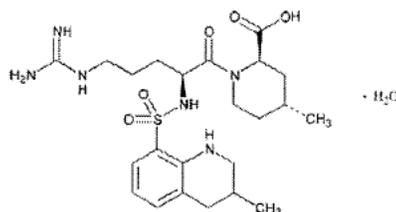
9. **LEGAL BASIS FOR SUBMISSION:** 505(b)(2)
10. **PHARMACOL. CATEGORY:** Prophylaxis and treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT); and anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
11. **DOSAGE FORM:** Injection
12. **STRENGTH/POTENCY:** 50 mg/250 mL (large volume parenteral)
13. **ROUTE OF ADMINISTRATION:** IV infusion
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:**

Molecular Formula  $C_{23}H_{36}N_6O_5S \cdot H_2O$   
 Molecular Weight 526.65 amu  
 Molecular Structure



17. **RELATED/SUPPORTING DOCUMENTS:**

A. **Supporting DMFs:**

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS <sup>3</sup>
(b) (4)	II	(b) (4)	Bulk API	3	acceptable	last review 10/25/13	In support of Sandoz NDA



CMC Review Data Sheet

(b) (4)						(b) (4)
	III	(b) (4)	4			
	III		4			
	III		4			
	III		4			

<sup>1</sup> 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")

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

<sup>3</sup> Include reference to location in most recent CMC review

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND (b) (4)	Teva	Drug Product	N/A	N/A	preNDA meeting

**18. CONSULTS/CMC-RELATED REVIEWS:**

CONSULTS	SUBJECT	DATE FORWARD	REVIEWER	STATUS
EES	GMP for CMC sites		OC	Approval in Panorama
Clinical Pharmacology	Biowaiver based on PD study		Y.Moon	Review Pending
Quality Microbiology	Process Qualification Studies		J.Cole	Approval; review dated 08/19/14

## Executive Summary Section

# The CMC Review for NDA 206,769

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The proposed application is APPROVABLE from the CMC perspective in that complete and acceptable information has been provided. The request for biowaiver is pending completion of the evaluation of the in vitro bridging study by the Office of Clinical Pharmacology.

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

No PMCs or PMAs are proposed for CMC.

### II. Summary of CMC Assessments

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

##### DRUG PRODUCT

This is a 505(b)(2) application which references the Sandoz product (argatroban injection, 1 mg/mL) which was FDA-approved on 09 May 2011 under NDA 22485. Composition of the dosage solutions for the Teva and Sandoz products are identical. The Sandoz product is 125 mL dosage solution in a glass vial within a carton. The proposed Teva product is 250 mL dosage solution in a large volume parenteral (LVP) with an overpouch within a carton.

Unit and batches formulation are described in sufficient detail. No excipient is of human or animal origin, or novel. Specifications for the excipients are acceptable. Manufacture is by preparation of bulk solution, (b) (4)

The manufacturing operations, process parameters and in process controls are described in sufficient detail and are acceptable to assure continuous product quality. Copies of executed batch records for the NDA registration batches, and the master production record for the commercial process and controls are provided. Microbiological qualification studies address container closure integrity and sterility assurance; microbiology reviewer found the studies acceptable. Process (b) (4) are qualified for extractables and leachables; non-clinical reviewer found the study results to be acceptable. The proposed sites for product manufacture, testing, packaging and storage have been found to meet cGMP requirements.

The proposed specification is acceptable. The tests are adequate to address appearance, identity, assay, purity, physicochemical attributes, microbiological quality and USP <1> requirements. The analytical methods are described in sufficient and shown to be valid for the intended purpose. The acceptance criteria are appropriately justified based on drug product batch analysis and stability data, USP requirements, and ICH requirements. Impurities are shown to be the same as observed in bulk drug substance and in the reference product at release and on stability.

The proposed Teva product presentation is a set of 5 LVPs within an aluminum foil laminate overpouch within a carton. The LVP consists of a polyolefin laminate bag with a single

## Executive Summary Section

(b) (4) infusion port, (b) (4) stopper and (b) (4) port cover. The LVP bag and carton are labeled. The packaging components are described in sufficient detail and the proposed specifications are acceptable. Product contact components are qualified for extractable and leachables; non-clinical reviewer found the studies to be acceptable.

The drug product batches and protocols for the primary, supportive and post approval studies are acceptable. The post approval commitment is acceptable. Primary stability study data is obtained from three NDA registration batches stored at 25°C/25%RH, 30°C/65%RH and 40°C/25%RH. Data from supportive photostability and freeze-thaw studies is also provided. Since the product is to be used without further dilution and administered over a short period, in-use stability is not mandated. The submitted primary and supportive study data is sufficient to support the proposed initial expiry period of 24 months with a label storage statement of "Store the bag in the 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".

The submitted carton label, LVP bag label and package insert are acceptable.

**DRUG SUBSTANCE**

CMC information is provided by reference to type II drug master file (DMF) (b) (4) from (b) (4) a signed and dated letter of authorization for the DMF is provided. (b) (4) The DMF was last reviewed 26 Nov 2013 and found acceptable to support an (b) (4). CMC amendments filed since this time do not alter the review conclusion.

Provided in the NDA is a summary of key CMC information taken from the referenced DMF including the (b) (4) specification, method validation studies and stability study conclusion for retest period and storage conditions. The proposed Teva sites for manufacture and testing have been found to meet cGMP requirements.

The proposed Teva specification uses the same tests, analytical methods and acceptance criteria as used as the (b) (4) specification. The proposed specifications adequately address identity, assay, impurities, residual solvents and microbiological quality. Teva method transfer study reports are sufficient for the intended purpose. Impurities observed at release and on stability are described in sufficient detail. Batch analysis data is provided for three drug substance lots which were used to manufacture the NDA exhibit drug product batches.

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

The product is intended to be administered in adults by IV infusion without further dilution.

**C. Basis for Approvability or Not-Approval Recommendation**

The proposed application is APPROVABLE from the CMC perspective in that complete and acceptable information has been provided regarding the drug substance, drug product and labeling, and the manufacturing and controls sites have been shown to meet cGMP requirements. The request for biowaiver is pending completion of the evaluation of the in vitro bridging study by the Office of Clinical Pharmacology.



Executive Summary Section

**III. Administrative**

**A. Reviewer's Signature:**

William M. Adams  
CMC Reviewer/Branch II/DNDQA I/ONDQA

Digitally signed by William M. Adams -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300006782, cn=William M. Adams -A  
Date: 2014.11.18 14:30:02 -05'00'

**B. Endorsement Block:**

Ali al Hakim, Ph.D.  
Chief/Branch II/DNDQA I/ONDQA

**Ali H. Al- Hakim - S**  
Digitally signed by Ali H. Al- Hakim -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093815, cn=Ali H. Al- Hakim -S  
Date: 2014.11.18 14:34:04 -05'00'

**C. CC Block: entered electronically in DFS**

DHP/RPM/N.Kormanik  
DNDQA I/PMQ/J.Martin  
DNDQA I/CMC Lead/J.Brown

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**Memorandum**

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

Date: 06-Aug-2014

From: Janice Brown, M.S.  
CMC Lead  
DNDQA I/ONDQA

Through: Ali Al-Hakim, Ph.D.  
Chief, Branch II  
New Drug Quality Assessment Division II  
ONDQA

To: NDA 206769  
Argatroban Injection

Subject: Risk Assessment

As per a new policy, each NDA with GRMP dates on or after August 1, 2014 will include a risk assessment in the Executive summary. This will be based on an initial risk assessment that would be captured in all IQAs written for NDAs received on or after June 1, 2014. It was decided that the CMC Lead would perform a retrospective risk assessment for those NDAs received prior to June 1, 2014 that had GRMP dates after August 1, 2014.

The following IQA template was provided:

**ONDQA Risk Assessment  
Template for Initial Quality  
Assessments of Original NDAs**

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment

In an email dated 30-May-2014, Dr. Ramesh Sood provided follow-up guidance on how to fill out the required IQA template that is used to populate the NDA template. The guidance provided templates for the most common dosage forms.

This memo captures both the table that would normally be in the IQA and populates the first three columns of the NDA template that will be filled in by the primary CMC reviewer.

### IQA RISK ASSESSMENT

Product attribute/ CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment	Risk
Sterility	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						(b) (4)
Endotoxin (b) (4)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						
Assay (API), stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						
Uniformity of Dose (Fill Volume/ Deliverable volume)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						
Osmolality	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						
pH- (High)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						
pH- (Low)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						
Leachable extractables	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						
Appearance (Color/turbidity)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>						

The evaluation from the IQA table was transferred to the following NDA table that can be used by the primary reviewer as a part of the NDA review.

NDA RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations / Comments
Sterility	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	(b) (4)			
Endotoxin (b) (4)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				
Assay (API), stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				
Uniformity of Dose (Fill Volume/ Deliverable volume)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				
Osmolality	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				
pH- (High)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				
pH- (Low)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				
Leachable extractables	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				
Appearance (Color/turbidity)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>				

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE T BROWN  
08/18/2014

ALI H AL HAKIM  
08/18/2014

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

<b>NDA Number</b>	206-769
<b>Submission Date</b>	February 28,2014
<b>Product name, generic name of the active</b>	Argatroban
<b>Dosage form and strength</b>	Injection 250 mg/250 mL (1 mg/mL)
<b>Indication</b>	-for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) -an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
<b>Applicant</b>	TEVA Pharmaceutical Works Private Limited Company
<b>Clinical Division</b>	DHP
<b>Type of Submission</b>	505 (b) (2)
<b>Biopharmaceutics Reviewer</b>	Houda Mahayni, Ph.D.
<b>Biopharmaceutics Team Leader</b>	Angelica Dorantes, Ph.D.

### I. SUBMISSION OVERVIEW

NDA 206769 was submitted in accordance with Section 505(b) (2) of the FDC Act. To support the approval of the proposed product, Argatroban Injection 250 mg/250 mL, the Applicant is relying on FDA's previous finding of safety and effectiveness for the Listed Drug (LD) (Sandoz's approved drug product Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125mL, NDA 022485).

The Applicant described the differences between the proposed drug product and the LD as follows:

*1) The total drug content per container (strength)*

The LD Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125 mL, has a total drug content per container (strength) of 125 mg/125mL. The proposed product has total drug content per container (strength) of 250 mg/250 mL. The proposed drug product will have the same concentration, 1 mg/mL, as the LD product, but will be packaged as a different strength (total drug content per container) of 250 mg/ 250 mL.

*2) Packaging components*

The LD is packaged in a single-use vial, while the proposed drug product is packaged in a (b) (4) bag. The Applicant stated that the use of a (b) (4) bag is more suited for the proposed drug product because the total fill volume of the drug product solution would be two times that of the LD product, Sandoz's Injection (in 0.9% Sodium Chloride), 125 mg/125 mL.

The Applicant stated that the proposed changes in the drug product strength (total drug content per container) and packaging components do not pose questions of safety or efficacy because the formulation, the indications, the doses, and the route of administration of the proposed drug product are the same as those of the LD.

FDA informed the Applicant at the IND stage (IND (b) (4)), in response to the Applicant's question about waiving the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence, to submit a request for a waiver at

## **PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW**

the time of the NDA submission. FDA advised the Applicant to provide the following in support of the biowaiver request:

1. Data from an in vitro bridging study assessing the in vitro equivalence of the anticoagulant pharmacodynamic (PD) activity between the LD product and the proposed product.
2. A comparative side-by-side table listing the components and composition of the LD and the proposed product including the pH and osmolarity values for each.

The Applicant provided the above information and is requesting a waiver of evidence of in-vivo bioavailability requirements for Argatroban Injection, 250 mg/250 mL (1 mg/mL) in accordance with 21 CFR §320.22(b) (1).

### **II. BIOPHARMACEUTICS SUMMARY INFORMATION**

The drug substance for Argatroban Injection, 250 mg/250 mL (1 mg/mL) is Argatroban Monohydrate. Argatroban is a synthetic direct thrombin inhibitor. It is indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) and as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

Argatroban Monohydrate manufactured by [REDACTED] (b) (4) was used for the development and for the manufacture of the finished drug product.

The Applicant stated that Argatroban is very soluble in acetic acid, sparingly soluble in ethanol, very slightly soluble in water, practically insoluble in acetone, ethyl acetate, chloroform and diethylether. Also, Argatroban is non-hygroscopic and has [REDACTED] (b) (4).

The Applicant aimed to develop a drug product that has the same drug substance, formulation, dosage form, route of administration and conditions of use as the LD. The development was performed using a Quality by Design (QbD) approach.

The proposed drug product is supplied in 250 mL [REDACTED] (b) (4) bag with single port, closed by stopper and cap, placed into aluminum foil overpouch with clear window. Argatroban Injection, 250 mg/250 mL is administered as intravenous infusion. The drug product should not be diluted prior to administration.

The components and composition of the drug product are shown in table below.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

**Table 1: Unit Composition for Argatroban Injection, 250 mg /250 mL (1 mg/mL)**  
(source: Module 2.3. Quality Overall Summary Part C)

Components	Concentration (mg/mL)	Each 250 mL bag contains <sup>2)</sup> (mg)	Function	Reference to quality standard
Argatroban (as Argatroban monohydrate)	1.0 (1.035)	250.0 (258.75)	Active ingredient	In-house
Sorbitol	3.0	750.0	(b) (4)	NF
Sodium chloride	9.0	2250.0		USP
Water for Injections	Ad to 1 mL <sup>1)</sup>	Ad to 250 mL <sup>1)</sup>		USP
(b) (4)				

The proposed drug product differs from the LD in total drug content per container and packaging components. The LD is supplied as two single use vials in a package, each vial containing 125 mL of Argatroban Injection (1 mg/mL). The proposed presentation is a bag product containing 250 mL of Argatroban Injection (1 mg/mL).

According to the Applicant the proposed drug product meets the waiver criteria for the following reasons:

1. Argatroban Injection, 250 mg/ 250 mL (1 mg/ mL), is a parenteral drug product intended for administration by injection.
2. The proposed drug product contains the same active and inactive ingredients in the same concentration as LD. A comparative side-by-side table listing the components and composition of the LD product and the proposed drug product is provided in Table 2. The pH and osmolarity values for each are provided in Table 3.
3. An in vitro bridging study demonstrated in vitro equivalence of the anticoagulant pharmacodynamic (PD) activity between LD and the proposed product.

**Table 2: Components and Composition Comparison of the RLD and Teva's Argatroban Injection, 250 mg/250 mL (Source: Module 2.3 Quality Overall Summary Part C)**

Components	Innovator Product: Argatroban Injection in 0.9% Sodium chloride, 125 mg/125 mL (1 mg/mL)		TEVA product: Argatroban Injection, 250 mg/250 mL (1 mg/mL)	
	Concentration / 1.0 mL	Concentration /125.0 mL	Concentration /1.0 mL	Concentration /250.0 mL
Argatroban (as Argatroban monohydrate)	1.0 mg (1.035 mg)	125.0 mg (129.38 mg)	1.0 mg (1.035 mg)	250.0 mg (258.75mg)
Sorbitol	3.0 mg	375.0 mg	3.0 mg	750.0 mg
Sodium chloride	9.0 mg	1125.0 mg	9.0 mg	2250.0 mg
Water for injections	ad 1.0 mL	ad 125.0 mL	ad 1.0 mL	ad 250.0 mL

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

**Table 3: pH and Osmolarity Results of Teva’s Argatroban Injection, 250 mg/250 mL and the RLD**

Test	Method	Requirement	Results			
			Innovator product	TEVA product		
			Batch Number: CC2823	Batch number: K1151012	Batch number: K2871112	Batch number: K2881112
pH	USP<791> DFA-241	3.2 – 7.5	6.1	5.6	6.0	6.4
Osmolarity	USP<785> DFA-116	270-330 mOsmol/kg	309	315	313	312

The Biopharmaceutics review will evaluate the data provided in support of the biowaiver request.

The pharmacodynamic (PD) in vitro bridging study (Study No. 6000133) performed to demonstrate the in vitro equivalence of the anticoagulant pharmacodynamic (PD) activity between LD and the proposed product will be reviewed by OCP.

### III. POTENTIAL REVIEW ISSUES – DAY 74 LETTER COMMENTS

The following parameters for the ONDQA’s Product Quality - Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		x	Solution product – Not Applicable.
2.	Is the dissolution test part of the DP specifications?		x	Solution product – Not Applicable.
3.	Does the application contain the dissolution method development report?		x	Solution product – Not Applicable.
4.	Is there a validation package for the analytical method and dissolution methodology?		x	Solution product – Not Applicable.
5.	Does the application include a biowaiver request?	x		Pursuant to 21 CFR §320.22 (b) (1), the Applicant requests a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data. The proposed drug product contains the same active and inactive ingredients in the same concentration as LD.
6.	Does the application include an IVIVC model?		x	Not applicable.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

7.	<p>Is there a modified-release claim? If yes, address the following:</p> <p style="margin-left: 20px;">a) Is there information submitted to support the claim in accordance with 320.25 (f)?</p> <p style="margin-left: 20px;">b) Is there information on the potential for alcohol-induced dose dumping?</p>	x	Not applicable.
8.	Is information such as BCS classification mentioned, and supportive data provided?	x	Not applicable.
9.	Is information on mixing the product with foods or liquids included?	x	Not applicable.
10.	Is there any <i>in vivo</i> BA or BE information in the submission?	x	Not applicable.
11.	Is there any design space proposed using <i>in vitro</i> release as a response variable?	X	Not applicable. However, this NDA does contain QbD elements.
12.	Is the control strategy related to <i>in vitro</i> drug release?	X	Not applicable.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
13.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		<ul style="list-style-type: none"> <li>The NDA is fileable from Biopharmaceutics Perspective.</li> <li>The acceptability of the biowaiver request is a review issue.</li> </ul>
14.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not Applicable.
15.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	

*{See appended electronic signature page}*

Houda Mahayni, Ph.D.

Biopharmaceutics Reviewer

Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader

Office of New Drug Quality Assessment

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HOUDA MAHAYNI  
04/22/2014

ANGELICA DORANTES  
04/22/2014

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

**IQA and Filing Review Cover Sheet**

**1. NEW DRUG APPLICATION NUMBER:** 206769

**2. DATES AND GOALS:**

Letter Date: 28-Feb-2014	28-Feb-2014
Filing: 29-Apr-2014 74 Day Filing Issues: 05/13/2014 PDUFA Goal Date: 28-Dec-2014	

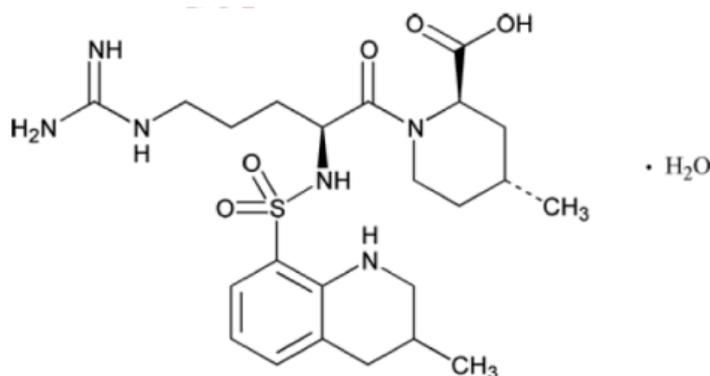
**3. PRODUCT PROPERTIES:**

Trade or Proprietary Name:	None
Established or Non-Proprietary Name (USAN):	Argatroban Injection
Dosage Form:	Injection, Solution
Route of Administration	Intravenous
Strength/Potency	250 mg/250 mL (1 mg/mL)
Rx/OTC Dispensed:	Rx

**4. INDICATION:**

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

**5. DRUG SUBSTANCE STRUCTURAL FORMULA:**



**Molecular formula:** C<sub>23</sub>H<sub>36</sub>N<sub>6</sub>O<sub>5</sub>S · H<sub>2</sub>O

**Molecular Weight:** 526.65 g/mol

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

**6. NAME OF APPLICANT (as indicated on Form 356h):** Teva Pharmaceuticals  
USA

**7. SUBMISSION PROPERTIES:**

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 5
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DHP

**8. CONSULTS:**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		Entered on 16-Dec-2013
Pharmacology/Toxicology	X		Leachable report for the container closure was forwarded to the nonclinical reviewer for evaluation
Methods Validation		X	Not required per IQP 5105
Environmental Assessment	X		A claim of categorical exclusion from the requirement to submit an Environmental Assessment (EA) was provided
CDRH		X	
Other			N.A.

**9. QUALITY REVIEW TEAM:**

Discipline	Reviewer
CMC	William (Mike) Adams
Biopharmaceutics	Houda Mahayni, Ph.D.
Microbiology	Jessica Cole, Ph.D.
Facilities	Vipul Dholakia, Ph.D.

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

**Overall Filing Conclusions and Recommendations**

**CMC:**

<b>Is the Product Quality Section of the application fileable from a CMC perspective?</b> Yes
CMC Filing Issues: None

<b>Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?</b> No
CMC Comments for 74-Day Letter: None

**Microbiology:**

<b>Is the Product Quality Section of the application fileable from a Microbiology perspective?</b> Yes
Microbiology Filing Issues: See Microbiology Filing Review for details and for any potential Microbiology review issues.

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

**Summary of Initial Quality Assessment**

<b>Does the submission contain any of the following elements?</b>			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	

**CMC Summary of Critical Issues and Complexities**

Drug Substance

1. Since impurities are tested using Impurities (b)(4) and Impurities (b)(4) in the DMF holder’s release specification, recommend including testing for impurity using both methods in the stability specification.

Drug Product

2. There is a significant difference in the impurity profile between Teva’s and Sandoz’s Argatroban injection. Teva has identified one impurity and Sandoz has limits for four impurities. (b)(4)  
 (b)(4) The formulation for both Argatroban drug products (b)(4) suggests that Teva’s impurities are underreported. Recommend looking into forced degradation studies have identified all impurities/degradants and confirm that the impurity method is able to detect these impurities.
3. The applicant performed an evaluation of the leachables from the container closure (bag) and numerous leachables were identified. A toxicological qualification was performed on four substances found to be either above the (b)(4) threshold or contain structural alerts. This report was forwarded to nonclinical reviewer for their assessment on leachable levels.
4. The applicant is requesting a 24 month shelf life for Argatroban Injection stored at 20° to 25° C (68° to 77°F) based on 12 month shelf life. (b)(4)  
 (b)(4)
5. The drug product is light sensitive. Results were out of the proposed limits for assay, impurity, appearance, visible particles and color in light exposed samples.

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

**CMC FILING REVIEW CHECKLIST**

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

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

<b>B. FACILITIES*</b>				
* <b>If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			N.A.

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

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

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

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

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

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

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

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Argatroban DS	(b) (4)	--
	III		(b) (4)		--
	III				
	III				
	III				--

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

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page  
 Janice Brown M.S.  
 CMC Lead  
 Division 1  
 Office of New Drug Quality Assessment

{See appended electronic signature page}  
 Ali Al-Hakim, Ph.D.  
 Branch Chief  
 Division 1  
 Office of New Drug Quality Assessment

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

**Initial Quality Assessment**

**SUMMARY**

This 505(b)(2) application relies on the FDA’s finding of safety and effectiveness for the reference listed drug, Argatroban Injection marketed by Sandoz under the approved NDA 22485. Teva’s Argatroban Injection, has the same active and inactive ingredients, strength, dosage form, route of administration, and conditions of use as listed drug in NDA (b) (4). The proposed drug product differs from the listed drug in total drug content per container and packaging components. The reference product is supplied as two single use vials, each vial containing 125 mL of Argatroban Injection (1 mg/mL). Teva’s presentation is a bag containing 250 mL of Argatroban Injection (1 mg/mL). A comparison of the composition of Teva’s and the Sandoz Argatroban injection is reproduced in table 1.

Table 1: Components and Composition Comparison of the LD and Teva’s Argatroban Injection, 250 mg/250mL

Components	Listed drug: Argatroban Injection in 0.9% Sodium chloride, 125 mg/125 mL (1 mg/mL)		TEVA product: Argatroban Injection, 250 mg/250 mL (1 mg/mL)	
	Conc./ 1.0 mL	Conc. /125.0 mL	Conc./1.0 mL	Conc./250.0 mL
Argatroban (as Argatroban monohydrate)	1.0 mg (1.035 mg)	125.0 mg (129.38 mg)	1.0 mg (1.035 mg)	250.0 mg (258.75mg)
Sorbitol	3.0 mg	375.0 mg	3.0 mg	750.0 mg
Sodium chloride	9.0 mg	1125.0 mg	9.0 mg	2250.0 mg
Water for injections	ad 1.0 mL	ad 125.0 mL	ad 1.0 mL	ad 250.0 mL

This NDA contains both CMC and a biopharmaceutics section. The submission did not include clinical, clinical pharmacology and nonclinical sections.

**DRUG SUBSTANCE**

- Argatroban is a direct thrombin inhibitor derived from L-arginine that reversibly binds to the thrombin active site. Argatroban has 4 chiral carbons. (b) (4)  
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 applicant provided a letter of authorization from (b) (4) allowing the agency to review the confidential information in DMF No. (b) (4) for the agratroban drug substance.

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

The DMF was found adequate by the primary reviewer; however, a four item information request was sent to the holder on 11/26/2013. The holder responded to the IR on 1/31/2014. This DMF amendment along with two annual reports requires a review; otherwise the DMF has been found adequate.

3. Based on the maximum daily dose of (b)(4) of argatroban, dosing for an average adult weight of 70 kg is (b)(4). Based on the maximum daily dose of (b)(4), the ICH Q3A(R2) qualification threshold for a drug substance impurity is (b)(4)%. The argatroban drug substance impurity limits are below the (b)(4)% qualification threshold.

Attachment 4 is a comparison of Teva's and DMF Holder's Argatroban Drug Substance Specification as reported in the NDA (module 2). Note that although Teva states that their drug substance specification is (b)(4), there are some differences in the (b)(4) specification as reported in the DMF (see yellow highlights). Although (b)(4) limits for some drug substance impurities are higher, the levels remain below the (b)(4)% qualification threshold.

4. Argatroban drug substance is manufactured by:

(b)(4)

A complete list of manufacturing facilities is appended in attachments 1 and 2.

5. To support filing of this NDA, the drug substance stability data is summarized below. In the most current DMF amendment, SD #16, eCTD # 0000, the holder submitted 60 month drug substance stability update for batches +AGT07L002, +AGT07L003, +AGT07L004. The remaining lots are the annual stability batches. Long-term and accelerated stability results met the proposed acceptance criteria. The results are somewhat unusual since there are no detected impurities or degradants up to 60 months. Since impurities are tested using Impurities (b)(4) and Impurities (b)(4) in the DMF holder's specification, recommend also including both methods in the stability specification.

A summary of the drug substance batches is shown in table 2.

**ONDQA Filing Review and Initial Quality Assessment (IQA)  
NDA 206769, Argatroban Injection, Teva Pharmaceuticals, Inc.**

Table 2: Drug Substance Stability Studies

Drug Substance Batch No.	Manufacture Date	Batch Size	Amount of Stability Data		Comments
			25°C±2°C/ 60%±5% RH	40°C/75% RH	
+AGT07L002	(b) (4)	(b) (4)	60 months	6 months	Testing for impurities was not performed using HPLC (b) (4)
+AGT07L003			60 months	6 months	
+AGT07L004			60 months	6 months	
+AGT08L003			48 months	None	
+AGT09L006			36 months	None	
2218325			24 months	None	
2283222			12 months	None	
2302891			0 months	None	

**DRUG PRODUCT**

6. Instead of a traditional QOS, the applicant is using the OGD QBR format in module 2 which is worth a look through. Reproduced in table 2.3.P.2-4 are the critical material attributes of the argatroban drug substance and the associated risk on the drug product critical quality attributes (CQA). The applicant has reduced the high risk (red squares) attributes by implementing a limit in the drug product specification. The revised risk assessment is reproduced in Table 2.3.P.2-6 based on the drug substance and/or drug product specification controls. (b) (4)

(b) (4)

These CMAs were evaluated during the laboratory studies and are described in section 3.2.P.2.3. A similar risk assessment was performed on the manufacturing process. Both are described in the following sections:

- 32p2.2.- Formulation development
- 32p2.3.- Manufacturing development

The applicant stated that development was performed by a Quality by Design (QbD) approach; however, no regulatory relief is requested.

Included in Table 2.3.P.2-6 below is the revised risk assessment based on the DS and/or DP specification controls

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Table 2.3.P.2-6 Potential impact of Drug Substance CMAs on Drug Product CQAs

CQA	CMA
	API
<i>Appearance</i>	(b) (4)
<i>Assay</i>	
<i>Related substances</i>	
<i>pH</i>	
<i>Osmolality</i>	
<i>Sterility</i>	
<i>Bacterial endotoxins</i>	
<i>Particulate matter</i>	
<i>Container content</i>	
<i> </i>	
Low <sup>1</sup> risk	Risk reduced by appropriate DS and/or DP specification
Low risk	Low/no impact on quality attributes. No further investigation is needed.
High risk	Affects quality attributes. Further investigation and control are needed in order to reduce the risk.

7. Argatroban Injection, 250 mg/250 mL (1 mg/mL) is supplied as a clear, colorless to pale yellow solution, packaged in 250 mL (b) (4) bag with single port which is contained in an aluminium foil overpouch with clear window. The drug product should not be diluted prior to administration.
8. Argatroban Injection is manufactured and tested by Teva Pharmaceutical Works in Hungary. The facilities listed in attachment 2 are involved in the manufacture, testing, labeling, packaging, and distribution of the drug product.
9. The composition of the Argatroban Injection is reproduced in the table 3. All excipients in the product are within IIG limits (b) (4) to the listed drug produced by Sandoz (NDA-022485).

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Table 3: Composition and IIG Limits for Argatroban Injection, 250 mg/250 mL (1 mg/mL)

Ingredients	Amount mg/mL	Amount mg/bag (in 250 mL)	Amount mg/bag with overfill (in 265 mL)	Function	Reference to quality standard	IIG Limit or Other Source; FDA / ANDA Quantity
Argatroban (as Argatroban monohydrate)	1.0 (1.035)	250.0 (258.75)	(b) (4)	Active ingredient	In-house	--
Sorbitol, NF	3.0	750.0	(b) (4)		NF	Up to (b) (4) % IV (Infusion); Injection
Sodium Chloride, USP	9.0	2250.0	(b) (4)		USP	Up to (b) (4) % IV (Infusion); Injection
Water for Injection, USP	q.s	q.s	(b) (4)		USP	N/A

10. The drug product manufacturing flow diagram and drug product specification are reproduced in attachments 5 and 6, respectively. The drug product is (b) (4)
11. The applicant has identified a single impurity, related (b) (4). Reproduced in table 4 is a comparison of the impurity profiles of Teva’s Argatroban injection and the Sandoz Argatroban drug product. Teva’s exhibit batches were stored at 25±2°C/40±5% RH for 12 months and LD lot was stored at ambient room temperature.

Table 4: Comparison of Teva’s and LD (Sandoz) the Impurity Profiles

Tests	Teva Lot K1151012[2]	Teva Lot K2871112[2]	Teva Lot K2881112[2]	RLD Lot CC2823[3]
Related (b) (4) %	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Any unknown impurity, %	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total impurities, %	(b) (4)	(b) (4)	(b) (4)	(b) (4)

There is a significant difference in the impurity profile between Teva’s and Sandoz’s Argatroban injection. Teva has identified one impurity and Sandoz has limits for 4 impurities. (b) (4)

(b) (4) Further, the formulation for both Argatroban drug products (b) (4) suggests that Teva’s related substances are underreported. Recommend looking into forced degradation studies in the method validation to see if the applicant has identified related substances.

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Included below are the impurities extracted from review #1 for Sandoz's Argatroban.

Impurities  (release and stability)	(b) (4)
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12. The container closure system for Argatroban Injection is reproduced in table 5. The applicant performed an evaluation of the leachables from the bag and a numerous leachables were identified. A toxicological qualification was performed on four substances found to be either above the (b) (4) threshold or ones that contain structural alerts. This report was forwarded to nonclinical reviewer for their assessment.

Table 5: Container/closure system

Component	Description	Supplier <sup>1</sup>
Bag	(b) (4)	
Ink		
Stopper		
Port		
Cap		

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Component	Description	Supplier <sup>1</sup>
Overpouch	(b) (4)	

13. The applicant submitted 12 months long term (25°C/60% RH), 12 months at 30°C/65% RH, and 6 months of accelerated (40°C/75% RH) stability data generated on three pilot registration batches. Note that commercial scale will be performed at (b) (4). A summary of the batches used to support the shelf life is shown in table 6. The stability specification is reproduced in attachment 7.

Table 6: Stability Studies Conducted on Argatroban Injection, 250mg/250mL (1mg/mL)

Drug Product Batch No.	Drug Substance Batch No.	Batch Size	Batch Use	Amount of Stability Data		
				25°C/60 % RH	30°C/65 % RH	40°C/75 % RH
K1151012	B2/017169	(b) (4)	Stability	12 mos	12 mos	6 mos
K2871112	B2/017173		Stability	12 mos	12 mos	6 mos
K2881112	B2/022418		Stability	12 mos	12 mos	6 mos

13.1 All test stability data meets the proposed specification under all conditions. No significant changes were seen in the stability-indicating parameters, such as assay, impurities, or pH for any of the pilot registration batches under long-term, intermediate and accelerated storage conditions.

13.2 The applicant is requesting a 24 month shelf life for Argatroban Injection stored at 20° to 25° C (68° to 77°F) based on 12 month shelf life. (b) (4)

13.3 Photo Stability - The drug product is light sensitive. Results were out of the proposed limits for assay, impurity, appearance, visible particles and color in light exposed samples. No difference in the tested parameters was observed between any of the light exposed samples with the overpouch and the unexposed controls.

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/s/  
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JANICE T BROWN  
04/11/2014

ALI H AL HAKIM  
04/12/2014