

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208374Orig1s000

PRODUCT QUALITY REVIEW(S)

1.12.14 Environmental Analysis

1. ENVIRONMENTAL ANALYSIS

1.1 Categorical Exclusion

Pursuant to 21 CFR § 25.31(b), Celerity Pharmaceuticals, LLC (Celerity) hereby claims a categorical exclusion from the requirements of an environmental impact analysis statement. Under 21 CFR § 25.31(b), a categorical exclusion exists for Action on an NDA if the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. Refer to 1.1.1 for calculations.

Consequently, Celerity submits that an environmental impact analysis statement is not required with this application and, therefore, requests that it be categorically excluded from the requirement to submit an environmental impact analysis.

1.1.1 Expected Introduction Concentration (EIC) of an Active Moiety into the Aquatic Environment

According to the *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications* (July 1998), the expected introduction concentration (EIC) of the active moiety, bivalirudin, into the aquatic environment is calculated as follows:

$EIC\text{-Aquatic (ppb)} = A \times B \times C \times D$; where



The estimate of the kilogram/year active moiety should be based on or include (1) the highest quantity of the active moiety expected to be produced for direct use in any of the next five years. Produced for direct use means the quantity intended for use in humans during a given year (i.e., excludes any quantity produced for inventory buildup), (2) the quantity used in all dosage forms and strengths included in the application, and (3) the quantity used in an applicant's related applications.

As it applies to Celerity and 505(b)(2) NDA 208374, the highest quantity of the active moiety expected to be produced for direct use in any of the next five years is (b) (4) kg.

This quantity includes all dosage forms and strengths (two codes/two strengths) and the quantity used in an applicant's related applications (Celerity has no other related applications).

Utilizing (b) (4) kg/year in the calculation above, EIC-Aquatic (ppb) = (b) (4) which is (b) (4).

1.2 Extraordinary Circumstances

In accordance with 21 CFR § 25.15(d), Celerity Pharmaceuticals, LLC (Celerity) additionally states that to the best of our knowledge, no extraordinary circumstances exist that would significantly affect the quality of the human environment and would warrant the preparation of an Environmental Assessment for bivalirudin under 21 CFR § 25.21.

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/s/

BRIDGET E KANE
12/27/2017

NDA 208374; Bivalirudin in 0.9% Sodium Chloride Injection

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Bivalirudin in 0.9% Sodium Chloride Injection
Strength	250 mg/50 mL, and 500 mg/100 mL
Route of Administration	Injection\
Rx/OTC Dispensed	Rx
Applicant	Celerity Pharmaceuticals, LLC

Submissions (s) Reviewed	NDA 208374, DMFs, and all the submitted CMC amendments
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Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Rajan Pragani	ONDP/DNDPI/NDPBI
Drug Product/Environmental Assessment (EA)	Dan Berger	ONDP/DNDPI/NDPBI
Process	Mark Johnson	OPQ/OPF/DPAI/PABI
Facility	Jonathan Swoboda	OPF/DIA/IABI
Biopharmaceutics	Banu Zolnik	ONDP/DB/BBI
Microbiology	Alifiyia Ghadiyala r	OPQ/OPF/DMA/MABII
Regulatory Business Process Manager	Grafton Adams & Dahlia Woody	OPRO DRBPMI/RBPMBI
Laboratory (OTR)	N/A	
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

1. RELATED/SUPPORTING DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
<u>Type II DMF</u>	(b) (4)	The DMF was reviewed in the context of this NDA submission.
Type III DMF		The DMF was reviewed in the context of this NDA submission.

2. CONSULTS: N/A

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 208374 (Bivalirudin in 0.9% Sodium Chloride Injection) is recommended for approval.

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

Not applicable.

II. Summary of Quality Assessments

The applicant, Celerity Pharmaceuticals LLC, has sought U.S. marketing approval for Bivalirudin in 0.9% Sodium Chloride Injection under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act and 21 CFR. Bivalirudin, a peptide, is a direct thrombin inhibitor indicated for use as an anticoagulant in patients under specified conditions. The applicant has made reference to the listed drug Angiomax® (bivalirudin) for Injection under NDA 020873 held by The Medicines Company. Celerity's proposed bivalirudin drug product is qualitatively and quantitatively similar to Angiomax® (bivalirudin) for Injection drug product after reconstitution and further dilution. However, Angiomax® contains mannitol (generally found in lyophilized products (b)(4)) as an additional inactive ingredient, which is not present in Celerity's proposed formulation. (b)(4)

The drug product is formulated in strengths of 250 mg/50 mL and 500 mg/ 100 mL.

A. Drug Substance (Bivalirudin) Quality Summary

Bivalirudin is a synthetic 20-amino acid hygroscopic peptide. It is an amorphous material; however, given that the drug product is compounded as an injectable solution, this drug substance attribute is not critical. The CMC information for the drug substance is cross-referenced to (b)(4) Type II DMF (b)(4), which has been previously reviewed and found adequate (for details, please refer to DMF# (b)(4) quality review, dated 7/26/2017, by M. Ethirajan). Briefly, the drug substance critical quality attributes (CQAs) are mainly controlled via release specification. In compliance with ICH 6QA, two identification tests i.e., HPLC (identification by retention time), and IR spectrometry (USP <197A>) are used. In addition, bioassay (validated for thrombin inhibition) is routinely performed on release. Because ICH (b)(4) does not directly apply to (b)(4), the applicant has relied on identification

threshold of (b) (4)% and qualification threshold of (b) (4)% per Chapter (b) (4) of the *European Pharmacopoeia* (b) (4). However, the proposed acceptance limits for impurities were deemed acceptable based on Agency's prior experience with toxicological qualification of these impurities for the listed drug Angiomax®. (b) (4)

B. Drug Product Quality Summary

The drug product Bivalirudin in 0.9% Sodium Chloride Injection is a frozen, iso-osmotic, sterile, nonpyrogenic premixed 50 mL or 100 mL solution containing 250 mg or 500 mg bivalirudin, respectively, in the GALAXY container (PL 2040 Plastic). Sodium chloride, USP is added to adjust the osmolality (0.9 g/100 mL). The reference drug ANGIOMAX® (bivalirudin) for Injection is currently approved under NDA 020873 as a sterile, lyophilized powder in single-dose, glass vials. Each vial contains 250 mg of bivalirudin. After reconstitution and further dilution, the ANGIOMAX® drug product is a sterile solution for intravenous administration (injection and infusion). The preclinical safety of bivalirudin injection is well established. The inactive ingredients used are compendial and do not exceed the IID levels for the intravenous infusion route of administration based on Maximum Daily Intake (MDI). The pharmaceutical development studies included evaluation of critical quality attributes such as pH, drug concentration (assay), related substances, and bioactivity. Identified degradants include (b) (4) which have acceptance limits of (b) (4)%, respectively based on the amounts observed over manufacturing and following changes over shelf life for the developmental and registration batches. The applicant has shown that the levels of these impurities are comparable to those observed for the RLD following storage for 12 months (frozen) (b) (4). Additionally, the levels of these degradation impurities are less than or equal to levels qualified in toxicity studies under RLD NDA 20873. Thus, the levels of these degradation impurities are considered acceptable. All CQAs for the product i.e., identity, assay, sterility, bioactivity, osmolality, bacterial endotoxins, (b) (4) and fill volume are controlled by appropriate release specification.

Bioassay for drug substance and drug product bivalirudin: The bioassay to test bioactivity has been developed in the context of following important considerations:

(b) (4)

Given that one of the critical evaluation considerations for adequacy of a bioassay is that it be clinically meaningful i.e., relevant to the mechanism of therapeutic action, the proposed validated bioassay with justified acceptance limits does meet this criterion, and is thus considered acceptable for the intended use.

Manufacturing: The manufacturing process involves [REDACTED] (b) (4)

[REDACTED] (b) (4)

Adequate control strategies are in place to ensure consistent batch-to-batch product quality.

Microbiological Aspects: Container closure integrity has been confirmed using validated container closure integrity methods, which demonstrate that the port/closure subassembly, port-to-bag seal, and main bag seals are all integral microbial barriers. Validations of the sterilization and decontamination processes, including filter integrity testing are adequate. The drug product release specification includes testing for sterility (USP <71>), and bacterial endotoxins (USP <85>).

Biopharmaceutics Aspects: Based on review of biopharmaceutics aspects, it is determined that there is an adequate bridge between the listed and proposed drug products per CFR 320.24(b)(6). The absence of mannitol in the proposed formulation is not likely to significantly impact the pharmacokinetic property of bivalirudin from the proposed injectable solution. In addition, the proposed drug product has been shown to have equivalent coagulation as compared to Angiomax®, as supported by results of statistical analysis showing that the 90% confidence intervals for geometric mean ratios for all three coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], and thrombin time [TT]) are all within the 80%-125% BE acceptance range.

Container Closure System: Bivalirudin in 0.9% Sodium Chloride Injection is packaged in (b) (4) 50 mL and 100 mL single-port PL 2040 Plastic (GALAXY) container closure system. The GALAXY container is fabricated from a specially designed (b) (4) plastic (PL 2040). Based on container closure testing, including USP physicochemical and biological tests, characterization of extractables/leachables (under worst-case-scenario), safety assessment, and formulation compatibility, the commercial container closure system is adequate to protect the drug product during its proposed shelf-life.

Expiration Date & Storage Conditions: The proposed product shelf-life of 12 months, when stored frozen (-20°C/-4°F) in commercial container closure system, (b) (4)

C. Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended overall approval for all the currently listed manufacturing facilities concerning this NDA.

III. Summary of Drug Product and Intended Use

Proprietary Name of the Drug Product	Not applicable
Non Proprietary Name of the Drug Product	Bivalirudin in 0.9% Sodium Chloride Injection
Active ingredient	Bivalirudin
Route of Administration	Injection: Intravenous Infusion
Strength(s)	250 mg/50 mL and 500 mg/100 mL

Proposed Indication(s)	<div style="background-color: #cccccc; height: 40px; width: 100%;"></div> <p>3. For use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).</p> <div style="background-color: #cccccc; height: 40px; width: 100%;"></div>
Maximum Daily Dose/ Duration of Treatment	Bivalirudin Injection is intended for intravenous bolus injection and continuous infusion. The dose to be administered is adjusted according to the patient's weight.
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation: The applicant has not request an official BCS designation.
2. Biowaivers/Biostudies: Per 21 CFR 320.22 (a), the applicant has requested a biowaiver
3. IVIVC: N/A.

E. Any Special Product Quality Labeling Recommendations: N/A

F. Life Cycle Knowledge Information

(Please see the next page)

Final Risk Assessment-

NDA 208374 (Bivalirudin in 0.9% Sodium Chloride Injection)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	H (High)	Container closure integrity has been confirmed using validated container closure integrity methods. Validations of the sterilization and decontamination processes, including filter integrity testing are adequate. Drug product release specification includes testing for sterility (USP <71>).	Acceptable	Given that the product sterility is the high risk attribute, any proposed changes in (b) (4) manufacturing process or microbiological testing-related product specification may need to be carefully evaluated.
Endotoxin (b) (4)	Formulation Container Closure Process Parameters Scale/equipment/ Site	M (Moderate)	Endotoxin testing is performed on product release per USP<85>, and acceptance limits have been set in compliance with USP requirements based on the maximum total daily dose.	Acceptable	Any proposed changes in acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)	Stability of the API and the drug product, and suitability of commercial container closure system have been well demonstrated. Manufacturing process is reasonably well-controlled.	Acceptable	
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))	The strategy for overfill is aligned with the USP <1> . Controls have been established on the identified critical steps of the manufacturing process i.e., (b) (4) Specifications for fill volume are established to ensure delivery of not less than the labeled volume over the shelf life of the product, taking into consideration residual volume in the container.	Acceptable	
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	Osmolality is monitored per USP <785> on release with acceptance limits (270-340 mOsm/kg) within the physiological range.	Acceptable	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	Product pH, a CQA (because it impacts the degradation rate of bivalirudin as well as the formation of related substances in the finished product over time) with acceptance limits of (b) (4) is monitored on release.	Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	M (Moderate)	Particulate matter (b) (4) is monitored on release per USP <788>.	Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	Based on extractables and leachables studies under worst-case-scenario, and USP physicochemical and biological tests, and formulation compatibility studies, the commercial container closure system is adequate for the intended use.	Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)	The product appearance is routinely monitored on release.	Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 208374 (Bivalirudin in 0.9% Sodium Chloride Injection) is recommended for approval.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products (Actg)
ONDP/DNDPI/NDPBI

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LABELING**NDA 208374****R Regional Information****1.14 Labeling***Immediate Container Label (amended 250 mg per 50 mL shown, submitted 11/6/2017)*

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The product is identified by the established name only.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration (21.CFR 201.100(b)(3))		Adequate
Net contents* (21 CFR 201.51(a))		Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		Adequate
Lot number per 21 CFR 201.18	The lot number was not present in the initial submission. In response to an Information Request, the Applicant provided the intended location for the lot number on the immediate container label.	Adequate
Expiration date per 21 CFR 201.17	The expiration date was not present in the initial submission. In response to an Information Request, the Applicant provided the intended location for the expiration date on the immediate container label.	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)	In response to an Information Request, the Applicant revised the storage statement to: “Store frozen at or below -20°C/-4°F.”	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)		Adequate
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate
Others		

*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.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label.

**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.

Reviewer's Assessment: Adequate

Information Requests were sent to the Applicant on October 27, 2017 for container label deficiencies: 1) The lot number must be added per CFR 201.18, 2) The expiration date must be added per CFR 201.17, 3) Revise storage statement to: "Store frozen at or below -20°C/-4°F."

As the requested revisions were provided in a response sent by the Applicant on November 6, 2017, the container label is considered to be adequate from a CMC perspective.

Carton Labeling (amended 250 mg per 50 mL shown, submitted 11/6/2017)

(b) (4)

Reviewer's Assessment:

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))	The product is identified by the established name only.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18	The lot number was not present in the initial submission. In response to an Information Request, the Applicant provided the intended location for the lot number on the immediate container label.	Adequate
Expiration date per 21 CFR 201.17	The expiration date was not present in the initial submission. In response to an Information Request, the Applicant provided the intended location for the expiration date on the immediate container label.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables) 201.10(a), 21CFR201.100(d)(2)]		Adequate
Sterility Information (if applicable)		Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions	In response to an Information Request, the Applicant revised the storage statement to: "Store frozen at or below -20°C/-4°F."	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)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
“See package insert for dosage information” (21 CFR 201.55)	Equivalent statement included	Adequate
“Keep out of reach of children” (optional for Rx, required for OTC)		Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		Adequate

Reviewer’s Assessment: Inadequate

Information Requests were sent to the Applicant on October 27, 2017 for carton label deficiencies: 1) The lot number must be added per CFR 201.18, 2) The expiration date must be added per CFR 201.17, 3) Revise storage statement to: “Store frozen at or below -20°C/-4°F.”

As the requested revisions were provided in a response sent by the Applicant on November 6, 2017, the carton label is considered to be adequate from a CMC perspective.

List of Deficiencies:

1. None

Primary Drug Product Reviewer Name and Date:

Dan Berger 11/6/2017

Secondary Drug Product Reviewer Name and Date:

Wendy Wilson-Lee 11/6/2017



Dan
Berger

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Wendy
Wilson- Lee

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Date: 11/07/2017 09:01:07AM
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BIOPHARMACEUTICS**Product Background:**

NDA: 208374

Drug Product Name / Strength: Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg/500 mL and 500 mg/100 mL

Route of Administration: Injection, intravenous infusion

Applicant Name: Celerity Pharmaceuticals

List Submissions being reviewed:

Seq.0000 Original submission dated 02/28/2107

Seq.0002 dated 05/30/2017

Review Summary

This Biopharmaceutics Review evaluated the overall data in support of the Applicant's biowaiver request and for the equivalence of in vitro plasma coagulation parameters to the Listed Drug Angiomax[®], as detailed below:

1) The Applicant's biowaiver request:

Based on the comparative physicochemical data and the similarity between the formulations, except for the absence of mannitol in the proposed drug product, it is determined that there is an adequate bridge between the listed and proposed drug products per CFR 320.24(b)(6). The absence of mannitol is not likely to significantly impact the pharmacokinetic property of bivalirudin from the proposed injectable solution.

2) Findings of the in vitro plasma coagulation equivalence studies:

The proposed drug product has shown equivalent coagulation as compared to Angiomax[®], as supported by results of statistical analysis showing that the 90% confidence intervals for geometric mean ratios for all three coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], and thrombin time [TT]) were all within the 80%-125% BE acceptance range.

Recommendation:

From the Biopharmaceutics perspective, NDA 208374 for Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg/500 mL and 500 mg/100 mL, is recommended for APPROVAL.

Signatures:

Primary Reviewer
Banu S. Zolnik, Ph.D.
11/8/2017

Secondary Reviewer
Ta-Chen Wu, Ph.D.
11/8/2017

Background

Celerity Pharmaceuticals is seeking approval under section of 505(b)(2) of Federal Food, Drug and Cosmetic Act for Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg/500 mL and 500 mg/100 mL for use as an anticoagulant in patients:

- (b) (4)
- Undergoing percutaneous coronary intervention (PCI) (b) (4)
- (b) (4)

The Applicant is relying on the FDA's findings of safety of efficacy for Angiomax[®] (bivalirudin), 250 mg/vial for injection to support the approval of the proposed drug product.

Biopharmaceutics Assessment

DRUG SUBSTANCE

Bivalirudin is a synthetic, 20 amino acid peptide drug. Bivalirudin is an amorphous drug substance, (b) (4).

Solubility: Bivalirudin is soluble in water (b) (4).

Permeability: Since the drug product is an injectable solution, permeability studies were not conducted.

BCS Designation: BCS class designation is not applicable

DRUG PRODUCT

Bivalirudin in 0.9% sodium chloride injection is a frozen, isosmotic, sterile, premixed 50 mL or 100 mL solution containing bivalirudin 250 mg or 500 mg, respectively. Table 2 shows the composition information of the proposed drug product. The thawed injectable solution results in pH range in between pH 5.2 and pH 6.0.

Table 1. Composition Information

Component	Quality Standard	Function	Component Quantity	
			250 mg/50 mL ^a (D3-15-75-304)	500 mg/100 mL ^b (D3-15-75-304)
Bivalirudin ^c	In house	Active ingredient	250 mg	500 mg
Sodium Chloride	USP	(b) (4)	(b) (4)	
Hydrochloric Acid ^d	NF			
Sodium Hydroxide ^d	NF			
Water for Injection	USP			

USP = United States Pharmacopeia; NF = National Formulary; QS = Quantity Sufficient

^a Labeled volume: 50 mL. Fill volume:

(b) (4)

^b Labeled volume: 100 mL. Fill volume

^c

(b) (4)

1) Is the Applicant’s biowaiver request for the proposed drug product acceptable?

Per 21 CFR 320.22 (a), the Applicant requested a waiver of in vivo Bioavailability/Bioequivalency requirements for Bivalirudin in 0.9% sodium chloride injection.

The differences in formulation between the proposed drug product and Listed Drug product (Angiomax®) are shown in Table 2. Note that the Listed Drug product is a lyophilized powder and contains mannitol as an inactive ingredient, whereas the proposed drug product is a frozen premixed solution and does not contain mannitol. The maximum dose of mannitol from Angiomax® ((b) (4) body weight, infused with 100 mL solution) is (b) (4) times lower than the labeled amount of mannitol diuretic dose (b) (4) for lowering intraocular pressure or result in any significant diuresis. Given that, the absence of mannitol in the proposed drug product is not expected to have significant impact on the drug disposition or offer unique benefits.

Angiomax® is administered either as intravenous bolus injection or as continuous infusion after reconstitution and dilution to yield final concentration of 5 mg/mL. The proposed drug product is thawed prior to use and requires no further reconstitution or dilution. The reconstituted and diluted Angiomax® and the proposed drug products have the same final pH range of pH 5-6. Comparative osmolality data between the Listed Drug and the proposed drug products are shown in Table 3.

Table 2. Comparison Between The Proposed Drug Product and Listed Drug Product-Angiomax® (after reconstitution with Sterile Water for Injection and further dilution with 0.9% Sodium Chloride For Injection)

Component	Angiomax® (After Reconstitution and Further Dilution)	Proposed Drug Product	
		250 mg	500 mg
Strength	250 mg or 500 mg ^a	250 mg	500 mg
Fill Volume	50 mL or 100 mL ^a	50 mL	100 mL
Bivalirudin	5 mg/mL	5 mg/mL	
Mannitol, USP	(b) (4)	none	
Sodium Hydroxide, NF	pH adjustment to 5-6 ^b	pH adjustment to 5.6 ^c	
Sodium Chloride, USP	0.9% (9 mg/mL)	9 mg/mL	
Water for Injection, USP	q.s.	q.s.	

^a The Angiomax® Prescribing Information [1] allows 1 vial in 50 mL and 2 vials in 100 mL for preparation of the lyophilized vial, thus demonstrating clinical use of these strengths and volumes. It also includes instructions for preparation of a 1250 mg/250 mL dilution (5 mg/mL) as well as a 250 mg/500 mL (0.5 mg/mL) dilution; the proposed drug product will not be offered in these configurations.

^b Angiomax® pH is after reconstitution but prior to dilution.[1]

^c Proposed pH limits for the drug product are 5.2 – 6.0.

Table 3. Comparison of Osmolality Data for Registration Stability Batches and Listed Drug

Product	Release Result (mOsm/kg)	Additional Testing Condition	Result (mOsm/kg)
Celerity Lot # 75254	304	12 months frozen ^a	301
Celerity Lot # 75255	305	12 months frozen ^a	302
Celerity Lot # 75256	303	12 months frozen ^a	300
Celerity Lot # 75257	304	12 months frozen ^a	300
Celerity Lot # 75258	305	12 months frozen ^a	302
Celerity Lot # 75259	303	12 months frozen ^a	300
TMC Lot # 2177995	N/A	Expiration Date: 09/2015; Test Date: 09/2015 ^b	292
TMC Lot # 00104	N/A	Expiration Date: 05/2018; Test Date: 11/2016 ^c	291
TMC Lot # 00109	N/A	Expiration Date: 06/2018; Test Date: 11/2016 ^c	290
TMC Lot # 00086	N/A	Expiration Date: 11/2017; Test Date: 11/2016 ^c	290

TMC = The Medicines Company’s Angiomax®; N/A = Not Applicable

^a Tested following 12 Months at -20°C + 24 hours at room temperature (25°C)

^b Tested after reconstitution followed by further dilution in 0.9% sodium chloride per labeling instructions

^c Tested using maximum labeling storage conditions (reconstituted solution stored at 2-8°C for 24 hours followed by further dilution in 0.9% sodium chloride and stored at room temperature (25°C) for 24 hours)

In addition, the Applicant submitted comparative assay, impurity profiles (b) (4)

Largest Other Related Substance, and Total Related Substance data for the proposed drug product and Listed

Drug product. Bioassay via thrombin inhibition is also part of the drug substance and drug product specification and is reviewed by the Drug Product Reviewer. Refer to the CMC review for the detailed assessment of the impurity profile.

Proposed drug product and Listed Drug have the comparable physicochemical properties and formulation similarity, except for the absence of mannitol in the proposed drug product. It is determined that the absence of mannitol is not likely to significantly impact the pharmacokinetic property of bivalirudin from the proposed injectable solution. Based on the requirements in CFR 320.24(b)(6), this Reviewer concludes that there is an adequate bridge between the listed and proposed drug products.

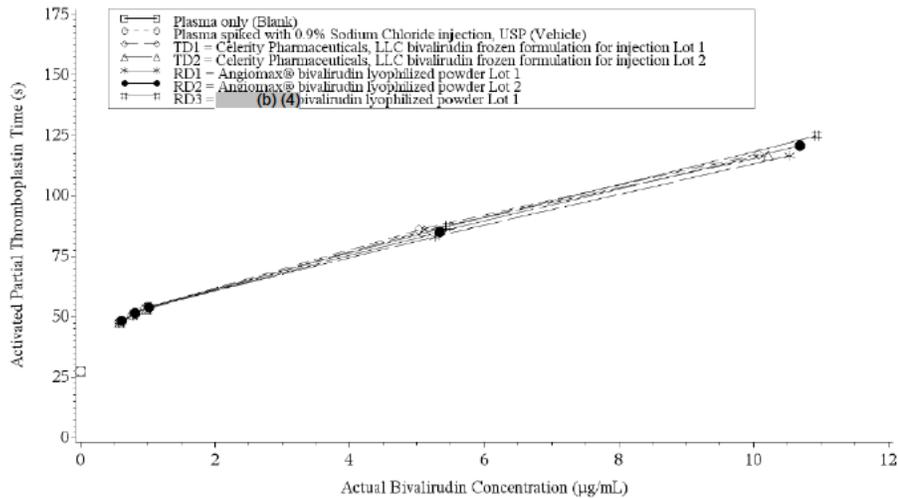
2) What are the findings of the in vitro plasma coagulation parameter equivalence studies?

Study CA17943: In Vitro Pilot Study to assess the selected range of plasma bivalirudin concentration for aPTT, PT, and TT clotting test

In response to the IR request letter dated May 10, 2017, the Applicant submitted the findings of selecting bivalirudin concentration ranges from an in vitro pilot study (Study CA17943) for the subsequent in vitro equivalency study. In vitro coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], and thrombin time [TT] were assessed following exposure of plasma to increasing concentrations (0.6, 0.8, 1, 5, 10 and 20 µg/mL) of the proposed formulation and the reconstituted and diluted Angiomax[®]. Additionally, lower concentrations (0.1, and 0.3 µg/mL) were used for TT assay. Three pooled plasma samples obtained from 36 subjects were tested for the selected coagulation parameters. The Applicant compared 2 Test lots (i.e., proposed drug product (TD1 and TD2) and 3 Reference drug, including RD1 and RD2 for Angiomax[®] and RD3 for ^{(b) (4)} bivalirudin product.

For aPTT assay, coagulation times increased with increasing bivalirudin concentration over the 0.6-10 µg/mL concentration range, as illustrated in Figure 1. Coagulation times were not reportable for the highest 20 µg/mL.

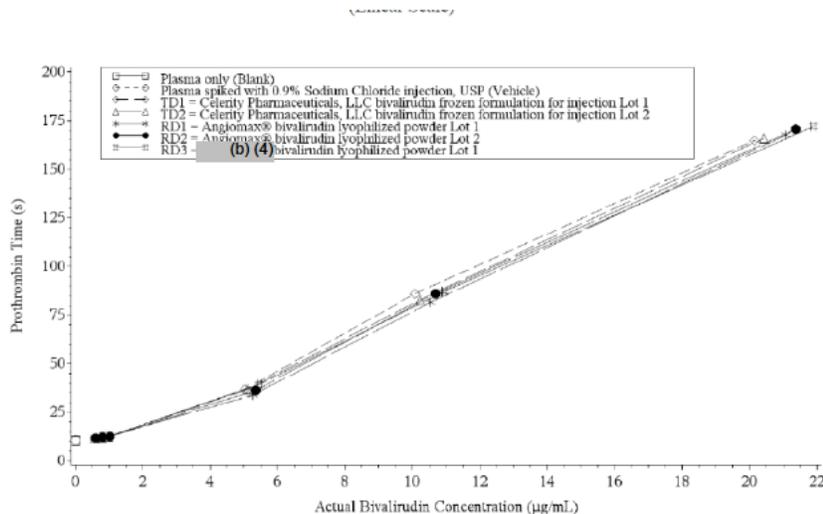
Figure 1 Mean Activated Thromboplastin Times vs Bivalirudin Concentration



No coagulation occurred at the 20 µg/mL nominal bivalirudin concentration for any study drug lot.
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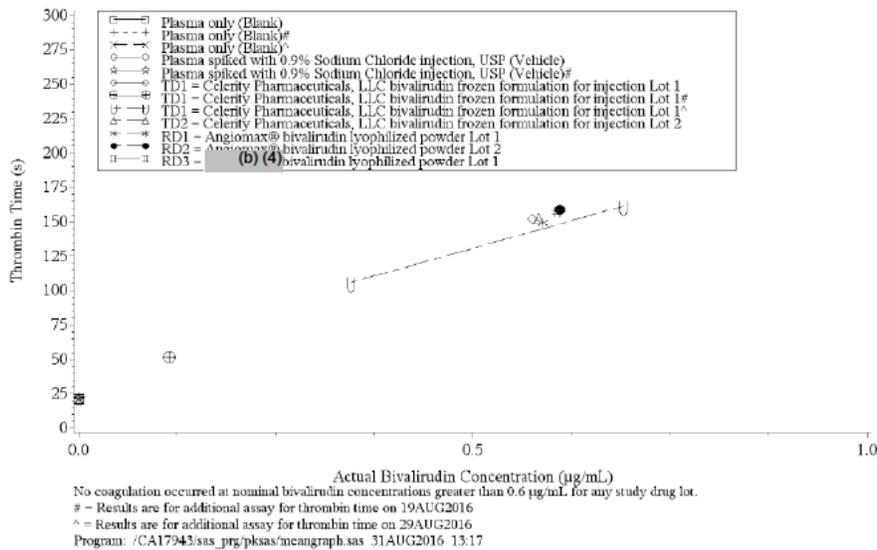
For PT assay, coagulation times increased with increasing bivalirudin concentration over the 5-10 µg/mL concentration range; quantifiable results were obtained up to 20 µg/mL, as illustrated in Figure 2. The lowest concentrations of 0.6 to 1.0 µg/mL resulted in slightly longer coagulation times than the blank (plasma only).

Figure 2 Mean Prothrombin Time vs Bivalirudin Concentration



For TT assay, coagulation times increased with increasing bivalirudin concentration for both test and reference formulations over the 0.1 to 0.6 µg/mL concentration range, as illustrated in Figure 3. At 0.8 µg/mL, coagulation occurred at a time over the limit set for all samples. No coagulation was observed for the reference and test formulations for all samples over 0.8-20 µg/mL.

Figure 3 Mean Thrombin Time vs Bivalirudin Concentration



The following bivalirudin concentration ranges for three coagulation parameters: 0.6-5 µg/mL for aPTT and PT, and 0.1-0.6 µg/mL for TT, were selected to be used in the in vitro coagulation equivalency study (Study CA17944), as described in the section below.

Study CA17944-In Vitro Study Comparing the Proposed Drug Product to the Angiomax on aPTT, PT, and TT clotting parameters

The Applicant assessed in vitro coagulation parameters (aPTT, PT, and TT) following exposure of plasma to increasing concentration of the proposed drug product (Test) and the reconstituted and diluted Angiomax® (Reference). The following concentration ranges, based on findings in the pilot study, were used in this study:

- For aPTT and PT: 0.6, 2 and 5 µg/mL,
- For TT: 0.1, 0.3, and 0.6 µg/mL

Blood samples were collected from 100 healthy subjects to obtain 10 pooled plasma (10 subjects for each). For each pooled plasma, aliquots of plasma were either spiked with bivalirudin of various concentrations or used as Blank (Plasma only) or Control (Plasma spiked with 0.9% NaCl). The aliquot of the Blank, or Control, and spiked plasma were analyzed to determine the aPTT, PT and TT values. The test samples included the drug product at release and at the end of shelf-life of 12 months. Results are presented and discussed below.

Comparative data on Activated Partial Thromboplastin Time:

Figure 4 Mean Activated Thromboplastin Time vs Bivalirudin Concentration

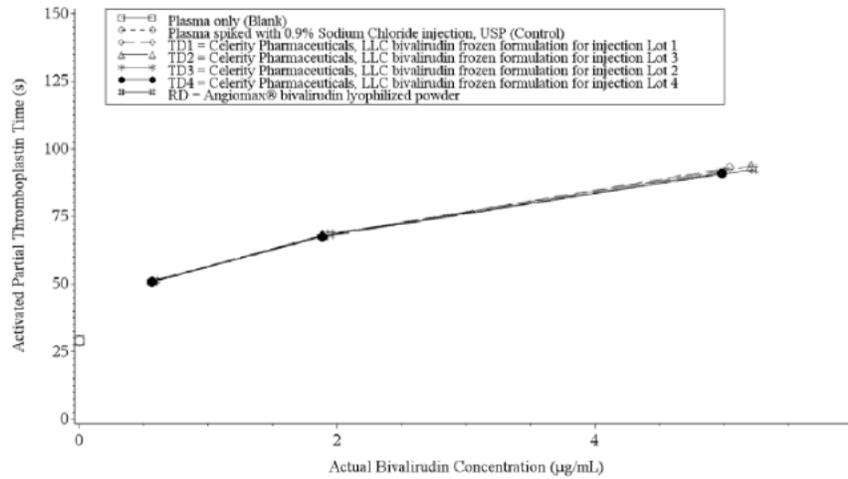


Table 4 Statistical Comparisons of aPTT between Proposed Drug Product (Test) and Angiomax® (Reference)

Comparison	Geometric LS Means		% Geometric LS Mean Ratio (Test/Reference)	Confidence Intervals (90% Confidence)
	Test (n)	Reference (n)		
Test Lot 1 vs Reference	68.54 (30)	68.10 (30)	100.65	98.27 - 103.08
Test Lot 2 vs Reference	68.52 (30)	68.10 (30)	100.62	98.25 - 103.06
Test Lot 3 vs Reference	68.33 (30)	68.10 (30)	100.34	97.97 - 102.77
Test Lot 4 vs Reference	68.14 (30)	68.10 (30)	100.06	97.70 - 102.48

TD1 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 1
 TD2 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 3
 TD3 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 2
 TD4 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 4
 RD: Angiomax® bivalirudin lyophilized powder
 Parameters are ln-transformed prior to analysis
 Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
 % Geometric Mean Ratio = 100*(Test/Reference)
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Comparative data on Prothrombin Time

Figure 5 Mean Prothrombin Time vs Bivalirudin Concentration

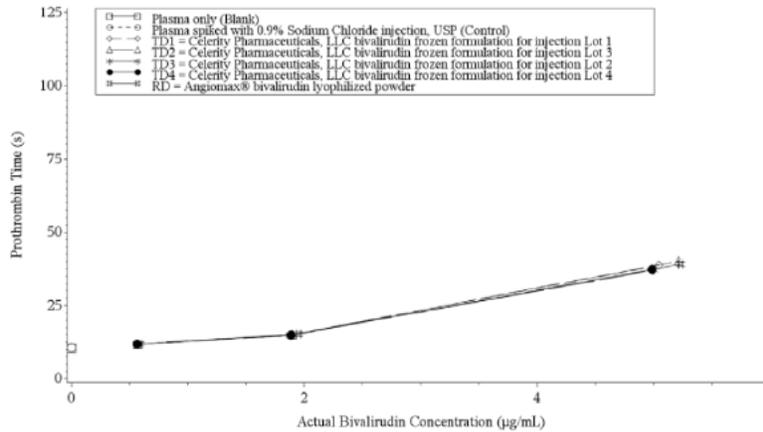


Table 5 Statistical Comparisons of PT between Proposed Drug Product (Test) and Angiomax® (Reference)

Comparison	Geometric LS Means		% Geometric LS Mean Ratio (Test/Reference)	Confidence Intervals (90% Confidence)
	Test (n)	Reference (n)		
Test Lot 1 vs Reference	19.02 (30)	18.81 (30)	101.12	98.30 - 104.02
Test Lot 2 vs Reference	19.05 (30)	18.81 (30)	101.28	98.47 - 104.20
Test Lot 3 vs Reference	18.83 (30)	18.81 (30)	100.11	97.35 - 103.02
Test Lot 4 vs Reference	18.93 (30)	18.81 (30)	100.64	97.85 - 103.54

TD1 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 1
 TD2 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 3
 TD3 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 2
 TD4 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 4
 RD: Angiomax® bivalirudin lyophilized powder
 Parameters are ln-transformed prior to analysis
 Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
 % Geometric Mean Ratio = 100*(Test/Reference)

Comparative data on Thrombin Time

Figure 6 Mean Thrombin Time vs Bivalirudin Concentration

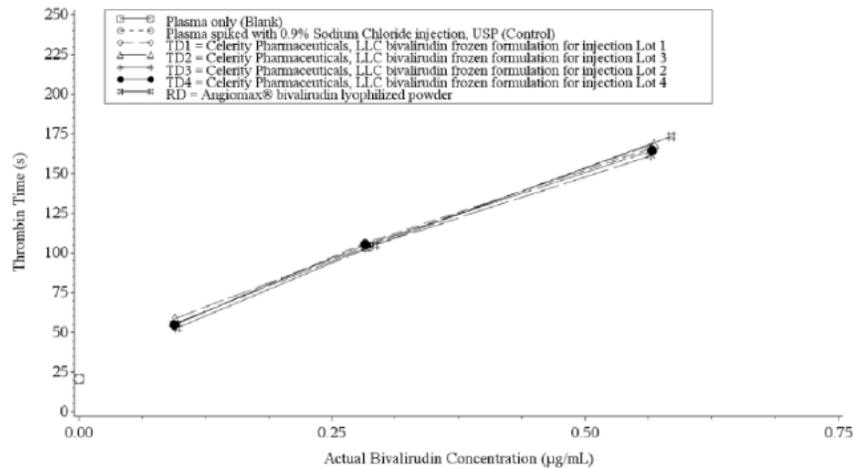


Table 6 Statistical Comparisons of TT between Proposed Drug Product (Test) and Angiomax® (Reference)

Comparison	Geometric LS Means		% Geometric LS Mean Ratio (Test/Reference)	Confidence Intervals (90% Confidence)
	Test (n)	Reference (n)		
Test Lot 1 vs Reference	99.30 (30)	96.76 (30)	102.63	97.21 - 108.33
Test Lot 2 vs Reference	100.29 (30)	96.76 (30)	103.65	98.19 - 109.41
Test Lot 3 vs Reference	97.74 (30)	96.76 (30)	101.01	95.68 - 106.62
Test Lot 4 vs Reference	98.75 (30)	96.76 (30)	102.06	96.68 - 107.73

TD1 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 1
 TD2 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 3
 TD3 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 2
 TD4 = Celerity Pharmaceuticals, LLC bivalirudin frozen formulation for injection Lot 4
 RD: Angiomax® bivalirudin lyophilized powder
 Parameters are ln-transformed prior to analysis
 Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
 % Geometric Mean Ratio = 100*(Test/Reference)

Reviewer’s Comment:

Statistical analysis results show that the 90% confidence intervals for geometric mean ratios for all three coagulation parameters were all within the 80%-125% BE acceptance range indicating that the proposed drug product has shown equivalent coagulation as compared to Angiomax®. It should be noted that the same statistical approach and limits have been employed for other bivalirudin applications, including the supplemental application for Angiomax®.

3) Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

There are no changes in the formulation, manufacturing process or manufacturing sites that require bridging to the commercial product.



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Zolnik

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Wu

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MICROBIOLOGY

Product Background:

NDA: 208374

Drug Product Name / Strength: Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg/50mL and 500 mg/100mL

Route of Administration: Intravenous

Applicant Name: Celerity Pharmaceuticals, LLC

Manufacturing Site: Baxter Healthcare Corporation
25212 W. Illinois Route 120
Round Lake, IL 60073, United States

Method of Sterilization: (b) (4)

Review Summary:

List Submissions being reviewed:

Submit	Received	Review Request	Assigned to Reviewer
02/28/2017	02/28/2017	N/A	03/06/2017
08/04/2017*	08/04/2017	N/A	N/A

Submissions on 04/10/2017, 05/30/2017, 06/12/2017, 07/19/2017 and 08/03/2017 are noted but not reviewed as there are not relevant updates.

* IR response

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining:

There are no deficiencies identified based on the information submitted.

Supporting/Related Documents:

- DMF microbiology reviews D^{(b) (4)}M03R01.doc dated 08/01/2016 (inadequate) and D^{(b) (4)}M03R02.doc dated 09/27/2016 (adequate) by Yarery C. Smith, and D^{(b) (4)}M05R01.doc dated 10/23/2017 (adequate) by Alifiya H. Ghadiali are referenced for relevant sterility assurance information.

The submission is **recommended** for approval on the basis of sterility assurance.

P.1 Description of the Composition of the Drug Product

Description of drug product –

Drug product is a frozen, iso-osmotic, sterile, non-pyrogenic premixed 250 mg/50mL or 500 mg/100mL API solution in the Galaxy container (PL 2040 Plastic).

Drug product composition –

Ingredient	Content (250mg/50mL)	Content (500mg/100mL)	Function
Bivalirudin, In-house	250 mg	500 mg	API
Sodium Chloride, USP			(b) (4)
Hydrochloric Acid, NF	*	*	pH adjuster
Sodium Hydroxide, NF	*	*	pH adjuster
Water for Injection, USP	qs	qs	(b) (4)

* Added as 1N solution, if necessary, for pH adjustment

Description of container closure system – single patient container

Configuration	Component	Description	DMF	Manufacturer
250mg/50mL; 500mg/100mL	Container	50mL and 100mL single-port PL 2040 Plastic (GALAXY)	(b) (4)	(b) (4)
	Closure	(b) (4) Elastomeric closure		

Reviewer's Assessment: Adequate

The applicant has provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package Integrity -**

Information regarding container closure integrity testing has been reviewed in DMF microbiology review D (b) (4) M05R01.doc dated 10/23/2017 (adequate) by Alifiya H. Ghadiali.

Reviewer's Assessment: Adequate

DMF (b) (4) contains adequate information regarding the proposed container closure integrity testing.

- **Antimicrobial Effectiveness Testing -**

Not applicable.

Reviewer's Assessment: Adequate

The subject drug product is single-dose and does not contain any preservatives. Antimicrobial effectiveness test is not required.

P.3 Manufacture

P.3.1 Manufacturers

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Alifiya
Ghadiali

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Bryan
Riley

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