CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211215Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 211215

Angiomax RTU (Bivalirudin) Injection

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Bivalirudin Injection
Strength	5 mg/mL (250 mg/50 mL)
Route of Administration	Parenteral (IV infusion)
Rx/OTC Dispensed	Rx
Applicant	Maia Pharmaceuticals, Inc.
Submissions (s) Reviewed	NDA 211215, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Raymond Frankewich	ONDP/DNDPI/NDPBI
Drug Product/Environmental Assessment (EA)	Kambhampati Rao	ONDP/DNDPI/NDPBI
Process and Facility	Kumar Janoria	OPQ/OPF/DPAI/PABI
Biopharmaceutics	Gerlie Gieser	ONDP/DB/BBI
Microbiology	Denise Miller	OPQ/OPF/DMA/MABII
RBPM	Grafton Adams	OPRO/ DRBPMI
Application Technical Lead (ATL)	Mohan Sapru	ONDP/DNDPI/NDPBI

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 211215 {Angiomax RTU (Bivalirudin) Injection} is recommended for approval. An expiration period of 11 months is granted for the product when stored at 2°C – 8°C (36 - 46°F) in the commercial packaging. Product excursions are permitted to (b) (4)

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

Not applicable.

II. Background, and Quality Assessment Summary

The applicant, MAIA Pharmaceuticals, Inc., has sought U.S. marketing approval for Angiomax RTU (Bivalirudin) Injection, 5 mg/mL for intravenous infusion in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Angiomax RTU is a direct-thrombin-binding anticoagulant indicated for use in patients undergoing percutaneous coronary intervention (PCI). The proposed Bivalirudin Injection (5mg/mL) is supplied as a refrigerated, ready-to-use (RTU), sterile solution in single-dose, glass 50 mL vials. This NDA for Bivalirudin Injection relies for approval, in part, on the FDA's findings of efficacy and safety for the Listed Drug (LD), Angiomax® (Lyophilized Powder) for Injection (NDA 020873). The LD is a lyophilized drug product that must be first reconstituted in Water for Injection (nominal concentration of 50 mg/mL), and subsequently diluted in either 0.9% Sodium Chloride Injection or 5% Dextrose Injection (nominal concentration of 5 mg/mL) prior to use. The proposed Angiomax RTU (bivalirudin) Injection has the same active ingredient as the LD, with the same trifluoroacetate salt content. The scientific bridge between the LD and the proposed Angiomax RTU (Bivalirudin) Injection has been established based on the results of the applicant's studies that demonstrate equivalence in terms of *in vitro* anticoagulant activities, *in vitro* hemolytic potential, and general *in vivo* animal systemic toxicity profiles, as well as the FDA's evaluation of submitted medical and nonclinical literature. From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, sterility, potency, and stability.

A. Drug Substance (Bivalirudin) Quality Summary

Bivalirudin is a single chain linear 20-amino acid peptide analog of hirudin (a naturally occurring peptide in the salivary glands of blood-sucking leeches that has a blood anticoagulant property) consisting of the hirudin active site-binding domain and the fibrinogen-binding domain linked together with a linker containing four glycine residues. All amino acid residues except the achiral Gly and the N-terminal D-Phe are in the L-configuration. All CMC information, including structural

characterization, manufacturing, batch analysis and stability data have been cross-referenced to DMF (b) (4) held by (b) (4)). The DMF (b) (4) has been reviewed in support of this NDA and found adequate. Based on CMC information provided in the NDA, the drug substance, available as a trifluoroacetate salt (range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents), is freely soluble in water. Bivalirudin is very hygroscopic as it absorbs more than 23% (m/m) of water by an increase in relative humidity from 0% to 95% at 25°C.

Manufacturing**:** Per submitted information in the NDA, Bivalirudin drug substance is manufactured (b) (4)

Control of Drug Substance**:** The drug substance is controlled for its identity using three methods (IR, ESI-MS and Amino acid analysis). It is also controlled for its potency (Assay) and the impurities that are process related and/or degradation products, including residual solvents. Other attributes that are tested at release include description, appearance of solution, thrombin inhibition, trifluoroacetic acid content, water content, microbial count and residual (b) (4) solvents. As appropriate for a drug substance intended for use in a parenteral product, Bivalirudin is also controlled for endotoxin at NMT (b) (4) EU/mg, well below the target limit for the drug product. (b) (4) The combined data from HPLC RT, ESI-MS, Amino Acid Analysis, Thrombin Inhibition Activity by UV-V provide adequate information about API identification, including sequence confirmation. The proposed drug substance specification is adequate. The analytical procedures have been adequately validated.

Container Closure System: The drug substance is stored in (b) (4) Container closure is suitable for use and provides adequate protection over the proposed retest period.

Retest Period: The drug product manufacturer (Gland Pharma Ltd.) has established a retest period of (b) (4) months when stored below (b) (4) °C (b) (4)). This retest period is supported by the stability data generated by the drug substance manufacturer, as noted above.

B.1. Product Design, and Release Specification:

Bivalirudin Injection is intended for the use as an anticoagulant in patients undergoing Percutaneous Coronary Intervention (PCI). The dosage form of Bivalirudin Injection is a ready-to-use parenteral

solution. Each mL of Bivalirudin Injection contains 5 mg of bivalirudin (equivalent to an average of 5.5 mg bivalirudin trifluoroacetate) and the following inactive ingredients: 0.8 mg sodium acetate (trihydrate), 100 mg polyethylene glycol 400, and Water for Injection, q.s to 1 mL, and sodium hydroxide (NF)/glacial acetic acid (NF) for pH adjustment. The recommended clinical dose and dosage regimen for proposed Bivalirudin Injection is identical to the LD. (b) (4) (b) (4) All proposed excipients are compendial grade. No novel or human/animal origin excipients were proposed. All the inactive ingredients are below the levels provided in Inactive Ingredients Database (IID) maintained by FDA. Polyethylene glycol 400 (b) (4)) is used as (b) (4) in this formula. The Inactive Ingredients Database lists the use of PEG 400 as high as 75.58% for solution, injection and it is controlled in the formulation as per the USP-NF monograph. Critical material attributes of the excipients employed in the formulation are controlled as per the relevant USP/NF monographs. The material attributes of the excipients do not directly impact the quality attributes of the finished product. Product release specification, involving testing of product critical quality attributes such as identity, pH, osmolality, particulate matter, sterility, elemental impurities (per USP <232>/ICH Q3D requirements), bacterial endotoxins, and bivalirudin related substances (organic impurities), is adequate. The analytical procedures have been adequately validated.

B.2. Manufacturing: The manufacturing process is (b) (4) Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

B.3. Microbiological Aspects: The manufacturing of the drug product is adequately controlled for microbiological attributes (b) (4) container closure package integrity, is adequate. The drug product is tested for sterility and is controlled for endotoxins against an acceptable limit of

NMT (b) (4) EU/mg of Bivalirudin. The applicant has demonstrated the container closure package integrity of Bivalirudin Injection, 5 mg/mL, packaged in 50 mL clear glass (b) (4) vial (with 32 mm neck, stoppered with 32 mm grey (b) (4) rubber stoppers, and sealed with 32-mm aluminum seals with a (b) (4) flip-off cap/button). Testing for bacterial endotoxins is appropriately performed according to USP <85>, and Total Viable Aerobic Count (TVAC) testing according to USP <61>.

B.4. Biopharmaceutics Aspects: The proposed to-be-marketed drug product Angiomax RTU (Bivalirudin) Injection is not quantitatively and qualitatively the same as the LD Angiomax® for Injection (NDA 20873). The differences from the LD include replacement of mannitol with polyethylene glycol 400 (b) (4), higher osmolality, and relatively higher level of degradant impurities at end-of-shelf-life in the proposed product. However, the proposed drug product and the LD have the same active ingredient (5 mg/mL bivalirudin) with the same trifluoroacetate salt content. The recommended clinical dose and dosage regimen for the proposed Bivalirudin Injection is identical to the LD i.e., a bolus injection (0.75 mg/kg) followed by a continuous intravenous infusion (1.75 mg/kg/h) lasting up to 8 hours (maximum PCI procedure duration of 4 hours and up to 4 hours post-procedure). To establish the scientific bridge to the LD, data from comparative *in vitro* pharmacodynamic, nonclinical (repeat dose animal toxicity), and *in vitro* hemolysis studies, as well as additional justification, have been provided. Specifically, the proposed Bivalirudin Injection intentionally degraded (at 30 °C for 10 days) demonstrated equivalence to the reconstituted/diluted LD in terms of prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT) over the therapeutic bivalirudin concentration range. Based on in *vitro* anticoagulation parameter study results for the initial and the end-of-shelf life, no trends in the thrombin inhibition activity of the registration batches of the proposed Bivalirudin Injection have been observed. Based on prior agreement with the Agency, no *in vivo* bioequivalence studies have been performed. The Agency has previously agreed that a study to assess the equivalence of the pharmacodynamic activity between the proposed product and the LD can be used to support the approval of the biowaiver request. In addition, these studies also serve to establish the scientific "bridge" between the proposed drug product and the LD to support the 505(b)(2) application and the reliance on FDA's determination of safety and efficacy of the LD. The data from applicant's two *in vitro* human plasma studies to assess equivalence of the anticoagulant (pharmacodynamic) activity of the proposed product and the LD are adequate. MAIA has not conducted clinical studies for bivalirudin. However, to supplement the known safety profile of bivalirudin from approved labeling for the LD, additional safety and tolerability information from recent published literature and from analysis of FAERS reports have been evaluated. Overall, the evaluation of the recent published literature for bivalirudin safety information did not identify any new safety information which would change the drug's known safety profile. In summary, biopharmaceutics information provided is adequate.

B.5. Container Closure System: The drug product is packaged in a 50 mL clear (b) (4) glass vial with a 32-mm neck, stoppered with a 32-mm grey (b) (4) rubber stopper, and sealed with a 32-mm aluminum seal with a (b) (4) flip-off button. Based on study of leachables and extractables, and pharmaceutical development studies, the applicant has demonstrated compatibility with the active ingredient, excipients, container and closure components, and dosing components. The product stability data also indicate suitability of the proposed container closure system for the intended use.

B.6. Product Stability. The applicant provided data from stability studies from three registration batches stored in the intended commercial packaging under long-term conditions (5±3°C) for up to 24 months and accelerated conditions (25±2°C) for 3 months.

B.6. 1. Potential Impact of End-of-Shelf-Life Levels of Degradant Impurities on Product Quality and Safety:

- The applicant indicated higher end-of-shelf-life levels of degradant impurities in the Bivalirudin Injection (ready-to-use product) compared to the LD (lyophilized powder).

- To qualify the systemic and local safety of the higher end-of-shelf-life levels of degradant impurities in the proposed Bivalirudin Injection compared to the LD, a 14-day continuous infusion toxicity study in rats has been carried out by the applicant. The repeat-dose animal toxicity study has evaluated up to 258 mg/kg/day continuous IV infusion doses of intentionally heat-degraded Bivalirudin RTU Solution (worst-case scenario product degradation with a total level of degradants at (b) (4) %). Based on Pharmacology and Toxicology review of results from this study, there is no indication that the higher level of degradant impurities induce any new toxicities or exacerbate the known toxicities of bivalirudin. The Pharmacology and Toxicology reviewer concluded that the "continuous infusion study using bivalirudin subject to accelerated degradation produced no findings of toxicological significance".

- The Office of Biotechnology Products (OBP) review team had concerns because of potential immunogenicity risk that may be associated with the higher end-of-shelf-life levels of degradant impurities in the Bivalirudin Injection compared to the LD. To address these potential concerns, the applicant agreed to CMC-recommended mitigation strategy i.e., a): to revise the proposed drug product shelf-life specification by tightening the acceptance criteria for product impurities (b) (4) , b) to reduce the requested expiry period to 11 months, which is adequately supported by long-term stability data in conformity with revised/tightened shelf-life specification limits, and c) use post-approval mechanisms to justify wider acceptance limits for product impurities and support a post-approval submission, for extending the product expiry period beyond 11 months, based on evaluating, via *in vitro* comparative immunogenicity studies, the potential immunogenicity risk associated with the higher end-of-shelf-life levels of degradant impurities in the Bivalirudin Injection compared to the LD.

- Based on alleviation of immunogenicity concern due to applicant's tightening of the acceptance criteria for product impurities (listed in the finished product shelf life specifications) (b) (4) and shortening of the proposed shelf life to 11 months, the OBP review team has recommended approval for this NDA (for details, please refer to Immunogenicity Consult Review, dated 9-27-2018).

- Post-approval, (b) (4)

(b) (4)

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- It is noted that the only degradant with a change in the primary sequence (b) (4) is already controlled (b) (4) and is below the level specified in the LD (less than (b) (4)%) and is hence the degradant is unlikely to pose any additional risk from an immunogenicity standpoint.

- The applicant's initial proposal for (b) (4) has been reviewed by the OBP review team and their recommendations regarding the design of these studies are currently being finalized.

B.6.2. Expiration Date and Storage Conditions: Based on evaluation of long-term and accelerated stability data in view of the revised/tightened shelf-life specification limits for product impurities, an expiration period of 11 months is granted for the product when stored in the commercial packaging at the long-term storage condition of 2°C – 8°C (36 - 46°F). Product excursions are permitted to (b) (4) Photostability of the proposed product has been demonstrated. Study of product stability under temperature cycling (Freeze –Thaw) conditions does not show any significant change with respect to all evaluated parameters. The post-approval stability commitments are appropriate to confirm the initially assigned expiry period of 11 months and to ensure the quality of the drug product over the proposed shelf-life.

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.

D. The applicant has claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) on the basis that no extraordinary circumstances exists under 21 CFR 25.15(d) that would warrant preparation of an environmental assessment. The applicant's claim of categorical exclusion is acceptable.

III. Summary of Drug Product and Intended Use

Proprietary Name	Angiomax RTU
Non-Proprietary Name	Bivalirudin Injection
Active ingredient	Bivalirudin
Route of Administration	Intravenous Infusion

Strength	5 mg/mL (250 mg/50 mL)
Proposed Indication(s)	Angiomax RTU is a direct thrombin inhibitor indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).
Maximum Daily Dose/ Duration of Treatment	The recommended dose and dosage regimen for ANGIOMAX RTU (bivalirudin) Injection is identical to Angiomax: a bolus injection (0.75 mg/kg) followed by a continuous intravenous infusion (1.75 mg/kg/h) for the duration of the PCI procedure and up to 4 hours post-procedure.
Alternative Methods of Administration	N/A

E. OPQ's all labeling recommendations are reflected in the most recent version of the product labeling.

F. Life Cycle Knowledge Information

Final Risk Assessment (Next Page)

NDA 211215 {Angiomax RTU (Bivalirudin) Injection}

Final Risk Assessment

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)**	Drug product release specification includes sterility (USP <71>) and bacterial endotoxin (USP <85>) testing. The applicant has demonstrated the container closure package integrity, and the product manufacturing is adequately controlled for microbiological attributes at various stages of the process.	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 Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**	The proposed acceptance limit of NMT (b) (4) EU/mg of Bivalirudin endotoxins (USP <85>) is adequate.	Acceptable	Any proposed changes concerning 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))	Per release specification, the product must meet the the requirement of USP <1> for Injections	Acceptable	

Final Risk Assessment (Continued, Next Page)

Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	Osmolality is monitored on release per USP <785>	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	The pH is monitored per USP <791> on release with acceptance limit of (b) (4) (b) (4)	Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M** **(Moderate)**	Particulate matter (Particles ≥ 10 µm: NMT (b) (4) Particles ≥ 25 µm: NMT (b) (4) is monitored on release per USP <788>.	Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	The extractables and leachables studies indicate no product quality risk from container closure system used to package the proposed drug product.	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

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 211215 {Angiomax RTU (Bivalirudin) Injection} is recommended for approval.

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

Mohan K. Sapru -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -S, 0.9.2342.19200300.100.1.1=2000589315
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LABELING

NDA 211215

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Angiomax RTU (bivalirudin) Injection
Dosage form, route of administration	Injection, intravenous
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Yes

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not applicable

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Injection
Strengths: in metric system	250 mg/50 mL (5 mg/mL)
Active moiety expression of strength with equivalence statement (if applicable)	Not usually placed in this section
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Yes
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Yes
Statement of being sterile (if applicable)	Yes
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Yes

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Not applicable
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: ***Adequate***

The Prescribing Information complies with all regulatory requirements from a CMC perspective.

R Regional Information

1.14 Labeling

Immediate Container (vial) Label

(b) (4)

Reviewer's Assessment: Adequate.

The vial label comply with all regulatory requirements from a CMC perspective.

Carton Labeling

(b) (4)

Reviewer's Assessment: Adequate.

Carton label complies with all regulatory requirements from a CMC perspective.

List of Deficiencies: None

QUALITY ASSESSMENT

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 5-20-19

Secondary Reviewer Name and Date:

Rao Kambhampati

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Date: 5/20/2019 05:48:54PM
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Wendy Wilson- Lee

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BIOPHARMACEUTICS

Product Background:

NDA: 211215

Drug Product Name / Strength: Angiomax® Ready-To-Use (RTU) (bivalirudin) Injection, 250 mg/50 mL

Route of Administration: For Intravenous (IV) Injection
Proposed Indication: Use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI)
Recommended Dosage: 0.75 mg/kg IV bolus dose followed immediately by 1.75 mg/kg/h IV infusion for the duration of the procedure and up to 4 hours post-procedure. Five minutes after the bolus dose, perform activated clotting time (ACT) test, and if needed, administer 0.3 mg/kg IV bolus

Applicant Name: Maia Pharmaceuticals

Review Recommendation: *APPROVAL*

Review Summary:
This 505(b)(2) NDA for Bivalirudin (Ready-To-Use Solution) Injection relies for approval, in part, on the FDA's findings of efficacy and safety for the Listed Drug product, Angiomax® (Lyophilized Powder) for Injection.

Per 21 CFR 320.24(b)(5)/(6), the scientific bridge between the Listed Drug (LD) and the proposed commercial RTU solution injectable drug product was established based on the results of the Applicant's conducted studies that demonstrated equivalence in terms of *in vitro* anticoagulant activities, *in vitro* hemolytic potential, and general *in vivo* animal systemic toxicity profiles, as well as the FDA's evaluation of submitted medical and nonclinical literature data and additional approved drug product labeling as related to excipient safety, notwithstanding the proposed drug product's differences from the LD with respect to formulation composition (i.e., replacement of mannitol with polyethylene glycol 400 (b) (4)), certain physicochemical properties (i.e., higher osmolality), and higher measured level of impurities/degradants at end-of-shelf-life.

At the currently proposed shelf-life (11 months when stored under refrigerated conditions), the proposed RTU solution drug product is anticipated to contain approximately up to 2-fold higher level of total impurities/degradants as compared to the Listed Drug Product during its shelf-life. However, based on NDA Review Team deliberations, such difference in bivalirudin degradant levels was not considered a safety concern particularly from the perspective of *relative immunogenicity risk* for the following reasons: 1) The observed total impurities and individual impurities levels of the RTU product at 11 months are numerically lower than those approved for the Listed

Drug Product at the end of its approved shelf-life (18 months). 2) (b) (4) . 3) Per FDA recommendation, (b) (4) the total/individual impurities limits and extension of the RTU product's shelf-life can only be justified based on the favorable results of adequately designed *in vitro*/*in silico* immunogenicity testing.

List of Submissions reviewed:
SDN-1, 9/27/2018 (Original NDA)
SDN-2, 12/28/2018 (Response to Biopharmaceutics Information Request)
SDN-7, 03/22/2019 (Response to Biopharmaceutics Information Request)
SDN-8, 3/29/2019 (Response to FDA Information Request/Immunogenicity and Degradants)
SDN-9, 4/8/2019 (Response to FDA Information Request/Viscosity)

Concise Description Outstanding Issues Remaining:
None

Bridging of Formulations

Reviewer's Assessment: *NOT APPLICABLE*

Bridging of formulations of the proposed solution drug product is not necessary since clinical studies/trials were not conducted, and there were no reported formulation and manufacturing process changes that occurred after initiation of the primary registration/stability studies. Additionally, the proposed to-be-marketed solution formulation/drug product (prior to and after intentional degradation) was evaluated in the submitted non-clinical studies.

Scientific Bridging to the Listed Drug Product *- ADEQUATE*

This NDA for Bivalirudin Injection relies for approval on the FDA's findings of efficacy and safety for the Listed Drug product, Angiomax® [NDA 020873]. Maia's Bivalirudin Injection is not quantitatively and qualitatively the same as Angiomax. However, no *in vivo* BE studies and clinical efficacy/safety studies were performed, per prior agreement with FDA. To establish the scientific bridge to the Listed Drug, data from comparative *in vitro* pharmacodynamic, nonclinical (repeat dose animal toxicity), and *in vitro* hemolysis studies, as well as additional justification, were submitted.

The proposed drug product is a Ready-To-Use (RTU) Solution for IV bolus or infusion, whereas the Listed Drug Product (Angiomax®) is a lyophilized powder for reconstitution and further dilution prior to intravenous bolus injection or infusion. Table 1 highlights the similarities and notable differences between the proposed and the listed drug products. Note that the proposed RTU solution drug product has the same drug concentration as the Listed Drug following reconstitution and further dilution per the approved labeling instructions.

Table 1. Comparison of the Proposed and Listed Drug Products

Attribute	**Listed Drug Product** [Angiomax® (bivalirudin) For Injection]	**Proposed Drug Product** [Maia's (bivalirudin) **RTU** Injection]
Presentation	Lyophilized powder for reconstitution and further dilution (250 mg/vial)	Ready-To-Use Solution (250 mg/50 vial)
Strength	50 mg/mL bivalirudin (upon reconstitution with 5 mL of SWFI) 250 mg/50 mL (= 5 mg/mL, upon further dilution with either 0.9% NaCl Injection or 5% Dextrose Injection per labeling instructions)	 250 mg/50 mL = 5 mg/mL Label states: "Do Not Dilute"*
Formulation Composition	250 mg bivalirudin (equivalent to 275 mg bivalirudin trifluoroacetate) 125 mg mannitol NaOH for pH adjustment	250 mg bivalirudin (equivalent to 275 mg bivalirudin trifluoroacetate) 40 mg sodium acetate trihydrate, 5 g polyethylene glycol 400, WFI, NaOH/glacial acetic acid for pH adjustment
	"Single-Dose"/Single-Use Vial	"Single-Dose" Vial 50 mL USP (b) (4) clear glass (b) (4) Vial (with a 32-mm neck, stoppered with a 32-mm grey (b) (4) (b) (4) rubber stopper, and sealed with a 32-mm aluminum seal with a (b) (4) flip-off button)
Recommended Storage	USP Controlled Room Temperature (20 – 25 °C)	Refrigerated (5 °C)
Final pH	(b) (4) Approved: 5.0 – 6.0	(b) (4) Proposed: (b) (4) release); **5.00 – 5.50** (shelf-life)
Osmolality	(b) (4)	
Viscosity		
Fill volume		
Total impurities		

	(b) (4)
Total fragments	
Thrombin Inhibition Assay	

*No difference in recommended dosage and administration route
[a] expiry period is 18 months for Angiomax® Powder, per the NDA 020873 Action Package
[b] per FDA request, (b) (4)"
[c] currently proposed expiry period for proposed RTU solution: 11 months when stored under refrigeration
[d] per FDA request, (b) (4)
[e] reported elsewhere as (b) (4)% (NDA 208374)

Impact of Formulation Difference on In Vitro Pharmacodynamic (Anti-Coagulant) Activity

To justify reliance on the FDA's findings of **efficacy** for the Listed Drug, equivalence between the proposed (i.e., both the initial and the end-of-shelf life) and the listed drug products was established mainly in terms of *in vitro* anticoagulant activity comparison, per 21 CFR 320.24(b)(5)/(6).

- This Reviewer's own analysis confirms the Applicant's report that the bivalirudin RTU solution intentionally degraded (at 30 °C for 10 days) demonstrated equivalence to the reconstituted/diluted Listed Drug product in terms of Prothrombin time (PT), activated partial thromboplastin time (aPTT), and Thrombin time (TT) over the therapeutic bivalirudin concentration range. Specifically, the geometric mean ratios of test-to-reference were within the protocol-specified BE acceptance criterion of 90.0% to 111.0% for all coagulation parameters (and the standard BE acceptance criterion of 80% to 125%) at all tested concentration levels for *all evaluable samples* (Table 2) and for *all samples with observations* (data not shown). See also the Reviewer's Figure 1 and Figure 2 for the plots of aPTT, PT and TT as a function of the nominal bivalirudin concentrations and the observed bivalirudin concentrations, respectively. The intentionally degraded test material contained (b) (4)% total impurities (vs. (b) (4)% for the Listed Drug; see Table 4) whereas the reported total impurities levels for the three registration batches of the proposed RTU solution after (b) (4) months of long-term (2 – 8 °C) storage ranged from (b) (4)%. (b) (4) . For comparison, the Applicant's *in vitro* anti-coagulant equivalence analysis of the freshly manufactured bivalirudin RTU solution is excerpted below (see Table 3).

Table 2.

Statistical Comparison of the *In Vitro* Anticoagulant Activities of *Intentionally Degraded (or End-of-Shelf life)* Bivalirudin RTU Solution Drug Product versus reconstituted/diluted Angiomax® Powder

Coagulation Parameter	Bivalirudin Concentration (µg/mL)	Number of Subjects	Least Squares Mean (Standard Error) in Log Scale		Geometric Means		
			Test	Reference	Test (second)	Reference (second)	Ratio, % (90% Confidence Interval)
PT	0*	50	2.3874 (0.0067)	2.3629 (0.0062)	10.89	10.62	102.5 (102.2, 102.8)
	5.0	50	3.6140 (0.0190)	3.5932 (0.0188)	37.12	36.35	102.1 (100.9, 103.4)
	10.0	47	4.2865 (0.0170)	4.2655 (0.0173)	72.71	71.20	102.1 (101.2, 103.0)
	15.0	48	4.6584 (0.0180)	4.6460 (0.0179)	105.46	104.17	101.2 (100.2, 102.4)
	20.0	46	4.9147 (0.0176)	4.8985 (0.0176)	136.28	134.08	101.6 (100.6, 102.7)
aPTT	0*	50	3.2648 (0.0087)	3.2352 (0.0085)	26.17	25.41	103.0 (102.7, 103.3)
	1.0	39	4.0142 (0.0137)	4.0097 (0.0138)	55.38	55.13	100.5 (100.1, 100.8)
	2.5	46	4.2664 (0.0126)	4.2577 (0.0131)	71.26	70.65	100.9 (100.4, 101.3)
	5.0	50	4.4687 (0.0120)	4.4636 (0.0121)	87.25	86.80	100.5 (100.2, 100.9)
	10.0	47	4.6802 (0.0135)	4.6796 (0.0121)	107.79	107.73	100.1 (98.9, 101.3)
	20.0	43	4.9390 (0.0129)	4.9295 (0.0136)	139.64	138.31	101.0 (100.5, 101.4)
TT	0*	50	3.0322 (0.0116)	3.0125 (0.0104)	20.74	20.34	102.0 (101.4, 102.6)
	0.5	38	5.5305 (0.0250)	5.5170 (0.0245)	252.27	248.88	101.4 (100.2, 102.6)
	0.75	45	5.8244 (0.0210)	5.8146 (0.0214)	338.47	335.17	101.0 (99.7, 102.3)
	1.0	30	6.0138 (0.0238)	5.9939 (0.0223)	409.02	400.98	102.0 (100.5, 103.5)

* Test = Blank (plasma only); Reference = Vehicle (0.9% sodium chloride)

Adapted from Table 29 of Pivotal Study Report CLOT-003

Table 3.

Statistical Comparison of the *In Vitro* Anticoagulant Activities of *Freshly Manufactured* Bivalirudin RTU Solution Drug Product versus reconstituted/diluted Angiomax® Powder

Coagulation Parameter	Bivalirudin Concentration (µg/mL)	Number of Subjects	Least Squares Mean (Standard Error) in Log Scale		Geometric Means		
			Test	Reference	Test (second)	Reference (second)	Ratio, % (90% Confidence Interval)
PT	0*	16	2.3886 (0.0133)	2.3642 (0.0122)	10.90	10.64	102.5 (102.0, 102.9)
	5.0	16	3.5289 (0.0246)	3.5746 (0.0264)	34.09	35.68	95.5 (93.4, 97.7)
	10.0	16	4.2201 (0.0231)	4.2758 (0.0270)	68.04	71.94	94.6 (93.2, 96.0)
	15.0	16	4.6033 (0.0259)	4.6340 (0.0259)	99.82	102.92	97.0 (95.7, 98.3)
	20.0	16	4.8563 (0.0261)	4.8832 (0.0268)	128.55	132.05	97.4 (96.1, 98.7)
aPTT	0*	16	3.2061 (0.0102)	3.1724 (0.0103)	24.68	23.86	103.4 (102.9, 104.0)
	1.0	16	3.8937 (0.0130)	3.9008 (0.0139)	49.09	49.44	99.3 (99.0, 99.6)
	2.5	16	4.1239 (0.0139)	4.1355 (0.0160)	61.80	62.52	98.8 (98.3, 99.4)
	5.0	16	4.3222 (0.0145)	4.3353 (0.0160)	75.36	76.35	98.7 (98.0, 99.4)
	10.0	16	4.5450 (0.0155)	4.5556 (0.0172)	94.16	95.17	98.9 (98.4, 99.5)
	20.0	16	4.7833 (0.0171)	4.7968 (0.0186)	119.50	121.12	98.7 (98.1, 99.2)
TT	0*	16	2.8279 (0.0190)	2.8039 (0.0199)	16.91	16.51	102.4 (101.4, 103.5)
	0.5	16	5.2003 (0.0341)	5.2472 (0.0309)	181.33	190.03	95.4 (91.4, 99.7)
	0.75	16	5.5216 (0.0351)	5.5570 (0.0390)	250.03	259.05	96.5 (94.9, 98.2)
	1.0	16	5.7496 (0.0382)	5.7832 (0.0377)	314.05	324.79	96.7 (94.5, 99.0)

* Test = Blank (plasma only); Reference = Vehicle (0.9% sodium chloride)

Adapted from Table 18 of Pivotal Study Report CLOT-004

Table 4.
Comparison of the Test and Reference Products used in Pivotal Study Reports CLOT-003 and CLOT-004

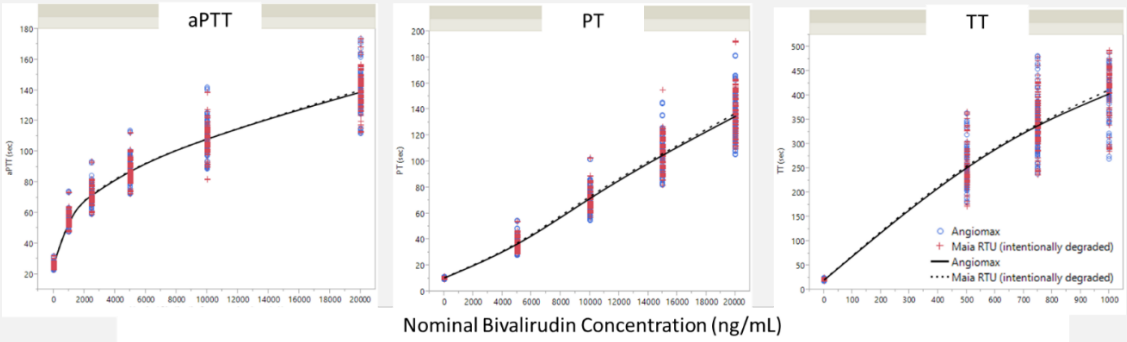
	Study CLOT-003		Study CLOT-004	
	TEST: Proposed RTU Solution Batch AJZ602[a] (5 mg/mL, *intentionally degraded* at 30 °C for 10 days)	**REFERENCE:** Angiomax• (Bivalirudin for Injection) 250 mg; Lot# 00111, Exp. 06/18	**TEST**: Proposed RTU Solution Batch BVN-19-001 (5 mg/mL, *freshly manufactured* (values at batch release and at completion of CLOT-004 study)	**REFERENCE:** Angiomax• (Bivalirudin for Injection) 250 mg; Lot# 00142, Exp. 02/21
Human thrombin inhibition assay (%, average)	45	ND	47%	ND
pH	5.22	5.23	5.23, 5.35	5.23
Assay	4.86 mg/mL 93.9 % of label claim	5.12 mg/mL	100.1%, 98.7% of label claim	102% of label claim
Total Impurities (%)				
Total Peptide Fragments				
Osmolality (mOsm/kg of water)	414	ND	411, 415	ND

(b) (4)

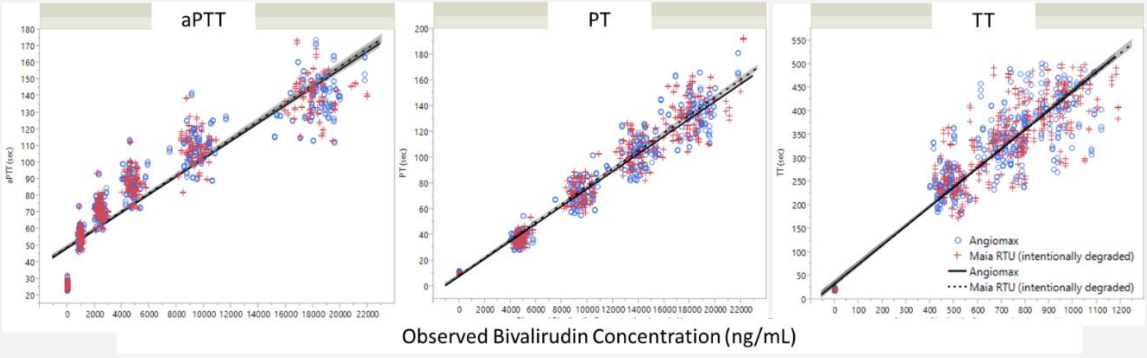
ND – not determined;

[a] Undegraded Lot AJZ602 was included in the primary registration stability studies.

Reviewer Figure 1. Anticoagulant activities of the test and the reference drug products as a function of the nominal/target bivalirudin concentration



Reviewer Figure 2. Anticoagulant activities of the test and the reference drug products as a function of the observed/measured bivalirudin concentration



These *in vitro* anticoagulation parameter study results for the initial and the end-of-shelf life RTU solution drug products are in line with the Applicant's report that no trends in the thrombin inhibition activity of the registration batches of the proposed RTU solution were observed, as all results on stability (44 – 46%) met the proposed acceptance range ((b) (4)%) and were comparable to the results at the initial time point.

Impact of Formulation Difference on Bivalirudin PK and the Proposed Product's Safety

To justify reliance of this 505(b)(2) NDA on the **bivalirudin PK and associated systemic safety** findings for the LD, the Applicant provided data/information (1) to support the conclusion that the PEG 400 (or in other words, the substitution of 125 mg mannitol with 5 grams PEG 400 per 50 mL) in the proposed RTU solution would not impact the PK of bivalirudin, and (2) to support the safety of the inactive ingredients (sodium acetate trihydrate (40 mg/50 mL) (b) (4), and PEG 400 (b) (4) not present in the LD. The Applicant's complete justification for the presence and the levels of these two mandatory inactive ingredients in the proposed drug product are summarized in the 12/28/2018 Response to the Biopharmaceutics Information Request included in the 74-Day Letter.

Based on the data provided in this NDA, this Reviewer concludes that there appears to be no indication that the types and levels of excipients in the proposed drug product could result in differences in the bivalirudin PK (disposition) and safety of the proposed RTU solution as compared to those of the Listed Drug, for the following reasons:

- Bivalirudin and its degradation products are eliminated (b) (4) The presence , and the level of mannitol in the Listed Drug are not expected to impact the disposition of bivalirudin from the plasma because (as stated in the Biopharmaceutics Review of NDA 208374 for an approved Bivalirudin Injection) the *"maximum dose of mannitol from Angiomax® (0.0042 g/60 kg body weight, infused with 100 mL solution) is 357 to 476 times lower than the labeled amount of mannitol diuretic dose (1.5 to 2.0 g/kg) for lowering intraocular pressure or result in any significant diuresis"*. Thus, the absence of mannitol is not anticipated to impact the disposition of bivalirudin from the body following administration of the proposed RTU solution drug product.
- The Applicant reported (and the Pharmacology/ Toxicology Reviewer, Dr. Elizabeth Hausner confirmed) that in the 14-day toxicology study (BS92RH), the bivalirudin injection vehicle continuously infused at 6000 mg/kg/day PEG 400 [3-fold higher dose than the human equivalent dose of 968 mg/kg] had so far not shown an apparent effect on kidney function.
- The Applicant also noted that [their safety findings are consistent with the observation that] the maximum daily dosage (MDD) of PEG 400 from BUSULFEX (busulfan) Injection is higher compared to that for proposed bivalirudin RTU solution (0.36 mL/kg/day versus 0.265 mL/kg/day; 406.8 mg/kg/day versus 300 mg/kg/day). Similarly, the MDD of sodium acetate trihydrate (b) (4) an "exception" inactive ingredient) is also higher for BREVIBLOC (esmolol

hydrochloride) Injection than for the proposed bivalirudin RTU solution (120.96 mg/kg/day versus 2.4 mg/kg/day). Of note, Dr. Hausner also confirmed that the nonclinical data/information provided in the NDA supports the Applicant's statements about qualification of the levels of sodium acetate and PEG 400 in the proposed formulation. Regarding the renal adverse events (e.g., BUN increased) listed in the BUSULFEX USPI, in a follow up email discussion, the Medical Reviewer (Dr. Rekha Kambhampati) stated that "alkylating agents, such as ifosfamide, are well-known in causing direct renal injury. Given that busulfan is an alkylating agent, it is quite possible that busulfan itself (without the PEG 400) would cause some of the nephrotoxic effects observed through direct renal toxicity."

- The therapy duration of the already approved parenteral product (BUSULFEX) is 4 days whereas for bivalirudin injections when used as indicated in the PCI setting, it is usually up to 8 hours as one-time therapy or possibly intermittent usage depending on the patient. Additionally, any impact of the added PEG 400 in renal elimination of bivalirudin may be offset by the fact the labeling recommendation to monitor anticoagulant activity (i.e., ACT) as early as 5 min post-initial dose thereby allowing for earlier dosage adjustment if required.
- Regarding the literature clinical case report (Laine et al. 1995) of acute tubular necrosis (ATN) following receipt of high dose lorazepam IV injection that delivered a total PEG 400 dose of 220 mL over 45 days or a daily dose range of 0.04 – 0.123 mL/kg/day, the Applicant concluded that it may not be accurate to consider that the ATN observed in the patient is due to the PEG 400 exposure because the lorazepam injection also contained propylene glycol which is known to have renal effects, and the patient had a history of alcohol abuse. Additionally, the FDA Medical Review by Dr. Rekha Kambhampati states: "In summary, the [Laine] case does not raise concern for the renal-safety of the dosage of PEG 400 in the MAIA bivalirudin product."
- To support the local safety of the proposed RTU solution despite the numerically higher osmolality value of the proposed RTU solution relative to the LD ((b) (4) mOsmol/kg versus (b) (4) mOsmol/kg), in addition to the difference in inactive ingredients, an *in vitro* hemolysis study using the proposed RTU drug product was performed. Per the Applicant, the *in vitro* hemolysis study with whole human blood showed no evidence of hemolysis at a blood-to-test material ratio of 1:0.75, corresponding to a final bivalirudin concentration of 2.14 mg/mL. Additionally, the Applicant reported that both the pH and osmolality of the proposed RTU solution did not show any significant change from the initial value at any storage condition tested. The Pharmacology/Toxicology reviewer considers the test concentration adequate, and Dr. Hausner's review states: "The *in vitro* hemolysis study did not show appreciable differences in hemolysis of human blood when compared to Angiomax."
- The Applicant reported that the measured pH ranges of the test RTU solution product and the reference solutions (following reconstitution and dilution of the lyophilized powder) were essentially the same, i.e., 5.2 – 5.3 and 5.4 – 5.5, respectively.

Impact of Higher Level of Bivalirudin Degradants During Storage on the Proposed Product's Safety

- To qualify the systemic and local safety of the higher-than-end-of-shelf-life levels of impurities in the proposed RTU solution compared to the LD (a lyophilized powder), a repeat-dose animal toxicity study was conducted. Study BS92RH evaluated up to 258 mg/kg/day continuous IV infusion doses of intentionally heat-degraded bivalirudin RTU Solution (with a total impurities level of (b) (4)%). Per the Applicant there was no indication that the higher level of degradants induced new toxicities or exacerbated known toxicities of bivalirudin. Additionally, Dr. Hausner stated that the "continuous infusion study using bivalirudin subject to accelerated degradation produced no findings of toxicological significance".
- With respect to the immunogenicity risk potentially associated with the higher level of impurities that could be present in the proposed bivalirudin RTU solution, the Applicant indicated (b) (4) and that there were no signs of an active immune response against the drug and its degradants in the conducted animal toxicity study. However, this Reviewer acknowledges that due to species difference, the (lack of an) immunogenic response in animals does not necessarily translate to humans. In the 3/12/2019 teleconference meeting with FDA representatives (including Dr. Mohan Sapru/CMC, Dr. Haoheng Yan/OBP and the Dr. Norman Stockbridge/OND) informed the Applicant about the FDA's concerns regarding the potential increase of immunogenicity in the proposed bivalirudin (ready-to-use) product due to its higher product related impurities compared to the Listed Drug. On 3/29/2019, the Applicant (1) updated the finished product QC specifications to tighten the proposed drug product acceptance criteria for impurities (during product shelf-life) (b) (4) . The Applicant's response was deemed acceptable by the CMC Reviewers, (b) (4)

Biowaiver Request

Reviewer's Assessment: *NOT APPLICABLE*

The Applicant requested a waiver of *in-vivo* bioavailability/bioequivalence studies pursuant to 21 CFR 320.22(d)(3) and/or 21 CFR 320.24(b)(6).

Since the proposed RTU injectable solution drug product is not qualitatively and qualitatively the same as the Listed Drug (Angiomax®), a waiver to conduct *in vivo* BA/BE studies per the CFR is not applicable.

List of Deficiencies:

None

Gerlie Gieser

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Jing Li

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MICROBIOLOGY

Product Background: This is a direct thrombin inhibitor indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention. The product is packaged as a single use product in a ready to use formulation that will not require any dilution prior to use.

NDA: 211-215

Drug Product Name / Strength: Angiomax RTU/205 mg/50 mL (5 mg/mL)

Route of Administration: Intravenous

Applicant Name: MAIA Pharmaceuticals, Inc.

Manufacturing Site: Gland Pharma Limited, India

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: This is a sterile (b) (4) product. The review covered the (b) (4) process and the stability program. The (b) (4) manufacturing process included the (b) (4) .

List Submissions Being Reviewed:
Original submission dated 27 September 2018
CMC Information Response dated 29 March 2019

Note: there were no quality microbiology information requests.

Highlight Key Outstanding Issues from Last Cycle:

Remarks: None

Concise Description Outstanding Issues Remaining: None

Supporting Documents:
DMF (b) (4)**:** LOA dated 09/19/18 for Record (b) (4). Recently reviewed by DMA on 10/31/17 (D (b) (4) Adequate and supports subject NDA.

List Number of Comparability Protocols (ANDA only): 0

S Drug Substance – NA

(b) (4)

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** This is a sterile non-pyrogenic solution that is clear to slightly opalescent and colorless to slightly yellow.
- **Drug product composition –** The drug product is a solution of bivalirudin in sodium acetate trihydrate and polyethylene glycol 400. The final volume is quantum suffice using water for injection.
- **Description of container closure system –**
  - Vials – 50 mL clear glass (b) (4) vial with 32mm neck from (b) (4)
  - Stopper – 32 mm grey (b) (4) stoppers (b) (4)

Reviewer's Assessment: ***Adequate***

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure Integrity

Dye Ingress

CCIT by dye ingress was performed on product vials with the commercial container closure system. The samples were Bivalriudin Injection 5 mg/mL in 50 mL vials with 32 mm stopper, three batches #AJZ601, AJZ602 and AJZ603.

Dye: Methylene blue (0.1% w/v)

The dye detection method is by UV-Visible spectrophotometer with Limit Of Detection (LOD) of 0.05 ug/mL of dye in the product (< 2.5 uL of dye in 50 mL of product). The positive control is a stopper compromised with a 26-gauge ½ inch needle and samples spiked with dye at the LOD.

The challenge parameters were dye immersion under a vacuum of 360 mm of Hg for 30 minutes.

Acceptance Criteria:

a) Challenged vials absorbance should be < LOD

b) Positive controls should show blue color and absorbance > the LOD

c) Spiked positive controls absorbance at the LOD

Reviewer's Assessment: ***Adequate,*** the three lots tested met the acceptance criteria and supports the integrity of the container closure system.

Antimicrobial Effectiveness Testing: NA

Reviewer's Assessment: None; product is not preserved as it is single use.

P.3 Manufacture

P.3.1 Manufacturers

Gland Pharma, Limited India

Reviewer's Assessment: ***Adequate***

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

(b) (4)

Reviewer's Assessment: ***Adequate.***

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Denise Miller

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Bryan Riley

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Mohan Sapru

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