CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211215Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA:	211215
Drug:	ANGIOMAX RTU (bivalirudin), for intravenous use
Class:	Direct thrombin inhibitor
Applicant:	MAIA Pharmaceuticals
Indication:	For use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI), including patients with heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis syndrome.
FDA Received:	27 September 2018
Approval date:	25 July 2019
PDUFA date:	27 July 2019

❖ REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products

- Norman Stockbridge, MD, PhD - Director
- Aliza Thompson - Deputy Director/Nephrology Team Leader
- Mary Ross Southworth, PharmD - Deputy Director for Safety
- Michael Monteleone, MS, RAC - Associate Director of Labeling
- Rekha Kambhampati, MD - Clinical Reviewer
- Xuan Chi, PhD – Non-Clinical Team Leader
- Elizabeth Hausner, PhD - Non-clinical Reviewer
- Bridget Kane, MS - Regulatory Health Project Manager

Office of Product Quality

Office of New Drug Products

- Mohan Sapru, PhD (Cross-Disciplinary Team Leader)
- Raymond Frankewich, PhD (Drug Substance)
- Rao Kambhampati, PhD (Drug Product)
- Gerlie Geiser, PhD (Biopharmaceutics)

Office of Process and Facilities

- Kumar Janoria, PhD (Process/Facilities)
- Denise Miller, PhD (Microbiology)

Office of Biotechnology Products, Division of Biotechnology Review and Research IV

- Haoheng Yan, PhD – Product Quality Reviewer
- Bazarragchaa Damdinsuren, PhD – Team Leader

Office of Surveillance and Epidemiology

- Sarah Thomas, PharmD (DMEPA)

*Office of Medical Policy, Office of Prescription Drug Promotion (*OPDP)

- Zarna Patel, PharmD

❖ BACKGROUND

MAIA pharmaceuticals (the applicant) submitted NDA 211215 pursuant to section 505(b)(2) of the FD&C act. The application was received by the Division of Cardiovascular and Renal Products (the Division) on 27 September 2018 and filed on 26 November 2018. MAIA Pharmaceuticals sought approval for ANGIOMAX RTU, an alternative dosage form of the reference listed drug (RLD) Angiomax (bivalirudin). ANGIOMAX RTU is a premixed, ready-to- use solution consisting of 250 mg of active ingredient, bivalirudin, in a 50 mL single-dose vial. The applicant relied on the Agency's findings of safety and effectiveness of RLD Angiomax (bivalirudin) for injection (NDA 20873, the Medicines Company) approved in 2000. MAIA's product will be supplied as a 5 mg/ml concentration – the same as the RLD after reconstitution. The recommended dosage for ANGIOMAX RTU is identical to the RLD, a bolus injection (0.75 mg/kg) followed by a continuous intravenous infusion (1.75 mg/kg/h) (b) (4)

To support the NDA submission, MAIA conducted a 14-day continuous intravenous infusion toxicity and toxicokinetic study to qualify the bivalirudin injection degradation products as well as an in vitro study (MAIA-BVN-17-CLOT-003) to bridge the pharmacodynamic activity of their ready-to-use product to the reference listed drug. This approach was agreed to by the Division at the pre-NDA meeting held on 24 July 2018 (meeting minutes dated 1 August 2018) under PIND 126394. The applicant did not open an IND since no clinical studies were conducted to support this application.

During the review, the Office of Biotechnology Products (OBP) was consulted to review the immunogenetic potential of ANGIOMAX RTU. OBP conveyed concerns to the Division related to higher levels of impurities in MAIA's product compared to the RLD. The Division conveyed these concerns to the applicant via teleconference on 12 March 2019 and advice letter on 15 March 2019. To mitigate these concerns, the applicant agreed to tighten the product shelf-life specification by tightening the acceptance criteria for product impurities (b) (4) The applicant submitted these revisions (b) (4) on 29 March 2019 for review. The Division found the shelf-life specification revisions acceptable. (b) (4)

This application was cleared by the 505(b)(2) committee on 17 June 2019.

❖ REGULATORY TIMELINE

- PIND meeting (pre-NDA): 24 July 2018
- NDA received: 27 September 2018
- Filing meeting: 13 November 2018

- NDA filed: 26 November 2018
- 74-day letter issued: 5 December 2018
- Team meeting: 22 January 2019
- Mid-cycle meeting: 28 February 2019
- Team meeting: 6 March 2019 (immunogenicity)
- T-con with sponsor: 12 March 2019 (immunogenicity)
- Team meeting: 28 June 2019 (immunogenicity)
- PDUFA date: 27 July 2019
- Action: 25 July 2019

❖ USER FEE

The user fee for this application was paid in full on 24 September 2018 (User fee ID #3017436).

❖ PEDIATRIC REVIEW COMMITEE (PeRC)

This application did not trigger PREA (21 U.S.C. 355c) because there is already an approved pre-mixed formulation of bivalirudin.

❖ ADVISORY COMMITTEE

N/A

❖ TRADE NAME

The applicant's proposed proprietary name, ANGIOMAX RTU, was found acceptable on 12 December 2018.

❖ REVIEW STATUS

This application was considered a standard review (10-month review cycle).

❖ FACILITIES

Per the Integrated Quality Assessment (16 June 2019), the Office of Process and Facilities has recommended approval for all listed manufacturing facilities for NDA 211215. Prior to taking action on this application, I confirmed with the facilities reviewer that the facilities remained in good standing.

❖ LABELING REVIEW

Labeling discussions began 3 April 2019 and concluded on 18 July 2019. See attached label in tracked changes to view all changes made to the applicant's proposed labeling.

❖ DISCIPLINE REVIEWS

Below are the conclusions reached by the review team members, organized by role and/or discipline.

CDTL memorandum (18 July 2019 – Sapru, Stockbridge)

Dr. Sapru agreed with the review teams' findings and summarized the basis for approval of ANGIOMAX RTU injection, concluding that the bridge to the RLD was adequate as were the in-vitro studies comparing the pharmacodynamic activity of ANGIOMAX RTU to the RLD. Dr. Stockbridge concurred with Dr. Sapru's summary and conclusions.

Office of Product Quality Integrated Review (16 June 2019 – Multiple reviewers)

Recommended action: Approval

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 211215 is recommended for approval. This integrated review also includes the microbiology and biopharmaceutics reviews. See full review located in Panorama for full assessment of each CMC aspect.

Office of Biotechnology Products Consult Review (23 May 2019 – Yan/Damdinsuren)
Recommended action: Approval
OBP was consulted to evaluate the immunogenetic potential of ANGIOMAX RTU. See Background section above and full review in Panorama for details.

Clinical Review (15 February 2019 – Kambhampati/Thompson)
Dr. Kambhampati, at the request of Biopharmaceutics, reviewed the information provided by the applicant related to polyethylene glycol (PEG) 400, an excipient of ANGIOMAX RTU, and risk of nephrotoxicity. The nephrology team did not believe that the amount of PEG 400 seen in the proposed bivalirudin dosage would pose a risk to renal safety. See review for further details.

Non-clinical review (7 November 2017 – Hausner/Chi)
Recommended action: Approval
Dr. Hausner concluded that "The continuous infusion study using bivalirudin subject to accelerated degradation produced no findings of toxicological significance. The in vitro hemolysis study did not show appreciable differences in hemolysis of human blood when compared to Angiomax."

❖ CONSULT REVIEWS

Please see the following reviews and their corresponding dates:

- OSE/DMEPA: Thomas/Tu – 18 March 2019; 25 February 2019
- OPDP: Patel – 22 May 2019

❖ CONCLUSION

After considering the primary and consult reviews for NDA 211215, the Division issued an approval letter. This letter was signed by Dr. Norman Stockbridge, Division Director, on 25 July 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRIDGET E KANE
07/25/2019 08:34:23 AM

U.S. FOOD & DRUG ADMINISTRATION

Immunogenicity Consult Review

STN:	NDA211215
Subject:	Immunogenicity Consult Review
Submission Date:	9/27/2018
Review/Revision Date:	5/15/2019, 5/22/2019
Primary Reviewer:	Haoheng Yan, MD, PhD Product Quality Reviewer, OPQ/OBP/DBRR IV
Secondary Reviewer:	Bazarragchaa Damdinsuren, MD, PhD Team Leader, OPQ/OBP/DBRR IV
Consults:	Immunogenicity
Applicant:	MAIA Pharmaceuticals
Product:	Angiomax RTU (bivalirudin) Injection, 5mg/mL
Indications:	Use as an anticoagulant in patients undergoing percutaneous coronary intervention
Action Due Date:	7/27/2019

- Unless otherwise noted, figures and tables in the review were adapted or copied directly from the submission.
- Reviewer's comments are shown in italic fond.
- The "guidance" cited in the review refer to "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin, Draft Guidance, October 2017"

Summary:

From the immunogenicity perspective, I recommend approval of this NDA. The ready to use (RTU) bivalirudin product has increased levels of product-related impurities in long term storage condition that have the potential to increase immunogenicity of the product. In order to alleviate this immunogenicity concern, the applicant tightened the acceptance criteria for impurities in the finished product shelf life specifications (b) (4) and shortened the proposed shelf life. The NDA review team concludes that the tightened shelf life specifications with shorter shelf life adequately addressed the immunogenicity concern. (b) (4) .

Consult Request

OPQ Biopharm requested an OBP immunogenicity consult for this NDA regarding the immunogenicity potential associated with the higher impurities/degradants levels in the proposed RTU product (liquid in vial presentation) as compared to Angiomax Powder. Specifically, the

Biopharm reviewer would like to get an expert opinion regarding the Applicant's justifications regarding immunogenicity risk.

Background and Precedent case

This is a 505(b)(2) NDA application for Angiomax RTU (ready-to-use bivalirudin solution). Bivalirudin is a synthetic peptide that is a direct thrombin inhibitor. The application referenced Angiomax (NDA20873) as the reference listed drug (RLD), originally approved on 12/15/2000. Unlike the RLD, which is lyophilized, Angiomax RTU is a liquid formulation. The stability data shows that the active ingredient degrades faster in the liquid formulation (in comparison with the lyophilized drug). At the end of proposed shelf life of (b) (4) months under long term storage condition, the Angiomax RTU product showed significant higher level of impurity compared to the RLD.

Precedent Case: On 3/17/2016, FDA issued a Complete Response Letter for NDA 208298, a 505(b)(2) application for Kangio (a RTU bivalirudin solution) due to an immunogenicity concern. This is the only CR comment for the application (copied below).

(b) (4)

Review

Comparison of the DP composition between Angiomax (RLD) and Angiomax RTU is summarized in the following table by the reviewer:

Parameter	RLD (Angiomax)	Proposed Drug (Angiomax RTU)
Presentation	250 mg/vial, lyophilized	250 mg/50 mL (5 mg/mL)
Active Ingredient	Bivalirudin	Bivalirudin
Inactive Ingredients	Mannitol Sodium Hydroxide Water for Injection (removed during lyophilization)	Sodium Acetate Trihydrate Polyethylene Glycol 400 (PEG400) Sodium Hydroxide Glacial Acetic Acid Water for Injection

Reviewer's Comment:

Compared to the RLD Angiomax, the proposed RTU drug includes PEG400 as an excipient. PEG can be immunogenic and may induce anti-PEG antibody in vivo. However, PEG400 is not a novel excipient, and the immunogenicity risk in the current case is negligible.

The applicant (MAIA Pharmaceuticals) submitted a Request for Waiver of In Vivo Bioavailability Studies, which contains an immunogenicity risk assessment section. Based on the data provided in Table 6 of the Request document (shown below), the impurities levels of MAIA RTU product at the end of the proposed shelf life are significantly higher than Angiomax.

(b) (4)

As part of immunogenicity risk assessment, the applicant states that although the levels of impurities in the RTU drug are higher than whose were observed in Angiomax, these impurities are not novel. (b) (4)

Reviewer's Comment:

(b) (4) *FDA clinical pharmacology reviewer commented that "The metabolites of bivalirudin have not been specifically characterized in humans.* (b) (4) *."*

The higher levels of impurities observed in the MAIA's RTU bivalirudin product compared to Angiomax have potential to increase the immunogenicity of the product. This immunogenicity concern was extensively discussed with the entire NDA review team during internal meetings on 2/28/2019 (mid-cycle) and 3/6/2019. The 3/6/2019 meeting focused specifically on the immunogenicity issue for MAIA's RTU bivalirudin product and the history of the precedent case NDA208298 was also presented. Dr. Mohan Sapru (ONDP), Drs. Haoheng Yan, Bazarragchaa Damdinsuren, William Hallett, Christopher Downey, Susan Kirshner (all OBP), Drs. Ann Farrell, Stephen Grand, Norman Stockbridge, Ms. Bridget Kane (OND) and other reviewers in

the NDA211215 review team attended the meeting. During the meeting, OBP suggested that the applicant may conduct one of the following studies to alleviate the immunogenicity concern considering the precedent case:

- *a non-inferiority clinical safety study comparing MAIA RTU bivalirudin and Angiomax for immunogenicity* (b) (4)
- *in silico analysis and in vitro tests that evaluate the relative immunogenicity risk associated with the RTU product and any product-related impurities that are new or present in increased amounts relative to RLD. Information on this type of approach can be found in the FDA draft guidance: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin.*

OBP explained that although the scope of the guidance is limited to certain synthetic peptide drug products that are seeking to submit ANDA, the scientific rational can be applied to the current MAIA's NDA. After extensive discussion, the review team decided that the immunogenicity concern will be limited if the impurity levels of the RTU drug are limited to (b) (4) *Additionally, the in vitro immunogenicity studies maybe performed to address the immunogenicity concern.*

On 3/12/2019, the applicant and FDA (including Dr. Mohan Sapru (ONDP, ATL of the applications), Drs. Haoheng Yan, Bazarragchaa Damdinsuren, Christopher Downey, Susan Kirshner (all OBP) and Dr. Norman Stockbridge and Bridget Kane (OND) held a T-con "to discuss the potential for increased immunogenicity of bivalrudin RTU because of increased product-related impurities not observed in the RLD and the approaches to resolve the uncertainty, including tightening shelf life acceptance limits or additional studies". During the T-con, FDA informed the applicant about the FDA's concerns regarding the potential increase of immunogenicity in the proposed RTU product due to its higher product related impurities compared to the RLD. The Agency and the applicant reached agreement that the applicant would limit the shelf-life specification (b) (4) *to alleviate immunogenicity concern and propose shorter shelf life. In addition, the applicant can submit in silico and in vitro immunogenicity testing data post-approval to expand the shelf life limit.*

On 3/29/2019, the Applicant submitted an amendment containing:

(1) updated the finished product shelf life specifications to tighten the proposed acceptance criteria for impurities (b) (4) and shorter shelf life,

(b) (4)

Reviewer's Comment: *The applicant's response was deemed acceptable by CMC reviewers. As discussed above, the immunogenicity risk of the RTU product is acceptable with the revised finished drug shelf life specifications. I recommend approval of this NDA from the immunogenicity perspective.*

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Haoheng Yan

Digitally signed by Haoheng Yan
Date: 5/23/2019 04:27:38PM
GUID: 54e4d29c0006b60003d1272740430bcc

Bazarragchaa Damdinsuren

Digitally signed by Bazarragchaa Damdinsuren
Date: 5/23/2019 04:50:42PM
GUID: 50afa2ce0005f62310093b8bdc00b898

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 22, 2019

To: Bridget Kane, MS
Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director for Labeling, (DCRP)

From: Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ANGIOMAX RTU (bivalirudin) injection, for intravenous use

NDA: 211215

In response to DCRP consult request dated November 27, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for ANGIOMAX RTU (bivalirudin) injection, for intravenous use.

PI: OPDP has reviewed the attached draft substantially complete Prescribing Information received by electronic mail from DCRP (Bridget Kane) on May 15, 2019, and we do not have any additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 12, 2019, and we do not have any additional comments at this time.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov .

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ZARNA PATEL
05/22/2019 01:57:53 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 18, 2019
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 211215
Product Name and Strength:	Angiomax RTU (bivalirudin) Injection, 250 mg per 50 mL (5 mg per mL)
Applicant/Sponsor Name:	MAIA Pharmaceuticals, Inc. (MAIA)
FDA Received Date:	March 12, 2019
OSE RCM #:	2018-2186-1
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for Angiomax RTU (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We note that MAIA incorporated most of our recommendations, with the exception of moving the "Discard unused portion." statement from the side panel to the principal display panel (PDP) on the container label. MAIA states in their March 12th submission that due to space limitations on the container label, they are unable to relocate the statement. We find their rationale acceptable. The revised container label and carton labeling for Angiomax RTU are acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Thomas S. Label and Labeling Review for Angiomax RTU (NDA 211215). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 25. RCM No.: 2018-2186.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH E THOMAS
03/18/2019 03:42:13 PM

CHI-MING TU
03/18/2019 05:27:31 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 25, 2018
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 211215
Product Name and Strength:	Angiomax RTU (bivalirudin) Injection, 250 mg per 50 mL (5 mg per mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	MAIA Pharmaceuticals, Inc. (MAIA)
FDA Received Date:	September 27, 2018
OSE RCM #:	2018-2186
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the 505(b)(2) NDA review process, this review evaluates the proposed Angiomax RTU container label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

Angiomax (bivalirudin) for Injection has been marketed under NDA 020873 since 2000 by Sandoz Inc. as a sterile, lyophilized powder in 250 mg single-dose, glass vials requiring reconstitution and dilution prior to intravenous injection. Angiomax is indicated for use as a direct thrombin inhibitor anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA), undergoing percutaneous coronary intervention (PCI) with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) as in the REPLACE-2 study, and with or at risk of heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI.[a]

MAIA Pharmaceuticals, Inc. submitted a 505(b)(2) NDA on September 27, 2018 for Angiomax RTU (bivalirudin), proposing a sterile, (b) (4) solution in a 250 mg/50 mL clear glass, ready-to-use, single-dose vial. The listed drug is Angiomax, NDA 020873. Per the September 27, 2018 proprietary name submission, MAIA Pharmaceuticals Inc. has obtained authorization from Sandoz Inc. to use the trademark Angiomax in connection with NDA 211215 for a bivalirudin injection ready to use product not requiring reconstitution or dilution.[b] We note that the proposed container label and carton labeling provide Sandoz as the distributor. Angiomax RTU is identical to Angiomax with respect to the active ingredient, strength, route of administration, and PCI indication, but does not require reconstitution or dilution prior to intravenous injection. The proposed Angiomax RTU product may help reduce the need for Bivalirudin preparation from a vial and help to ensure aseptic conditions.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B

[a]Angiomax product found in Drugs@FDA database. Accessed November 29, 2018 online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020873s036lbl.pdf.

[b]Angiomax RTU September 27, 2018 Proprietary Name Submission, Sandoz Authorization Letter for Use of ANGIOMAX Trademark accessible at: \\cdsesub1\evsprod\nda211215\0001\m1\us\118-proprietary-names\sandoz-authorization-angiomax-trademark.pdf.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Label and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the materials submitted identified areas where the label and labeling may be improved to promote the safe use of the product.

(b) (4)

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling, and PI for Angiomax RTU may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)
   1. Highlights, Dosage Forms and Strengths
      a. Replace the word (b) (4) " with "vial" in the following phrase for consistency purposes with Full PI, Section 3, Dosage Forms and Strengths (underlining and bolding intended to highlight change and not for implementation):
      "250 mg/50 mL (5 mg/mL) in a single-dose <u>vial</u>. Ready-to-use."
   2. How Supplied/Storage and Handling Section
      a. In Section 16, add appropriate information to facilitate identification of the injection (e.g., description from Section 3: "clear to slightly opalescent, colorless to yellow sterile solution"), as well as provide the

concentration for the injection and the NDC numbers for both proposed cartons, as follows:

"ANGIOMAX RTU is supplied as a refrigerated, ready-to-use, clear to slightly opalescent, colorless to yellow, sterile solution in 250 mg/50 mL (5 mg/mL) single-dose, glass vials. The single-dose vials are available as follows:

- NDC 70511-141-50: Carton containing 1 ANGIOMAX RTU single-dose vial
- NDC 70511-141-84: Carton containing 10 ANGIOMAX RTU single-dose vials"

b. We recommend adding the room temperature storage information for Angiomax RTU [redacted (b) (4)] to Section 16.2 as well, and revise the temperature provided to include a room temperature range per USP. Ensure that the revised temperature ranges per USP are also applied to the storage information provided on the container label and carton labeling.

4.2 RECOMMENDATIONS FOR MAIA PHARMACEUTICALS, INC. (MAIA)

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Label & Carton Labeling)

1. Remove the statement "[redacted (b) (4)]" on the side panel(s). Alternatively, revise the statement to read "Single-Dose Vial" and provide your rationale for the need of this duplicate statement when it's already provided on the PDP.
2. Revise the statement, "[redacted (b) (4)]." to the following: "Usual Dose: See prescribing information."
3. Revise the storage information to "[redacted (b) (4)]" and increase the prominence on the container label and carton labeling by bolding the font and/or relocating this statement from the side panels to the principal display panels (PDP). This revision will ensure consistency in the provision of storage information across the PI, container label, and carton labeling, as well as help to alert end-users to the change in storage for the proposed Angiomax RTU when compared to the listed drug Angiomax and other marketed bivalirudin for injection products.
4. If space allows, we recommend relocating the "Discard unused portion." statement from the side panels to the principal display panels of the container label and carton labeling after the "Single-Dose Vial" statement.

5. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[c] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

B. Container Label

1. As currently presented, the format for the expiration date is not defined. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.[d]

C. Carton Labeling

1. We note that the lot number and expiration date are missing on the proposed carton labeling. Ensure the lot number and expiration date are presented on the carton labeling in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17, and ensure that they are clearly differentiated from one another.[e] Ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[f] Also see comment B.1 above for the expiration date format.

---

[c] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

[d] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

[e] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[f] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Angiomax RTU received on September 27, 2018 from MAIA Pharmaceuticals, Inc. (MAIA), and the listed drug (LD), Angiomax.

Table 2. Relevant Product Information for Angiomax RTU and the Listed Drug		
Product Name	Angiomax RTU (bivalirudin) injection (NDA 211215)	Angiomax (Bivalirudin) for Injection (NDA 020873)[g]
Initial Approval Date	N/A	December 15, 2000
Active Ingredient	bivalirudin	bivalirudin
Indication	Direct thrombin inhibitor indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).	Direct thrombin inhibitor indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI) including patients with heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS).
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	250 mg per 50 mL (5 mg per mL)	250 mg per vial
Dose and Frequency	•The recommended dosage is a 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the procedure. Five minutes after the bolus dose has been administered, an activated clotting time (ACT) should be performed and an additional bolus of 0.3 mg/kg should be given if needed.	•The recommended dosage is a 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the procedure. Five minutes after the bolus dose has been administered, an activated clotting time (ACT) should be performed and an additional bolus dose of 0.3 mg/kg should be given if needed. •Extending duration of infusion post-procedure up to 4 hours

[g] Angiomax [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 NOV 29. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020873s036lbl.pdf.

	•Consider extending duration of infusion post-procedure up to 4 hours in patients with ST segment elevation MI (STEMI).	should be considered in patients with ST segment elevation MI (STEMI).
How Supplied	ANGIOMAX RTU is supplied as a refrigerated, ready-to-use, sterile solution in single-dose, glass 50 mL vials. NDC 70511-141-50 Each vial contains 250 mg of bivalirudin (equivalent to an average of 275 mg bivalirudin trifluoroacetate*). **The range of bivalirudin trifluoroacetate is 270 to 280 mg based on a range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents.*	Angiomax is supplied as a sterile, lyophilized powder in single-dose, glass vials. Each vial contains 250 mg of bivalirudin equivalent to an average of 275 mg of bivalirudin trifluoroacetate*. **The range of bivalirudin trifluoroacetate is 270 to 280 mg based on a range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents*.
Storage	Store ANGIOMAX RTU dosage units refrigerated at 5°C (41°F).	Store Angiomax dosage units at 20 to 25°C (68 to 77°F). Excursions to 15 to 30°C permitted [see USP Controlled Room Temperature].
Container Closure	Vial	Vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 6, 2018, we searched the L:drive and AIMS for previous DMEPA reviews relevant to this current review using the terms, bivalirudin, Angiomax, and NDA "211215". Our search identified 8 previous reviews[h, i, j, k, l, m, n, o] involving similar bivalirudin products or Angiomax (LD) and their associated labels and labeling. We considered our previous recommendations to see if they are applicable for this current review.

[h] Lee L. Label and Labeling Review for Angiomax Injection NDA 020873. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2000 FEB 24. RCM No.: 00-0061.

[i] Hamilton-Stokes, D. Label and Labeling Review for Angiomax Injection NDA 020873/S-022. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 JUL 12. RCM No.: 2010-851.

(b) (4)

[n] Thomas, S. Label and Labeling Review for Bivalirudin (NDA 208374). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 2. RCM No.: 2017-457.

[o] Thomas, S. Label and Labeling Review for Bivalirudin (NDA 208374). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 8. RCM No.: 2017-457-1.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 6, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR
Search Strategy and Terms	Match Exact Word or Phrase: bivalirudin

D.2 Results

Our search retrieved 4 newsletters, and none are relevant to this label and labeling review. Of note, bivalirudin is listed on ISMP's List of High Alert Medications.[p]

[p] ISMP's List of High-Alert Medications [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2014 [cited 2018 DEC 6]. Available from: http://www.ismp.org/tools/highalertmedications.pdf.

APPENDIX G. LABEL AND LABELING

G.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[q] along with postmarket medication error data, we reviewed the following Angiomax RTU label and labeling submitted by MAIA Pharmaceuticals, Inc. (MAIA).

- Container label received on September 27, 2018
- Carton labeling received on September 27, 2018
- Prescribing Information (Image not shown) received on September 27, 2018

G.2 Label and Labeling Images

Container Label

(b) (4)

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[q] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH E THOMAS
02/25/2019 12:18:00 PM

CHI-MING TU
02/25/2019 12:24:44 PM