

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208374Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA: 208374
Drug: bivalirudin in 0.9% sodium chloride injection, 250 mg/50 mL and 500 mg/100 mL
Class: Direct thrombin inhibitor
Applicant: Celerity Pharmaceuticals

Indication: Bivalirudin Injection is an anticoagulant for use in patients undergoing percutaneous coronary intervention (PCI).

FDA Received: 28 February 2017
Approval date: 21 December 2017
PDUFA date: 28 December 2017

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
 - Norman Stockbridge, MD, PhD (Director)
 - Stephen Grant, MD (Deputy Director)
 - Mary Ross Southworth, PharmD (Deputy Director for Safety)
 - Michael Monteleone, MS, RAC (Associate Director of Labeling)
 - Karen Hicks, MD (Clinical reviewer, labeling)
 - Gowra Jagadeesh, PhD (Non-clinical reviewer, labeling)
 - Bridget Kane, MS (Regulatory Health Project Manager)
- Office of Clinical Pharmacology
 - Martina Sahre, PhD (Cross-Disciplinary Team Leader)
 - Snehal Samant, PhD (Reviewer)
- Office of Product Quality
 - Mohan Sapru, PhD (Application Technical Lead)
 - Rajan Prajani, PhD (Drug Substance)
 - Dan Berger, PhD (Drug Product)
 - Mark Johnson, PhD (Process)
 - Jonathan Swoboda, PhD, RAC (Facilities)
 - Alifiyia Ghadiyala, PhD (Microbiology)
 - Banu Zolnik, PhD (Biopharmaceutics)
 - Ta-Chen Wu, PhD (Biopharmaceutics)
- Office of Surveillance and Epidemiology
 - Sarah Thomas, PharmD (DMEPA)
- Office of Medical Policy
 - Office of Prescription Drug Promotion (OPDP)
 - Zarna Patel, PharmD
- Division of Pediatric and Maternal Health

- Christos Mastroyannis, MD (Labeling review)

❖ **BACKGROUND**

Celerity Pharmaceuticals (the applicant) submitted NDA 208374 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 28 February 2017 and filed on 29 April 2017. Celerity Pharmaceuticals sought approval for an alternative dosage form of the RLD Angiomax (bivalirudin) - a premixed solution (bivalirudin in 0.9% sodium chloride) for injection in two strengths, 250 mg/50 mL and 500 mg/100 mL for injection. 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.

The applicant's product is a parenteral solution intended solely for administration by injection and is qualitatively and quantitatively similar to The Medicines Company's Angiomax® (bivalirudin) for Injection drug product after reconstitution and further dilution; however, Angiomax® contains mannitol as an additional inactive ingredient. Mannitol is commonly found in lyophilized products (b)(4). Since the proposed drug product is produced and intended for market as a frozen premixed IV solution, mannitol is not required for this formulation.

All pre-NDA correspondence/activity was conducted under PIND 126428; the applicant did not open an IND since no clinical studies were conducted. To prepare for this submission, Celerity discussed a bio-waiver for in-vivo bioavailability/bioequivalence studies during a PIND (126428) meeting on 30 June 2015 (minutes dated 28 July 2015). The Division agreed to the company's request for a bio-waiver. This NDA submission did not contain clinical data; however an in-vitro study, entitled "A Two Site In Vitro Study Comparing a Frozen Formulation of Bivalirudin to the Lyophilized Formulation of Bivalirudin (Angiomax®) on Activated Partial Thromboplastin Time, Prothrombin Time, and Thrombin Time over the Therapeutic Range in Male Human Plasma", was submitted to provide the requested evidence (Pre-IND CMC meeting, minutes dated 12 February 2016) to show that at physiologically relevant bivalirudin concentrations, the in vitro coagulation parameters (aPTT, PT, and TT) for bivalirudin premixed injection (at batch release and at the end of its shelf-life) were within ±20% of those measured for Angiomax®.

The application was cleared by the 505(b)(2) committee on 19 December 2017.

❖ **REGULATORY TIMELINE**

- PIND meeting: 30 June 2015
- PIND meeting (CMC WRO): 12 February 2016
- NDA received: 28 February 2017
- Filing meeting: 17 April 2017
- NDA filed: 29 April 2017
- 74 day letter issued: 10 May 2017
- Mid-cycle meeting: 31 July 2017
- 505(b)(2) committee cleared: 19 December 2017
- PDUFA date: 28 December 2017
- Action: 21 December 2017

❖ **USER FEE**

The user fee for this application was paid in full on 24 February 2017 (ID 3016706).

❖ **PEDIATRIC REVIEW COMMITTEE (PeRC)**

The PeRC meeting to discuss this application was held on 15 November 2017. The PeRC and the Division agreed with the applicant that pediatric studies with bivalirudin would be impossible or

highly impracticable because the disease/condition does not exist in pediatric patients. Thus, a full pediatric waiver was granted for this application (PeRC minutes dated 28 November 2017).

❖ **ADVISORY COMMITTEE**

N/A

❖ **TRADE NAME**

The applicant did not submit a trade name for this product.

❖ **REVIEW STATUS**

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

❖ **FACILITIES**

Per the Integrated Quality Assessment (13 November 2017), the Office of Process and Facilities has recommended approval for all listed manufacturing facilities for NDA 208374.

❖ **LABELING REVIEW**

Labeling discussions began 30 November 2017 and concluded on 19 December 2017. Significant labeling revisions were made and agreed to by the Division and the Applicant; see attached for all changes made to the applicant's proposed label. The intent of the changes was to modernize the label and update the content to reflect current American practice in the PCI setting. For a summary and rationale for these changes, see labeling review (Grant, 20 December 2017).

❖ **DISCIPLINE REVIEWS**

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

CDTL Memorandum/Divisional Memo (15 December 2017 – Sahre, Stockbridge)

Dr. Sahre agreed with the review teams' findings and summarized the basis for approval of bivalirudin in 0.9% sodium chloride injection, stating that the review team considered the bridge to the RLD adequate and that the in-vitro study conducted by the applicant showed that the coagulation markers were similar between the RLD and the applicant's drug product. The labeling changes were also summarized. Dr. Stockbridge concurred with Dr. Sahre's summary.

Clinical Pharmacology Review (7 November 2017 - Samant)

Recommended action: Approval

See review.

Office of Product Quality Integrated Review (13 November 2017 – Sapru)

Recommended action: Approval

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 208374 is recommended for approval. This includes the biopharmaceutics review that states that there is an adequate bridge between the listed and proposed drug products per CFR 320.24(b)(6). See review for details.

❖ **CONSULT REVIEWS**

Please see the following reviews and their corresponding dates:

- OSE/DMEPA: Thomas – 2 October 2017 & 8 November 2017
- DPMH: Mastroyannis – 20 November 2017
- OPDP: Patel - 8 December 2017

❖ **CONCLUSION**

After considering the primary and consult reviews for NDA 208374, the Division issued an approval letter. This letter was prepared and signed by Dr. Norman Stockbridge, Division Director, on 21 December 2017.

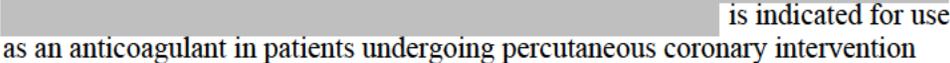
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/s/

BRIDGET E KANE
12/21/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 208374	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: N/A Established/Proper Name: bivalirudin in 0.9% sodium chloride Dosage Form: premixed injection Strengths: 250 mg/50 mL and 500 mg/100 mL		
Applicant: Celerity Pharmaceuticals		
Date of Receipt: 28 February 2017		
PDUFA Goal Date: 28 December 2017		Action Goal Date (if different): N/A
RPM: Bridget Kane		
Proposed Indication(s):  (b) (4)		
1.2 Percutaneous Coronary Intervention (PCI)		
Bivalirudin Injection  (b) (4)  is indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).  (b) (4)  (b) (4)		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 20873 – Angiomax (bivalirudin)	FDA’s previous finding of safety and effectiveness (clinical and non-clinical)
Published literature	Sections 6, 8, 14 of FPI

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The 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), we conclude that there is an adequate bridge between the listed and proposed drug products.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If “NO,” proceed to question #5.

Information from multiple recently published studies identified by the Division was used to support the following changes to the PI for bivalirudin:





(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Angiomax (bivalirudin)	20873	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.
If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a premixed form of the RLD – bivalirudin in 0.9% NaCl, 250 mg/50 mL and 500 mg/100 mL injection.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):	7582727	7/27/2028
	7582727*PED	1/27/2029
	7598343	7/27/2028
	7598343*PED	1/27/2029

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): **7582727, 7582727*PED, 7598343, 7598343*PED**

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO
If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO
If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): **June 5, 2017**

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

BRIDGET E KANE
12/21/2017



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: 20 December 2017

From: Stephen M. Grant, M.D.
Deputy Director
Division of Cardiovascular and Renal Products /CDER

To: File

Subject: Label NDA 208374

Pertinent literature and other references:

1. Shahzad A *et al.*; Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet*. 2014 Nov 22;384(9957):1849-1858. doi: 10.1016/S0140-6736(14)60924-7. Erratum in: *Lancet*. 2014 Nov 22;384(9957):1848.
2. Han Y *et al.*; BRIGHT Investigators. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA*. 2015 Apr 7;313(13):1336-46. doi: 10.1001/jama.2015.2323.
3. Erlinge D, *et al.*; Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. *N Engl J Med*. 2017 Sep 21;377(12):1132-1142. doi: 10.1056/NEJMoa1706443.
4. Valgimigli M *et al.*; MATRIX Investigators. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. *N Engl J Med*. 2015 Sep 10;373(11):997-1009. doi: 10.1056/NEJMoa1507854.
5. Cavender, M *et al.*; Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. *Lancet*, 2014; (9943): 599 – 606. doi: 10.1016/S0140-6736(14)61216-2
6. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention
7. Bivalirudin label, March 2016 (accessed 19 December 2017)

Celerity Pharmaceuticals LLC has submitted NDA 208374 under section 505(b)(2) of the FDC&A seeking approval for a new formulation of bivalirudin that relies on the finding of safety and efficacy of the reference listed drug (RLD) Angiomax® (NDA 20873). 21 CFR 201.56(a) requires that:

- (1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.
- (2) The labeling must be informative and accurate and neither promotional in tone nor false

or misleading in any particular. In accordance with 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

The Division reviewed current literature and concluded the label required updating to conform to the requirements of 21 CFR 201.56(a). This memo serves to describe the bases for changes to the currently approved label for the RLD.

Description and Rationale for Specific Changes to the Label

The primary impetuses for the changes were two: 1) revising the label conform to contemporary labeling practices, which emphasize concision as an aid to clarity and 2) excising information not pertinent to contemporary American medical practice. In particular, there have been changes in the performance of percutaneous coronary intervention (PCI) (b) (4)

[Redacted content]

It should be noted that the marketing authorization holder for the Angiomax brand of bivalirudin (The Medicines Company) is not listed as the sponsor for any of the studies cited above in clinicaltrials.gov. A search under the NDA for Angiomax (# 020873) in DARRTS revealed that none of the studies had been submitted for review.

The primary revisions to the label are described below by section.

Section 1 INDICATIONS AND USAGE:

The current indication was made more concise by simply indicating that bivalirudin is effective for providing anticoagulation during the performance of percutaneous coronary intervention (PCI). (b) (4)

[Redacted content]

Section 5 WARNINGS AND PRECAUTIONS:

[Redacted content] (b) (4)

(b) (4)

Section 6 ADVERSE REACTIONS:

The primary changes in this section are deletion of information

(b) (4)

(b) (4)

Section 14 CLINICAL STUDIES:

The primary change in this section is deletion of information

(b) (4)

(b) (4)

Interactions with Applicant

A label with the changes described above was sent to the applicant. The applicant agreed with all changes suggested by the Division except for removal from [REDACTED] (b) (4)

[REDACTED] The Division's rationale for not including that information in the PI was explained, as noted above. The Division invited the applicant to conduct a review of the literature and other sources to determine [REDACTED] (b) (4)

[REDACTED] After consideration, the applicant chose not to conduct a review but rather to accept the Division's suggested changes.

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/s/

STEPHEN M GRANT
12/20/2017

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

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

Memorandum

Date: December 8, 2017

To: Bridget Kane, MS, 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, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for BIVALIRUDIN in 0.9% Sodium Chloride Injection, for intravenous use

NDA/BLA: 208374

In response to DCRP's consult request dated April 13, 2017, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for BIVALIRUDIN in 0.9% Sodium Chloride Injection, for intravenous use .

PI: OPDP has reviewed the attached draft PI and we do not have any comments. OPDP's review is based on the draft PI received by electronic mail from DCRP on November 30, 2017.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 6, 2017, and we do not have any comments.

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

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/s/

ZARNA PATEL
12/08/2017



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: November 9, 2017 **Date consulted:** March 17, 2017

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Bivalirudin Injection

Drug Class: Anticoagulant

NDA: 208374

Applicant: Celerity Pharmaceuticals, LLC

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication: Bivalirudin Injection is indicated for use in patients [REDACTED] (b) (4)
[REDACTED]

Materials Reviewed:

- DPMH consult request dated March 17, 2017 in DARRTS (Reference ID 4071437)
- Applicant's submission for NDA 208374 and Prescribing Information (PI) for Bivalirudin Injection dated February 28, 2017

Consult Question:

DCRP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling sub-sections to comply with PLLR format.

INTRODUCTION

On February 28, 2017, Celerity Pharmaceuticals, LLC (Celerity) submitted a New Drug Application (NDA) 208374 for Bivalirudin in 0.9% Sodium Chloride Injection (250 mg/50 mL and 500 mg/100 mL). It is a 505(b)(2) NDA submission based on literature and refers to the listed drug Angiomax (bivalirudin) for Injection (NDA 020873) for safety and efficacy. Bivalirudin is a premixed drug product in a single-dose Galaxy container. No new studies are submitted.

The Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) on March 17, 2017, to provide input for appropriate labeling of the pregnancy and lactation subsections of bivalirudin in 0.9% Sodium Chloride Injection, for intravenous use to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND

Bivalirudin is indicated in patients, (b) (4) .

(b) (4)

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

(b) (4)

Regulatory History

Angiomax (bivalirudin) for Injection (NDA 020873), the reference listed drug (RLD), was approved on December 15, 2000, for use as an anticoagulant with concomitant use of aspirin (because clinical studies with the RLD were conducted only in patients receiving concomitant aspirin) for the following indications:

- in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).
- with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) in patients undergoing percutaneous coronary intervention (PCI).
- in patients with, or at risk of, heparin induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI.

Bivalirudin Drug Characteristics¹

- Bivalirudin is a specific and reversible direct thrombin inhibitor.
- Bivalirudin is a synthetic, 20 amino acid peptide
- The molecular weight of bivalirudin is 2180 daltons (anhydrous free base peptide)
- Half-life, in patients with normal renal function, of 25 min.
- Bivalirudin does not bind to plasma proteins (other than thrombin) or to red blood cells.
- Bivalirudin is cleared from plasma by a combination of renal mechanisms and

¹ Angiomax (bivalirudin) labeling last approved on March 21, 2016 and Bivalirudin applicant's proposed labeling, Sections 11 and 12

- proteolytic cleavage.
- Difference between Angiomax and Celerity's bivalirudin: Angiomax contains mannitol (b) (4) an inactive ingredient that is common in lyophilized products. The proposed drug product is produced and intended for market as a frozen premixed IV solution; therefore, mannitol is not required for the formulation.

Current RLD Labeling

The current labeling for RLD, Angiomax, as of March 21, 2016, is in Physician Labeling Rule format (PLR), but has not yet complied with PLLR. It states²:

FULL PRESCRIBING INFORMATION: CONTENTS

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

FULL PRESCRIBING INFORMATION

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day, (1.6 times the maximum recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the maximum recommended human dose based on body surface area). These studies revealed no evidence of impaired fertility or harm to the fetus attributable to bivalirudin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Angiomax is intended for use with aspirin [see *Indications and Usage (1.3)*]. Because of possible adverse effects on the neonate and the potential for increased maternal bleeding, particularly during the third trimester, Angiomax and aspirin should be used together during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether bivalirudin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Angiomax is administered to a nursing woman.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of bivalirudin. Bivalirudin displayed no genotoxic potential in the *in vitro* bacterial cell reverse mutation assay (Ames test), the *in vitro* Chinese hamster ovary cell forward gene mutation test (CHO/HGPRT), the *in vitro* human lymphocyte chromosomal aberration assay, the *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) assay, and the *in vitro* rat micronucleus assay. Fertility and general reproductive performance in rats were unaffected by subcutaneous doses of bivalirudin up to 150 mg/kg/day, about 1.6 times the dose on a body surface area

² Angiomax (bivalirudin) labeling last approved ON March 21, 2016

basis (mg/m²) of a 50 kg person given the maximum recommended dose of 15 mg/kg/day.

REVIEW

As per applicant, Celerity has not performed any clinical or nonclinical studies on the potential effects of bivalirudin in 0.9% Sodium Chloride Injection on pregnancy, lactation, and females and males of reproductive potential. There is no pharmacovigilance database nor pregnancy registry by Celerity.

PREGNANCY

Animal Data

Celerity makes reference to the listed drug Angiomax[®] (bivalirudin) for Injection (NDA 020873) held by The Medicines Company for nonclinical information supporting the proposed product. Therefore, no nonclinical studies have been performed for this product. No new information was provided by the applicant.

Review of Literature

Applicant's Review

On April 10, 2017, the applicant provided a review of the literature and summary of the available information in response to FDA's information request of March 9, 2017, to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential (PLLR) subsections of labeling. A literature search of PubMed with keywords "bivalirudin AND pregnancy", "bivalirudin AND fertility", "bivalirudin AND lactation", "bivalirudin AND breast feeding", "bivalirudin AND milk", "bivalirudin AND reproduction", and "bivalirudin AND teratogenic" was performed. This search includes all publications available in the PubMed database to date (from 1965 to 15 March 2017). Additional searches were performed using Toxnet database (toxnet.nlm.nih.gov) with "bivalirudin within the last 6 years from the search date and 5 years from the latest revision of the approved labeling for the RLD, Angiomax[®], (from March 2011 to March 2017) as well as all relevant abstracts. There were no relevant publications that were identified.

DPMH Review

In addition to the search by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases³ for bivalirudin and use in pregnancy. No publications were identified. GG Briggs and RK Freeman⁴ in *Drugs in Pregnancy and Lactation* report that "in animal studies there was no evidence of impaired fertility or fetal harm. It is not known if bivalirudin crosses the placenta. The molecular weight of 2180 and the short elimination half-life, suggest that little, if any, of the peptide will cross the placenta".

As per the applicant and consistent with the RLD, bivalirudin [REDACTED] (b) (4)

[REDACTED] (b) (4)

³ TERIS and ReproTox databases, Truven Health Analytics, Micromedex Solutions, 2016.

⁴ Briggs GG and Freeman RK, *Drugs in Pregnancy and Lactation*, Wolters Kluwer, Philadelphia, PA. 2015

LACTATION

(b) (4)

Review of Literature

Neither the applicant nor this reviewer could identify any publications about bivalirudin and lactation. There are no reports in *Medication's and Mother's Milk* by Thomas Hale, LactMed, or *Drugs in Pregnancy* by GG Briggs and RK Freeman. Lactation studies have not been conducted to assess the presence of bivalirudin in human milk, the effects on the breastfed infant, or the effects on milk production. The short half-life and molecular weight of 2180 daltons suggest that little, if any drug, will be present in the breast milk. Bivalirudin,

⁵ Mastroyannis, C. Yosprala (aspirin and omeprazole) review in DARRTS, Dated August 29, 2016, Reference ID: 3977490. The literature referenced in the DPMH consult review is supportive and/or for background purposes only.

⁶ Truven health Analytics-Micromedex Solutions

as a peptide, will likely be digested in the breastfed infant's digestive system, thus minimizing further the infant's exposure to the drug.

Summary

It is not known if bivalirudin is present in the breast milk. There is no data to inform of any effects on milk production or effects on the breastfed infant. Bivalirudin characteristics (molecular weight, short half-life, and being a peptide) make it likely that the breastfed infant would experience a very low, if any, exposure to bivalirudin. However, physicochemical characteristics alone are not sufficient to determine the transfer of a drug into breastmilk.

(b) (4)

Animal data

Reproductive studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day, (1.6 times the maximum recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the maximum recommended human dose based on body surface area). These studies revealed no

(b) (4)

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Review of Literature

Neither the applicant nor this reviewer could identify any publications about bivalirudin and females and males of reproductive potential.

Summary

There is no human or animal information regarding bivalirudin's effects on fertility in females and males of reproductive potential. Therefore, contraception and pregnancy testing during treatment with bivalirudin are not recommended. Subsection 8.3 will be omitted from labeling because there is nothing to be reported.

CONCLUSIONS

Bivalirudin labeling has been edited to comply with the PLLR. There is no published literature in humans; therefore, there is no identified association between bivalirudin use during the 1st trimester and adverse developmental outcomes, and adverse pregnancy or lactation-related outcomes.

DPMH revised subsections 8.1, 8.2, and 8.3 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

The Pregnancy and Lactation subsections of bivalirudin labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**

- The "Pregnancy" subsection of bivalirudin labeling was formatted in the PLLR format to include: "Risk Summary", (b) (4) and "Data" headings.

- **Lactation, Subsection 8.2**

- The "Lactation" subsection of bivalirudin labeling was formatted in the PLLR format to include the "Risk Summary" (b) (4) headings.

(b) (4)

RECOMMENDATIONS

DPMH has the following recommendations for bivalirudin labeling.

FULL PRESCRIBING INFORMATION: CONTENTS

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on use of Bivalirudin Injection in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Reproduction studies in rats and rabbits administered subcutaneously (SC) doses up to 1.6 times and 3.2 times the maximum recommended human dose (MRHD) based on body surface area (BSA), respectively, revealed no evidence of fetal harm when dosed during organogenesis (*see Data*).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Reproductive studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day, (1.6 times the maximum recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the maximum recommended human dose based on body surface area) administered during organogenesis). There was no harm to the fetus or any adverse developmental outcomes.

At 500 mg/kg/day subcutaneously, litter sizes and live fetuses in rats were reduced. Fetal skeletal variations were also noted. Some of these changes could be attributed to maternal toxicity observed at high doses.

8.2 Lactation

Risk Summary

It is not known whether bivalirudin is present in human milk. No data are available on the effects of bivalirudin on the breastfed child or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of bivalirudin to a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Bivalirudin Injection and any potential adverse effects on the breastfed infant from Bivalirudin Injection or from the underlying maternal condition.

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/s/

CHRISTOS MASTROYANNIS
11/09/2017

TAMARA N JOHNSON
11/10/2017

LYNNE P YAO
11/20/2017

MEMORANDUM

REVIEW OF REVISED LABELS 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: November 8, 2017
Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number: NDA 208374
Product Name and Strength: Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg/50 mL and 500 mg/100 mL (5 mg/mL)
Applicant/Sponsor Name: Celerity Pharmaceuticals, LLC (Celerity)
Submission Date: November 6, 2017
OSE RCM #: 2017-457-1
DMEPA Safety Evaluator: Sarah Thomas, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels and carton labeling for Bivalirudin (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

The revised container labels and carton labeling for Bivalirudin are acceptable from a medication error perspective. We have no further recommendations at this time.

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

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/s/

SARAH E THOMAS
11/08/2017

CHI-MING TU
11/08/2017

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:	October 2, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 208374
Product Name and Strength:	Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg/50 mL and 500 mg/100 mL (5 mg/mL)
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Celerity Pharmaceuticals, LLC (Celerity)
Submission Date:	February 28, 2017 and May 30, 2017
OSE RCM #:	2017-457
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As a part of the 505(b)(2) NDA review, this review evaluates the proposed container labels, carton labeling, and prescribing information (PI) for bivalirudin in 0.9% Sodium Chloride Injection submitted on February 28, 2017 and May 30, 2017, for areas of vulnerability that could lead to medication errors.

Celerity submitted a 505(b)(2) New Drug Application (NDA 208374) for Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg/50 mL and 500 mg/100 mL, premixed drug product in a single-dose GALAXY container. The listed drug is Angiomax (bivalirudin) for Injection. The proposed Bivalirudin in 0.9% Sodium Chloride Injection will 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
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels 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

While Angiomax is only supplied as 250 mg/vial, Celerity's proposed Bivalirudin in 0.9% Sodium Chloride Injection will be available in 250 mg/50 mL and 500 mg/100 mL, making the 500 mg/100 mL packaging configuration a higher strength product. However, because the concentration of the proposed 500 mg/100 mL premixed bag remains the same 5 mg/mL as Angiomax after dilution, we do not anticipate an increase in risk of dosing confusion errors with the introduction of this higher strength Bivalirudin product.

The proposed packaging configuration for Bivalirudin in 0.9% Sodium Chloride Injection is (b) (4) 12 single-dose GALAXY containers inside a very small carton (VSC), (b) (4)

(b) (4) Our review found that this unique packaging configuration is already used for multiple, currently marketed products in Galaxy containers (e.g., oxacillin, nafcillin, and cefazolin injection products packaged in Galaxy containers (b) (4) and so we do not object to the proposed packaging configuration.

Aside from the higher strength and the packaging configuration, our review of the proposed container labels, carton labeling, and prescribing information (PI) for bivalirudin in 0.9% Sodium Chloride Injection identified areas of the labels and labeling that may be improved to promote the safe use of the product. We provide our recommendations in Section 4.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling for Bivalirudin in 0.9% Sodium Chloride Injection drug product may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. In Section 2.1, we note the abbreviation, “min” used, and we recommend spelling out the word “minutes” as follows: “Five minutes after the bolus...”
2. In Section 2.2, revise the format of dosing information in renal impairment to improve clarity, such as via line spacing and sub-headers. We received post-marketing errors associated with prescribing the wrong dose or rate of infusion in patients with renal impairment.
3. In Section 3 and 16, we recommend adding the 5 mg/mL concentration following the total mg per total mL strengths.
4. In Section 16, add appropriate information to facilitate identification of the injection (e.g., description from Section 3: “clear and colorless solution”).

4.2 RECOMMENDATIONS FOR CELERITY PHARMACEUTICALS, LLC

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

A. General Comments for Container Labels and Carton Labeling

1. Revise the statement, “(b) (4)” to the following: “Usual Dose: See prescribing information.”
2. Revise the storage statement on the PDP to read as follows: “Store frozen at or below -20°C/-4°F.”
3. Revise the statement “(b) (4)” to read “For intravenous use only. Do Not Dilute.” As proposed, (b) (4) is undefined, but it appears your intention is to inform end users not to further dilute the proposed product.

4. Revise and highlight the following statements on the container label and carton labeling to emphasize the changes in storage and infusion rate for the proposed Bivalirudin when compared to the currently marketed RLD, Angiomax:
 - i. “Store frozen at or below -20°C/-4°F.”
 - ii. “For intravenous use only. Do Not Dilute.”

This will help to bring attention to these important changes on the labels and labeling to the end-users of this product.

5. Consider highlighting the strength statement in a (b) (4) color for the 500 mg per 100 mL container label and carton labeling. This will help increase the prominence of the strength presentation among the other (b) (4) font writing on the container label and carton labeling, similar to how the 250 mg per 50 mL (5 mg/mL) strength is prominent with the pink highlight on the associated container label and carton labeling.^a
6. We note the use of sequential numbers for the product code (middle digits) of the NDC for the of 250 mg per 50 mL and 500 mg per 100 mL strengths, which is not an effective differentiating feature. The middle digits are traditionally used by healthcare providers to check the correct product and strength, and so similarity of product code numbers has led to selection and dispensing errors of the wrong strength. Therefore, revise the middle digits of the NDC numbers for the two strengths on the container labels and carton labeling.^b
7. We note the absence of a lot number and expiration date on the proposed container labels and carton labeling. The lot number is required per 21 CFR 201.10(i). USP requires the label of an official drug product to bear an expiration date. Therefore, we also strongly recommend including the product’s expiration date on the container labels too.^c
 - i. Revise the container labels to include the lot number per 21 CFR 201.10(i), and to bear the expiration date per USP.
 - ii. Ensure the lot number and expiration date are presented on the carton labeling in accordance with 21 CFR 201.10(i) and 21 CFR 201.17, and ensure that they are clearly differentiated from one another.^d Ensure

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

^d Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

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.^e

^e 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 MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bivalirudin that Celerity Pharmaceuticals, LLC submitted on May 30, 2017 and the listed drug (LD), Angiomax.

Table 2. Relevant Product Information for Bivalirudin in 0.9% Sodium Chloride Injection and the Listed Drug		
Product Name	Bivalirudin in 0.9% Sodium Chloride Injection (NDA 208374)	Angiomax (Bivalirudin) for Injection (NDA 020873)
Initial Approval Date	N/A	December 15, 2000
Active Ingredient	Bivalirudin	Bivalirudin
Indication	<p>Bivalirudin Injection is a direct thrombin inhibitor indicated for use as an anticoagulant in patients:</p> <ul style="list-style-type: none"> •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. •With, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), undergoing PCI. •Bivalirudin Injection is intended for use with aspirin. 	<p>Angiomax is a direct thrombin inhibitor indicated for use as an anticoagulant in patients:</p> <ul style="list-style-type: none"> •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. •With, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), undergoing PCI. •Angiomax is intended for use with aspirin.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	250 mg/50 mL and 500 mg/100 mL	250 mg/vial
Dose and Frequency	<p><i>For patients who do not have HIT/HITTS:</i></p> <ul style="list-style-type: none"> •PCI/PTCA: 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the PCI/PTCA procedure. See FPI for remainder of 	<p><i>For patients who do not have HIT/HITTS:</i></p> <ul style="list-style-type: none"> •PCI/PTCA: 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the PCI/PTCA procedure. See FPI for

	<p>monitoring and dosing information.</p> <p><i>For patients who have HIT/HITTS:</i></p> <ul style="list-style-type: none"> •PCI: 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the procedure. See FPI for remainder of monitoring and dosing information. <p><i>For patients with STEMI:</i></p> <ul style="list-style-type: none"> •Consider extending duration of infusion post-procedure up to 4 hours. 	<p>remainder of monitoring and dosing information.</p> <p><i>For patients who have HIT/HITTS:</i></p> <ul style="list-style-type: none"> •PCI: 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the procedure. See FPI for remainder of monitoring and dosing information. <p><i>For patients with STEMI:</i></p> <ul style="list-style-type: none"> •Consider extending duration of infusion post-procedure up to 4 hours.
How Supplied	Bivalirudin Injection is supplied as a frozen, premixed, iso-osmotic, sterile, nonpyrogenic, single-dose solution packaged in the GALAXY container.	250 mg of sterile, lyophilized bivalirudin powder in a single-dose, glass vial for reconstitution
Storage	GALAXY containers should be stored frozen at or below -20°C/-4°F. Handle frozen product containers with care. Product containers may be fragile in the frozen state.	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	PL 2040 GALAXY container with two components: <ul style="list-style-type: none"> •PL 2040 film •Fitment (administration port/closure subassembly): PL 2504 polyolefin administration port and elastomeric closure 	Vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 24, 2017, we searched the L:drive and AIMS using the terms, bivalirudin, Angiomax, and NDA# “208374,” to identify relevant reviews previously performed by DMEPA.

B.2 Results

Our search identified 6 relevant reviews^{f, g, h, i, j, k} involving similar bivalirudin products or Angiomax (RLD) and their associated labels and labeling. We applied the relevant recommendations from those reviews to this label and labeling review.

^f 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.

(b) (4)

^j Ayres, E. Label and Labeling Review Memo for Angiomax (Bivalirudin) (NDA 20873/S-036). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 27. RCM No.: 2015-2414.

(b) (4)

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On July 24, 2017, 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 labels and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Searched the Acute Care, Community, and Nursing Newsletters.
Search Strategy and Terms	Match Any of the words: bivalirudin

D.2 Results

Our search retrieved 3 newsletters, and none are relevant to this label and labeling review. Of note, bivalirudin is listed on ISMP's List of High Alert Medications.¹

¹ ISMP's List of High-Alert Medications [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2014 [cited 2017 JULY 24]. Available from: <http://www.ismp.org/tools/highalertmedications.pdf>.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On July 25, 2017, we searched FAERS using the criteria in the table below. The date of search was limited from the last search date June 1, 2015 in a previous review.^m Our search identified 6 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.ⁿ We excluded 4 cases because 1 case described a potential product quality issue related to Angiomax, 1 case had an unclear narrative, 1 case involved diluting Angiomax in wrong diluent volume, and 1 case involved a discrepancy in the labeling of the Sandoz Bivalirudin product for the 0.5 mg/mL strength.

Criteria Used to Search FAERS	
Initial FDA Received Dates:	From 6/1/2015 to 7/25/2017
Product Name:	N/A
Product Active Ingredient (PAI):	Bivalirudin
Event:	SMQ <i>Medication errors</i> (Narrow)
Country (Derived):	USA

E.2 Results

Our search identified 6 cases, of which 2 describe errors relevant to this review. The 2 cases described prescribers who prescribed the wrong rate or dose in patients receiving dialysis. Both cases describe the patients experiencing fatal bleeding events.

We reviewed the proposed Bivalirudin PI and note the format of dose adjustment in renal impairment may be improved for clarity.

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case Number	Manufacturer Control Number
11777798	US-THE MEDICINES COMPANY-US-MDCO-14-00246
11777841	US-THE MEDICINES COMPANY-US-MDCO-15-00272

^m

(b) (4)

ⁿ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^o along with postmarket medication error data, we reviewed the following Bivalirudin labels and labeling submitted by Celerity Pharmaceuticals, LLC.

- Container labels submitted February 28, 2017
- Carton labeling submitted February 28, 2017
- Prescribing Information (Image not shown) submitted May 30, 2017
- Picture images of how the proposed container labels and carton labeling are fitted on the container closure system by using representative Cefazolin product submitted August 3, 2017^p

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

^o Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

^p Celerity Pharmaceutical's August 3, 2017 response to our July 27, 2017 information request.
<\\CDSESUB1\evsprod\NDA208374\208374.enx>

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

/s/

SARAH E THOMAS
10/02/2017

CHI-MING TU
10/02/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208374	NDA Supplement #: S- N/A	Efficacy Supplement Category: N/A <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: N/A Established/Proper Name: bivalirudin in 0.9 Sodium Chloride Dosage Form: injection Strengths: 250 mg/50 mL and 500 mg/100 mL Route(s) of Administration: Intravenous Infusion		
Applicant: Celerity Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A		
Date of Application: 28 February 2017 Date of Receipt: 28 February 2017 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA Goal Date: 28 December 2017	Action Goal Date (if different): N/A	
Filing Date: 29 April 2017	Date of Filing Meeting: 17 April 2017	
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication: <div style="background-color: #cccccc; height: 20px; width: 100%;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>		
Anticoagulant in patients undergoing percutaneous coronary intervention (PCI) <div style="background-color: #cccccc; height: 15px; width: 150px; display: inline-block;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>		
<div style="background-color: #cccccc; height: 20px; width: 100%;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	N/A	

<p>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</p>				
<p>Type of BLA</p> <p>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</p>		N/A		
<p>Review Classification:</p> <p>The application will be a priority review if:</p> <ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? N/A		Resubmission after refuse to file? N/A		
<p>Part 3 Combination Product? N/A</p> <p>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</p>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)			
<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation (set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager) <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: N/A	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <ul style="list-style-type: none"> <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) 			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): 126428				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic</i>				

<i>archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		N/A
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		User fee ID: 3016706 Submitted 2/24/17
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted questions below:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input checked="" type="checkbox"/>										
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>										
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>20873</td> <td>Angiomax</td> <td>*PED</td> <td>1/27/29</td> </tr> </tbody> </table> <p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	20873	Angiomax	*PED	1/27/29	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Unexpired pediatric exclusivity.
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration									
20873	Angiomax	*PED	1/27/29									
<ul style="list-style-type: none"> If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If no, include template language in the 74-day letter.</p> <p><i>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</i></p> <p><i>Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		The RLD, Angiomax, is a pharmaceutical alternative since it is a different dosage form.								
Exclusivity	YES	NO	NA	Comment								
Does another product (same active moiety) have orphan	<input type="checkbox"/>	<input checked="" type="checkbox"/>										

<p>exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i></p>				
<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?</p> <p>If yes, # years requested: N/A</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p><i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i></p> <p><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>Forms and Certifications</p> <p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Form 3542a will be requested in 74-day letter.
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Submission is electronic.

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p>For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		New dosage form.
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Agreed iPSP 12/2/2016
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Waiver requested.
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/05/2016

8

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSL/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	DPMH consult submitted 3/17/17. Requested from applicant on 3/9/2017; submitted 4/10/17.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult submitted 4/13/17.
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 6/30/15	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PIND meeting 6/30/15 (minutes 7/28/15); CMC PIND WRO 2/12/16
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 17 April 2017

BACKGROUND: Celerity Pharmaceuticals submitted an NDA for bivalirudin in 0.9% Sodium Chloride injection (250 mg/50 mL and 500 mg/100 mL) pursuant to Section 505(b)(2) of the FD&C act. Celerity is proposing an alternative dosage form, a premixed solution for injection, and is relying on the safety and effectiveness findings of RLD Angiomax (bivalirudin) for injection (NDA 20873, the Medicines Company) approved in 2000.

Celerity’s proposed product is a parenteral solution intended solely for administration by injection and is qualitatively and quantitatively similar to The Medicines Company’s Angiomax® (bivalirudin) for Injection drug product after reconstitution and further dilution; however, Angiomax® contains mannitol as an additional inactive ingredient. Mannitol is commonly found in lyophilized products as a (b) (4). Since the proposed drug product is produced and intended for market as a frozen premixed IV solution, mannitol is not required in the formulation.

To prepare for this submission, Celerity discussed a bio-waiver for in-vivo bioavailability/bioequivalence studies during a PIND (126428) meeting; minutes dated 28 July 2015. The Division agreed to the company’s request for a bio-waiver. This NDA submission does not contain clinical data; however an in-vitro study, entitled “A Two Site In Vitro Study Comparing a Frozen Formulation of Bivalirudin to the Lyophilized Formulation of Bivalirudin (Angiomax®) on Activated Partial Thromboplastin Time, Prothrombin Time, and Thrombin Time over the Therapeutic Range in Male Human Plasma”, was submitted to provide the requested evidence (minutes dated 12 February 2016) that at physiologically relevant bivalirudin concentrations the in vitro coagulation parameters (aPTT, PT, and TT) for your proposed drug products (at batch release and at the end of its shelf-life) are within ±20% of those measured for Angiomax®.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Bridget Kane	N
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Martina Sahre		Y
Division Director	Norman Stockbridge		Y
Deputy Division Director	Stephen Grant		Y
Clinical	Reviewer:	Karen Hicks	Y
	TL:		
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Snehal Samant	Y
	TL:	Sudharshan Hariharan	N
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Mohan Sapru	Y
	RBPM:	Grafton Adams	Y
• Drug Substance	Reviewer:	Rajan Pragani	N
• Drug Product	Reviewer:	Dan Berger	N
• Process	Reviewer:	Mark Johnson	Y
• Microbiology	Reviewer:	Alifiyia Ghadiyala	N
• Facility	Reviewer:	Jonathan Swoboda	Y
• Biopharmaceutics	Reviewer:	Banu Zolnik	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sarah Thomas	Y

	TL:	Alice Tu	N
OSE/DPV	Reviewer:	Mohamed Mohamoud	Y
	TL:	Alice Tu	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
Division of Pediatric & Maternal Health	Reviewer:	Christos Mastroyannis	Y
	TL:	Tamara Johnson	N
Other attendees	Colleen Locicero, ODE 1 ADRA		Y
	Alexis Childers, RPM		Y
	Ta-Chen Wu, Biopharmaceutics TL		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> <p>The sponsor provided two forms of information attempting to show that their application can rely on</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
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<p>the finding of safety and efficacy of the listed drug.</p> <p>(1) In lieu of a BA/BE study, the sponsor submitted a biowaiver based on 21 CFR 320.22(a) and (b)(1)(i) and (ii). For a parenteral solution to be administered via injection, bioequivalence can be considered self-evident if the concentration of active and inactive ingredients is the same as the listed drug.</p> <p>(2) An in vitro study to support similar potency of the new product.</p>	
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain: N/A</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: N/A</p>	<input checked="" type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: N/A
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: No filing issues; no 74-day letter comments.</p> <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: No 74-day letter comments; no facilities inspections.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity</u> (NDAs only)</p> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>Environmental Assessment</p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments: request located in Section 1.12.14	
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Comments: no planned inspections at this time	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments: N/A	<input checked="" type="checkbox"/> Not Applicable
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
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REGULATORY PROJECT MANAGEMENT

Signatory Authority: Norman Stockbridge, MD, PhD, Division Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: N/A

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

BRIDGET E KANE
05/03/2017