

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208374Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.5.2 Patent Certification

PARAGRAPH IV CERTIFICATIONS [21 CFR § 314.50(i)(1)(i)(A)(4)(i)]

U.S. Patent No. 7,582,727, assigned to The Medicines Company and listed in the current Orange Book¹ for ANGIOMAX Injectable, 250 mg /vial (bivalirudin), expires on July 27, 2028 with a pediatric exclusivity period under 21 USC § 355a(c)(2)(A) expiring on January 27, 2029. On behalf of Celerity Pharmaceuticals, LLC, I hereby certify that U.S. Patent No. 7,582,727 is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg base/50 mL or Bivalirudin in 0.9% Sodium Chloride Injection, 500 mg base/100 mL for which this 505(b)(2) application is submitted.

U.S. Patent No. 7,598,343, assigned to The Medicines Company and listed in the current Orange Book for ANGIOMAX Injectable, 250 mg /vial (bivalirudin), expires on July 27, 2028 with a pediatric exclusivity period under 21 USC § 355a(c)(2)(A) expiring on January 27, 2029. On behalf of Celerity Pharmaceuticals, LLC, I hereby certify that U.S. Patent No. 7,598,343 is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Bivalirudin in 0.9% Sodium Chloride Injection, 250 mg base/50 mL or Bivalirudin in 0.9% Sodium Chloride Injection, 500 mg base/100 mL for which this 505(b)(2) application is submitted.

Celerity further certifies that it will comply with the requirements of 21 CFR § 314.52(a) with respect to providing a notice to the holder of each patent identified above and to the NDA holder for the reference listed drug; with the requirements of 21 CFR § 314.52(b) with respect to the sending of such notice; and with the requirements of 21 CFR § 314.52(c) with respect to the contents of such notice.



Daniel S. Robins
President, Celerity Pharmaceuticals, LLC



Date

¹ U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Information Technology, Division of Data Management and Services. *Approved Drug Products with Therapeutic Equivalence Evaluations* (Electronic Orange Book).

1.3.3 Debarment Certification

Celerity Pharmaceuticals, LLC 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.

Signed: Ambareen Sheriff
Ambareen Sheriff
Vice President, Regulatory Affairs and Quality Assurance
Celerity Pharmaceuticals, LLC

Date: Feb 2, 2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208374	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: N/A Established/Proper Name: bivalirudin in 0.9% sodium chloride Dosage Form: injection		Applicant: Celerity Pharmaceuticals Agent for Applicant (if applicable): N/A
RPM: Bridget Kane		Division: Cardiovascular and Renal Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 12/21/17</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>28 December 2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information were issued 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) (link)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees (link)	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval -12/21/2017
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	N/A
<ul style="list-style-type: none"> Original applicant-proposed labeling 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	N/A
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input checked="" type="checkbox"/> 12/21/17 DMEPA: <input checked="" type="checkbox"/> 10/2/17, 11/8/17 DMPP/PLT (DRISK): N/A OPDP: <input checked="" type="checkbox"/> 12/8/17 SEALD: N/A CSS: N/A Product Quality: 11/13/17 DPMH: <input checked="" type="checkbox"/> 11/9/17 Deputy Director: <input checked="" type="checkbox"/> 12/20/17
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	RPM Filing review – 5/3/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	505(b)(2) committee clearance - 12/19/2017
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>15 November 2017</u> If PeRC review not necessary, explain: N/A 	DARRTS Pediatric Page included
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	NDA Acknowledgement letter – 3/9/17 NDA 74-day letter – 5/10/17 Information Request – 10/27/17 Information Requests (DMEPA) – 7/27/17
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Memo-Application Transfer-IND 126428, 4/30/15
Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	Pre-IND meeting – 6/30/15 Post-meeting email – 8/28/17 CMC meeting (pre-IND) – 2/12/16
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> See CDTL Memo
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 12/15/17 (Joint review - Sahre, Stockbridge)
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None

Clinical <input checked="" type="checkbox"/> None	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	N/A
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	N/A - 505(b)2 application
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> N/A
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	N/A
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	Primary Review (Samant), 11/7/17; Filing Review (Samant) 4/27/17
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	IQA, 11/13/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	IQA, 13 Nov 2017 (Berger) Applicant's Environmental Assessment included
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	N/A
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	N/A
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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
12/27/2017



NDA 208374

INFORMATION REQUEST

Celerity Pharmaceuticals, LLC
Attention: Brent Yurschak
Senior Regulatory Affairs Manager
9450 W. Bryn Mawr Ave., Suite 640
Rosemont, IL 60018

Dear Mr. Yurschak:

Please refer to your New Drug Application dated 28 February 2017, received 28 February 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for bivalirudin in 0.9% sodium chloride injection.

After review of your proposed carton and container labeling, we have the following recommendations. Please submit revised carton and container labeling by **Monday, 6 November 2017**.

1. Please 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, (b) (4) 250 mg per 50 mL (5 mg/mL) strength is prominent with the pink highlight on the associated container label and carton labeling.¹

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, consider revising the middle digits of the NDC numbers for the two strengths on the container labels and carton labeling.²
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.³
 - 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.⁴ Ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.⁵

If you have any questions, please contact Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

¹ 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>.

² 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>.

³ 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>

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

⁵ Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

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/s/

NORMAN L STOCKBRIDGE
10/27/2017

Blaus, Alison

From: Blaus, Alison
Sent: Friday, August 28, 2015 10:46 AM
To: 'Brent Yurschak'
Cc: Amber Sheriff
Subject: RE: Bivalirudin Injection pre-IND 126428 Meeting Minutes-Question 4 Follow-up

Hi Brent

In response to the below question and referencing our meeting minutes from our 30Jun15 pIND Meeting (minutes dated 28Jul15), we have the following response to your 19Aug15 email:

- Given the long-term stability of the RLD, and composition of your proposed formulation, you have not provided any valid justification to explain why the long-term stability of your proposed formulation at the recommended storage conditions is not be studied beyond the (b) (4) time point to support a commercially viable product expiration dating period.
- Given that the product expiration period is determined based on review evaluation of quality and quantity of stability data, including the multi-time point data trends, providing only (b) (4) stability data does not necessarily guarantee granting a (b) (4) expiration dating period for your proposed product.
- It is important to point out that the current state of knowledge and understanding of issues in any scientific field, including the regulatory sciences continuously undergo evolution. Hence decisions concerning regulatory practices are made in the context of our current understanding and not necessarily by dogmatic adherence to past practices unless justified by strong scientific rationale. Viewed in this context, your listing of some of the (b) (4) products which have been approved in the past with shorter expiration periods does not necessarily provide adequate justification for your current proposal to provide reduced stability data to support shorter expiration dating period.
- As previously communicated, please note that the Agency's expectation is that the NDA will include at least twelve (12) months of long-term stability data at the time of submission as per ICH QIA(R2). In addition, any proposal for short-term excursions or product thawing outside the proposed label storage conditions needs to be supported by appropriate stability data. Lastly, according to the Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (GRMPs), all NDAs are to be complete in the original submission.

****Please retain this email as formal documentation of this advice as it will be made part of the administrative file for this IND.****

Do not hesitate to contact me if you have any questions!
Alison

Alison Blaus, RAC

Senior Regulatory Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
alison.blaus@fda.hhs.gov
Office:(301) 796-1138
Blackberry: (240) 204-4562
Fax:(301) 796-9838

Address for desk and courtesy copies:
Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4158
Silver Spring, MD 20993

Address for official submissions to your administrative file:
Division of Cardiovascular and Renal Products
FDA, CDER, HFD-110
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

From: Brent Yurschak [mailto:byurschak@celeritypharma.com]
Sent: Wednesday, August 19, 2015 3:27 PM
To: Blaus, Alison
Cc: Amber Sheriff
Subject: Bivalirudin Injection pre-IND 126428 Meeting Minutes-Question 4 Follow-up

Hello Alison,

Thank you again for speaking with Celerity on Thursday, August 13 regarding pIND 126428. As agreed at the conclusion of our discussion, I am sending along additional information to support our request for submission of the NDA with 9 months of data (Question 4).

Summary of August 13, 2015 Discussion

Celerity Participants: Amber Sheriff, Vice President of Regulatory Affairs; Brent Yurschak, Senior Regulatory Affairs Manager
FDA Participant: Alison Blaus, Senior Regulatory Project Manager

Celerity indicated that we still weren't certain, based on the meeting minutes, if submission of the NDA with 9 months data would be acceptable. Ms. Blaus said that in her opinion the expectation was clear that the original submission should include 12 months of data. Celerity noted that our development partner, (b) (4), manufactures frozen drug products that are marketed with (b) (4) or less expiration dating period. Ms. Blaus stated that if these products were originally submitted with less than (b) (4) data at time of submission, that would be potentially helpful for our question, as the Division does not wish to set a precedent. Celerity indicated that they would reach out to (b) (4) and ask them to inform us if the submissions were made with less than (b) (4) data, and Celerity would subsequently provide that information to Ms. Blaus by email. Once the information is provided, Ms. Blaus will go back to the OPQ reviewer for his clarification. Ms. Blaus additionally indicated that Celerity would not receive an official communication but that her email response would be placed on file.

Additional Supportive Information

FDA's Post-Meeting Note to Question 4 is duplicated below in **bold** font, with additional Celerity comments interspersed in regular font.

Given the composition of your proposed formulation, it is not clear why the long-term stability of your proposed formulation is not to be studied beyond the (b) (4) time point. As indicated in our preliminary response to Q4, it is important that the proposed expiration period ensures that the drug product is commercially viable.

As Celerity indicated in our conversation with Ms. Blaus on August 13, our development partner, (b) (4), currently manufactures several frozen premixed drug products that have an expiration dating period of (b) (4). Please refer to the table below.

Drug Product	NDA	Expiry
--------------	-----	--------

		(months)
CLAFORAN	050596	(b) (4)
FORTAZ	050634	(b) (4)
TIMENTIN	050658	(b) (4)
ZOSYN	050750	(b) (4)
Cefepime Injection	050817	(b) (4)

Cefepime Injection is a Baxter-owned drug product and the original submission was filed with 6 months of real time data and upon approval of the application was marketed with (b) (4) expiration dating period. (b) (4)

We note that you intend to market your product with only (b) (4) expiry period, and do not plan to submit any additional stability data during the NDA review period for extending the proposed (b) (4) expiry period. We recommend providing adequate long-term and accelerated stability data to support your proposed expiry period. As indicated earlier, we will evaluate the proposed expiration period based on the quantity and quality of the stability data provided in the submission.

As noted in ICH Q1A(R2), frozen drug products do not have an accelerated storage condition. ICH Q1A(R2) further reads "For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition." In accordance with this guidance, Celerity intends to provide real time data obtained at the long-term storage condition (b) (4) as well as providing additional short-term data at each time point. Testing will be scheduled as follows:

(b) (4)

Regards,
Brent

Brent Yurschak
Senior Regulatory Affairs Manager
Celerity Pharmaceuticals, LLC
9450 W. Bryn Mawr Ave.
Suite 640
Rosemont, IL 60018
Direct/Fax/SMS: +1 (847) 999-0492
Email: byurschak@celeritypharma.com

CELERITY PHARMACEUTICALS, LLC CONFIDENTIALITY NOTICE: The information transmitted is intended only for the person(s) or entity to which it is addressed and may contain confidential and/or legally privileged material. Delivery of this message to any person other than the intended recipient(s) is not intended in any way to waive privilege or confidentiality. Any review, retransmission, dissemination or other use of, or taking of any action in reliance upon, this information by entities other than the intended recipient is prohibited. If you receive this in error, please contact the sender and delete the material from any computer. This communication does not reflect an intention by the sender to conduct a transaction or make any agreement by electronic means.

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/s/

ALISON L BLAUS
08/28/2015

Lyons, Darrell

From: Lyons, Darrell
Sent: Thursday, July 27, 2017 9:21 AM
To: 'byurschak@celeritypharma.com'
Cc: Kane, Bridget
Subject: Labeling Information Request (IR) for NDA 208374

Dear Mr. Yurschak,

This communication is in reference to your February 28, 2017 submission.

You submitted Bivalirudin injection container labels and carton labeling, but we cannot visualize how the "back panel" of the container label fits on the container closure system and how the panel pieces of carton labeling fit together. Submit the following to the application via the electronic gateway within 5 business days from date of request:

1. Picture of the proposed Bivalirudin product with container label, such that we can visualize how the container label will be applied to the intravenous bag.
2. Complete carton labeling in its entirety. For example, your submission included the Angiomax carton labeling in its entirety (snapshot below).

9. THE MEDICINES COMPANY'S REFERENCE LISTED DRUG 250 MG CARTON

(b) (4)



Best regards,

Darrell Lyons, BSN, RN
Commander, USPHS
Safety Regulatory Project Manager
Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology
U.S. Food and Drug Administration
Tel: (301) 796-4092
darrell.lyons@fda.hhs.gov



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/s/

DARRELL LYONS
07/27/2017

Lyons, Darrell

From: Lyons, Darrell
Sent: Thursday, July 27, 2017 9:26 AM
To: byurschak@celeritypharma.com
Cc: Kane, Bridget
Subject: Proprietary Name for NDA 208374

Dear Mr. Yurschak,

If you intend to have a proprietary name for the above-referenced product, you should submit a request for proprietary name review within **7 days** of this communication.

When submitting a proprietary name request for review to the Agency, it is crucial to include the statement “**REQUEST FOR PROPRIETARY NAME REVIEW**” in bold capital letters, at the top of your cover letter and on the first page of the main submission document (refer to the complete submission guidance link below). The review of this name will be initiated when the new submission is received.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

Best regards,

Darrell Lyons, BSN, RN
Commander, USPHS
Safety Regulatory Project Manager
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
U.S. Food and Drug Administration
Tel: (301) 796-4092
darrell.lyons@fda.hhs.gov



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/s/

DARRELL LYONS
07/27/2017



NDA 208374

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Celerity Pharmaceuticals, LLC
Attention: Brent Yurschak
Senior Regulatory Affairs Manager
9450 W. Bryn Mawr Ave., Suite 640
Rosemont, IL 60018

Dear Mr. Yurschak:

Please refer to your New Drug Application dated 28 February 2017, received 28 February 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for bivalirudin in 0.9% sodium chloride injection.

We also refer to your amendment dated 10 April 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is 28 December 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by 28 November 2017.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug and contains a paragraph IV certification, this filing communication is the "paragraph IV acknowledgment letter" described in 21 CFR 314.52(b) and the "postmark" is 4 calendar days after the date on which this letter is signed. Notice of the paragraph IV certification must be sent to the persons described in 21 CFR 314.52(a) no later than 20 days after the date of the postmark on this paragraph IV acknowledgment letter and must contain the information described in 21 CFR 314.52(c).

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Product Quality

- Please submit an updated form 356h and applicable section of Module 3 to include all final drug substance and final drug product manufacturing facilities as well as all drug substance and drug product testing facilities.

Biopharmaceutics

- We could not locate the pilot in-vitro study report (CA17943) in your submission. We request that you indicate the location of this study report, if it has been submitted, or submit the complete study report to the NDA for the Agency's review.

Regulatory

- Per 21CFR Part 314.53(c) and (d), please submit a completed FDA Form 3542a for each patent that claims a drug substance (active ingredient), drug product (formulation or composition), and/or method of using the proposed drug product. If there are no relevant patents for this pending NDA, please complete Section 5 of the form.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug, we recommend that the cover letter for amendments to your unapproved 505(b)(2) application either: 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. In the Highlights of Prescribing Information (HPI), please change the name of the drug product to **BIVALIRUDIN** in the Highlights limitation statement. The statement should read: **These highlights do not include all the information needed to use BIVALIRUDIN safely and effectively. See full prescribing information for BIVALIRUDIN.**

2. Please remove the 'RECENT MAJOR CHANGES' section in the HPI as these changes are greater than one year old. Please also remove the vertical line in the respective sections of the Full Prescribing Information.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **Friday, 2 June 2017**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are

required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
05/10/2017



NDA 208374

NDA ACKNOWLEDGMENT

Celerity Pharmaceuticals, LLC
Attention: Brent Yurschak
Senior Regulatory Affairs Manager
9450 W. Bryn Mawr Avenue, Suite 640
Rosemont, IL 60018

Dear Mr. Yurschak:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Bivalirudin in 0.9% Sodium Chloride Injection

Date of Application: February 28, 2017

Date of Receipt: February 28, 2017

Our Reference Number: NDA 208374

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 29, 2017 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling 21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is required for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
03/09/2017

Form Approved: OMB No. 0910 - 0297 Expiration Date: March 31, 2019. See instructions for OMB Statement, below.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm>

1. APPLICANT'S NAME AND ADDRESS

CELERITY PHARMACEUTICALS LLC
Brent Yurschak
9450 BRYN MAWR AVE STE 640
ROSEMONT
IL
IL
US 600185276
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

208-374

2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE

847-9990492

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

Bivalirudin in 0.9% Sodium Chloride Injection

6. USER FEE I.D. NUMBER

PD3016706

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? YES NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736

(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
 THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
 YES NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

Privacy Act Notice:

This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online: <http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm>.

OMB Statement:

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
Brent Yurschak <i>Brent Yurschak</i>	Senior Regulatory Affairs Manager	2/20/2017

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
 \$1,019,050.00

Form FDA 3397 (03/16)

**INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET
FORM FDA 3397**

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency, unless specifically exempted below. Form FDA 3397 should be placed in the first volume of the application with the application (FORM FDA 356(h)) form. Form FDA 3397 is to be completed on-line at https://userfees.fda.gov/OA_HTML/pdufaCAcdLogin.jsp. If you need assistance in completing the form call 301-796-7200 or email: userfees@fda.gov.

NOTE: Form FDA 3397 need not be submitted for:

CDER

- 505(j) applications
- Supplements to 505(j) applications
- 351(k) applications

CBER

Any supplement that does not require clinical data for approval.
Applications and supplements for:

- * Products for further manufacturing use only
- * Whole blood or blood components for transfusion
- * Bovine blood product for topical application licensed before September 1, 1992
- * A crude allergenic extract product
- * An in vitro diagnostic biological product licensed under Section 351 of the PHS Act
- * 351(k) applications

ITEM NO.	INSTRUCTIONS
1-2.	Self-explanatory
3.	PRODUCT NAME: Include generic or proper name and trade name, as applicable.
4.	BLA STN / NDA NUMBER - FOR AN ORIGINAL BIOLOGIC LICENSE APPLICATION (BLA) - Indicate the 6-digit BLA number (Submission Tracking Number (STN)) if pre-assigned, otherwise leave blank. For A SUPPLEMENT enter the BLA STN. FOR DRUG PRODUCTS: Indicate the new drug application (NDA) number. NDA numbers can be obtained by completing the information at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm .
5.	CLINICAL DATA: The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf .
6.	USER FEE I.D. NUMBER: Please include the ID number (generated when completing Form FDA 3397) on the application payment check.
7.	PRIORITY REVIEW VOUCHER: If you are redeeming a priority review voucher awarded to a sponsor of a tropical disease product application (see section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), please include the priority review voucher number assigned when the voucher was initially granted. See FDA's Guidance for Industry: Tropical Disease Priority Review Vouchers for further information. FDA's guidance can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf .
8.	EXCLUSIONS: The application is for an orphan drug product. Under section 736(a) (1) (F) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	WAIVER: Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.

Form FDA 3397 (03/16) (BACK)

[Close Print Cover sheet](#)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 126428

MEETING MINUTES

Celerity Pharmaceuticals, LLC
Attention: Brent Yurschak
Senior Regulatory Affairs Manager
9450 W. Bryn Mawr Ave, Suite 640
Rosemont, IL 60018

Dear Mr. Yurschak:

Please refer to your Pre-Investigational New Drug Application (PIND) file for bivalirudin injection.

We also refer to the teleconference between representatives of your firm and the FDA on 30 June 2015. The purpose of the meeting was to discuss your development plans for this product.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call:

Alison Blaus, RAC
Senior Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

Meeting Minutes
Sponsor's Slide



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-IND
Meeting Date and Time: 30 June 2015 from 1400 to 1500 EST
Meeting Location: Teleconference
Application Number: PIND 126428
Product Name: bivalirudin injection
Proposed Indication: [REDACTED] (b) (4)

2. Percutaneous Coronary Intervention (PCI)
Bivalirudin Injection [REDACTED] (b) (4)
[REDACTED] indicated for use as
an anticoagulant in patients undergoing percutaneous coronary
intervention (PCI). [REDACTED] (b) (4)

[REDACTED] (b) (4)

Sponsor Name: Celerity Pharmaceuticals, LLC
Meeting Chair: Norman Stockbridge, MD, PhD
Meeting Recorder: Alison Blaus, RAC

FDA ATTENDEES

* Office of New Drugs I, Division of Cardiovascular and Renal Products

Norman Stockbridge, MD., PhD	Director
Stephen Grant, MD	Deputy Director
Edward Fromm, RPh, RAC	Chief Project Management Staff
Alison Blaus, RAC	Senior Regulatory Health Project Manager
Brian Procter	Regulatory Health Project Manager

* Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Martina Sahre, PhD	Reviewer, Clinical Pharmacology
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* Office of Pharmaceutical Quality (OPQ), Division of Biopharmaceutics

Angelica Dorantes, PhD	Acting Branch Chief, Biopharmaceutics
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SPONSOR ATTENDEES

Daniel Robins, PhD
Amber Sheriff

President
Vice President, Regulatory Affairs & Quality Assurance
Senior Regulatory Affairs Manager
Senior Product Development Manager
Product Development Scientist
RPh, Regulatory Consultant

Brent Yurschak
George Monen
Jay Mowli
Gordon Johnston
Consultant

(b) (4)

1.0 BACKGROUND

Bivalirudin Injection is a direct thrombin inhibitor approved under the trade name Angiomax® (b) (4). Celerity intends to seek approval of Bivalirudin Injection via the 505(b)(2) NDA pathway with reference to FDA's finding of safety and effectiveness for Angiomax® for Injection (lyophilized powder in single-use, glass vials - After reconstitution, each vial delivers 250 mg of Angiomax). The proposed Celerity drug products are premixed, frozen iso-osmotic solutions comprised of 250 mg/50 mL and 500 mg/100 mL of bivalirudin in 0.9% sodium chloride in a GALAXY plastic container.

FDA sent Preliminary Comments to Celerity Pharmaceuticals on 26 June 2015.

2. DISCUSSION

2.1. Questions for the Agency

Clinical Pharmacology

1. In accordance with 21 CFR § 320.22(a), Celerity Pharmaceuticals, LLC intends to request a waiver for the requirement to submit in vivo bioavailability/bioequivalence data for the proposed Bivalirudin Injection drug product. This request is based on 21 CFR § 320.22(b), which states that for certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident provided:
 - (1) The drug product:
 - (i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and
 - (ii) Contains the same active and inactive ingredients (b) (4) as a drug product that is the subject of an approved full new drug application.

While the proposed drug product and Angiomax® are not identical, they are very similar upon reconstitution and dilution of Angiomax®; the absence of mannitol in the proposed drug product is not expected to lead to clinical differences. Further, the route of administration and concentration (after reconstitution and dilution of Angiomax®) of the proposed product are the same as Angiomax®. Does the Agency concur with this position?

FDA Preliminary Comment

We agree with your proposal to request a biowaiver for your proposed drug product.

Discussion during the Teleconference

No further discussion.

2. If the Agency concurs with the position presented in Question 1, does the Agency agree that from the clinical pharmacology perspective the provided information supports the sponsor's request for a waiver of the CFR requirement to submit *in vivo* bioavailability/bioequivalence data for their product, and that the proposed product is eligible for a biowaiver upon the forthcoming submission of the 505(b)(2) NDA?

FDA Preliminary Comment

As stated in our response for Q1, a biowaiver request is appropriate for your proposed drug product. Please include the biowaiver request in your NDA submission and provide the following supporting information/data;

- A justification with supporting data demonstrating that the formulation differences between your product and the listed product do not have an impact on the on the disposition, efficacy, and safety of your drug product when they are compared to those of the listed drug product (published literature, study data, etc.)
- The physicochemical data and other supporting information for your drug product compared to the information/data of the listed drug product. An *in vitro* equivalency study assessing the pharmacodynamic (PD) activity of bivalirudin between your product and listed drug product. Please note that for the *in vitro* study the 90% confidence interval for the ratios of geometric means between your product and the listed drug product should meet the 90-110% confidence range for observed aPTT, and PT at clinically relevant bivalirudin concentrations, and TT measurements can be conducted at diluted as appropriate concentrations covering at least 3 concentration points (i.e., between ^{(b) (4)} μg/mL).

Be aware that FDA does not grant waivers of the required bioavailability (BA) and bioequivalence (BE) studies during the IND stage. Therefore, our recommendation on granting the biowaiver for your product will be made during review of the NDA.

Discussion during the Teleconference

The sponsor referred the Agency to the slide provided as an appendix. The sponsor desired to study the bioactivity of the molecule as part of the stability program instead of the *in vitro* equivalency study. The Agency mentioned that they were open to a new test, but would need to see (1) a validation report to see how well this new test performs, and (2) a document clearly laying out the argument for reliance on thrombin only.

3. Celerity believes that a half-PDUFA fee is appropriate, as the application will not contain clinical data as noted in Section 5. Does the Agency agree?

FDA Preliminary Comment

It appears that there will be no clinical data needed for this potential 505(b)(2), and therefore a half-PDUFA fee would be appropriate. However, a final determination will be made at the time of the NDA. At the time of the pre-NDA meeting, if you would like to submit a draft label and a synopsis of why no clinical data are needed, we can review and make a determination at that time.

Discussion during the Teleconference

No further discussion.

Chemistry, Manufacturing, and Controls

4. Celerity intends to request (b) (4) expiration dating (shelf life) for the proposed drug product in the original NDA filing. According to Section II.B.7.e of FDA's Stability Testing guidance, "for drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition."

Additionally, FDA's Stability Testing for New Dosage Forms (b) (4) data from ongoing studies) may be acceptable in certain justified cases."

Taking into consideration the guidance documents referenced, Celerity proposes to submit (b) (4) of stability data for the proposed drug product in the original NDA filing. These (b) (4) of stability data will consist of real time data over the requested shelf life at the long-term storage condition (frozen). Does the Agency agree with this proposal?

FDA Preliminary Comment

No, we do not agree. First, ICH Guidance (b) (4) is not applicable in this situation. ICH Guidance (b) (4) (Stability Testing for New Dosage Forms) allows (b) (4), and is applicable to new dosage forms by the owner of the original application. Second, according to the Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (GRMPs), all NDAs are to be complete in the original submission.

It is our expectation that the NDA will include at least twelve (12) months of long-term stability data at the time of submission. Furthermore, in the absence of an accelerated storage condition for your proposed drug product, intended to be stored in a freezer, testing at an elevated temperature ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$) for an appropriate time period should be conducted to support: a) your proposed thawed labeled storage conditions i.e., 24 hours at room temperature ($25^{\circ}\text{C}/77^{\circ}\text{F}$)" and b) short-term excursions outside the proposed label storage conditions. The proposed expiration period should ensure that the drug product is commercially viable. We will evaluate the proposed expiration period based on the quantity and quality of the stability data provided in the submission.

Discussion during the Teleconference

The sponsor clarified that they only seek a (b) (4) expiration date, so they only proposed sending in (b) (4) of stability data. The sponsor also plans to provide both short-term and long-term frozen time points, including data on thawed product and how long it was stable. Dr. Stockbridge did not anticipate that this would be a problem, but deferred to our OPQ reviewer to opine in a post-meeting note.

Post-Meeting Note

Given the composition of your proposed formulation, it is not clear why the long-term stability of your proposed formulation is not to be studied beyond the (b) (4) time point. As indicated in our preliminary response to Q4, it is important that the proposed expiration period ensures that the drug product is commercially viable. We note that you intend to market your product with only (b) (4) expiry period, and do not plan to submit any additional stability data during the NDA review period for extending the proposed (b) (4) expiry period. We recommend providing adequate long-term and accelerated stability data to support your proposed expiry period. As indicated earlier, we will evaluate the proposed expiration period based on the quantity and quality of the stability data provided in the submission.

5. Celerity proposes to include stability data from three (3) registration stability batches of the proposed Bivalirudin Injection drug product in the NDA submission. Two (2) registration stability batches of the 250 mg/50 mL presentation and one (1) registration stability batch of the 500 mg/100 mL presentation will be manufactured at not less than (b) (4) of commercial batch size using multiple drug substance lots in the commercial manufacturing facility with equipment and processes representative of commercial production.

Celerity believes that a total of three (3) registration stability batches is justified and adequate to support the proposed expiration dating for the proposed product presentations in the 505(b)(2) NDA submission, and proposes to include two (2) registration stability batches of the 250 mg/50 mL presentation and one (1) registration stability batch of the 500 mg/100 mL presentation. Refer to Section 14 for supportive information. Does the Agency agree with this position?

FDA Preliminary Comment

No, we do not agree. ICH Q1A (R2) guidance stipulates stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied. You are proposing to market only 250 mg/50 mL and 500 mg/100 mL presentations and hence a bracketing or matrixing approach is not relevant. For additional details regarding granting of expiration period, refer to our response to question 4.

Discussion during the Teleconference

Celerity explained that their proposal for stability testing on three batches, not six, was based on previous experience they had manufacturing a product for (b) (4) that was similar to their product in terms of equipment and manufacturing process. They felt the only relevant difference between their product and the (b) (4) Product was volume and headspace. Dr. Stockbridge suggested the sponsor submit a rationale for the proposed deviation from guidance and it will be reviewed by OPQ.

Post-Meeting Note

In the absence of CMC details concerning the (b) (4) product i.e., formulation, manufacturing process, and control strategies in the meeting package, we cannot evaluate the adequacy of your proposal for reduced stability studies at this stage. However, you have the option to request a type C CMC-only meeting to discuss this proposal in detail with the Agency.

6. Section II.B.2 of FDA's Stability Testing guidance² states that "Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B." ICH Q1B4 requirements are tailored to products that are not significantly thermally sensitive.

Frozen drug products are sensitive to temperature and will degrade significantly from exposure to room temperature, thus they are stored long term in a freezer. The proposed frozen Bivalirudin Injection drug product units are packaged in cardboard cartons and it is unlikely that the product receives any significant light exposure during long-term label storage in the freezer. Further, the guidance "...does not cover the photostability of drugs after administration (i.e., under conditions of use)". During the thawed labeled storage conditions proposed for Bivalirudin Injection of (b) (4) in a hospital setting, it is also unlikely that the product receives any significant light exposure other than to ambient light.

Therefore, photosensitivity studies are not appropriate and Celerity proposes not to conduct photostability studies in support of the NDA. Does the Agency concur?

FDA Preliminary Comment

No, we do not agree. The thawed labeled storage conditions proposed for Bivalirudin Injection include (b) (4) in a hospital setting. It is not clear why photostability testing (with use of appropriate controls) cannot be performed reliably. In general, evaluating the photostability characteristics of drug substances and products is important to demonstrate that light exposure does not result in unacceptable degradation during thawing of the drug product and administration to the patient. Hence, we recommend that you perform ICH Q1B -compliant photostability testing.

Discussion during the Teleconference

The sponsor acknowledged that they would perform in use stability testing with (b) (4) light exposure.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development

lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

If the sponsor would like to discuss the post-meeting notes captured under Questions 4/5, a Type C CMC-only Meeting or Written Response Only can be submitted to the IND.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Division was to follow-up with the CMC reviewer, Dr. Mohan Sapru, regarding the discussion under question 4 and 5. Those post-meeting notes are captured above.	FDA	To be included in these minutes - Completed

6.0 ATTACHMENTS AND HANDOUTS

The sponsor had one slide they presented to the FDA. This slide is attached as an appendix to these minutes.

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/s/

NORMAN L STOCKBRIDGE
07/28/2015



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PIND 126428

**MEETING REQUEST-
WRITTEN RESPONSES**

Celerity Pharmaceuticals, LLC
Attention: Brent Yurschak
Senior Regulatory Affairs Manager
9450 W. Bryn Mawr Ave., Suite 640
Rosemont, IL 60018

Dear Mr. Yurschak:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Bivalirudin Injection.

We also refer to your submission dated December 24, 2016, containing a Type B meeting request. The purpose of this meeting is to discuss consideration by the DCRP that the determination of bioactivity, measured at all-time points during the stability testing of the registration batches, is sufficient to demonstrate in vitro bioequivalence between the proposed Celerity drug products and Angiomax®.

Further reference is made to our Meeting Granted letter dated January 5, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your January 29, 2016 background package.

If you have any questions, call Maryam Changi at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Wendy Wilson-Lee, Ph.D.
Branch Chief, Branch 1 (Acting)
Division of New Drug Product 1
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-IND

Application Number: 126428
Product Name: Bivalirudin Injection
Indication: (b) (4)
2. Percutaneous Coronary Intervention (PCI)

Sponsor: Celerity Pharmaceuticals, LLC

1.0 BACKGROUND

The purpose of this meeting is to discuss consideration by the DCRP that the determination of bioactivity, measured at all-time points during the stability testing of the registration batches, is sufficient to demonstrate in vitro bioequivalence between the proposed Celerity drug products and Angiomax®.

2.0 QUESTIONS AND RESPONSES

Question 1:

Reference is made to the pre-IND 126428 meeting minutes ^[2] from a teleconference held on 30 June 2015 between Celerity and FDA's Division of Cardiovascular and Renal Products (DCRP) regarding Bivalirudin Injection. Specifically, the DCRP indicated it would be "open to a new test" for bioavailability (BA)/bioequivalence (BE) if certain additional information was provided (Question 2).

Based on the validation report, bioactivity results for the proposed Celerity products and Angiomax®, and additional justification laying out the argument for reliance on the thrombin inhibition bioassay only, Celerity proposes that the determination of bioactivity, measured at all time points during the stability testing of the registration batches, is sufficient to demonstrate in vitro bioequivalence between the proposed Celerity products and Angiomax®. Does the Agency agree?

FDA Response to Question 1

Based on the data provided, we do not agree that comparative testing of your proposed drug product versus Angiomax® using the thrombin-inhibition (stability-indicating) bioassay alone is sufficient to support the biowaiver request for the proposed premixed, frozen iso-osmotic solutions of bivalirudin, 250 mg/50 mL and 500 mg/100 mL. Therefore, in the NDA submission include a biowaiver request and include the following supporting information:

- (1) A summary table comparing (side by side) the composition, pH, osmolarity, assay potency, thrombin inhibition activity, impurity profiles, etc. of the proposed ready-to-use/ready-to-dilute solution products at batch release vs. the Listed Drug upon reconstitution and upon further dilution per labeling instructions.*

- (2) *The rationale for why you believe the differences (e.g., formulation composition, type of dosage form, etc.) between your product vs the Listed Drug will not impact the disposition of bivalirudin, and the efficacy and safety of your product.*
- (3) *Evidence 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 $\pm 20\%$ of those measured for Angiomax®.*

Note that the acceptability of your request to waive the requirement to conduct in vivo BA/BE studies will be determined upon review of the NDA.

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/s/

WENDY I WILSON-LEE
02/12/2016

MEMORANDUM

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

TO: Alison Blaus
Division of Cardio-Renal Products

FROM: Jacquin Jones
Division of Hematology Products

SUBJECT: Application Transfer

APPLICATION: IND 126428
Bivalirudin/Indicated as an anticoagulant in patients (b) (4) undergoing
percutaneous (b) (4) coronary (b) (4) intervention.

In the line with the OND policy of placing administrative responsibility of applications within the Division that reviews the principal clinical research activity of the drug, we are transferring IND 126428 for your acceptance. If you do not concur, please include the reason as a signature comment. If you have any questions, call me at 301-(240) 402-4590.

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/s/

JACQUIN L JONES
04/30/2015