

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206426Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206426

SUPPL # 000

HFD # 530

Trade Name RAPIVAB

Generic Name peramivir injection

Applicant Name BioCryst Pharmaceuticals, Inc.

Approval Date, If Known

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

Original 505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND #                      YES                       ! NO   
! Explain:

Investigation #2  
IND #                      YES                       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES                       ! NO   
Explain:                      ! Explain:

Investigation #2  
YES                       ! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Elizabeth Thompson, M.S.  
Title: Chief, Project Management Staff  
Date: December 18, 2014

Name of Office/Division Director signing form: Debra Birnkrant, M.D.  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH G THOMPSON  
12/18/2014

DEBRA B BIRNKRANT  
12/18/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 206426	NDA Supplement # N/A (Original NDA)	If NDA, Efficacy Supplement Type: N/A (Original NDA) <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: RAPIVAB Established/Proper Name: peramivir injection Dosage Form: intravenous		Applicant: BioCryst Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Elizabeth Thompson		Division: DAVP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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 style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> <p>Date of check: _____</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"> <li>Proposed action</li> <li>User Fee Goal Date is <b>December 23, 2014</b></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> For resubmissions, (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).

<sup>3</sup> 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 1  
 (*confirm chemical classification at time of approval*)

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Fast Track: Granted 1-5-2006 | <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        |   |

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: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ 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> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other (Information Advisory)
❖ Exclusivity	
• 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)	
• 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.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ 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> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval; December 19, 2014
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included (November 17, 2014; sponsor proposed)
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included (December 23, 2013)
❖ 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"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> 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"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included (November 17, 2014)
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	Acceptable: March 4, 2011 (IND 69038); March 6, 2014 (NDA 206426) Review: March 4, 2011 (IND 69038); March 4, 2014 (NDA 206426)
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input checked="" type="checkbox"/> None PLR Format: May 1, 2014 DMEPA: October 20, 2014; November 7, 2014 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: November 12, 2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	February 27, 2014
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed with the respective discipline.

❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP                     <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<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"> <li>• Date reviewed by PeRC <u>October 29, 2014</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	12-27-2013, 1-2-2014, 1-3-2014, 1-14-2014, 1-28-14 (3), 1-31-2014, 2-1-2014, 2-12-2014, 2-14-2014, 2-24-2014, 2-27-2014 (3), 3-5-2014, 3-7-2014, 3-18-2014, 3-25-2014 (2), 3-31-2014, 4-18-2014, 4-30-2014, 5-2-2014, 5-14-2014, 5-21-2014, 5-30-2014, 6-6-2014, 6-17-2014, 7-31-2014 (2), 8-26-2014, 8-29-2014 (Labeling), 9-4-2014, 9-10-2014, 9-15-2014, 9-22-2014, 10-1-2014, 10-7-2014, 10-24-2014, 10-28-2014, 11-12-2014 (PMR/PMCs), 11-13-2014 (Labeling), 11-14-2014 (Labeling), 12-2-2014 (PMR/PMCs), 12-15-14 (Labeling), 12-17-2014 (PMR/PMCs)
❖ 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)	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	June 28, 2013
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	June 5, 2014
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	September 16, 2014
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	July 11, 2013 (pediatric development); June 25, 2013 (clinical virology)

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	December 19, 2014
Division Director Summary Review ( <i>indicate date for each review</i> )	December 1, 2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	November 7, 2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	7
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review see CDTL review
• Clinical review(s) ( <i>indicate date for each review</i> )	2-3-2014 (filing) 8-22-2014 (clinical review)
• 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 type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Page 20 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> )	N/A
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	N/A
• 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> )	9-8-2014
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	Review: 7-29-2014 Letters: 5-20-2014, 6-19-2014, 7-7-2014, 8-12-2014, 9-2-2014 (2), 9-19-2014, 10-23-2014
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	1-29-2014 (filing) 8-21-2014 (clin micro review) 11-17-2014 (labeling)
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	1-27-2014 (filing) 8-22-2014 (stats review)

<b>Clinical Pharmacology</b> <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> )	1-30-2014 (filing) 8-22-2014 (clin pharm review)
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	8-1-2014
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	8-12-2014
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	2-3-2014 (filing) 8-20-2014 (nonclng review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	9-23-2014
❖ ECAC/CAC report/memo of meeting	6-12-2014 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	2-24-2014 (CMC and Biopharm filing) 8-19-2014 (CMC review) 12-18-14 (CMC addendum 1)
❖ Microbiology Reviews	1-28-2014 (CMC Micro filing) 8-5-2014 (CMC Micro review)
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> )	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <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> )	8-19-2014 (page 104 of CMC review)
<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"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup></i> )	Date completed: 12-18-14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ 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	<input checked="" type="checkbox"/> Done
❖ 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	<input checked="" type="checkbox"/> Done
❖ 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

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/s/  
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ELIZABETH G THOMPSON  
12/19/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: PMR/PMC revisions  
**Date:** Wednesday, December 17, 2014 9:42:17 AM  
**Importance:** High

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Elliott-

1. Please see below for the revised PMR/PMC for Rapivab. I need your agreement to these revisions submitted officially to the NDA.

### PMRs

2831-1 Conduct a clinical trial to evaluate the pharmacokinetics, safety, and antiviral activity of peramivir administration in pediatric subjects with acute uncomplicated influenza infection from birth to less than 18 years of age. Include characterization of peramivir resistance-associated substitutions in viral isolates from subjects with prolonged viral shedding.

Study Completion: 04/30/2018

Final Report Submission: 12/31/2018

2831-2 Analyze and submit the remainder of the clinical resistance data that were not included with the NDA. These include both the HA and NA data for trials BCX1812-201, BCX1812-211, and BCX1812-311.

Final Report Submission: 06/30/2016

2831-3 Conduct a study to determine the cross-resistance to oseltamivir and zanamivir for all of the HA peramivir resistance substitutions that have yet to be evaluated (A/H1N1 HA D129S, R208K; A/H3N2 HA G78D, K189E; B HA T139N, G141E, R162M, D195N, T197N, Y319H). Additionally, determine cross-resistance to oseltamivir/zanamivir resistance substitutions (A/H1N1 NA R152K, I122K/T, G248R+I266V, Q312R+I427T, R371K, A/H3N2 NA E41G, I222L/V, Q226H, S247P, HA A28T, K68R, E114K, R124M, N145S, S165N, S186F, N199S, K222T, B NA D198Y, A246D/S/T, G420S).

Final Protocol Submission: 04/30/2015

Study Completion: 04/30/2016

Final Report Submission: 10/31/2016

## PMCs

2831-4 Evaluate the impact of peramivir resistance-associated substitutions in hemagglutinin (HA) on the effectiveness of influenza vaccine in cell culture assays:

- Titrate the neutralization and hemagglutinin inhibition activity of the serum samples from multiple subjects vaccinated with the influenza virus vaccine against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus. A titration of the serum samples should be evaluated using established methods for determining hemagglutination inhibition (HI) as well as virus neutralization (e.g. plaque number reduction or % infected cells based on nuclear NP staining). We recommend performing neutralization assays using different input concentrations of virus to confirm that assay conditions are such that the EC50 value is independent of virus concentration.
- Titrate the neutralization and hemagglutinin inhibition activity of the baseline and end of treatment serum samples from multiple subjects treated with peramivir against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus.
- Compare the antigenicity of wild type (WT) and HA mutants, selected during peramivir treatment in cell culture, against immune serum (convalescent or vaccine-induced) from human subjects and from animal models vaccinated with inactivated WT virus. Antigenicity should be determined using both HI and neutralization assays.

Final Protocol Submission: 06/30/2015

Study Completion: 12/31/2018

Final Report Submission: 06/30/2019

2831-5 Submit clinical data from an adequate number of subjects to characterize the effectiveness of peramivir administration in patients with acute uncomplicated

influenza B virus infection. These data may be collected from the pediatric study required under PREA or from a new stand-alone clinical trial in a different population. Conduct genotypic resistance analysis of neuraminidase and hemagglutinin using samples directly from subjects without an intervening culture step. Conduct phenotypic analysis, including cross-resistance to approved neuraminidase inhibitors.

Final Analysis Plan Submission: 06/30/2015

Trial Completion: 04/30/2018

Final Report Submission: 12/31/2018

2831-6 Conduct a clinical trial to evaluate the pharmacokinetics, safety and antiviral activity of peramivir administration in a predominantly ambulatory setting in elderly subjects aged 65 years or older with influenza infection.

Final Protocol Submission: 06/30/2015

Trial Completion: 04/30/2018

Final Report Submission: 12/31/2018

2831-7 Conduct a clinical trial to evaluate the pharmacokinetics, safety and antiviral activity of peramivir administration in a predominantly ambulatory setting in subjects with influenza infection at higher risk for influenza complications, as defined by the U.S. Centers for Disease Control and Prevention (CDC).

Final Protocol Submission: 06/30/2015

Trial Completion: 04/30/2018

Final Report Submission: 12/31/2018

2. Also, please refer to the December 15, 2014 IR regarding revisions to the Package Insert, specifically to Section 14. As BioCryst has informed the FDA that package inserts have been printed and packaged already, and since these changes are minor, we agree to having these edits take place after action.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
12/18/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: Peramvir label clinical changes to Section 14  
**Date:** Monday, December 15, 2014 10:50:17 AM  
**Attachments:** [rapivab-prescribing-information \(FDA 12\\_11\\_2014\).docx](#)  
**Importance:** High

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Elliott-

The Division made some minor revisions to Section 14. Please see the attached label and tracked changes to that section. Please let me know asap if you agree to these changes. If BioCryst agrees, I will have you submit updated labeling. For now, hold off, as I still have minor edits to PMR/PMCs coming for your agreement as well.

Beth

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

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ELIZABETH G THOMPSON  
12/15/2014

**From:** Thompson, Elizabeth  
**To:** ["Berger, Elliott"](#)  
**Subject:** RE: NDA 206426 RAPIVAB PMR/PRC IR  
**Date:** Tuesday, December 02, 2014 12:55:00 PM

---

Elliott-

We have reviewed your comments and agree. We will not change the dates for PMC 4 but will remove the text you added.

Please submit the PMR/PMCs w/timelines to the NDA officially.

Regards,  
Beth

---

**From:** Berger, Elliott [mailto:[eberger@BIOCRYST.com](mailto:eberger@BIOCRYST.com)]  
**Sent:** Tuesday, December 02, 2014 9:33 AM  
**To:** Thompson, Elizabeth  
**Cc:** Sheridan, Bill; Taylor, Ray; Collis, Phil; Dobo, Sylvia; Wileman, Martin; McMillan, Nicole; Adair, Jason; Maetzel, Andreas; Bennett, Robert  
**Subject:** RE: NDA 206426 RAPIVAB PMR/PRC IR

Beth

Our response to the Division's comments regarding PMR/PMCs are in the attached document. Please let me know if you have any questions.

Best regards

Elliott

**Elliott T Berger, Ph.D.**  
**Sr. Vice President, Regulatory Affairs**  
**BioCryst Pharmaceuticals, Inc.**  
**4505 Emperor Blvd. Suite 200**  
**Durham NC 27703**  
**Phone (919) 859-7919**  
**Cell (b) (6)**  
**FAX (919) 859-1316**  
**[eberger@biocryst.com](mailto:eberger@biocryst.com)**

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**From:** Thompson, Elizabeth [mailto:[Elizabeth.Thompson@fda.hhs.gov](mailto:Elizabeth.Thompson@fda.hhs.gov)]  
**Sent:** Monday, December 01, 2014 2:44 PM  
**To:** Berger, Elliott  
**Subject:** RE: NDA 206426 RAPIVAB PMR/PRC IR

Elliott-

Do you have a proposed date to reply? We are working on getting clearance of these by

upper management.

---

**From:** Thompson, Elizabeth  
**Sent:** Friday, November 21, 2014 9:43 AM  
**To:** 'Berger, Elliott'  
**Cc:** Thompson, Elizabeth  
**Subject:** NDA 206426 RAPIVAB PMR/PRC IR

Elliott-

We are in agreement with your proposed dates and timelines on the proposed PMR/PMCs with the following comments:

- For PMC 2831-5 (flu B), you propose to submit an “analysis plan” by end of June 2015. Please clarify if this means that BioCryst plans to fulfill the PMC with one of the other protocols (the peds study or other)?
- We note the Dec 31, 2018 report submission for the PREA study. Given no formulation issues, can you clarify why you expect it to take 3-4 flu seasons to enroll pediatric subjects?

For PMC 2831=4 we do not agree with your revised text and we have the following comment:

We agree that the clinical relevance of the HA substitutions is unclear. However, we remain concerned of the possible impact on the effectiveness of influenza vaccines. While there was no pattern in the development of HA genotypic changes in you clinical studies, appropriate data were not collected in the trials for which FDA did not review the protocols. The HA was not genotyped in any of the studies conducted by Shionogi. Additionally, in studies in which HA was genotyped, the primary phenotypic assay that was used for characterization was the NAI assay which would not have detected changes in HA that could impact peramivir susceptibility. We acknowledge that substitutions in HA may be compensatory rather than conferring resistance to peramivir. Regardless of their function, substitutions in HA may accelerate antigenic escape from prevailing or vaccine-induced immunity. This could have significant public health implications and we respectfully request that you conduct this PMC.

---

**From:** Berger, Elliott [<mailto:eberger@BIOCRYST.com>]

**Sent:** Wednesday, November 19, 2014 8:53 AM  
**To:** Thompson, Elizabeth  
**Cc:** Sheridan, Bill; Collis, Phil; Taylor, Ray; Dobo, Sylvia;  
Wileman, Martin; McMillan, Nicole; Adair, Jason; Maetzel,  
Andreas  
**Subject:** NDA 206426 RAPIVAB BioCryst PMR/PRC Response

Good Morning Beth,

Attached is our response to the PMR/PMC requests you provided via email on 12 NOV 2014. Please let me know if you have any questions regarding the responses or if any additional discussion is required.

Best regards,

Elliott

**Elliott T Berger, Ph.D.**  
**Sr. Vice President, Regulatory Affairs**  
**BioCryst Pharmaceuticals, Inc.**  
**4505 Emperor Blvd. Suite 200**  
**Durham NC 27703**  
**Phone (919) 859-7919**  
**Cell (b) (6)**  
**FAX (919) 859-1316**  
**[eberger@biocryst.com](mailto:eberger@biocryst.com)**

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ELIZABETH G THOMPSON  
12/05/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical labeling comments  
**Date:** Friday, November 14, 2014 12:47:40 PM  
**Attachments:** [11-14 DAVP proposed rapivab-prescribing-information.docx](#)  
**Importance:** High

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Elliott-

Here are our clinical comments regarding labeling. As discussed yesterday, the clinical virology comments are included as well, even though they were sent under separate correspondence. Please let me know if you have any questions.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
11/14/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical virology label changes  
**Date:** Thursday, November 13, 2014 3:46:02 PM  
**Attachments:** [11-13 FDA proposed rapivab-prescribing-information.docx](#)  
**Importance:** High

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Elliott-

Attached are the current DAVP recommendations in the Clinical Virology section of the PI, along with a comment providing explanation of why the changes were made. Please let me know if you have any questions. I hope to have the final PI to you tomorrow.

**Comment:** We appreciate the suggestions that you have made to the resistance and cross-resistance tables. We agree with separating the substitutions that were observed in surveillance studies. We also agree that substitutions selected by oseltamivir and/or zanamivir should only be in the cross-resistance table (Table 5). However, we believe the following substitutions should still be included in the tables:

- NA S246N (H1N1): This substitution was originally identified in surveillance studies and reported as a neuraminidase inhibitor resistance substitution ([Hurt et al., 2011](#)). Influenza A virus (H1N1) with the NA S247N substitution has been detected in community specimens ranging from ~1% to ~30% in the US, Europe, Asian and Australia. While the substitution alone did not confer a significant reduction in inhibition of neuraminidase, the combination with H275Y substitution resulted in a substantially greater reduction in inhibition of neuraminidase than either substitution alone.
- NA P139S (flu B): We acknowledge that this substitution was expanded during passaging in MDCK cells ([Fujisaki et al., 2013](#)). However, this substitution was present at baseline prior to amplification, The IC<sub>50</sub> values of peramivir, oseltamivir, and zanamivir were reduced by 322-fold, 10-fold, and 25-fold, respectively against the P139S strain. The authors also conclude that this substitution is resistance-associated. At a minimum, P139S is a resistance-associated polymorphism and should be included in the surveillance section.
- HA N63K and N145D (H3N2): The EC<sub>50</sub> values of peramivir, oseltamivir, and zanamivir were <0.001 mM, 0.01 mM, and <0.001 mM, respectively, against the WT virus (study report dd00048-pre-clinical-study-report). The EC<sub>50</sub> values of peramivir, oseltamivir, and zanamivir were 100 mM, >100 mM, and >100 mM, respectively, against the double mutant virus.

Regards,

Beth

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
11/13/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: PMR/PMC request for information  
**Date:** Wednesday, November 12, 2014 10:27:40 AM  
**Attachments:** [NDA 206426 PMRs PMCs.docx](#)  
**Importance:** High

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Elliott-

Attached please find our proposed PMRs and PMCs for RAPIVAB, as discussed at the Late Cycle Meeting. If you have any clarification questions, please provide them by email so we can correspond and finalize before submitting officially to the NDA.

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

**Pediatric Postmarketing Requirement (PREA):**

XXXX-1 Conduct a clinical trial to evaluate the pharmacokinetics, safety, and antiviral activity of peramivir administration in pediatric subjects with acute uncomplicated influenza infection from birth to less than 18 years of age. Include characterization of peramivir resistance-associated substitutions in viral isolates from subjects with prolonged viral shedding.

Protocol Submission:  
Trial Completion:  
Final Report Submission:

**Postmarketing Requirements:**

XXXX-2 Submit the remainder of the clinical resistance data that were not included with the NDA. These include both the HA and NA data for studies BCX1812-201, BCX1812-211, and BCX1812-311.

Protocol Submission: Completed  
Trial Completion: Completed  
Final Report Submission:

XXXX-3 Determine the cross-resistance to oseltamivir and zanamivir for all of the HA peramivir resistance substitutions that have yet to be evaluated (A/H1N1 HA D129S, R208K; A/H3N2 HA G78D, K189E; B HA T139N, G141E, R162M, D195N, T197N, Y319H). Additionally, determine cross-resistance to oseltamivir/zanamivir resistance substitutions (A/H1N1 NA R152K, I122K/T, G248R+I266V, Q312R+I427T, R371K, A/H3N2 NA E41G, I222L/V, Q226H, S247P, HA A28T, K68R, E114K, R124M, N145S, S165N, S186F, N199S, K222T, B NA D198Y, A246D/S/T, G420S).

Protocol Submission:  
Trial Completion:  
Final Report Submission:

**Postmarketing Commitments:**

XXXX-4 Evaluate the impact of peramivir resistance-associated substitutions in hemagglutinin (HA) on the effectiveness of influenza vaccine in cell culture assays:

- Titrate the neutralization and hemagglutinin inhibition activity of the serum samples from multiple subjects vaccinated with the influenza virus vaccine against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus. A titration of the serum samples should be evaluated

using established methods for determining hemagglutination inhibition (HI) as well as virus neutralization (e.g. plaque number reduction or % infected cells based on nuclear NP staining). We recommend performing neutralization assays using different input concentrations of virus to confirm that assay conditions are such that the EC50 value is independent of virus concentration.

- Titrate the neutralization and hemagglutinin inhibition activity of the baseline and end of treatment serum samples from multiple subjects treated with peramivir against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus.
- Compare the antigenicity of wild type (WT) and HA mutants, selected during peramivir treatment in cell culture, against immune serum (convalescent or vaccine-induced) from human subjects and from animal models vaccinated with inactivated WT virus. Antigenicity should be determined using both HI and neutralization assays.

Protocol Submission:

Trial Completion:

Final Report Submission:

XXXX-5

Submit clinical data from an adequate number of subjects to characterize the effectiveness of peramivir administration in patients with acute uncomplicated influenza B virus infection. These data may be collected from the pediatric study required under PREA or from a new stand-alone clinical trial in a different population. Conduct genotypic resistance analysis of neuraminidase and hemagglutinin using samples directly from subjects without an intervening culture step. Conduct phenotypic analysis, including cross-resistance to approved neuraminidase inhibitors.

Protocol Submission:

Trial Completion:

Final Report Submission:

XXXX-6

Conduct a clinical trial to evaluate the pharmacokinetics, safety and antiviral activity of peramivir administration in a predominantly ambulatory setting in elderly subjects aged 65 years or older with influenza infection.

Protocol Submission:

Trial Completion:

Final Report Submission:

XXXX-7 Conduct a clinical trial to evaluate the pharmacokinetics, safety and antiviral activity of peramivir administration in a predominantly ambulatory setting in subjects with influenza infection at higher risk for influenza complications, as defined by the recommendations of the (b) (4)

Protocol Submission:  
Trial Completion:  
Final Report Submission:

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ELIZABETH G THOMPSON  
11/12/2014

**From:** [Thompson, Elizabeth](mailto:Thompson, Elizabeth)  
**To:** "[Berger, Elliott](mailto:Berger, Elliott)"  
**Cc:** [Thompson, Elizabeth](mailto:Thompson, Elizabeth)  
**Subject:** FW: NDA 206426: Carton/Container Labeling Comments  
**Date:** Tuesday, October 28, 2014 1:03:01 PM

---

Elliott-

Here are our responses to your questions.

BioCryst Questions:

1. There is a small overage in each vial so the "total drug content per vial" is actually slightly greater than 200 mg (b) (4) This will allow the health care professional preparing the infusion to withdraw a full 200 mg dose. Please confirm that we should still state 200 mg/20 mL as the total drug content per vial.

**Agency response: Please use 200 mg/20 mL as total drug content per vial.**

2. The Agency commented that on the carton top panel we should apply the same format as other parts of the carton, i.e., the total drug content and strength should follow below the proprietary and established names. Due to the narrowness of the carton top this may result in a very small font size. Can the information on total drug content and strength be placed to the side of the proprietary and established names?

**Agency response: Your proposal to place this information to the side of the names is acceptable.**

---

**From:** Berger, Elliott [<mailto:eberger@BIOCRYST.com>]  
**Sent:** Monday, October 27, 2014 12:47 PM  
**To:** Thompson, Elizabeth  
**Cc:** Sheridan, Bill; Taylor, Ray; Adair, Jason; Bennett, Robert; Wileman, Martin; McMillan, Nicole  
**Subject:** RE: NDA 206426: Carton/Container Labeling Comments

Beth

We have reviewed the comments on the Carton/Vial Label and have a couple of questions for clarification regarding the carton:

FDA Comment:

The strength on the carton labeling should reflect the total drug content in each vial. Thus the strength should be expressed as 200 mg/20 mL per vial. Additionally, move the expression of strength higher up on the PDP so it is immediately below the established name and **ensure the strength presentation includes the total drug content per vial** followed by the concentration in a smaller sized font in accordance with USP General

Chapter <1> requirements. **Apply this to the carton top panel as well** which has the strength expression separate from the proprietary and established names.

BioCryst Questions:

1. There is a small overage in each vial so the “total drug content per vial” is actually slightly greater than 200 mg ( (b) (4) ). This will allow the health care professional preparing the infusion to withdraw a full 200 mg dose. Please confirm that we should still state 200 mg/20 mL as the total drug content per vial.
2. The Agency commented that on the carton top panel we should apply the same format as other parts of the carton, i.e., the total drug content and strength should follow below the proprietary and established names. Due to the narrowness of the carton top this may result in a very small font size. Can the information on total drug content and strength be placed to the side of the proprietary and established names?

Thanks very much

Elliott

**Elliott T Berger, Ph.D.**  
**Sr. Vice President, Regulatory Affairs**  
**BioCryst Pharmaceuticals, Inc.**  
**4505 Emperor Blvd. Suite 200**  
**Durham NC 27703**  
**Phone (919) 859-7919**  
**Cell (b) (6)**  
**FAX (919) 859-1316**  
**[eberger@biocryst.com](mailto:eberger@biocryst.com)**

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**From:** Thompson, Elizabeth [<mailto:Elizabeth.Thompson@fda.hhs.gov>]  
**Sent:** Friday, October 24, 2014 9:50 AM  
**To:** Berger, Elliott  
**Cc:** Thompson, Elizabeth  
**Subject:** NDA 206426: Carton/Container Labeling Comments  
**Importance:** High

Elliott-

In consultation with ONDQA and DMEPA, please find our comments regarding carton/container labeling below:

**General**

Consider revising the proprietary name so it appears in title case (e.g. Tradename) to optimize the readability of the proprietary name (refer to the Guidance link below).

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

FDA Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize*

*Medication Errors*. See Section IV(A). pg. 9.

The abbreviation 'I.V.' which is listed on the Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations (see link below) is used on the carton labeling and container label. Replace 'I.V.' with the word "Intravenous" throughout all labels and labeling to help prevent misinterpretation.

[www.ismp.org/tools/errorproneabbreviations.pdf](http://www.ismp.org/tools/errorproneabbreviations.pdf).

### **Carton Labeling**

[REDACTED] (b) (4)

Additionally, on the carton's principal display panel (PDP), revise the statement [REDACTED] (b) (4)

[REDACTED] to read similar to "Dosage: See accompanying package insert for complete product information".

Before the statement "Contains no preservative", add the statement "Single-use vial, discard unused portion." to provide additional information that any medication left in the vial after removal should be discarded.

3. The strength on the carton labeling should reflect the total drug content in each vial. Thus the strength should be expressed as 200 mg/20 mL per vial. Additionally, move the expression of strength higher up on the PDP so it is immediately below the established name and ensure the strength presentation includes the total drug content per vial followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements. Apply this to the carton top panel as well which has the strength expression separate from the proprietary and established names.

For example:

Rapivab

(peramivir) injection

200 mg/20 mL per vial

(10 mg /mL)

Include a carton net quantity statement on the bottom of the PDP such as: "Carton contains 3 vials."

Move the statement “For Intravenous Infusion Only. Dilute Before Use” to below the strength statement on the PDP in order to increase the prominence of this important information.

**Container Label**

Because there is more than one dose for this product, revise the dosage statement to read “Dosage: See accompanying package insert for complete product information.”

Move the expression of strength to immediately below the established name and ensure the strength presentation includes the total drug content per vial followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements.

For example:

Rapivab

(peramivir) injection

200 mg/20 mL per vial

(10 mg /mL)

Revise the statement (b) (4) to read “Single-Use Vial. Discard unused portion.” Additionally, swap the placement of the two statements “Single-Use Vial. Discard unused portion” and “For Intravenous Infusion. Dilute Before Use” to ensure the critical route of administration information has increased prominence and is near other critical information like the established name and strength.

Please let me know if you have any questions regarding our comments.

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
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ELIZABETH G THOMPSON  
10/28/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: Carton/Container Labeling Comments  
**Date:** Friday, October 24, 2014 9:50:08 AM  
**Importance:** High

---

Elliott-

In consultation with ONDQA and DMEPA, please find our comments regarding carton/container labeling below:

### **General**

1. Consider revising the proprietary name so it appears in title case (e.g. Tradename) to optimize the readability of the proprietary name (refer to the Guidance link below).

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

FDA Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. See Section IV(A). pg. 9.

2. The abbreviation 'I.V.' which is listed on the Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations (see link below) is used on the carton labeling and container label. Replace 'I.V.' with the word "Intravenous" throughout all labels and labeling to help prevent misinterpretation.

[www.ismp.org/tools/errorproneabbreviations.pdf](http://www.ismp.org/tools/errorproneabbreviations.pdf).

### **Carton Labeling**

1. [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] Additionally,  
on the carton's principal display panel (PDP), revise the statement [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] to read similar to "Dosage: See accompanying package insert for complete product information".

2. Before the statement "Contains no preservative", add the statement "Single-use vial, discard unused portion." to provide additional information that any medication left in the vial after removal should be discarded.

3. The strength on the carton labeling should reflect the total drug content in each vial. Thus the strength should be expressed as 200 mg/20 mL per vial. Additionally, move the expression of strength higher up on the PDP so it is immediately below the established name

and ensure the strength presentation includes the total drug content per vial followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements. Apply this to the carton top panel as well which has the strength expression separate from the proprietary and established names.

For example:

Rapivab

(peramivir) injection

200 mg/20 mL per vial

(10 mg /mL)

4. Include a carton net quantity statement on the bottom of the PDP such as: “Carton contains 3 vials.”
5. Move the statement “For Intravenous Infusion Only. Dilute Before Use” to below the strength statement on the PDP in order to increase the prominence of this important information.

### **Container Label**

1. Because there is more than one dose for this product, revise the dosage statement to read “Dosage: See accompanying package insert for complete product information.”
2. Move the expression of strength to immediately below the established name and ensure the strength presentation includes the total drug content per vial followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements.

For example:

Rapivab

(peramivir) injection

200 mg/20 mL per vial

(10 mg /mL)

3. Revise the statement “(b) (4)” to read “Single-Use Vial. Discard unused portion.” Additionally, swap the placement of the two statements “Single-Use Vial. Discard unused portion” and “For Intravenous Infusion. Dilute Before Use” to ensure the critical route of administration information has increased prominence and is near other critical information like the established name and strength.

Please let me know if you have any questions regarding our comments.

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
10/24/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: Virology PMC clarification comment  
**Date:** Tuesday, October 07, 2014 9:47:57 AM

---

Elliott-

Please refer to the proposed PMC from the LCM background package that read "Evaluate the impact of the peramivir resistance substitutions in HA on the effectiveness of influenza vaccine". We have the following additional information to provide clarity and our current thinking regarding that PMC.

- Please titrate the neutralization and hemagglutinin inhibition activity of the serum samples from multiple subjects vaccinated with the influenza virus vaccine against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus. A titration of the serum samples should be evaluated using established methods for determining hemagglutination inhibition (HI) as well as virus neutralization (e.g. plaque number reduction or % infected cells based on nuclear NP staining). We recommend performing neutralization assays using different input concentrations of virus to confirm that assay conditions are such that the EC50 value is independent of virus concentration.
- Please titrate the neutralization and hemagglutinin inhibition activity of the baseline and end of treatment serum samples from multiple subjects treated with peramivir against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus.
- Please compare the antigenicity of WT and HA mutants, selected during peramivir treatment in cell culture, against immune serum (convalescent or vaccine-induced) from human subjects and from animal models vaccinated with inactivated WT virus. Antigenicity should be determined using both HI and neutralization assays.
- For additional information, please refer to the following vaccine Guidance:  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091990.pdf>

Please let me know if you have any further questions. As we continue our review, we will work to finalize the wording for this PMC and will request protocol submission, study completion, and final study report submission dates from you.

Regards,

**Beth**  
Chief, Project Management Staff  
FDA/CDER/OAP/DAVP  
301-796-0824

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/s/  
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ELIZABETH G THOMPSON  
10/07/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: labeling comments  
**Date:** Wednesday, October 01, 2014 4:16:18 PM  
**Attachments:** [10-1 FDA proposed.docx](#)  
**Importance:** High

---

Elliott-

As discussed at the LCM, here are the Division's latest comments regarding labeling. Please let me know if you have any questions or need clarifications.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
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ELIZABETH G THOMPSON  
10/01/2014

**From:** [Berger, Elliott](#)  
**To:** [Thompson, Elizabeth](#)  
**Cc:** [Wileman, Martin](#); [McMillan, Nicole](#); [Taylor, Ray](#); [El Kattan, Yahya](#); [Sheridan, Bill](#); [Stonehouse, Jon](#); [Bennett, Robert](#)  
**Subject:** RE: NDA 206426: CMC Information Request  
**Date:** Monday, September 22, 2014 3:54:34 PM  
**Attachments:** [emfalert.txt](#)

---

Beth

We have not yet manufactured our launch product. We intend to use the validation lots that will be manufactured at (b) (4) for launch. Current timing is to manufacture 3 lots on (b) (4) Line 1 in October and 3 lots on (b) (4) Line 2 in November. Product should be released 4-6 weeks after manufacture.

Please let me know if you have any other questions.

Regards

Elliott

**Elliott T Berger, Ph.D.**  
**Sr. Vice President, Regulatory Affairs**  
**BioCryst Pharmaceuticals, Inc.**  
**4505 Emperor Blvd. Suite 200**  
**Durham NC 27703**  
**Phone (919) 859-7919**  
**Cell (b) (6)**  
**FAX (919) 859-1316**  
**[eberger@biocryst.com](mailto:eberger@biocryst.com)**

---

**From:** Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]  
**Sent:** Monday, September 22, 2014 12:43 PM  
**To:** Berger, Elliott  
**Cc:** Thompson, Elizabeth  
**Subject:** NDA 206426: CMC Information Request  
**Importance:** High

Elliott-

Our CMC/Compliance team has the following information request:

Please provide a list of your current intended launch product to include lot numbers and when manufactured.

Regards,

**Beth**  
Chief, Project Management Staff  
FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
09/22/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** FW: NDA 206426 RAPIVAB (Peramivir Injection) - Labeling Question  
**Date:** Monday, September 15, 2014 8:57:50 AM  
**Importance:** High

---

Elliott-

The clinical virology team has reviewed your question below and wants to provide this in advance of our meeting tomorrow.

Please see attached the references for each of the amino acid substitutions. We used a liberal definition for 'surveillance' as any resistance-associated substitutions that were reported that were not identified in peramivir cell culture selection or clinical studies. We acknowledge that these could be further defined (e.g. identified in natural isolates, identified in clinical isolates from other NAI treated patients, cell culture selection by other NAIs). We welcome other suggestions for representing these data.

H1N1	
E119G/V	Pizzorno A et al, 2011, Abed Y et al 2006
Q136K	Okomo-Adhiambo M et al, 2010
D151G/N	Okomo-Adhiambo M et al, 2010
Y155H	McKimm-Breschkin et al, 2013
D199G	Pizzorno A et al, 2011, McKimm-Breschkin JL et al, 2012
I123M/R/V	Pizzorno A et al, 2011, Pizzorno A et al, 2012, Nguyen HT et al, Clin Infect Dis, 2010, van der Vries E et al, 2010, Eshagi A et al, 2011, Hurt AC et al, 2009
S247N	Hurt AC et al, 2011, Seibert CW et al, 2012
N295S	Abed Y et al 2006, Kiso M et al, 2004
H3N2	
E119G/I/V	Abed Y et al 2006, zurcher T et al, 2006, Okomo-Adhiambo M et al, AAC, 2010, Tamura D et al, 2011, Ison MG et al, 2006, Simon P et al, 2011, Sheu TG et al, 2008, Monto AS et al, 2006, Mishin VP et al, 2005, Carr S et al, 2011, Richard M et al, 2011
T148I	Tamura D et al, 2013
D151A/E/G/N/V	Study report S-021812-EB-133-N
Flu B	
E105K	Fujisaki S et al, 2012
E116A/D/G/V	Jackson et al., 2005
P139S	Fujisaki S et al, 2013
G140R	Okomo-Adhiambo M et al, 2013, Fujisaki S et al, 2013
R149K	Gubareva LV et al 1998, Jackson D et al, 2005, Yen HL et al, 2006, Mishin VP et al, 2005
D197E/N/Y	Hatakeyama S et al, 2007, Sheu TG et al, 2008, Ison MG et al, 2006, Mishin VP et al, 2005, Study Report S-021812-EB-133-N
I221T/V	Sleeman et al, 2011, Study Report S-021812-EB-133-N

R292K	Jackson D et al, 2005
R371K	Study report S-021812-EB-133-N

---

**From:** Berger, Elliott [<mailto:eberger@BIOCRYST.com>]  
**Sent:** Sunday, September 07, 2014 10:26 PM  
**To:** Thompson, Elizabeth  
**Cc:** Wileman, Martin; McMillan, Nicole; Taylor, Ray; Collis, Phil; Katyna Borroto-Esoda ([kborrotoesoda@gmail.com](mailto:kborrotoesoda@gmail.com)); Sheridan, Bill  
**Subject:** NDA 206426 RAPIVAB (Peramivir Injection) - Labeling Question

Beth

We went over the Division's labeling comments last week and we were not sure what the sources were for Tables 3 and 4 of the Microbiology Section. The text mentions community surveillance studies (Table 3) and cross resistance from cell culture assays (Table 4) – are there references you can provide us so we can understand the data behind the tables and associated labeling text.

I am also working on a brief list of topics for the three-way CMC discussion. You will have them by Tuesday at the latest.

Best regards

Elliott

**Elliott T Berger, Ph.D.**  
**Sr. Vice President, Regulatory Affairs**  
**BioCryst Pharmaceuticals, Inc.**  
**4505 Emperor Blvd. Suite 200**  
**Durham NC 27703**  
**Phone (919) 859-7919**  
**Cell (b)(6)**  
**FAX (919) 859-1316**  
**[eberger@biocryst.com](mailto:eberger@biocryst.com)**

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ELIZABETH G THOMPSON  
09/15/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: 3 way compliance discussion  
**Date:** Thursday, September 04, 2014 1:56:11 PM  
**Importance:** High

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Elliott-

Our team met internally and have concluded that we can proceed forward with a three-way conversation between FDA, (b) (4) and BioCryst. Here's what needs to be done:

1. BioCryst needs to reach out to (b) (4) to see if they are willing to have this discussion.
2. Have (b) (4) contact the (b) (4) to notify them of the intent to have this discussion, and to provide my name as the person from FDA (DAVP) who will coordinate and set this up.
3. BioCryst should provide names of people from both (b) (4) and BioCryst that will be involved in the call.
4. I will work with you on finding dates/times. The best case scenario would be to try to hold this before our Late Cycle Meeting, however, logistically I'm not sure that will happen. If it does, great. If it does not, you will see some general remarks/discussion areas related to Compliance for the LCM that we can discuss, but not on the same level as we would with the three-way.

Please let me know if you have any questions.

Regards,

Beth

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
09/04/2014



NDA 206426

## LABELING PMR/PMC DISCUSSION COMMENTS

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) dated December 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RAPIVAB (peramivir injection) for intravenous use.

We also refer to our March 5, 2014, letter in which we notified you of our target date of August 30, 2014 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

We received your proposed labeling submission to this application, dated and received May 8, 2014, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by September 12, 2014. The resubmitted labeling will be used for further labeling discussions.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

If you have any questions, call Elizabeth Thompson, Chief, Project Management Staff at (301) 796-0824.

Sincerely,

*{See appended electronic signature page}*

Elizabeth Thompson, M.S.  
CDR, U.S. Public Health Service  
Chief, Project Management Staff  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE: Division labeling comments

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ELIZABETH G THOMPSON  
08/29/2014

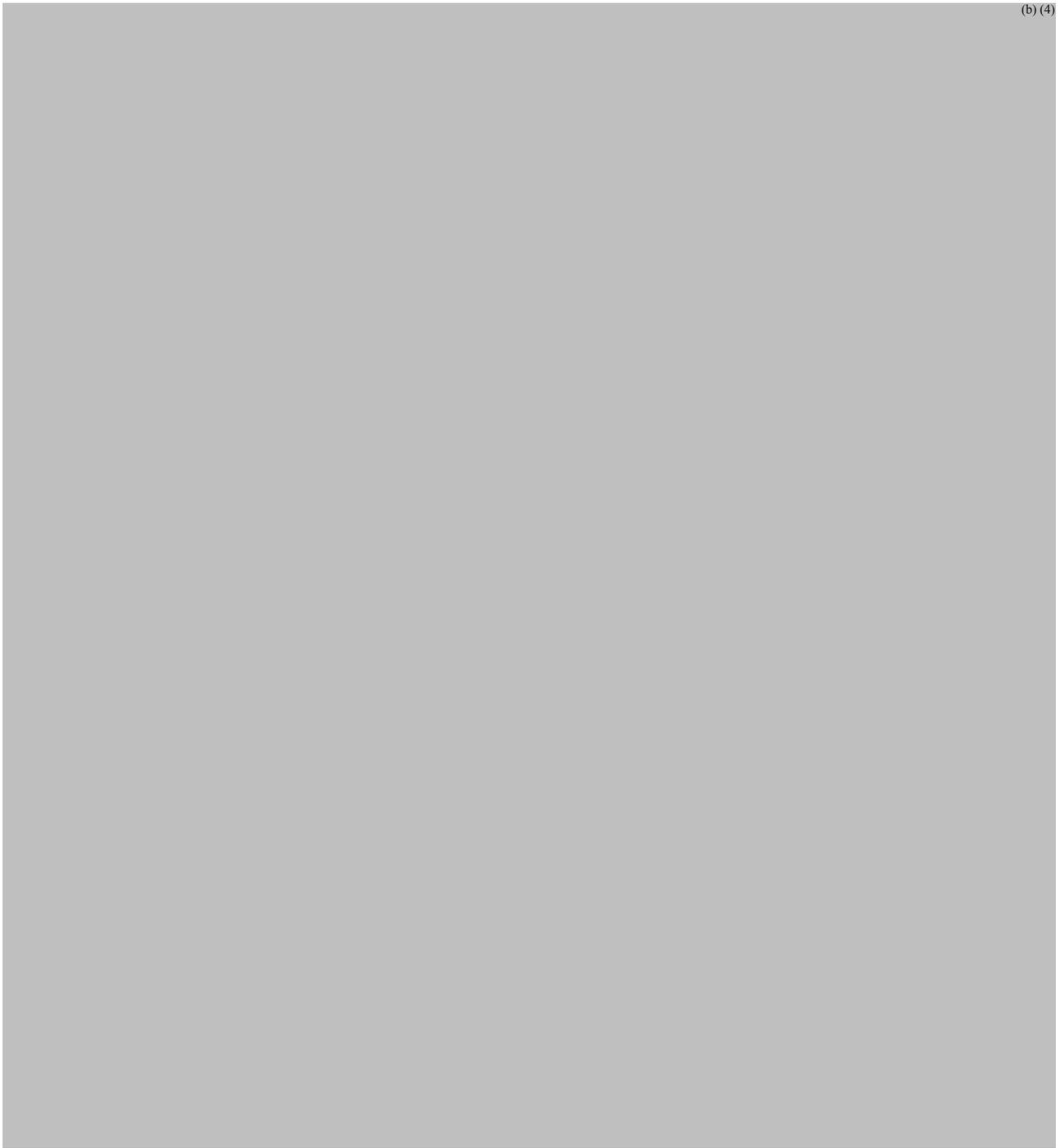
**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: Peds Plan and Protocol Comments  
**Date:** Tuesday, August 26, 2014 3:31:40 PM  
**Importance:** High

---

Elliott-

We have discussed your proposed pediatric plan with our FDA Pediatric Review Committee and agree with your request for deferred pediatric studies and timeline. In addition, we discussed your proposed pediatric protocol and have the following recommendations:

(b) (4)



Please submit a revised pediatric plan and protocol for further review and comments from the Division.

Regards,

*Beth*

Elizabeth Thompson, M.S.  
CDR, U.S. Public Health Service  
Chief, Project Management Staff  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6334  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
[elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov)

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ELIZABETH G THOMPSON  
08/26/2014

**From:** [Thompson, Elizabeth](#)  
**To:** [Berger, Elliott](#)  
**Cc:** [Wileman, Martin](#); [Wileman, Martin](#); [Sheridan, Bill](#); [Taylor, Ray](#); [Thompson, Elizabeth](#)  
**Subject:** RE: NDA 206426 Peramivir - IR regarding Influenza B  
**Date:** Thursday, July 31, 2014 10:41:07 AM

---

Elliott-

The Division review team has already evaluated the information in the NDA that you propose summarizing below. Therefore, the Division does not feel this information needs to be submitted to your pending NDA for review.

Regards,

**Beth**

Chief, Project Management Staff  
FDA/CDER/OAP/DAVP  
301-796-0824

---

**From:** Berger, Elliott [mailto:eberger@BIOCRYST.com]  
**Sent:** Wednesday, July 30, 2014 2:27 PM  
**To:** Thompson, Elizabeth  
**Cc:** Wileman, Martin; Wileman, Martin; Sheridan, Bill; Taylor, Ray  
**Subject:** RE: NDA 206426 Peramivir - IR regarding Influenza B

Beth

The information we would submit will not contain any data that was not included in the NDA but rather would be a concise summary on the information in the NDA on Flu B that will include the following;

- In vitro susceptibility data (IC50) compared to oseltamivir and zanamivir
- Virology data from controlled clinical trials (change in viral titer and TCID50)
- Clinical Outcome data in subjects with Flu B (time to alleviation of symptoms, time to resolution of fever)
- Comparison of available data on peramivir compared with the data used for approval of oseltamivir and zanamivir

If the reviewers think this will be helpful for their review we will put the information together and submit it as soon as it is ready.

Best regards

Elliott

Elliott T Berger, Ph.D.  
Sr. Vice President, Regulatory Affairs  
BioCryst Pharmaceuticals, Inc.  
4505 Emperor Blvd. Suite 200  
Durham NC 27703  
Phone (919) 859-7919  
Cell (b) (6)  
FAX (919) 859-1316  
[eberger@biocryst.com](mailto:eberger@biocryst.com)

---

**From:** Thompson, Elizabeth [<mailto:Elizabeth.Thompson@fda.hhs.gov>]  
**Sent:** Tuesday, July 29, 2014 3:55 PM  
**To:** Berger, Elliott  
**Subject:** RE: NDA 206426 Peramivir - Manufacturing Update

Elliott-

In discussing the Influenza B question below, our team has requested some additional information to help us assess whether or not this information would be helpful for review.

Can you provide more information on where this additional information would be coming from? Is this new information that would be submitted, or is this information that exists in the NDA submission. If in the current submission, could you provide details on where/what trials you are considering pulling this information from?

Regards,

Beth

---

**From:** Berger, Elliott [<mailto:eberger@BIOCRYST.com>]  
**Sent:** Thursday, July 24, 2014 5:25 PM  
**To:** Thompson, Elizabeth  
**Cc:** Wileman, Martin; McMillan, Nicole; Taylor, Ray; El\_Kattan, Yahya  
**Subject:** NDA 206426 Peramivir - Manufacturing Update

Dear Beth

I want to provide you with some follow-up information on the situation at (b) (4). (b) (4) I don't recall if I had told you that (b) (4) had a face-to-face meeting with the FDA (b) (4) on June 27, 2014. The CDER Office of Compliance participated by phone led by (Victor) Ray Gaines. On July 15, (b) (4) provided an update to a previously submitted comprehensive response initially provided in response to FDA Form 483 inspectional observations issued on (b) (4) and to a presentation provided to FDA during the June 27, 2014 meeting. I believe these are the documents you alluded to during our call that would require approximately one month for review by Compliance. (b) (4) has committed to provide periodic updates to the (b) (4) as additional information relevant to the inspection observations becomes available. The next update is targeted for mid-September.

I also wanted to follow-up on the issue we discussed by phone regarding Influenza B, specifically if the Clinical and/or Virology reviewers feel a comprehensive summary of available information on Flu B would be of value.

One last question – Do we have an actual time established for the Late-cycle Review Meeting on September 16??

Best regards,

Elliott

**Elliott T Berger, Ph.D.**  
**Sr. Vice President, Regulatory Affairs**  
**BioCryst Pharmaceuticals, Inc.**  
**4505 Emperor Blvd. Suite 200**  
**Durham NC 27703**  
**Phone (919) 859-7919**  
**Cell [REDACTED] (b) (6)**  
**FAX (919) 859-1316**  
**[eberger@biocryst.com](mailto:eberger@biocryst.com)**

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ELIZABETH G THOMPSON  
07/31/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** RE: NDA 206426: request for information  
**Date:** Thursday, July 31, 2014 10:38:06 AM  
**Importance:** High

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Elliott-

I have an additional request to the one below.

During our review of your submission, we note that you have submitted a request for a pediatric waiver (to be submitted; see request below) and or deferral. However, we could not locate the certification that is required under 21, CFR 314.55. If you have submitted this information, please provide the location. If not, please submit this information no later than August 8, 2014.

---

**From:** Thompson, Elizabeth  
**Sent:** Wednesday, July 30, 2014 1:18 PM  
**To:** 'Berger, Elliott'  
**Cc:** Thompson, Elizabeth  
**Subject:** NDA 206426: request for information  
**Importance:** High

Elliott-

The Division is meeting with our pediatric review committee in mid-August and while reviewing your pediatric plan and deferral I noted that not all pediatric age groups were accounted for. Please submit a waiver request for (b) (4) 28 days and rationale for why this population will not be studied.

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
07/31/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** Authorization Request for (b) (4) discussions  
**Date:** Tuesday, June 17, 2014 11:16:36 AM

---

Elliott-

As discussed in the Mid-Cycle Communication teleconference, FDA is willing to further discuss the compliance issues with BioCryst and (b) (4). BioCryst will need to obtain an authorization letter from (b) (4) for this to occur. For the authorization letter, (b) (4) needs to specifically state that (b) (4) is authorizing FDA to discuss with BioCryst any issues related to the FDA483 observations, corrective action plans and BioCryst product-related issues.

Before we engage in discussions, please note that DAVP/Compliance will have further information requests to ensure a productive meeting.

Please let me know if you have any further questions.

Regards,

Beth  
Chief, Project Management Staff  
FDA/CDER/OAP/DAVP  
301-796-0824

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ELIZABETH G THOMPSON  
06/19/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: CMC information request  
**Date:** Friday, June 06, 2014 11:41:51 AM  
**Importance:** High

---

Elliott-

ONDQA and DAVP need the following information resolved concerning the facility site listed below:

(b) (4) **testing of drug substance**

Please confirm and submit details about the activities conducted at this site that has been submitted in the NDA application.

Regards,

**Beth**  
Chief, Project Management Staff  
FDA/CDER/OAP/DAVP  
301-796-0824

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ELIZABETH G THOMPSON  
06/16/2014



NDA 206426

**MID-CYCLE COMMUNICATION**

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RAPIVAB (peramivir injection) for intravenous use.

We also refer to the teleconference between representatives of your firm and the FDA on June 5, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Elizabeth Thompson, Chief, Project Management Staff at (301) 796-0824.

Sincerely,

*{See appended electronic signature page}*

Linda L. Lewis, MD  
Medical Team Leader  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** June 5, 2014; 1:00 PM Eastern Time  
**Application Number:** 206426  
**Product Name:** RAPIVAB (peramivir injection), for intravenous use  
**Indication:** **Treatment of acute, uncomplicated influenza**  
**Applicant Name:** BioCryst Pharmaceuticals, Inc.

**FDA ATTENDEES**

OND/OAP

Edward Cox, Director  
Barbara Styrt, Medical Reviewer

OND/OAP/DAVP

Debra Birnkrant, Division Director  
Jeff Murray, Deputy Division Director  
William Tauber, Acting Deputy Director of Safety  
Linda Lewis, Medical Team Leader  
Kim Struble, Medical Team Leader  
Peter Miele, Medical Reviewer  
Wendy Carter, Medical Reviewer  
Kuei-Meng Wu, Nonclinical Reviewer  
Jules O'Rear, Clinical Virology Team Leader  
Takashi Komatsu, Clinical Virology Reviewer  
Elizabeth Thompson, Chief, Project Management Staff  
Suzanne Strayhorn, Regulatory Project Manager

OTS/OB/DB4

Greg Soon, Biostatistics Team Leader  
Tom Hammerstrom, Biostatistician

OTS/OCP/DCP4

Islam Younis, Clinical Pharmacology Team Leader  
Elizabeth Lakota, Clinical Pharmacology Contractor  
Leslie Chinn, Clinical Pharmacology and Pharmacometrics Reviewer

ONDQA

Fuqiang Liu, CMC Reviewer

OPS

Neal Sweeney, CMC Microbiology Reviewer

Office of Surveillance and Epidemiology

Veronica Sansing, DEPI

Office of Compliance

Krishna Ghosh

Eastern Research Group Participants

(b) (4) Independent Assessor

**APPLICANT ATTENDEES**

BioCryst

Elliott Berger, Senior VP, Regulatory

(b) (4), Virology Consultant

Phil Collis, VP, Clinical Development

Sylvia Dobo, Executive Director, Product Safety and Clinical Development

(b) (4), Statistical Consultant

Yahya El-Kattan, VP, Drug Development CMC

Steve MacLennan, Executive Director, Toxicology

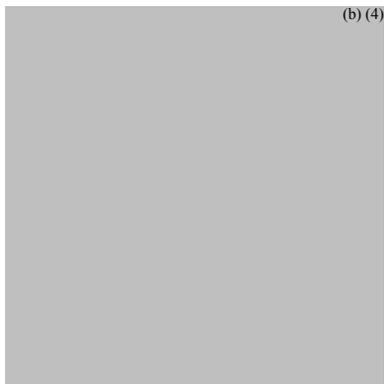
Nikki McMillan, Manager, Regulatory Affairs

Carrie Rivera, Director, Quality Assurance

William Sheridan, Senior VP, Chief Medical Officer

Jon Stonehouse, President, CEO

Ray Taylor, VP, Peramivir Project Leader



**1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If

you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

As stated earlier, the purpose of this meeting is not to discuss the issues identified, but in the spirit of transparency to provide a status update on the review of your application. The application is still under review and no regulatory decisions have been determined. The Division informed BioCryst that meeting minutes will be issued within 30 days.

The following issues were discussed:

### Compliance

FDA referenced the Type C CMC meeting request dated May 8, 2014, to discuss ongoing facility inspection issues. FDA noted that they are unable to engage in discussions surrounding the current inspection/deficiency issues or address the questions posed in the meeting request, except to say that all manufacturing and testing sites must be cGMP compliant and all corrective actions from any inspections have to be adequately addressed and reviewed by FDA/Compliance for an application to be approved. If any site is found to be noncompliant, it can have an impact on the approvability of the NDA.

Compliance noted that in order for submission of information to be considered in support of the NDA, it must occur during the current PDUFA review cycle which ends December 23, 2014. Compliance also stated that FDA would need time to review this information, so it should be submitted in a timely manner.

BioCryst noted the withdrawal of their Type C meeting request on May 20, 2014 and wanted to know what mechanisms they should utilize to further discuss unresolved compliance issues. FDA stated that they cannot address the FDA-483 observations related to (b) (4) but stated that while the issues are being resolved with (b) (4) it may be beneficial to BioCryst to establish diversity and redundancy in manufacturing. FDA is aware that BioCryst has begun to look for an additional CMO, but reiterated that they must adhere to the PDUFA timeline when providing this documentation, as FDA will need adequate review time before the action date. BioCryst stated that their primary intention was to resolve issues related to (b) (4) and that engaging an additional CMO is a secondary goal.

FDA stated that further discussions between BioCryst and FDA regarding manufacturing might be possible. BioCryst mentioned that they have weekly contact with (b) (4) and asked whether it would be helpful to submit an authorization letter from (b) (4) to initiate discussions between (b) (4) BioCryst and FDA. FDA stated this would be helpful.

### Clinical

FDA noted that they have been conducting the NDA review under the assumption that the IM and IV formulations of peramivir provide similar systemic peramivir exposures, and has therefore been using the clinical trials of IM peramivir to support the safety and efficacy of IV peramivir in adults with acute uncomplicated influenza; however, final confirmation of comparable bioavailability was pending based on the results of current OSI inspections. FDA had not identified any significant safety issues that would preclude approval with either formulation thus far, but was having internal discussions regarding the best way to display safety information collected during the EUA period and the post-marketing experience in Japan, specifically the cases of serious skin reactions and abnormal behaviour. FDA had also not found any significant differences between the peramivir 300 mg and 600 mg doses with respect to safety or efficacy, but acknowledged that there may be secondary evidence to support favoring the 600 mg dose.

FDA noted that the submitted clinical trials did not contain sufficient clinical evidence to support peramivir activity against influenza B, but that it had not yet made any determinations regarding how this will be addressed in labeling or whether post-marketing studies would be necessary to support an indication in influenza B.

### Clinical Virology

The submitted clinical trials enrolled fewer subjects infected with influenza B virus relative to the rates reportedly circulating in the study regions. The use of RAT assays as inclusion criteria may have played a role. The sensitivity of RAT assays varies across populations, but it is generally higher for influenza A virus than for influenza B virus infection (Chartrand et al., 2012). Additionally, the performance characteristics of the RAT assays used in these trials demonstrate less sensitivity against influenza B virus.

## **3.0 INFORMATION REQUESTS**

The Division notes the following pending information requests:

- Chemistry, Manufacturing, and Controls drug substance and drug product information request dated May 30, 2014

## **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

There are no major safety concerns identified at this time that warrant the need for a REMS.

## **5.0 ADVISORY COMMITTEE MEETING**

There are no plans for an AC meeting at this time.

## **6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

The Late-Cycle Meeting (LCM) is scheduled for September 16, 2014. The background package will be sent to applicant by September 11, 2014. The purpose of the LCM is to share information

and discuss any substantive review issues identified to date, as well as our objectives for the remainder of the review cycle.

The projected date that the Division will have initial proposed Post Marketing Requirements (PMRs), Post Marketing Commitments (PMCs), and labeling to the applicant will be August 30, 2014.

BioCryst noted they submitted a pediatric plan in the original NDA and wanted to know if the Division had a timeframe for providing a response. FDA stated that the internal review (by the Pediatric Review Committee) would be in October 2014. FDA asked if BioCryst needed feedback sooner. BioCryst stated it would be unlikely for them to get the study up and running in time for the next influenza season if FDA feedback is received in October. BioCryst asked if FDA would prefer the full pediatric protocol instead of the synopsis provided in the NDA. FDA stated it would be helpful to review. FDA also stated they would work with the Pediatric Review Committee to try to provide earlier feedback.

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/s/  
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LINDA L LEWIS  
06/13/2014

Executive CAC

Date of Meeting: June 10, 2014

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair  
Paul Brown, Ph.D., OND IO, Member  
Wendy Schmidt, Ph.D., OND IO, Alternate Member  
Hanan Ghantous, Ph.D., DAVP, Supervisor  
Kuei-Meng Wu, Ph.D., DAVP, Presenting Reviewer

Author of Minutes: Kuei-Meng Wu

The following information reflects a brief summary of the Committee discussion and its conclusions. Detailed study information can be found in the individual review.

NDA 206-426

Drug Name: Peramivir (RWJ-270201-162; BCX1812)

Sponsor: Biocryst Pharmaceutical Inc., AL

### Background

Peramivir is a viral neuraminidase inhibitor for influenza infection. The NDA included oral carcinogenicity studies in rats and mice. The mouse study was terminated without histopathology. The rat study is complete, which was performed under the protocol discussed and agreed upon by Exec CAC on 12/21/1999.

### Rat Study:

The drug was administered by oral gavage to Crl:CD®(SD)IGS rats at doses of 0 (water), 0 (untreated), 150, 1000, 3000 mg/kg/day for up to 2 years. The results showed some increases in pheochromocytoma of the adrenal medulla in males of 1000 and 3000 mg/kg/day groups, but the findings were not statistically significant.

### **Executive CAC Recommendations and Conclusions:**

#### Rat Carcinogenicity Study

The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol. The Committee concurred that there were no drug-related neoplasms in the study.

Abby Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\

/Division File, DAVP  
HGhantous/ Supervisor, DAVP  
KWu/Reviewer, DAVP  
EThompson /PM, DAVP  
/ASeifried, ONDIO

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/s/  
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ADELE S SEIFRIED  
06/12/2014

ABIGAIL C JACOBS  
06/12/2014



NDA 206426

## INFORMATION REQUEST

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RAPIVAB (peramivir injection) for intravenous use.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by June 13, 2014, in order to continue our evaluation of your NDA.

For Peramivir drug substance, we have the following recommendations:

- 1) In section 3.2.S.2.2, please carefully review and re-calculate the material amounts (crude peramivir, theoretical yield and actual yield) listed in Table 11 for the (b) (4) process and update the table – there appear to be multiple calculation errors. Specifically,
  - a. Clarify what solid form (b) (4) is used in the calculation of (b) (4) peramivir and the corresponding yields. It appears that at (b) (4) the yields were based on conversion from (b) (4) peramivir to the (b) (4) form, but we cannot tell how the yields were calculated at (b) (4). Since 3.2.S.3.1.4.10 indicates that the (b) (4) peramivir is isolated as a (b) (4) form, should the yield be calculated based on (b) (4) peramivir?
  - b. The theoretical yield range is stated to be (b) (4). Clarify how this range was determined. The upper limit of yield at (b) (4) seems to be much higher than (b) (4) % yield. Additionally, the actual yield amounts (b) (4) are not corresponding to the listed yield range of (b) (4) %. Clarify or correct these discrepancies.

- 2) In section 3.2.S.3.1, provide solid state characterization results including solubility data for Form B, as you did for Form A in sections 3.2.S.3.1 and 3.2.S.1.3. Please explain why you choose Form A (b)(4) over Form B (b)(4).
- 3) In section 3.2.S.4.5, you mentioned that Figure 4 was stability data of Impurity (b)(4) for the registration batches, but the figure shows (b)(4), instead of Impurity (b)(4). Please correct this discrepancy.
- 4) The proposed regulatory specification also applies to the drug substance under stability study; however, we noted that the stability reports listed in 3.2.S.7.3 use different acceptance criterion for specified impurities (b)(4)% as proposed in the NDA) and (b)(4) purity ((b)(4)% for the (b)(4) as proposed in the NDA). Revise future stability reports to reflect the current specifications.

For Peramivir drug product, we have the following recommendations:

- 5) The proposed drug product regulatory specification also applies to the drug product under stability study; however, we noted that the stability reports listed in 3.2.P.8.3 use different acceptance criterion for pH range ((b)(4) vs. 5.5 - 8.5 as proposed in the NDA) and total degradants ((b)(4)% as proposed in the NDA). Revise future stability reports to reflect the current specifications.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
05/30/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 206426

**MEETING REQUEST WITHDRAWN**

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RAPIVAB (peramivir injection) for intravenous use.

We also refer to your May 20, 2014 communication requesting withdrawal of your May 8, 2014 meeting request. Your meeting request is hereby withdrawn.

If you have any questions, call me at (301) 796-0824.

Sincerely,

*{See appended electronic signature page}*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Chief, Project Management Staff  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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ELIZABETH G THOMPSON  
05/21/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical information request (Study BCX1812-303)  
**Date:** Wednesday, May 14, 2014 4:27:05 PM  
**Importance:** High

---

Elliott-

The Division has the following clinical information request:

Two events of convulsion were identified in the AE database, both occurring in Study 303 (Subjects 131.100 and 153.013). Neither event was considered serious or related to study drug (per the datasets), but the case narratives for these two subjects omit any mention of seizures. Please provide any and all information you may have regarding these convulsion events.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
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ELIZABETH G THOMPSON  
05/14/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: P1 label format comments  
**Date:** Friday, May 02, 2014 9:07:16 AM  
**Attachments:** [rapivab-pi davn format edits.docx](#)  
**Importance:** High

---

Elliott-

Attached please find labeling format comments. Please address these comments and submit clean and annotated labeling by May 23, 2014. If you have any questions, please let me know.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
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ELIZABETH G THOMPSON  
05/02/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: nonclinical IR  
**Date:** Wednesday, April 30, 2014 9:43:11 AM  
**Attachments:** [Completely unexamined R.pdf](#)  
**Importance:** High

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Elliott-

Please refer to the Division's request for information dated March 31, 2014, and your response dated April 3, 2014. We have the following additional clarification question/request for additional information related to that original request.

Nonclinical

Please provide explanations as to why some males in rat carcinogenicity study were excluded from analysis (i.e., necropsy and histopathology exams) entirely (see attached list of animals that were completely unexamined). Our statisticians wanted to know the rationales or the underlying reasons for dropping these animals (e.g., based on any clinical conditions, or any random methodology [please reveal in details]).

Regards,

Beth

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Chief, Project Management Staff  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6334  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
[elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov)

<i>Species and sex</i>	<i>Dose group</i>	<i>Animal number</i>
Rats - Male	Control	B21021
		B21030
		B21031
		B21032
		B21034
		B21039
		B21041
		B21047
		B21048
		B21059
		B21060
		B21063
		B21064
		B21068
		B21072
		B21074
		B21080
		B21083
		B21084
		Low dose
B21169		
B21182		
B21183		
B21187		
B21190		
B21191		
B21193		
B21194		
B21198		
B21208		
Mid dose	B21215	
	B21226	
	B21229	
	B21234	
	B21244	
	B21255	
	B21262	
	B21266	
B21268		
High dose	B21280	
	B21294	

<i>Species and sex</i>	<i>Dose group</i>	<i>Animal number</i>
		B21296
		B21297
		B21299
		B21300
		B21305
		B21309
		B21311
		B21314
		B21317
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		B21343

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/s/  
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ELIZABETH G THOMPSON  
05/01/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical pharmacology information request  
**Date:** Friday, April 18, 2014 12:27:33 PM  
**Importance:** High

---

Elliott-

We have the following information request regarding your NDA currently under review, and are asking for a response by April 25, 2014.

**Clinical Pharmacology**

The final bioanalytical validation reports VR-1812-HP-BTMBA030 and VR-1812-HU-BTMBA033 establish plasma and urine long-term stability for 6-6.5 months and 6 months, respectively, at -80 degrees C. Please submit longer-term stability data (e.g. to cover the sample storage period in trial BCX1812-103 prior to analysis) if available. If such data have already been submitted, please provide the location in the NDA submission.

Regards,

*Beth*

Elizabeth Thompson, M.S.

LCDR, U.S. Public Health Service

Chief, Project Management Staff

FDA/CDER/OND/DAVP

10903 New Hampshire Avenue

Bldg #22, Rm 6334

Silver Spring, MD 20993

301-796-0824 (office); 301-796-9883 (fax)

[elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov)

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/s/  
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ELIZABETH G THOMPSON  
04/18/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: nonclinical information request  
**Date:** Monday, March 31, 2014 10:33:26 AM  
**Importance:** High

---

Elliott-

Our nonclinical review team has the following request for information:

In regards to the rat carcinogenicity study, there were significant portion of the males that were unexamined pathologically. Please provide in detail the reasons why those animals were not examined. This will allow us to determine how to interpret the results from this study.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
-----

ELIZABETH G THOMPSON  
04/07/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** RE: NDA 206426: clinical information request.  
**Date:** Tuesday, March 25, 2014 12:41:27 PM  
**Importance:** High

---

Elliott-

Please refer to the email below and your emailed response dated March 25, 2014. I know I mentioned this would be informal, but after further review, can you clarify if the information provided below was submitted with the Original NDA? If not, please submit your response officially to the NDA.

---

**From:** Thompson, Elizabeth  
**Sent:** Monday, March 24, 2014 3:15 PM  
**To:** 'Berger, Elliott'  
**Cc:** Thompson, Elizabeth  
**Subject:** NDA 206426: clinical information request.  
**Importance:** High

Elliott-

Please see the following IR. This can be emailed and does not need a formal response (submitted to NDA).

For Study 0815T0631, please provide a method for correlating the Subject IDs from the datasets to the those used in the CSR, narratives and CRFs. If this information has already been presented, please indicate where in the submission it may be found.

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
-----

ELIZABETH G THOMPSON  
03/25/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical information request regarding AEs  
**Date:** Tuesday, March 25, 2014 8:16:40 AM  
**Importance:** High

---

Elliott-

The clinical team has the following information request:

For Study 0815T0631, the ADSL dataset indicates that 28 subjects discontinued study prematurely due to an adverse event. However, in the ADAE dataset, only 14 subjects have AEs that are flagged "drug withdrawn" in the AEACN variable. Since it appears that most if not all of the peramivir-treated subjects in this cohort completed study drug dosing on Day 1, it is assumed that the "drug withdrawn" variable in this case refers to discontinuation from study. This is confirmed by review of the CRF for subject 0815T0631.013.JCD06 (or # 154-003 in the CRF) who discontinued study on Day 3 due to AEs of arthralgias/drug eruption noted on Day 2, but who did complete dosing on Day 1.

In contrast, Subject 0815T0631.082.JWQ09 (or #085-006 in the CRFs) discontinued study on Study Day 8 as per the ADSL dataset and CRF. The CRF indicates the reason for discontinuation was occurrence of adverse event, and refers to "acute bronchitis" as the specific AE. In the ADAE dataset, however, the AE of "acute bronchitis" is not flagged, and the AEACN variable for this event is "dose not changed". Without having cross-referenced the ADSL dataset and the CRF, which is labor intensive, this AE would have been missed as leading to premature study discontinuation.

Since these 28 subjects have 59 AEs reported among them, and since there appears to be variability in the way investigators coded the AEACN variable, it is difficult to identify the specific AEs that led to study discontinuation among the 14 subjects whose AEACN variables are not "drug withdrawn" without resorting to the CRFs. However, some of the submitted CRF's are incomplete (such as for Subject JVT01 or 077-02) and thus not helpful in this endeavor.

In order to obtain an accurate assessment of IV peramivir safety, please indicate the AEs that resulted in study drug discontinuation or study withdrawal in these 28 subjects, based on the CRF notation associated with the reason for discontinuation.

The subject ID listings (per the ADSL dataset) are as follows:

USUBJID

0815T0631.008.JAM02

0815T0631.011.JBH07

0815T0631.013.JCD06

0815T0631.026.JEH14

0815T0631.031.JFH01

0815T0631.041.JGP22

0815T0631.041.JGP23

0815T0631.041.JGP26

0815T0631.053.JPT02

0815T0631.056.JQH04

0815T0631.061.JRE01

0815T0631.066.JTJ04

0815T0631.066.JTJ05

0815T0631.070.JVD02

0815T0631.076.JVT01

0815T0631.077.JVU01

0815T0631.077.JVU03

0815T0631.077.JVU05

0815T0631.080.JWD03

0815T0631.082.JWQ09

0815T0631.085.JWY03

0815T0631.093.JXM02

0815T0631.095.JXV02

0815T0631.101.JZL03

0815T0631.117.KPM01

0815T0631.134.THA04

0815T0631.137.TLU30

0815T0631.139.TNZ17

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
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ELIZABETH G THOMPSON  
03/25/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** RE: NDA 206426 - clinical IR re: Subject BCX1812-311.613.002  
**Date:** Tuesday, March 18, 2014 7:48:12 AM

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Elliott-

The clinical reviewer was able to locate the problem and therefore does not need a response to this request.

---

**From:** Thompson, Elizabeth  
**Sent:** Friday, March 14, 2014 2:56 PM  
**To:** 'Berger, Elliott'  
**Cc:** Thompson, Elizabeth  
**Subject:** NDA 206426 - clinical IR re: Subject BCX1812-311.613.002  
**Importance:** High

Elliott-

We have the following clinical information request (IR):

The CSR for Study 311, and the integrated report for 211/311, indicate that all randomized subjects in Study 311 (N=82) received study drug. However, there is one subject, Subject 613002, in the ADSL dataset for Study 311 (as well as the pooled dataset for 211/311) who appears to have been randomized to placebo on 1/21/2008 but not treated. No CRF was submitted for this subject; furthermore, per the CSR for Study 311 (Table 14.1.1.1), no subjects were enrolled at Site 613. Please clarify this discrepancy between the datasets and study report.

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
03/18/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical information request  
**Date:** Friday, March 07, 2014 2:17:41 PM  
**Importance:** High

---

Elliott-

Please refer to NDA 206426 currently under review. We have the following clinical requests for information:

1. For the Shionogi Study 0722T0621, please provide the number of subjects screened and the number of screen failures (broken down by reason), as was reported for the BioCryst trials in acute uncomplicated influenza.
2. For Study BCX1812-212, please explain why the ITTI-A population was selected for the analysis of the primary efficacy endpoint.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
03/12/2014



NDA 206426

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

BioCryst Pharmaceuticals, Inc.  
4505 Emperor Boulevard, Suite 200  
Durham, NC 27703

ATTENTION: Elliott Berger, Ph.D.  
Senior Vice President, Regulatory Affairs

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) dated December 21, 2013, received December 23, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Peramivir Solution for Injection, 10 mg/mL.

We also refer to your correspondence dated December 21, 2013, received December 23, 2013, requesting review of your proposed proprietary name, Rapivab. We have completed our review of the proposed proprietary name Rapivab, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your December 21, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Elizabeth Thompson at (301) 796-0824.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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AZEEM D CHAUDHRY  
03/05/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR  
03/06/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical virology information request  
**Date:** Wednesday, March 05, 2014 8:48:11 AM  
**Importance:** High

---

Elliott-

Please refer to NDA 206426 (currently under review). We have the following request from our clinical virology team:

Clinical Virology

The primers/probes that were used to determine influenza A virus and influenza B virus by realtime RT-PCR appear to be the same for those that were used by Shionogi (study report BCX1812-621-VIR, pg. 12) and by (b) (4) (study report BCX1812-211/311-VIR, pg. 13). Furthermore, the procedure that was used for the primary virus culture (described in Section 6.2 for both study reports) appears to be identical. Please clarify whether the same primer/probes as well as the same procedures were used at both of these sites.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
03/05/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: nonclinical request for information  
**Date:** Thursday, February 27, 2014 10:30:54 AM  
**Attachments:** [Carci Data Format and Stat Guidance Info Sheets 07-16-09.pdf](#)  
**Importance:** High

---

Elliott-

Please refer to your pending NDA currently under review. We have the following request for information:

Nonclinical

In order to perform a statistical analysis, the FDA Biostatistics Review Team request you to submit rat carcinogenicity data in SEND standard format, or in FDA's own in-house data standard format (generally referred to as TUMOR.XPT - see the attached document for details) as soon as possible.

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
02/28/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical site inspection request  
**Date:** Thursday, February 27, 2014 1:49:19 PM  
**Importance:** High

---

Elliott-

Regarding the information you shared with me over the phone this morning, please provide an official communication to the NDA outlining the specifics of the problem encountered at the clinical site for Dr. Wise. In addition, please make note if BioCryst is aware of any other information FDA should be aware of regarding any other clinical sites (including but not limited to the 5 sites identified for inspection).

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
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ELIZABETH G THOMPSON  
02/28/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical and stats information request  
**Date:** Thursday, February 27, 2014 3:48:55 PM  
**Importance:** High

---

Elliott-

Please refer to your NDA currently under review. We have the following clinical and statistical request for information.

#### Clinical

1. Please submit sample patient diary forms for the four placebo-controlled trials (0722T0621, BCX1812-211, -212, and -311) and describe how subjects were instructed to record their daily assessments of influenza symptoms. Were subjects instructed to record the worst score for each symptom experienced in the previous twelve hours or current score at the time of the diary entry?
2. Please indicate how many protocol amendments were made to Study 0722T0621 and provide a description of the changes made with each amendment.

#### Statistics

3. There appear to be a number of errors/discrepancies in the five trials of acute uncomplicated influenza (0722T0621, 0815T0631, BCX1812-211, BCX1812-212, BCX1812-311) with respect to date and time of diary entries. As an example, when reviewing the ADSS dataset for the COMPOSITE SYMPTOM SCORE, we noted that these errors generally take one of the following three forms:
  1. There are 3 or 4 diary entries all on the same day with the next entry occurring two days later, or alternatively there are no entries for the previous day. We assume that the third and fourth entries on the same day are actually supposed to be for the next day when no entries are recorded for that day, In cases where the previous day has no entries recorded, we assume that the first two entries are supposed to be for the previous day.
  2. There are entries for morning and evening with both times later than noon; usually both are much later, around 6 – 9 PM. We assume a morning entry at 7 PM followed by an evening entry also at 7 PM or even at 6:30 PM should really be a morning entry at 7 AM followed by an evening entry at 7 PM.
  3. There are entries for morning and evening with both times before noon. We assume a morning entry at 7 AM followed by an evening entry also at 7 AM should really be a

morning entry at 7 AM followed by an evening entry at 7 PM.

The following subjects illustrates problems of the first type. ELAPSE time and CHANGE in ELAPSE time are variables created by FDA by subtracting the first ADTM from the later ones.

TRIAL\_212

Unique Subject Identifier=BCX1812-212.102.003

AVISIT CH_ELAPSE	ADTM	ELAPSE
DAY 1 PRE-DOSE	14AUG08:16:40	0.000
DAY 1 EVENING 1.3333	14AUG08:18:00	1.333
DAY 2 MORNING 15.2500	15AUG08:09:15	16.583
DAY 2 EVENING 10.7500	15AUG08:20:00	27.333
DAY 3 MORNING 13.0000	16AUG08:09:00	40.333
DAY 3 EVENING 11.0000	16AUG08:20:00	51.333
DAY 4 MORNING 15.3667	17AUG08:11:22	66.700
DAY 4 EVENING 11.1333	17AUG08:22:30	77.833
DAY 5 MORNING 12.5000	18AUG08:11:00	90.333
DAY 5 EVENING 9.5000	18AUG08:20:30	99.833
DAY 6 MORNING 11.2333	19AUG08:07:44	111.067
DAY 6 EVENING 12.7667	19AUG08:20:30	123.833
DAY 7 MORNING 11.2500	20AUG08:07:45	135.083
DAY 7 EVENING 12.7500	20AUG08:20:30	147.833
DAY 8 MORNING 14.5000	21AUG08:11:00	162.333

DAY 8 EVENING 9.5000	21AUG08:20:30	171.833	
DAY 9 MORNING 12.0000	21AUG08:08:30	159.833	-
DAY 10 MORNING 49.5000	23AUG08:10:00	209.333	
DAY 11 MORNING 23.7500	24AUG08:09:45	233.083	
DAY 12 MORNING 22.2500	25AUG08:08:00	255.333	
DAY 13 MORNING 24.0000	26AUG08:08:00	279.333	
DAY 14 MORNING 23.7500	27AUG08:07:45	303.083	
Unique Subject Identifier=BCX1812-212.300.003			
AVISIT	ADTM	ELAPSE	
CH_ELAPSE			
DAY 1 PRE-DOSE	15JUL08:12:00	0.000	.
DAY 1 EVENING 9.5000	15JUL08:21:30	9.500	
DAY 2 MORNING 10.5000	16JUL08:08:00	20.000	
DAY 2 EVENING 10.5000	16JUL08:18:30	30.500	
DAY 3 MORNING 39.0833	18JUL08:09:35	69.583	
DAY 3 EVENING 8.9167	18JUL08:18:30	78.500	
DAY 4 MORNING 10.0000	18JUL08:08:30	68.500	-
DAY 4 EVENING 11.0833	18JUL08:19:35	79.583	
DAY 5 MORNING 13.0833	19JUL08:08:40	92.667	
DAY 5 EVENING 10.7500	19JUL08:19:25	103.417	
DAY 6 MORNING 13.8333	20JUL08:09:15	117.250	
DAY 6 EVENING	20JUL08:19:30	127.500	

10.2500		
DAY 7 MORNING 15.2500	21JUL08:10:45	142.750
DAY 7 EVENING 9.5000	21JUL08:20:15	152.250
DAY 8 MORNING 14.5000	22JUL08:10:45	166.750
DAY 8 EVENING 8.4167	22JUL08:19:10	175.167
DAY 9 MORNING 15.7500	23JUL08:10:55	190.917
DAY 10 MORNING 23.3333	24JUL08:10:15	214.250
DAY 11 MORNING 25.0000	25JUL08:11:15	239.250
DAY 12 MORNING 21.9167	26JUL08:09:10	261.167
DAY 13 MORNING 22.8333	27JUL08:08:00	284.000
DAY 14 MORNING 23.2500	28JUL08:07:15	307.250

In the case of Subject BCX1812-212.300.003, for example, these discrepancies occur around the day the subject reportedly met the primary efficacy endpoint (Day 3 evening) and thus raise questions about the integrity of the data used for the efficacy analyses.

Please conduct a systemic review of the diary entry data for all five of the above mentioned trials and submit subject listings (per trial) for all subjects where such apparent discrepancies between Visit Day and date and time exist.

Also, please clarify how you handled these discrepancies in the conduct of your efficacy analyses since the analysis plans do not appear to account for these errors.

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
02/28/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: CMC request for information  
**Date:** Monday, February 24, 2014 8:55:48 AM  
**Importance:** High

---

Elliott-

Please refer to your NDA under review. We have the following CMC request for information:

We note that there are 4 facilities listed as performing (b) (4) testing of peramivir drug substance (in some case with additional testing responsibilities). Are all of those 4 facilities intended for future testing of commercial lots of the drug substance? In other words, were any of these 4 facilities only used for batches of peramivir drug substance that have already been manufactured, with no intent for future testing at that site?

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
02/24/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical and CMC information requests  
**Date:** Friday, February 14, 2014 11:04:53 AM  
**Attachments:** [Summary of Facilities listed in 356h.pdf](#)  
**Importance:** High

---

Elliott-

The review team has the following requests for information.

### Clinical

Given that data from the peramivir IM trials are being used to support the current NDA, please provide a risk-benefit assessment for the IV formulation versus the IM formulation and your reasons for abandoning the IM formulation. If this information is documented in the NDA submission, please indicate where it may be found.

### CMC

Please update the NDA with a statement that all CMC facilities that are listed in the 356h form are ready for inspection, or reference the location of this statement if already included in the NDA. Please also confirm that the site responsibilities listed in the attached summary are accurate, and whether this list includes all facilities used to manufacture, test, package and label the peramivir drug substance or drug product.

Please respond to the CMC portion of this request NLT January 20, 2014.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
02/18/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "[Berger, Elliott](#)"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: CMC request for information  
**Date:** Wednesday, February 12, 2014 9:44:21 AM  
**Importance:** High

---

Elliott-

The CMC team has the following request:

Please update the NDA with a statement that all CMC facilities are ready for inspection, or reference the location of this statement if already included in the NDA.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
02/12/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: clinical information request  
**Date:** Saturday, February 01, 2014 6:43:47 AM  
**Importance:** High

---

Elliott-

The clinical team has the following request for information:

For Study 0722T0621, please verify that the (b) (4) variable in the (b) (4) datasets represents neutrophil percentage. Were absolute neutrophil results collected in this study? If so, are those data available, as they are for the supportive BCX IM studies? The AE datasets report multiple events of "Neutrophil count decreased" or "Neutrophil percentage decreased" and it would be useful to have the laboratory data to correlate. Also, please define the "Stab" variable in the (b) (4) dataset.

Please let me know if you have any questions regarding this request.

Regards,

**Beth**  
Chief, Project Management Staff  
FDA/CDER/OAP/DAVP  
301-796-0824

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ELIZABETH G THOMPSON  
02/03/2014

**From:** [Thompson, Elizabeth](#)  
**To:** "Berger, Elliott"  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426 (peramivir injection): Clinical Information Request  
**Date:** Tuesday, January 28, 2014 7:12:16 PM  
**Attachments:** [Copy of NDA 206426 Report On Duplicate Records In Lab Data.xlsx](#)  
**Importance:** High

---

Elliott-

The Division has the following IR from the clinical review team:

We have noticed across multiple studies that numerous subjects have more than one laboratory test result reported for the same lab test name, date and time. This appears to affect predominantly the reporting of neutrophil counts and neutrophil/leukocyte ratios. Furthermore, the duplicated test results are widely divergent from one another for a given subject, lab test, date and time and also appear to use different reference ranges. These duplicated test results are not flagged in any easily identifiable manner, so that it would be difficult to extract them if necessary to conduct our analyses. The enclosed Excel spreadsheet includes the subjects, by subject ID and trial, and the laboratory tests we have identified with multiplicity of reported results.

Please explain the occurrence of these duplicate test results and the disparity in the reported results and reference ranges used. If there is a manner in which we can easily identify these instances of duplicate test reporting, please describe. If not, please resubmit the laboratory tabulation datasets with a flag variable to identify those instances of duplicate reporting, particularly for Studies BCX1812-211, -212, and -311. Also, when multiple results are reported for a given subject, test, date and time, please identify which result is to be relied upon for our review. Lastly, please define the "LOINC Code" variable, as the define file does not.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
01/31/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426 - clinical information request  
**Date:** Friday, January 31, 2014 11:57:10 AM  
**Importance:** High

---

Elliott-

The clinical team has the following request for information:

Please provide the following general study related information. If items are provided elsewhere in the NDA submission, please describe location or provide link to requested information.

1. Please include the following information in a tabular format for each of the supportive clinical trials (BCX1812-211, BCX1812-212, and BXC1812-311).

*By site*, please list:

- a. Number of subjects screened
- b. Number of subjects randomized
- c. Number of subjects excluded from study, include reasons not randomized
- d. Number of subjects randomized but not treated, include reasons not treated
- e. Number of subjects treated who prematurely discontinued study, include reasons for discontinuation
- f. Number of protocol violations, include descriptions of violations
- g. Number of AEs
- h. Number of SAEs
- i. Number of deaths
- j. Number of subjects who met primary endpoint efficacy parameter, include percentage of randomized subjects

FDA requests that this information be provided to the NDA NLT February 7, 2014. If BioCryst determines it will require more than one week to put this information together, please provide the information for a-e first, followed by the more complete data when available.

Please let me know if you have any questions regarding this request.

**Beth**

**Chief, Project Management Staff**

FDA/CDER/OAP/DAVP

301-796-0824

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ELIZABETH G THOMPSON  
01/31/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: CMC information request  
**Date:** Tuesday, January 28, 2014 12:54:27 PM  
**Importance:** High

---

Elliott-

The Division has the following urgent request from our CMC team.

Please confirm that all the manufacturing and testing facilities that are listed in the 356h attachment are ready for inspection.

Regards,

**Beth**

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/  
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ELIZABETH G THOMPSON  
01/28/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: Pharmacometrics Information Request  
**Date:** Tuesday, January 28, 2014 8:34:20 AM  
**Importance:** High

---

Elliott-

The Division has an information request regarding your new NDA for peramivir injection.

Pharmacometrics

Please provide the pharmacokinetic and pharmacodynamic datasets used to conduct the peramivir population PK and PK/PD analyses presented in BCX1812-PPK-1, as well as the code files used to generate the datasets and perform the analyses. If these items were included in the initial NDA submission, please provide the relevant pathways to their locations. Please provide the requested materials or a link to their location in the original NDA within two weeks.

Please let me know if you have any questions regarding this request.

Regards,

*Beth*

Elizabeth Thompson, M.S.

LCDR, U.S. Public Health Service

Chief, Project Management Staff

FDA/CDER/OND/DAVP

10903 New Hampshire Avenue

Bldg #22, Rm 6334

Silver Spring, MD 20993

301-796-0824 (office); 301-796-9883 (fax)

[elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov)

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/s/  
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ELIZABETH G THOMPSON  
01/28/2014



## ELECTRONIC MAIL CORRESPONDENCE: INFORMATION REQUEST/ADVICE

**Date:** January 14, 2014

**To:** Elliott Berger, Ph.D.  
Sr. Vice President, Regulatory Affairs, BioCryst Pharmaceuticals, Inc.

**From:** Elizabeth Thompson, MS  
Chief, Project Management Staff, DAVP

**NDA/Drug:** NDA 206426 (Peramivir)

**Subject:** Pending NDA information request

---

Reference is made to NDA 206426. The Division has the following information requests.

### Clinical Virology

1. It appears the LLOQ value of your TCID<sub>50</sub> assay is different between the studies sponsored by Shionogi. For example, for study 0815T0631 the LLOQ value is <0.8 log<sub>10</sub> while for study 0722T0621 the LLOQ value is <1.102 log<sub>10</sub>. Please clarify the difference. Were different assays used?
2. The LOD values for [REDACTED]<sup>(b) (4)</sup> RT-PCR assays were provided as Ct values (e.g. RPT-VAL034-Reproducibility-FNL). These values should be provided as 'copies/mL'. For clarity, please provide the LOD/LLOQ values for each TCID<sub>50</sub> assay, real-time RT-PCR assay, and genotypic assay that were used by both [REDACTED]<sup>(b) (4)</sup> and Shionogi. The values for the PCR assays should be provided as 'copies/mL'. Additionally, please provide your definition for 'LOD'.
3. Please identify all of the RAT assays that were used in your Clinical studies. If this information was included with your NDA submission, please identify the file. Additionally, please provide the performance characteristics of these assays if not included.

### Nonclinical

1. Please refer to the following nonclinical modules: Toxicology (Module 2.6.1, pages 1-10), Nonclinical PK/ADME (Module 2.6.5, pages 1-26), and Secondary and Safety Pharmacology (Module 2.6.3, pages 11-12). Please provide related IND submission number and date next to the studies in the respective table listing in these Modules.

Please feel free to contact me at 301-796-0824 if you have any questions regarding the contents of this correspondence.

*{See appended electronic signature page}*

---

Elizabeth Thompson, M.S.  
LCDR, USPHS  
Chief, Project Management Staff  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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ELIZABETH G THOMPSON  
01/14/2014

**From:** Thompson, Elizabeth  
**To:** "[Berger, Elliott](#)"  
**Cc:** [McMillan, Nicole](#); [Wileman, Martin](#); [Taylor, Ray](#); [Collis, Phil](#); [Jenna Elder](#); [Sheridan, Bill](#)  
**Subject:** RE: NDA 206426 RAPIVAB (Peramivir) - Response to 02 Jan 2014 Email Request  
**Date:** Friday, January 03, 2014 12:07:00 PM

---

Elliott-

After a quick review of your response, the clinical virologist has a clarification question.

For question 1 you propose:

1. To add in the time to resolution?
2. Format the dataset to visually identify fields as dates and times?

If this is correct, DAVP agrees to your proposal to update and resubmit datasets with these changes

For question 2: DAVP agrees to your proposal to provide RT-PCR results from studies BCX1812-301 and 303 in vp/mL

---

**From:** Berger, Elliott [mailto:[eberger@BIOCRYST.com](mailto:eberger@BIOCRYST.com)]  
**Sent:** Friday, January 03, 2014 11:27 AM  
**To:** Thompson, Elizabeth  
**Cc:** McMillan, Nicole; Wileman, Martin; Taylor, Ray; Collis, Phil; Jenna Elder; Sheridan, Bill  
**Subject:** NDA 206426 RAPIVAB (Peramivir) - Response to 02 Jan 2014 Email Request

Dear Beth,

The following is the response to the email you sent yesterday regarding virology datasets. If the responses are not clear we suggest a brief telecon with the Clinical Virology team to ensure that any new or updated information to be provided will meet their needs.

#### **FDA Comment 1**

In your virology datasets (gpvdata), there appears to be errors in the reporting for 'FRSTDSDT', 'FRSTDSTM', 'LASTDSDT', 'LASTDSTM', 'RESDT', and 'RESTM' as these values are different from those in the clinical dataset. For example, in the dataset for study 0722T0621, subject ID 0722T0621.AA1.061-3, these columns read: '17523', '59400', '17523', '59400', '17531', and '31200', respectively. Please submit revised datasets with the dates/times reported in the same format as in the clinical data sets (e.g., the data of resolution and time to resolution for subject ID 0722T0621.AA1.061-3 is '12/31/2007' and '184.16666667', respectively, in dataset ADTTE).

#### **BioCryst Response**

The virology dataset (GPVDATA) contains the same underlying data values for date of first dose (FRSTDSDT) and date of resolution (RESDT) as the ADTTE dataset has (STARTDT, ADT, respectively); these fields are SASDate fields. The only difference is the ADaM dataset ADTTE requires the date field to be formatted (current display is date9.) whereas the legacy dataset has no such requirement. The same is true for the other date fields in GPVDATA

(LASTDSDT and ISODATE) and time fields (FRSTDSTM, LASTDSTM, RESTM: These are SAS time fields, but are not formatted to time5.). The ADTTE dataset includes AVAL which is time to resolution, rather than RESTM which is time of resolution (the time of day resolution occurred on the date of resolution) . We can add a time to resolution in GPVDATA, but, as this field was not specified in the previous correspondence, it was not included in the current version of the GPVDATA dataset. We can also provide formats to the GPVDATA dataset to visually identify the fields as dates and times. **Please advise if you would like BioCryst to update and resubmit the datasets with these changes.**

Please note that there are subtle differences in definitions of certain variables used in the construction of the GPVDATA dataset and the ADSL datasets. These differences are noted in the data definition tables and in the differences in naming (INFSEAS in GPVDATA vs FLUSEAS in ADSL, for example). Additionally, the resolution date used is the date of resolution of the primary endpoint for a given study rather than the primary endpoint used in the NDA (ADTTE.PARAMCD='TFRSTAL').

### **FDA Comment 2**

Additionally, for all studies where viral load was evaluated by quantitative RT-PCR, please report the data as 'copies/mL' instead of the Ct values.

### **BioCryst Response**

Viral load was evaluated by quantitative RT-PCR only in studies BCX1812-212, 301 and 303. Our virology central lab, (b) (4), started to implement conversion of Cycle Time (Ct) to virus particles per mL (vp/mL) around the time of initiation studies BCX1812-301 and 303 by inclusion of vp/mL standard curves during sample analysis for these studies. This was not a part of their procedures during conduct of study BCX1812-212. We are able to provide vp/mL values for data from studies BCX1812-301 and 303 but not BXC1812-212. **Please advise if you would like BioCryst to provide the RT-PCR results from studies BCX1812-301 and 303 in virus particles per mL (vp/mL).**

Best regards,

Elliott

**Elliott T Berger, Ph.D.**  
**Sr. Vice President, Regulatory Affairs**  
**BioCryst Pharmaceuticals, Inc.**  
**4505 Emperor Blvd. Suite 200**  
**Durham NC 27703**  
**Phone (919) 859-7919**  
**Cell (b) (4)**  
**FAX (919) 859-1316**  
**[eberger@biocryst.com](mailto:eberger@biocryst.com)**

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/s/  
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ELIZABETH G THOMPSON  
01/03/2014

**From:** [Thompson, Elizabeth](#)  
**To:** ["Berger, Elliott"](#)  
**Cc:** [Thompson, Elizabeth](#)  
**Subject:** NDA 206426: pending NDA information request  
**Date:** Thursday, January 02, 2014 11:39:44 AM  
**Importance:** High

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Dr. Berger-

We have an information request from our clinical virology team:

In your virology datasets (gpvdata), there appears to be errors in the reporting for 'FRSTDSDT', 'FRSTDSTM', 'LASTDSDT', 'LASTDSTM', 'RESDT', and 'RESTM' as these values are different from those in the clinical dataset. For example, in the dataset for study 0722T0621, subject ID 0722T0621.AA1.061-3, these columns read: '17523', '59400', '17523', '59400', '17531', and '31200', respectively. Please submit revised datasets with the dates/times reported in the same format as in the clinical data sets (e.g., the data of resolution and time to resolution for subject ID 0722T0621.AA1.061-3 is '12/31/2007' and '184.16666667', respectively, in dataset ADTTE).

Additionally, for all studies where viral load was evaluated by quantitative RT-PCR, please report the data as 'copies/mL' instead of the Ct values.

Please let me know if you have any questions regarding this request. Please submit this information by January 17, 2014.

Regards,

*Beth*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Chief, Project Management Staff  
FDA/CDER/OND/DAVP  
10903 New Hampshire Avenue  
Bldg #22, Rm 6334  
Silver Spring, MD 20993  
301-796-0824 (office); 301-796-9883 (fax)  
[elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov)

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/s/  
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ELIZABETH G THOMPSON  
01/02/2014



NDA 206426

**NDA ACKNOWLEDGMENT**

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

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: Rapivab (peramivir) solution for IV infusion, 200 mg (20 mL) vials

Date of Application: December 19, 2013

Date of Receipt: December 23, 2013

Our Reference Number: NDA 206426

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 February 21, 2014, 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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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 Antiviral Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful 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](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824.

Sincerely,

*{See appended electronic signature page}*

Elizabeth Thompson, M.S.  
LCDR, U.S. Public Health Service  
Chief, Project Management Staff  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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ELIZABETH G THOMPSON  
12/27/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 69038

MEETING MINUTES

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard  
Nottingham Hall, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Peramivir Injection for Intravenous Administration.

We also refer to the teleconference between representatives of your firm and the FDA on July 11, 2013. The purpose of the teleconference was to discuss the proposed pediatric development plan.

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

If you have any questions, please contact Elizabeth Thompson, M.S., Chief, Project Management Staff, at (301) 796-0824 or via email at [elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

IND 69038  
OAP/DAVP  
Meeting Minutes  
Type C: Other (pediatric)

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type C  
**Meeting Category:** Other (pediatric development)

**Meeting Date and Time:** July 11, 2013; 10:00 AM - 11:00 AM Eastern Time  
**Meeting Location:** Teleconference

**Application Number:** IND 69038  
**Product Name:** Peramivir Injection for Intravenous Administration.  
**Indication:** **Treatment of acute uncomplicated influenza**  
**Sponsor/Applicant Name:** BioCryst Pharmaceuticals, Inc.

### FDA ATTENDEES

#### OND/OAP

Barbara Styrt, Medical Officer

#### OND/OAP/DAVP

Elizabeth Thompson, Chief, Project Management Staff

Debbie Birnkrant, Division Director

Jeff Murray, Deputy Division Director

Wendy Carter, Medical Officer

Yodit Belew, Medical Officer

Tafadzwa Vargas-Kasambira, Medical Officer

Alan Shapiro, Medical Officer

Kim Struble, Medical Officer Team Leader

Kuei-Meng Wu, Nonclinical Reviewer

Peyton Myers, Acting Nonclinical Team Leader

#### OTS/OCP/DCP4

Vikram Arya, Clinical Pharmacology Reviewer

Jeff Florian, Pharmacometrics Reviewer

Islam Younis, Clinical Pharmacology Team Leader

### SPONSOR ATTENDEES

#### BioCryst Pharmaceuticals, Inc.

Elliott Berger, Senior Vice President, Regulatory Affairs

William Sheridan, Senior Vice President and Chief Medical Officer

Phil Collis, Vice President Clinical Development

Nicole McMillan, Manager, Regulatory Affairs

Ray Taylor, Product leader

(b) (4) Statistics Consultant

IND 69038  
OAP/DAVP  
Meeting Minutes  
Type C: Other (pediatric)



## **1.0 BACKGROUND**

On May 31, 2013, the Division received a Type C meeting request/meeting package to discuss the proposed pediatric development plan. The Division granted a teleconference to be held on July 11, 2013.

The Division sent an information request on July 1, 2013 and preliminary meeting comments on July 10, 2013 (electronic correspondence). BioCryst provided a response to the July 1, 2013 information request on July 3, 2013.

## **2.0 DISCUSSION**

BioCryst noted that the two main points for discussion (which came from preliminary comments sent by the Division on July 10, 2013) were study design and targeting exposure to match the systemic exposures at the 600 mg adult dose.

(b) (4)



The Division asked if BioCryst had access to the full raw datasets from the Shionogi pediatric study, as this would help further determine how many additional US pediatric subjects will need to be enrolled in the various age groups for an adequate safety database, BioCryst acknowledged that they have full raw datasets available from the Shionogi pediatric trial (b) (4)

(b) (4) BioCryst asked the Division if they had an approximate number of how many subjects would be needed for safety. The Division noted that there are approximately (b) (4) subjects in their safety database already, and that there may be adequate data available for a certain age/weight range; (b) (4)

(b) (4) The Division stated that once the additional information is submitted for review, a more precise determination of target numbers needed across the various age groups could be provided.

(b) (4)

### 3.0 ACTION ITEMS

- (b) (4)
- 

### 4.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts associated with this teleconference.

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DEBRA B BIRNKRANT  
07/24/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 69038

MEETING MINUTES

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard  
Nottingham Hall, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Peramivir Injection for Intravenous Administration.

We also refer to the meeting between representatives of your firm and the FDA on June 28, 2013. The purpose of the meeting was to obtain agreement and discuss the content of the planned NDA submission.

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

If you have any questions, please contact Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824 or via email at [elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** preNDA

**Meeting Date and Time:** June 28, 2013; 11:00 AM - 12:30 AM Eastern Time  
**Meeting Location:** FDA/White Oak; Bldg 22, Room 1313

**Application Number:** IND 69038  
**Product Name:** Peramivir Injection for Intravenous Administration.  
**Indication:** **Treatment of acute uncomplicated influenza**  
**Sponsor/Applicant Name:** BioCryst Pharmaceuticals, Inc.

**FDA ATTENDEES**

OND/OAP

Dave Roeder, Associate Director, Regulatory Affairs  
Ed Cox, Office Director  
Barbara Styrt, Medical Officer

OND/OAP/DAVP

Karen Winestock, Chief, Project Management Staff  
Elizabeth Thompson, Senior Regulatory Project Manager  
Debbie Birnkrant, Division Director  
Jeff Murray, Deputy Division Director  
Wendy Carter, Medical Officer  
Kim Struble, Medical Officer Team Leader  
Kuei-Meng Wu, Nonclinical Reviewer  
Takashi Komatsu, Clinical Virology Reviewer  
Jules O'Rear, Clinical Virology Team Leader  
Kendall Marcus, Deputy Director for Safety

ONDQA

George Lunn, CMC Reviewer

OPS/NDMS

Steve Langille, Sterility Reviewer

OTS/OCP/DCP4

Vikram Arya, Clinical Pharmacology Reviewer  
Jeff Florian, Pharmacometrics Reviewer  
Islam Younis, Clinical Pharmacology Team Leader

IND 69038  
OAP/DAVP  
Meeting Minutes  
Type B: preNDA

OTS/OB/DB4

Tom Hammerstrom, Statistics Reviewer  
Greg Soon, Statistics Team Leader

OSE

Morgan Walker  
Jamie Wilkins Parker  
George Neyarapally  
Fred Sorbello

Office of Strategic Programs

Kimberly Taylor

Eastern Research Group

(b) (4)

**SPONSOR ATTENDEES**

BioCryst Pharmaceuticals, Inc.

Elliott Berger, Senior Vice President, Regulatory Affairs  
Jon Stonehouse, President and Chief Executive Officer  
William Sheridan, Senior Vice President and Chief Medical Officer  
Phil Collis, Vice President Clinical Development  
Nicole McMillan, Manager, Regulatory Affairs  
Ray Taylor, Product leader

(b) (4)

Statistics Consultant

Yarya El-Kattan, Executive Director, CMC

(b) (4)

## 1.0 BACKGROUND

On April 26, 2013, the Division received a Type B Pre-NDA meeting request. DAVP granted a face-to-face meeting to be held on June 28, 2013. A background package was received on May 31, 2013. The purpose of this meeting is to discuss and obtain agreement on the content of the planned NDA submission.

BioCryst Pharmaceuticals, Inc., is seeking an indication for Peramivir injection for intravenous use, for the treatment of acute uncomplicated influenza in patients 18 years and older. A Type C meeting was held on April 2, 2013, where the Division and BioCryst agreed that the Shionogi Study 0722T0621, in combination with pooled supporting data from BCX1812-211 and BCX1812-311, could be submitted to support an NDA (refer to FDA meeting minutes dated April 26, 2013).

## 2.0 DISCUSSION

The FDA noted that the NDA submission would be reviewed under the PDUFA V NME Program, which means that the application needs to be complete at the time of submission; therefore, one of the objectives of this meeting is to agree on what information is expected at the time of submission, and what information, if any, could be submitted as a minor amendment during the review. The FDA mentioned that a REMS is not anticipated for this application. In addition, a comprehensive list of clinical sites and manufacturing facilities should be provided at the time of application submission. The FDA stated they are working with the Office of Compliance and the Division of Scientific Investigations to determine if further clinical sites need to be investigated, as inspections were done under the EUA.

### CLINICAL

#### **Integrated Summaries of Efficacy (ISE) and Safety (ISS)**

**Question 1: Does the Division agree that the proposed content of the ISE and ISS provide adequate information to support NDA review?**

FDA Response to Question 1: Yes, the proposed content should be adequate to allow for NDA review; however, we request that you also submit a complete clinical study report for Trial 301 in the NDA. Additionally, because Trial 0815T0631 compares peramivir to oseltamivir in subjects infected with acute uncomplicated influenza, we recommend that this trial not be pooled with the placebo controlled trials for an overall analysis. Therefore, your ISE analyses would include analyses of the individual trials and an overall analysis of the pooled placebo-controlled trials.

*Meeting Discussion: No further discussion occurred.*

#### **Case Report Forms (CRFs) to be Included in the NDA Submission**

**Question 2: Does the Division agree with the proposal for inclusion of CRFs in the NDA?**

FDA Response to Question 2: Yes, we agree with your proposal for CRFs. Please also be aware of the need for complete, well documented narratives for required regulatory reporting of safety events and clearly hyperlinking the documents from the ISS and other pertinent study reports.

We request that narratives for deaths, nonfatal SAEs, AEs leading to discontinuation, and Grade 3/4 clinical Adverse Events considered at least possibly related to study drug be submitted. Additional individual narratives may be requested based on review of the safety data.

*Meeting Discussion: No further discussion occurred.*

**Waiver of Financial Disclosure Information for Shionogi Studies**

**Question 3: Does the Division agree that Financial Disclosure information will not be required for Shionogi Study 0722T0621?**

FDA Response to Question 3: No, despite the fact that Study 0722T0621 was not conducted under IND, you will be required to submit Financial Disclosure information for this study. This will also be reviewed as part of the filing review and is a necessary component for your NDA. Please see the following link for additional details regarding the Guidance regarding Financial Disclosure information:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf>

Reporting to the FDA is the responsibility of the Applicant. As stated in Question E.3 in the Guidance, an IND/IDE sponsor is responsible for collecting financial information from both foreign and domestic clinical investigators. If a sponsor did not collect this information, for example, because the sponsor conducted a foreign study that was not conducted under an IND/IDE and was not originally intended for submission to the FDA, the applicant is expected to contact the sponsor and/or clinical investigators to retrospectively obtain the financial disclosure information. See Questions F.2 and F.3 for additional information.

*Meeting Discussion: No further discussion occurred.*

**BioCryst Approach to Establishing Dosage Recommendations**

**Question 4: Does the Division agree with the proposed analyses to be conducted in support of dosage selection?**

FDA Response to Question 4: The proposed dose rationale seems reasonable. Please conduct the following additional analysis:

- The “Clinical Pharmacokinetics” sub section of the Dosing Rationale section suggests that the systemic clearance is higher in US subjects as compared with Japanese subjects, however, systemic exposure data from both the populations was not provided. As part of your NDA submission, please include a comparison of single

dose peramivir intravenous exposures for 300 mg and 600 mg in IV in both Japanese subjects and US subjects.

- We recommend performing exploratory exposure-response analyses for the following exposure metrics (AUC, C<sub>min</sub>, C<sub>max</sub>) versus time to alleviation of symptoms, time to resolution of fever, change in viral titer, and time to resumption of usual activities as well as any already planned exposure-response analyses. These analyses should highlight any identified relationship between peramivir exposure and the response metric and discuss whether any differences are predicted between exposures for peramivir 300 mg IV or 600 mg IV in US subjects.
- Please consider performing exploratory exposure-response safety analyses between peramivir exposures and common adverse events observed during treatment.
- Please submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:
  - a. All datasets used for population pharmacokinetic and pharmacokinetic/pharmacodynamic model development and validation should be submitted as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any datapoints and/or subjects who have been excluded from the analysis should be flagged and maintained in the datasets.
  - b. Model codes or control streams and output listings should be provided for all major model building steps, e.g. base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g. myfile\_ctl.txt, myfile\_out.txt, myfile\_sas.txt, myfile\_R.txt).

*Meeting Discussion: BioCryst presented slides summarizing the number of subjects administered peramivir with available sparse and intensive PK data, the peramivir dose that was administered, and whether the subjects were healthy volunteers or from the infected patient studies (hospitalized or uncomplicated). In Japanese subjects, they noted that body weight rather than race was correlated with exposure differences. However, BioCryst stated they would do further analyses to see if race was independently associated with exposure differences. BioCryst also noted that other characteristics, such as weight and serum creatinine, would be evaluated and submitted to the Division.*

*The Division acknowledged that body weight was previously identified as a significant covariate for peramivir exposure. However, the Division noted that the approved dose in Japan was 300 mg and that the differences in body weight between Japanese and US subjects would only amount to a 30% difference in peramivir exposure. The Division explained that the difference in body weight alone may not be sufficient justification for the 600 mg dose, and that the requested exploratory exposure-response analyses may assist in identify response metrics where the 600 mg dose offered benefit compared to the 300 mg dose.*

*BioCryst acknowledged the Division's request for exposure-response safety analyses for adverse events and proposed performing the analysis in a two-step approach. Initially, BioCryst would evaluate differences in the adverse event profile based on peramivir dose. If there were no apparent differences in adverse event rates with higher doses, no subsequent exposure-response safety analyses would be performed. However, if a dose-response relationship was observed for safety adverse event, BioCryst would consider exploratory exposure-response analyses for those safety events. The Division agreed with BioCryst's proposed exposure-response safety analysis plan.*

**Target Product Profile (Draft Labeling Concepts)**

**Question 5: BioCryst is interested in any feedback from the Division on the revised TPP?**

FDA Response to Question 5: We appreciate you providing the updated TPP. Your general proposals are appropriate with the expectation that some specific language and some proposals will change during the NDA review process, in particular for Trial 301. We agree that Trial 301 should be specifically described with a statement about the efficacy results showing no difference in the endpoint for the peramivir group compared to placebo. (b) (4)

The "draft labeling statements and concepts" document submitted with the Type C meeting package in March 2013 included dosing recommendations of peramivir for patients with varying degrees of renal impairment. However, the target product profile submitted with the pre-NDA meeting package indicates that (b) (4)

Please explain this discrepancy.

Please be aware that the Pregnancy and Lactation Labeling Rule may affect some formatting of the final label. Information regarding PLLR is available at:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

*Meeting Discussion: BioCryst commented on the target product profile discrepancy regarding dosing recommendations for subjects with renal impairment (March 2013 Type C meeting package versus the May 2013 preNDA meeting package). The sponsor stated the difference was due to the (b) (4) desire to simplify product labeling. The FDA requested BioCryst provide their rationale for this change in the NDA submission for review.*

**Virology Information for Inclusion in the NDA**

**Question 6: Does the Division agree with BioCryst's plan for discussion and agreement of the virology and resistance information to be included in the NDA?**

FDA Response to Question 6: This is being addressed as a separate meeting with separate comments/responses.

*Meeting Discussion: BioCryst referred to the teleconference on June 25, 2013 and the additional virology information provided by email to the FDA on June 26, 2013 for further discussion at the preNDA meeting (virology line listing and proposal for further sequencing analysis). BioCryst noted that their proposal was to include an additional 300 samples (75 subjects) of which 44 would be from Study 311 and the rest would come from Study 211 (300 mg and placebo). The FDA stated that they agreed with BioCryst's proposal to include an additional 75 subjects in the proposed NDA submission, however, the FDA wanted to counter propose the subjects to be selected for sequencing. The FDA explained that in order to maximize the data we can get from 75 subjects, we prioritized the list based on a) those subjects who were shedding virus the longest, b) capturing different influenza seasons, and c) capturing all of the influenza type/subtypes. The FDA stated they would provide the subject identification numbers and rationale for the algorithm used for their proposed 75 subjects, as well as a backup plan to choose additional subjects if any of those samples were not available. The sponsor agreed.*

*The FDA also requested that BioCryst store all of their samples as additional sequencing will be requested (under a Post Marketing Requirement/Commitment) if the drug is approved. The sponsor agreed.*

#### **Pediatric Plan**

**Question 7: Does the Division agree with BioCryst's plan for discussion and agreement of the planned pediatric program?**

FDA Response to Question 7: This is being addressed as a separate meeting with separate comments/responses.

*Meeting Discussion: No further discussion occurred.*

#### **Requirement for FDA-Approved Patient Labeling (Patient Information and Instructions for Use)**

**Question 8: Does the Division agree that FDA-Approved Patient Labeling will not be required?**

FDA Response to Question 8: We agree Patient Labeling will not be required because this is an intravenous product not for individual patient self-administration.

*Meeting Discussion: No further discussion occurred.*

#### **Requirement for 120-Day Safety Update Report**

**Question 9: Does the Division agree that the requirement for a 120-day Safety Update Report can be waived?**

FDA Response to Question 9: We agree the 120-Day Safety Update report can be waived because there are no ongoing clinical trials with peramivir.

*Meeting Discussion: No further discussion occurred.*

**Plan for Post-Marketing Risk Assessment**

**Question 10: Does the Division agree with BioCryst's proposed post-marketing risk assessment plan?**

FDA Response to Question 10: Your plan for routine post-marketing surveillance is acceptable; however, if a significant safety issue is identified during review of the NDA this recommendation could change.

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with peramivir following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.

*Meeting Discussion: No further discussion occurred.*

**NONCLINICAL**

**Question 11: Does the Division agree with BioCryst's plan for providing nonclinical information in the NDA?**

FDA Response to Question 11: Yes we agree with the plan for submission of the nonclinical data.

*Meeting Discussion: No further discussion occurred.*

**CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)**

**Specifications for Active Pharmaceutical Ingredient (API)**

**Question 12: Does the Division agree that the proposed specifications are appropriate for the release of the API?**

FDA Response to Question 12: The drug substance specification is an NDA review issue. However, you appear to be using the correct tests and the limits seem generally appropriate. At the time of the NDA submission please provide a justification for the (b) (4) % permitted variation in the HPLC retention time, which seems rather wide.

*Meeting Discussion: No further discussion occurred.*

**Specifications for the Drug Product**

**Question 13: Does the Division agree that the proposed specifications are appropriate for the release of the commercial drug product?**

FDA Response to Question 13: The drug product specification is an NDA review issue. However, you appear to be using the correct tests and the limits seem generally appropriate. Is the IR spectrum of an aqueous solution really a specific identity test?

Please note that we expect the product to confirm to the regulatory specification at release and throughout the labeled shelf-life. Additional release tests and tighter acceptance criteria on release are acceptable.

At the time of the NDA submission please address the following points:

Provide a justification for the (b) (4) % permitted variation in the HPLC retention time, which seems rather wide.

Consider changing the assay acceptance criterion to (b) (4) %.

Consider reducing the total degradant acceptance criterion from (b) (4) %.

Consider controlling osmolality by means of a release test or an in-process control.

Provide a report discussing the possibility of single chiral center inversion at each center and whether diastereomers so formed may be detected by the HPLC method.

Provide a report on the extractables and leachables testing that you have performed (we note that we have previously discussed the nature of this testing with you).

*Meeting Discussion: The sponsor referred to slide 6 regarding the IR identity test. A sample of the aqueous solution (b) (4) (b) (4) Therefore the IR test is a specific identity test. In Slides 8-11 the sponsor described the likelihood of the various (b) (4) (b) (4) will be detected by the HPLC method. In addition the sponsor noted that these points had been previously discussed in serial numbers 0044, 0055, and 0058 to IND 69,038. For both issues FDA agreed with the conclusions of the sponsor.*

**API Batches to Support Commercial Drug Product Stability**

**Question 14: Does the Division agree that the drug product manufactured from the batches described above will support an NDA filing with both sources of API?**

FDA Response to Question 14: Yes. We understand that the NDA will include 60 month data on peramivir injection solution. This will include 3 drug product batches made from each of the API

sources, with at least one from each site representing commercial scale production of the drug product.

*Meeting Discussion: No further discussion occurred.*

**Validation of Analytical method to Include Impurity at RRT**

**Question 15: Does the Division agree that no additional validation of the analytical method to include Impurity <sup>(b)</sup><sub>(4)</sub> in the validation report is to be conducted?**

FDA Response to Question 15: You should conduct a limited revalidation and include the results as an addendum to the original validation report. In this revalidation you should evaluate the specificity of the method and, if an authentic sample is available, you should evaluate linearity, accuracy, and precision for Impurity <sup>(b)</sup><sub>(4)</sub>.

*Meeting Discussion: No further discussion occurred.*

**Process Qualification for API**

**Question 16: Does the Division agree that the validation conducted at both suppliers is adequate and no further process qualification is needed for the API?**

FDA Response to Question 16: FDA does not approve process validation plan, protocols, or specific batches used in process validation studies. FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection. Process validation for drug substances is also enforceable under the FD&C Statute 501(a)(2)(b).

It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process performed at each API manufacturing site is capable of consistently delivering quality product. The number of lots included in a process validation study is not a performance criteria.

It is important to note that process validation involves a series of activities such as process design, process qualification and continuous process verification taking place over the lifecycle of the product and process. Prior to marketed product distribution, it is necessary for firms to justify and confirm earlier process design and development work for their proposed scale up to commercial scale. Firms need to have justification for their process parameters, component characteristics, and how these relate to the final product attributes, demonstrated at commercial scale. Process validation also includes routine commercial production in that firms must ensure that the process remains in a state of control and consistently produces high quality product.

For additional information, please refer to "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.

In addition, Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf>

*Meeting Discussion: No further discussion occurred.*

#### OTHER MEETING DISCUSSION

- BioCryst referred to the preliminary meeting comments for the virology teleconference held on June 24, 2013 and the issue regarding the provision of date and time in the virology datasets for the “onset of symptoms” variable. BioCryst provided a question to the FDA for statistical review (email dated June 26, 2013), noting that the date/time for “onset of symptoms” was captured in a 12 hour block, and asked if the FDA had a response. The FDA noted that it was appropriate to submit the date/time as a 12 hour block.
- BioCryst thanked the FDA for reviewing the sample datasets and providing preliminary comments. BioCryst noted that in patient diaries some of the fields were missing data. The datasets originally were not in SDTM, but were re-mapped, therefore they wanted to know the FDA’s preference for providing the missing data (should it have a place holder or be left blank). The FDA was agreeable to variables missing data that could not be imputed to be left blank (in SAS blanks in numeric fields may be represented by a ‘dot’). BioCryst asked the FDA their preference for missing for a different reason/data not captured (should they create an additional field or not submit the field; for example completion dates and visit dates). The FDA stated agreement to use the imputed variables when dates were known based on other captured variables and BioCryst agreed to describe the algorithm used to impute the data. BioCryst noted that for some screening failures they were unable to obtain demographic data for the datasets and wanted to know how to submit this information for instances where it is available. The FDA stated to submit the data in a separate listing for analysis. BioCryst also recognized that some data from Japanese studies did not translate well within several datasets and from the CRFs. BioCryst stated they would provide the SAS translation and would not submit Japanese characters. BioCryst also noted that all CRFs from Study 621 would be submitted in English.
- BioCryst noted that a request for tradename was submitted in 2010, and wanted to know if they needed to resubmit. FDA noted that tradenames reviewed under INDs are tentative approved and that these requests still need to be submitted under the NDA for final review.

- The FDA summarized the information expected at the time of submission under the PDUFA V NME Program requirements for a complete, reviewable application (efficacy and safety data outlined in the preNDA meeting package and previous correspondences, exposure response analysis, updated resistance plan, tradename request, and PREA waiver/deferral requests). The FDA noted that they would also like the complete study report for Study 301, and that datasets would not be required nor reviewed for efficacy. BioCryst noted that the datasets would be submitted, as they will provide these for safety. BioCryst will provide the virology data as described in their May 31, 2013 background package and the Agency's July 2, 2013 meeting minutes, with the exception that BioCryst agreed to the Agency's proposal for the 75 subjects to be analyzed.

### ADDITIONAL COMMENTS

#### *Chemistry, Manufacturing and Controls*

1. Please make sure that the NDA contains a Methods Validation package that contains a list of samples that can be supplied to an FDA laboratory upon request as well as links to the appropriate sections of the NDA.

### **3.0 ACTION ITEMS**

- The FDA will provide virology line listings and subject id's for the additional 75 subjects to be sequenced (this was provided to BioCryst in an advice/information request dated July 1, 2013)

### **4.0 ATTACHMENTS AND HANDOUTS**

The attached slides were shown by the sponsor during the meeting.

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DEBRA B BIRNKRANT  
07/10/2013



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type C  
**Meeting Category:** Other (Clinical Virology)

**Meeting Date and Time:** June 25, 2013; 9:30 AM - 11:00 AM Eastern Time  
**Meeting Location:** Teleconference

**Application Number:** IND 69038  
**Product Name:** Peramivir Injection for Intravenous Administration.  
**Indication:** **Treatment of acute uncomplicated influenza**  
**Sponsor/Applicant Name:** BioCryst Pharmaceuticals, Inc.

**FDA ATTENDEES**

OND/OAP/DAVP

Elizabeth Thompson, Senior Regulatory Project Manager  
Debbie Birnkrant, Division Director  
Jeff Murray, Deputy Division Director  
Wendy Carter, Medical Officer  
Kim Struble, Medical Officer Team Leader  
Takashi Komatsu, Clinical Virology Reviewer  
Jules O'Rear, Clinical Virology Team Leader

**SPONSOR ATTENDEES**

BioCryst Pharmaceuticals, Inc.

Elliott Berger, Senior Vice President, Regulatory Affairs  
Jon Stonehouse, President and Chief Executive Officer  
William Sheridan, Senior Vice President and Chief Medical Officer  
Phil Collis, Vice President Clinical Development  
Nicole McMillan, Manager, Regulatory Affairs  
Ray Taylor, Product leader

(b) (4), Statistics Consultant

(b) (4), Virology Consultant

(b) (4)

## 1.0 BACKGROUND

Reference is made to the sponsor's March 16, 2012 submission which requested a meeting to discuss the virology analysis plan for the Phase 3 studies in support of an NDA. The Division provided comments on May 29, 2012. BioCryst informed the Division that they would like to postpone the meeting until September 2012 to allow time to complete the Phase 2 virology reports and provide them to the Division for review. The Division provided additional comments on June 14, 2012 and requested that the meeting be cancelled until the Division has had time to review the Phase 2 virology data. BioCryst submitted a meeting cancellation request on June 27, 2012. BioCryst submitted a Type C meeting request/meeting package on May 31, 2013 to discuss the outstanding virology issues.

## 2.0 DISCUSSION

Introductions were made. The Division opened the discussion by thanking the sponsor for providing information outlining the additional subjects to be selected for sequencing.

### **Virology Analysis Plan for BioCryst Studies 301 and 303**

The virology analysis plan for studies BCX1812-301 and BCX1812-303 identifies three populations that will be selected for genotypic analysis. Direct genotyping of HA and NA will be performed by population sequencing of viruses under the following circumstances:

- a. Subjects with virus isolates that have an  $IC_{50} > 3x$  median baseline  $IC_{50}$
- b. Subjects with virus detectable at Day 5 by culture or PCR with  $CT < 32$
- c. Up to 20% random sample of subjects with  $IC_{50} < 3x$  median baseline  $IC_{50}$  with last detectable sample PCR  $CT < 32$

BioCryst believes that these populations address the Division's previous concerns that genotypic analyses were triggered solely based on phenotypic data.

### **Question 1:**

#### **Does the Division agree with this proposal?**

#### FDA Response to Question 1:

We have previously mentioned several concerns with using phenotypic data to identify samples for screening in your studies. The utility of the phenotypic analyses as a screen for resistance is suspect given the selection bias of the assay for wildtype virus when viruses in subject samples are amplified in cell culture prior to testing. Additionally, the assay itself can produce a WT result for a mixed population (Wetherall et al., 2003). Furthermore, a neuraminidase assay is not expected to detect resistance substitutions developing in HA.

Subjects will have enrolled in the studies at different times in the infection cycle. In previously submitted data, the NA H275Y amino acid substitution has been observed as early as Day 3 in peramivir treated subjects (e.g. studies BCX1812-211 and 0722T0621). Therefore, given the limited resistance data that have been provided, samples from all subjects who are RT-PCR positive at Days 3 and 4, in addition to later time points from subjects who continue to shed

virus, should be genotyped directly without an intervening culture step. Novel substitutions should be assessed for cross-resistance to oseltamivir and zanamivir. We recommend that you conduct a thorough resistance analysis for all of your clinical studies where you still have samples available (including studies BCX1812-201, BCX1812-211, and BCX1812-311).

**Meeting Discussion:**

*BioCryst referred to the preliminary comments for Question 1, in particular to the request for the genotyping at Days 3 and 4. BioCryst stated that this was a new request that would have implications on the timing of the NDA, and therefore wanted to know the rationale for this request. The Division stated that based on review of their recently submitted Phase 2 data, resistance to peramivir can be selected as early as Day 3. The data that have been submitted to date have relied on phenotypic analysis to trigger genotypic analysis so we do not have a clear understanding of all of the resistance pathways. The Division recommended starting with subjects that shed longest, but recent data indicate that selection for resistance can develop early. The recent recommendation was made to ensure a thorough resistance analysis is conducted.*

*BioCryst referred to the sequence Table they provided and noted the number of additional subjects to be selected for sequencing based off of Division comments. BioCryst noted that due to the number of additional samples to be sequenced (approximately 1400 assays) and the availability of the company that would be performing the sequencing, the NDA submission would be delayed by several months. BioCryst asked the Division if there were any alternatives and if it would be possible to submit data during the NDA review cycle. The Division asked if it was necessary to sequence all of the placebo samples from Studies 211 and 311. BioCryst stated they felt this was important to sequence as a comparator to see if the substitution(s) were random. BioCryst asked if the 150 mg samples from Study 211 could be excluded, as it is more than likely that the 600 mg will be marketed. The Division asked to see a proposal for additional sequencing (line-item listing) that included viral load, type/subtype, dose received, and availability of the samples). The Division also recommended that the sponsor include a comment explaining exclusion (e.g., no samples available or viral load too low to sequence). The Division noted that alternative proposals and what information would be available at NDA submission, along with the line-item listings, could be reviewed and discussed at the preNDA meeting to be held Friday, June 28, 2013. BioCryst noted that they will provide as much information as possible, but that analysis were still ongoing. In addition, for Studies 211/311, quantitative RT-PCR was not done. The viral load for these studies was determined by cell culture. The Phase 3 studies were assayed using quantitative RT-PCR. The Division noted that for applications reviewed under "the Program", all information needs to be complete at the time of NDA submission.*

### **Adequacy of Proposed Resistance Evaluation**

#### **Question 2:**

**Does the Division agree that the analyses from the clinical studies outlined herein, together with other sources of data from preclinical studies, independently conducted surveillance studies and post-marketing surveillance studies in Japan, that will be submitted in the NDA will support an adequate evaluation of the potential for resistance development to peramivir?**

FDA Response to Question 2:

Please see our response to question #1 above. We outlined above our recommendations for a thorough resistance analysis; a final evaluation will be a review issue. Additionally, you have not genotyped the HA in any of your Phase 2 studies.

Meeting Discussion:

*Please see discussion under Question 1.*

### **Adequacy of Virology datasets Previously Submitted to IND 69,038**

#### **Question 3:**

**Can the Division confirm that the format of the datasets provided is consistent with the Division's expectation for submission in the NDA?**

FDA Response to Question 3:

The overall format of the datasets is acceptable. However, we have a few additional comments:

- The data in the date/time of start of treatment and end of treatment columns are difficult to interpret. For example, first day of treatment reads "1517166000" for subject 104.001 in study BCX1812-201.
- Please have individual columns for the dates and times in "first day of treatment", "last day of treatment", "onset of symptoms", and "time to resolution". For example, instead of "22DEC07:23:00", please separate to individual columns for the "date" (12/22/07) and "time" (23:00). Also, the data in these columns should be reported in the continuous format.
- It is unclear whether the empty cells indicates no change compared to reference, missing (i.e., deletion), ambiguous, or sequence failure. Please report your data as follows:
  - o Blank = no change compared to reference.
  - o X = ambiguous codon leading to a non-interpretable translation (amino acid could not be called, but nucleotide information was present).
  - o ? = No sequence information due to region not sequenced or sequencing failure.
  - o Dash = missing amino acid compared to reference.

(b) (4)

IND 69038  
OAP/DAVP  
Meeting Minutes  
Type C: Other (clinical virology)

**Meeting Discussion:**

*BioCryst clarified that for “onset of symptoms”, they did not collect date/time, but captured this in a 12 hour block. BioCryst asked how this should be submitted to the Division. The Division asked BioCryst to provide this information in writing so that it could be discussed with the statisticians.*

*BioCryst clarified their understanding of the Division’s third bullet. The Division stated they had the correct understanding. BioCryst asked if the (b)(4) amino acids listed in bullet 4 should be listed separately. The Division noted that these are normally seen in the same cell. BioCryst asked if the recommendation outlined in bullet 4 refers to sequences containing mixture of viruses with different sequences. The Division stated yes and that these data should be reported in decreasing order of frequency. BioCryst stated that they would have to verify that the first amino acid listed is at the highest frequency, and agreed that they could provide the data for sequence mixtures in each cell.*

**DAVP Comment at Recent Type C Meeting Regarding “Unbiased” Resistance Assays**

**Question 4:**

**BioCryst would like further clarification as to any potential source(s) of bias that the Division has in mind that are not addressed by the proposals herein.**

FDA Response to Question 4:

Please see our response to Question #1.

**Meeting Discussion:**

*No further discussion occurred.*

**Location of Virology and Resistance Summary in the NDA (CTD) Submission**

**Question 5:**

**Does the Division agree with the proposed location of the Virology and Resistance Summary?**

FDA Response to Question 5:

The virology and resistance summary should be in section 2.7.2.4 (Special Studies) and the virology study reports and datasets in section 5.3.5.4 (Other studies).

**Meeting Discussion:**

*No further discussion occurred.*

**Additional Clinical Virology Comments:**

1. Please determine the antiviral activity of peramivir against viruses expressing oseltamivir/zanamivir resistance-associated substitutions (see drug labels for oseltamivir and zanamivir).
2. For the post-market surveillance studies in Japan from patients treated with IV peramivir, please provide the selection criteria that were used to trigger resistance analyses. Also, was the HA genotyped?
3. Please include the complete study reports and detailed descriptions of the methodologies for all of your non-clinical virology studies in your NDA submission. Of particular interest are studies of:
  - Mechanism of action
  - Antiviral activity in cell culture and animal models
  - Cytotoxicity
  - Cell culture combination antiviral activity relationships
  - Selection and characterization of resistant virus
  - Cross-resistance with other approved agents for influenza virus
4. In your NDA submission, please identify the RAT assay(s) that were used for each site in studies 0722T0621, BCX1812-211, BCX1812-212, and BCX1812-311 and provide the performance characteristics with geographically and temporally distinct isolates of the key influenza types and subtypes. Additionally, please provide all available information on all of the subjects who were screened in these studies but were excluded due to a negative RAT test.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

- Additional subjects to be sequenced
- Clinical virology data to be provided at time of NDA submission
- How to submit date/time for “onset of symptoms”

### **4.0 ACTION ITEMS**

- BioCryst will provide line listing of virology from Phase 2/3 studies (received via email correspondence on June 26, 2013; officially submitted to IND on June 27, 2013)
- BioCryst will provide information for statisticians to review regarding submitting date/time for “onset of symptoms” (received via email correspondence on June 26, 2013)

### **5.0 ATTACHMENTS AND HANDOUTS**

The attached Table was provided by electronic correspondence prior to the teleconference (A corrected Table of Sequencing Selection, Virology Line Listing for Phase 2/3 Studies, and a Virology Sequencing Proposal was submitted officially to the IND on June 27, 2013).

**BioCryst Pharmaceuticals  
Peramivir Sequencing**

<b>Study</b>	<b>Treatment Group</b>	<b>Subjects Randomized ITTI (N)</b>	<b>Subjects Already Selected for Sequencing</b>	<b>Add'l Subjects to be Selected for Sequencing*</b>	<b>Total Subjects Selected</b>
<b>Study 211</b>	<b>All</b>	<b>318</b>	<b>21</b>	<b>148</b>	<b>169</b>
	150mg	104	9	46	55
	300mg	105	9	37	46
	Placebo	109	3	65	68
<b>Study 311</b>	<b>All</b>	<b>80</b>	<b>0</b>	<b>44</b>	<b>44</b>
	300mg	55	0	29	29
	Placebo	25	0	15	15
<b>Study 201</b>	<b>All</b>	<b>122</b>	<b>30</b>	<b>32</b>	<b>62</b>
	200mg	41	13	10	23
	400mg	40	7	8	15
	OSE	41	10	14	24
<b>Study 301</b>	<b>All</b>	<b>338</b>	<b>90</b>	<b>105</b>	<b>195</b>
	600mg	222	62	64	126
	Placebo	116	28	41	69
<b>Study 303</b>	<b>All</b>	<b>127</b>	<b>16</b>	<b>28</b>	<b>44</b>
	600mg QD	70	12	15	27
	300mg BID	57	4	13	17
<b>Totals</b>		<b>985</b>	<b>157</b>	<b>357</b>	<b>514</b>

\* Based on the FDA Comments provided to BioCryst on June 20, 2013

Note: As specified in the current Virology Analysis Plan, pre-planned genotyping for Phase 3 studies includes both NA and HA and for Phase 2 studies includes only NA .

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DEBRA B BIRNKRANT  
07/02/2013



IND 069038

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

BioCryst Pharmaceuticals, Inc.  
4505 Emperor Boulevard  
Nottingham Hall, Suite 200  
Durham, North Carolina 27703

ATTENTION: Elliott Berger, Ph.D.  
Senior Vice President, Regulatory Affairs

Dear Dr. Berger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Peramivir Injection, 10 mg/mL.

We also refer to your September 8, 2010, correspondence, received September 8, 2010, requesting review of your proposed proprietary name, Rapivab. We have completed our review of the proposed proprietary name, Rapivab and have concluded that it is acceptable.

A request for proprietary name review for Rapivab should be submitted once the NDA is submitted.

If any of the proposed product characteristics as stated in your September 8, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

IND 069038

Page 2

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Elizabeth Thompson at (301) 796-0824.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
03/04/2011

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 206426

**LATE-CYCLE MEETING MINUTES**

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) dated December 19, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RAPIVAB (peramivir injection) for intravenous use.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 16, 2014.

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

If you have any questions, please contact Elizabeth Thompson, M.S., Chief, Project Management Staff, at (301) 796-0824 or via email at [elizabeth.thompson@fda.hhs.gov](mailto:elizabeth.thompson@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Linda L. Lewis, M.D.  
Cross-Discipline Team Leader  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** September 16, 2014; 11:00 am  
**Meeting Location:** FDA, White Oak, Bldg 22, Room 1417

**Application Number:** NDA 206426  
**Product Name:** RAPIVAB (peramivir injection)  
**Applicant Name:** BioCryst Pharmaceuticals, Inc.

**Meeting Chair:** Linda Lewis, MD  
**Meeting Recorder:** Elizabeth Thompson, MS

**FDA ATTENDEES**

OND/OAP

Edward Cox, Office Director

OND/OAP/DAVP

Elizabeth Thompson, Chief, Project Management Staff  
Debbie Birnkrant, Division Director  
Peter Miele, Medical Officer  
Linda Lewis, Medical Officer Team Leader  
Kuei-Meng Wu, Nonclinical Reviewer  
Will Ince, Clinical Virology Reviewer  
Eric Donaldson, Clinical Virology Reviewer  
Takashi Komatsu, Clinical Virology Reviewer

OTS/OCP/DCP4

Leslie Chinn, Clinical Pharmacology Reviewer  
Jeff Florian, Pharmacometrics Reviewer  
Islam Younis, Clinical Pharmacology Team Leader

OTS/OB/DB4

Tom Hammerstrom, Statistics Reviewer  
Greg Soon, Statistics Team Leader

OSE

Robert Pratt, DRISK  
James Schlick, DMEPA

ONDQA

Neal Sweeney, Product Quality-Microbiology Reviewer

## **EASTERN RESEARCH GROUP ATTENDEES**

(b) (4) Independent Assessor

## **APPLICANT ATTENDEES**

### BioCryst Pharmaceuticals, Inc.

Elliott Berger, Senior Vice President, Regulatory Affairs

William Sheridan, Senior Vice President and Chief Medical Officer

Phil Collis, Vice President, Clinical Development

Nicole McMillan, Manager, Regulatory Affairs

Ray Taylor, Product Leader

(b) (4), Statistics Consultant

Sylvia Dobo, Executive Director, Product Safety and Clinical Development

Jon Stonehouse, President and CEO

Andreas Maetzel, Vice President, Medical Affairs

Yahya El-Kattan, Vice President, CMC

(b) (4), Virology Consultant



## **1.0 BACKGROUND**

NDA 206426 was submitted on December 23, 2013 for RAPIVAB (peramivir injection) for intravenous use.

Proposed indication(s): Treatment of acute, uncomplicated influenza

PDUFA goal date: December 23, 2014

FDA issued a Background Package in preparation for this meeting on September 10, 2014.

## **2.0 DISCUSSION**

### **1. Introductory Comments**

FDA noted that the purpose of a Late-cycle Meeting (LCM) was to share and discuss any substantive review issues that have been identified to date and the plans for the remainder of the review cycle. FDA stated that discussions regarding labeling can occur, but that a formal

review of the most recent draft label proposed by the applicant had not been fully reviewed as of yet.

## 2. Discussion of Substantive Review Issues

### CMC/Compliance

FDA noted that CMC inspections and compliance evaluations for manufacturing sites provided in the NDA are ongoing. Reference was made to an upcoming three-way teleconference with FDA, BioCryst and (b) (4) for further compliance issues, and as such, those issues would not be discussed during this meeting.

### Clinical/Clinical Virology (b) (4)

FDA reminded the sponsor that the (b) (4) FDA pointed to the draft labeling recommendations that were sent to the sponsor for the current thinking regarding this issue.

FDA clarified their response to the sponsor's question regarding the clinical virology section of the label. FDA stated that the ultimate goal for labeling was to include all resistance substitutions, regardless of the source (i.e., sponsor's studies or reports from the literature). FDA has required this type of information in labeling for other drugs. FDA acknowledged that the 'other' sources could be clarified further (e.g., identified from circulating isolates, from patients who failed other neuraminidase inhibitors, selection studies using other neuraminidase inhibitors, etc.). The challenge of labeling to that degree of (b) (4), however, is that some of these substitutions have been identified through multiple sources and would make labeling confusing. FDA welcomed any suggestions for presenting the data more efficiently.

### Clinical Pharmacology (Renal dosing)

FDA reiterated its position that based on the anticipated 3.1- and 4.5-fold increases in peramivir AUC in patients with creatinine clearance 30-49 and <30 mL/min, respectively, dose reductions to 200 mg for patients with creatinine clearance 30-49 mL/min and 100 mg for patients with creatinine clearance less than 30 mL/min were necessary. FDA stated that the safety of exposures in the expected ranges had not been established; in addition, higher systemic peramivir exposures provided no additional benefit in terms of efficacy based on the primary endpoints evaluated in clinical trials. FDA also indicated that the benefit-risk assessment for peramivir use in patients with acute uncomplicated influenza was different than that for patients with complicated influenza and that less risk would be tolerated in the former patient population.

BioCryst agreed there were insufficient safety data to support the exposures expected in patients with creatinine clearance below 30 mL/min, but that a number of patients with complicated influenza received multiple doses of peramivir 600 mg daily. FDA noted that the majority of these patients had normal renal function and no systemic peramivir accumulation would be anticipated, and that the number of patients with renal impairment appeared to be limited and peramivir was dose-adjusted in these cases. BioCryst expressed their intent to

reexamine data from the TQT study, in which a supratherapeutic dose (1200 mg) of peramivir was evaluated, in order to support the standard 600 mg dose in patients with creatinine clearance 30-49 mL/min. The FDA emphasized that there would need to be a sufficient number of subjects with exposures in the anticipated range in order for safety at these exposures to be demonstrated. BioCryst responded that they understood and would review the numbers of subjects in the TQT study who had plasma exposures in the range of those expected in patients with creatinine clearance 30-49 mL/min.

3. Discussion of Upcoming Advisory Committee Meeting

FDA noted that no Advisory Committee meeting was planned.

4. REMS or Other Risk Management Actions

FDA noted that no issues related to risk management have been identified to date.

5. Postmarketing Requirements/Postmarketing Commitments

PREA

FDA noted that the review team, along with the Pediatric Review Committee (PeRC), had reviewed the proposed pediatric plan and protocol included in the original NDA submission. FDA had communicated previously that pediatric study requirements for ages birth to less than 18 years would be deferred for this application. Protocol comments were also provided earlier, and FDA acknowledged that further discussion may be warranted.

BioCryst acknowledged FDA's protocol comments and stated they would need to reassess the pediatric timeline and would provide this to the FDA for further review.

Clinical Virology PMR/PMCs

BioCryst acknowledged the virology PMRs outlined in the background package. Regarding the virology PMC, BioCryst asked for clarification. FDA stated they were concerned about the observed HA substitutions, which modeling indicates some are occurring at antigenic sites, and their possible impact on vaccine efficacy. FDA, including CBER, is currently considering options for appropriate studies to address this concern. FDA agreed to share that information when available.

BioCryst acknowledged the second PMC and stated they hoped to enroll a sufficient number of subjects with influenza B in the pediatric study, as well as in other studies they intend to conduct during postmarketing, in order to gain further knowledge of peramivir's clinical effectiveness against influenza B.

6. Major Labeling Issues

FDA provided labeling comments prior to the LCM (August 29, 2014) and received BioCryst's revised label, along with responses to FDA's comments on September 12, 2014.

FDA stated that the revised label had not been reviewed; however, a discussion regarding BioCryst's response document could occur at the LCM.

*Use in serious influenza requiring hospitalization (Limitations of Use)*

BioCryst noted that FDA revised the statement regarding peramivir efficacy not demonstrated in hospitalized influenza patients to state, "[REDACTED] (b) (4) patients with serious influenza requiring hospitalization". BioCryst was concerned that this statement might be interpreted to mean there is a safety-related concern, but such is not the case here. This statement could also impact the ability of getting peramivir on a hospital formulary. BioCryst noted their alternative wording in the response document. FDA agreed the proposed language seemed reasonable but that it would still need some minor revisions.

*Dosage adjustment in renal impairment (Section 12.3)*

BioCryst noted the earlier discussion on this topic and stated they would review internally.

*Dosing in geriatric patients (Section 2.3)*

BioCryst did not agree with [REDACTED] (b) (4). FDA stated that this type of non-action statement [REDACTED] (b) (4) is not usually included in this section. Sections 8 and 12 of labeling include the relevant information regarding use in the elderly. BioCryst requested to retain the language under Dosage and Administration. FDA stated they would review the matter further.

*Preparation of RAPIVAB for intravenous infusion (Section 2.4)*

BioCryst noted they reordered statements in this section and would have further edits. They noted that empty IV bags are not readily available in hospital pharmacies and that they would need further hospital pharmacy input before proposing further revisions.

*Serious skin/hypersensitivity reactions (Section 5.1)*

BioCryst acknowledged FDA's attempt to simplify the language in Section 5.1, but was concerned that it changed the interpretation of the findings. BioCryst noted there was only one case of SJS in postmarketing (Japan) but that erythema multiforme was observed in both clinical trials and postmarketing (Japan). FDA stated that a "rare" event has a specific regulatory meaning related to the rate of events. However, it is difficult to determine rates from postmarketing data. In addition, "very rarely" has no regulatory meaning. FDA understands BioCryst's concern and stated they would take this back for further review.

*Pregnancy (Section 8.1)*

BioCryst noted that FDA's proposed language failed to mention that peramivir [REDACTED] (b) (4). They asked whether there was any utility in describing this information. FDA noted that this type of information borders on being anecdotal and is not usually included in labeling as it is not the same caliber of information as that from a pregnancy registry or epidemiological studies. BioCryst stated they were working with the VAMPS program to get pregnancy information into labeling.



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/s/  
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LINDA L LEWIS  
10/07/2014



NDA 206426

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

BioCryst Pharmaceuticals, Inc.  
Attention: Elliott Berger, PhD  
Senior Vice President, Regulatory Affairs  
4505 Emperor Boulevard, Suite 200  
Durham, NC 27703

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RAPIVAB (peramivir injection) for intravenous use.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 16, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Elizabeth Thompson, Chief, Project Management Staff at (301) 796-0824.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** September 16, 2014  
**Meeting Location:** Teleconference

**Application Number:** NDA 206426  
**Product Name:** RAPIVAB (peramivir injection) for intravenous use  
**Indication:** Treatment of acute uncomplicated influenza  
**Sponsor/Applicant Name:** BioCryst Pharmaceuticals, Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### Discipline Review Letters

No Discipline Review letters have been issued to date.

#### Substantive Review Issues

The following substantive review issues have been identified to date:

#### *Chemistry, Manufacturing and Controls (CMC) and Compliance:*

Inspections and compliance evaluations for manufacturing sites submitted in the new drug application (NDA) for peramivir are ongoing.

We acknowledge the September 18, 2014 3-way teleconference with the FDA, BioCryst and (b) (4) to discuss outstanding manufacturing site deficiencies relevant to peramivir. At this time, we can reiterate our previous comments that all manufacturing and testing sites submitted in an application must be fully compliant and have closed all the corrective actions pertaining to any FDA 483 for the application to be approved. We always encourage sponsors to include redundancy in their manufacturing sites in order to lessen the impact on approvability should a site fail to comply with FDA regulations.

Clinical/Clinical Virology:

As conveyed to you during the mid-cycle briefing, the clinical evidence included in the NDA is insufficient to support a specific claim of effectiveness in acute uncomplicated influenza B virus infection. Please refer to draft labeling recommendations sent to you on August 29, 2014, for the Division's current thinking regarding labeling for influenza B virus.

Clinical Pharmacology:

Population PK simulations conducted using a model informed by data from the renal impairment study (BCX1812-105) predicted increases of approximately 3.1- and 4.5-fold in systemic peramivir exposures (based on AUC values adjusted to 600 mg) in patients with creatinine clearance 30-<50 and <30 mL/min, respectively, following a single dose of peramivir IV 600 mg. Because the safety of exposures in this range has not been established, the Division plans to recommend a reduction in peramivir IV dose to 200 mg and 100 mg for patients with creatinine clearance 30-<50 and <30 mL/min, respectively, as specified in the Division's revisions to the draft label sent to you on August 29, 2014.

The Division and the Office of Scientific Investigations have completed their reviews of the relevant clinical studies and concluded that the data demonstrating similar systemic exposures of peramivir IM and IV formulations are acceptable; therefore, the clinical trials in which IM peramivir was evaluated may be used to support the safety and efficacy of IV peramivir in adults with uncomplicated influenza.

**ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

**LCM AGENDA**

1. Introductory Comments – 5 minutes (Elizabeth Thompson, M.S./Linda Lewis, M.D.)  
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 15 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Chemistry, Manufacturing and Controls (CMC) and Compliance- Inspection issues
  - Clinical/Clinical Virology-influenza B
  - Clinical Pharmacology-renal impairment dosing
3. Postmarketing Requirements/Postmarketing Commitments – 10 minutes
    - a. Pediatric Postmarketing Requirement (PREA):
      1. The pediatric study requirement for ages birth to less than 18 years for this application will be deferred because adult studies are completed and the pediatric study has not been completed. Comments regarding your proposed pediatric study plan were recently forwarded. In general, we do not believe the small, single arm study proposed will be adequate to assess either safety or efficacy of peramivir in the pediatric population. We are willing to have further discussion of your proposed pediatric protocol in a separate correspondence or teleconference.
    - b. Postmarketing Requirements:
      1. Submit the remainder of the clinical resistance data that were not included with the NDA. These include both the HA and NA data for studies BCX1812-201, BCX1812-211, and BCX1812-311.
      2. Determine the cross-resistance to oseltamivir and zanamivir for all of the HA peramivir resistance substitutions that have yet to be evaluated (A/H3N2 HA G78D, K189E). Additionally, determine cross-resistance to oseltamivir/zanamivir resistance substitutions (A/H1N1 NA R152K, I122K/T, G248R+I266V, Q312R+I427T, R371K, A/H3N2 NA E41G, I222L/V, Q226H, S247P, B NA D198Y, A246D/S/T, G420S).
    - c. Postmarketing Commitments:
      1. Evaluate the impact of the peramivir resistance substitutions in HA on the effectiveness of influenza vaccine.
      2. Submit clinical data from a sufficient number of subjects with influenza B virus infection to adequately characterize the effectiveness of peramivir administration in this patient population. These data may be collected from the pediatric study required under PREA or from a new stand-alone clinical trial. Resistance data from these subjects should be collected in a manner consistent with previous FDA advice.
  4. Major labeling issues – 15 minutes
  5. Review Plans – 5 minutes
    - a. Await final inspection review
    - b. Continue with labeling review and discussions
  6. Wrap-up and Action Items – 5-10 minutes

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/s/  
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DEBRA B BIRNKRANT  
09/10/2014