

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206426Orig1s000

CHEMISTRY REVIEW(S)

NDA 206426

Rapivab

BioCryst Pharmaceuticals, Inc.

Fuqiang Liu, Ph.D.
Branch V, ONDQA
For the Division of Anti-Viral Products

CMC Addendum 1 to Review #1

REVIEW DATE: 18-Dec-2014

The Executive Summary

Recommendation and Conclusion on Approvability

NDA 206426 is recommended for approval from the CMC perspective. CMC information in the NDA has been reviewed and found satisfactory (Aug 19, 2014), and labeling has adequate CMC information. The Product Quality Microbiology review recommends approval (Aug 5, 2014), and the CMC/Biopharmaceutics Initial Quality Assessment (Feb 24, 2014) concluded that no Biopharmaceutics information needed to be reviewed. The overall recommendation from the Office of Compliance is ACCEPTABLE as of Dec. 18, 2014.



Overall Manufacturing Inspection Recommendation

| [Next task >](#)

NDA 206426-Orig1-New/NDA(1)

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Approve

Facility Inspection - Overall Application Re-evaluation Date

5/17/15

Carton and Vial Label:



(b) (4)

Administrative

A. Reviewer's Signature

Fuqiang Liu -S

Digitally signed by Fuqiang Liu -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Fuqiang Liu -S,
0.9.2342.19200300.100.1.1=2000778114
Date: 2014.12.18 15:45:48 -05'00'

Fuqiang Liu, Ph.D.
CMC Reviewer

B. Endorsement Block

**Stephen
Miller -A**

Digitally signed by Stephen Miller -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Stephen Miller -
A,
0.9.2342.19200300.100.1.1=1300087013
Date: 2014.12.18 16:01:16 -05'00'

“I concur, this NDA is recommended for approval from the CMC perspective.”

Stephen Miller, Ph.D.
CMC-Lead

**Rapti D.
Madurawe -A**

Digitally signed by Rapti D. Madurawe -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300220251,
cn=Rapti D. Madurawe -A
Date: 2014.12.18 16:04:47 -05'00'

Rapti Madurawe, Ph.D.
Branch Chief

NDA 206426

Rapivab

BioCryst Pharmaceuticals, Inc.

**Fuqiang Liu, Ph.D.
Branch V, ONDQA
For the Division of Anti-Viral Products**

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Chemistry Review Data Sheet

1. NDA 206426
2. REVIEW #: 1
3. REVIEW DATE: 19-Aug-2014
4. REVIEWER: Fuqiang Liu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

SDN# 008 Quality/Response to Information Request

SDN# 010 Quality/ Response to Information Request

SDN# 024 Quality/ Response to Information Request

SDN# 025 Quality/ Response to Information Request

SDN# 026 Quality/ Response to Information Request

Document Date

23-Dec-2013

20-Feb-2014

27-Feb-2014

05-Jun-2014

11-Jun-2014

24-Jun-2014

7. NAME & ADDRESS OF APPLICANT:

Name: BioCryst Pharmaceuticals, Inc.
Address: 4505 Emperor Boulevard, Suite 200
Durham, NC 27703
Representative: Elliott Berger, Ph.D., Senior VP of RA
Telephone: 919-859-7919

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rapivab
- b) Non-Proprietary Name (USAN): Peramivir
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiviral (acute uncomplicated influenza)

11. DOSAGE FORM: Solution for IV injection

12. STRENGTH/POTENCY: 200 mg (20 mL/vial)

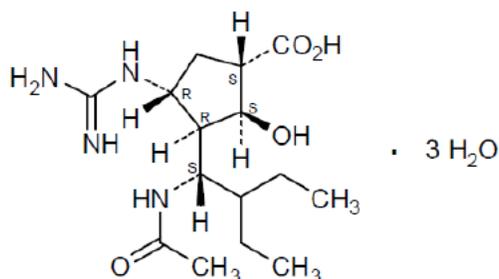
13. ROUTE OF ADMINISTRATION: IV infusion

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structural Formula:

Chemistry Review Data Sheet



Chemical Name: (1*S*,2*S*,3*R*,4*R*)-3-[(1*S*)-1-(acetylamino)-2-ethylbutyl]-4-(carbamimidoylamino)-2-hydroxycyclopentanecarboxylic acid, trihydrate

Molecular Formula: C₁₅H₂₈N₄O₄ · 3H₂O

Molecular Weight 382.45

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ₁	STATUS ²	DATE REVIEW COMPLETE D	COMMENTS
(b) (4)	V		(b) (4)	3	Adequate		Reviewed by Min Tang on Aug. 2013
	III			3, 4	Adequate		Reviewed by Xuhong Li for NDA 205596 on Feb. 2014
	II			4	Adequate		
	III			3, 4	Adequate		Reviewed by Don Klein for NDA 18780 on Sept. 2012

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

Chemistry Review Data Sheet

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69038	Peramivir IV
IND	(b) (4)	(b) (4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		Dr. Krishnakali Ghosh
Pharm/Tox	pending		Dr. Kuei-Meng Wu
Biopharm	Approval	24-Feb-2014	Dr. Banu S. Zolnik
LNC	N/A		
Methods Validation	Pending		
OPDRA	N/A		
EA	Request for categorical exclusion is granted		
Microbiology	See separate review		Dr. Neal Sweeney

The Chemistry Review for NDA 206426

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is not recommended for approval from the CMC perspective. CMC information in the NDA has been reviewed and found satisfactory, and labeling has adequate CMC information which will be finalized during team review of labeling. The Product Quality Microbiology review recommends approval (Aug 5, 2014), and the CMC/Biopharmaceutics Initial Quality Assessment (Feb 24, 2014) concluded that no Biopharmaceutics information needed to be reviewed. However, the establishment status is pending as of the date of this review. The only drug product manufacturer, (b) (4) was classified as OAI, and the Office of Compliance is recommending Withhold for this facility. This NDA cannot be approved until the (b) (4) issues have been resolved and an overall recommendation of Acceptable is made for the establishment. Alternatively, the applicant could select a different contractor, transfer the drug product manufacturing process, and submit appropriate information to the NDA (e.g., sterility assurance controls and data).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Peramivir is a new molecular entity (NME) filed under NDA 206426 by BioCryst. This NDA describes the manufacture and processing of Peramivir. The NDA contains relevant information regarding all aspects of the Peramivir drug substance.

Drug substance is manufactured and tested by (b) (4). Testing is also carried out at (b) (4).

The status of the (b) (4) facility is currently listed as Pending, and the (b) (4) facility shows a re-evaluation date of May 2014.

The Peramivir drug substance has five chiral centers and it is a (b) (4) form. The manufacturing process includes (b) (4).

Executive Summary Section

(b) (4) The drug substance specifications are adequate and include tests for appearance, identification, assay, impurity content, organic volatile impurities/residual solvents, ROI, heavy metals, (b) (4) water content, pH of solution, microbial limits and bacterial endotoxins, etc.

The submitted long term and accelerated stability data were reviewed, and were found to be within the proposed specification and acceptable. The levels of individual and total impurities have not increased and no degradation products have been observed during the long term and accelerated stability studies. Therefore, a retest period of (b) (4) months at (b) (4) % RH (long-term storage conditions) is granted.

Drug Product

The drug product, peramivir injection, is a clear, colorless, sterile and isotonic solution for intravenous (IV) administration. The product contains 10 mg/mL of peramivir in 0.9% sodium chloride solution. The inactive components include sodium chloride (NaCl), (b) (4) HCl (b) (4) (b) (4) NaOH (b) (4) and water for injection. The drug product (200 mg) is packaged in a 20 mL/20 mm clear, colorless (b) (4) vial of USP Type I (b) (4) glass with appropriate stopper and seals. Drug product is manufactured and tested by (b) (4) which is classified as OAI Alert, and the Office of Compliance is currently recommending Withhold for this facility.

The major manufacturing steps are: (b) (4)
(b) (4) The drug product specifications are reasonable and include description, identification, assay, degradation products, pH, osmolarity, particulate matter, sterility, bacterial endotoxin, etc.

The drug product is extremely stable. No degradation above the level of (b) (4) % is observed throughout the stability studies. The applicant provided acceptable stability data at long-term storage conditions for four peramivir injection registration lots through 60 months, and for two registration lots through 48 months. The stability data from the registration batches support the proposed 60 months of shelf-life of drug product manufactured using either supplier of drug substance. Therefore, a retest period of (b) (4) months at (b) (4) % RH (long-term storage conditions) is granted.

B. Description of How the Drug Product is Intended to be Used

RAPIVAB (Peramivir Injection) is a neuraminidase inhibitor indicated for the treatment of acute uncomplicated influenza in patients 18 years and older. The recommended dose in adults is single 600 mg dose, administered by intravenous infusion over a minimum of 15 minutes. The drug product is a clear, colorless, sterile and isotonic solution. The drug product is supplied in a carton containing 3 vials; each with 200 mg peramivir per 20 mL glass vials fitted with rubber stoppers and royal blue flip-off seals. The pH is adjusted to a target of (b) (4) with sodium hydroxide, USP

Executive Summary Section

and/or hydrochloric acid, USP if needed. The storage condition is “stored in original cartons at 20°C to 25°C (68 to 77°F). Excursions are permitted to 15°C to 30°C (59 to 86°F)” and the expiration dating period granted is 60 months.

C. Basis for Approvability or Not-Approval Recommendation

Information provided for NDA 206426 regarding the manufacturing, raw materials controls and specifications, analytical methods and stability for the drug substance and drug product is adequate to support the quality of both the drug substance and drug product through a shelf-life of 60 months. The labeling has adequate CMC information which will be finalized during team review of labeling.

At this time, this NDA is not recommended for approval due to the following: As of the date of this review, the overall recommendation for the manufacturing and testing facilities is PENDING. Approval of this NDA is contingent upon an overall evaluation of “acceptable” in EES and the acceptability of the final labeling.

Executive Summary Section

III. Lifecycle Knowledge Management

a) Drug Product – Initial Risk Identification (not included in original IQA)

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any
Sterility*	Formulation Raw materials Container closure Process parameters Scale/Equipment/Site	4	5	5	100	(b) (4)
Endotoxin*	See Sterility	2	4	4	32	
Particulate matter	See Sterility	3	5	3	45	Drug concentration of 10 mg/mL is half of the solubility of 20 mg/mL
Related substances	See Sterility	3	2	1	6	Extremely stable drug - no degradation from (b) (4)
Assay	See Sterility	2	3	1	6	Highly stable.
Appearance	See Sterility	3	3	1	9	
Leachable/extractable	See Sterility	2	4	3	24	
Osmolality	Formulation Raw materials Process Parameters	2	4	2	16	
pH	See Osmolality	2	2	1	4	Target pH 5.5-8.5.
Deliverable volume	Container closure Process parameter Equipment	3	4	3	36	Target fill volume: NLT (b) (4)mL.

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

* See Dr. Sweeney's Product Quality Microbiology review (Aug 5, 2014) for additional risk evaluation of sterility and endotoxin controls.

Executive Summary Section

b) Drug Product – Final Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	Formulation Raw materials Container closure Process parameters Scale/Equipment/Site	H	See Dr. Sweeney’s review (Aug 5, 2014)	Acceptable	See Dr. Sweeney’s review (Aug 5, 2014)
Endotoxin	See Sterility	M	See Dr. Sweeney’s review (Aug 5, 2014)	Acceptable	See Dr. Sweeney’s review (Aug 5, 2014)
Particulate matter	See Sterility	M	Formulated to 10 mg/mL with solubility of approximately 20 mg/mL Monitoring per USP<788>	Acceptable	Keep monitoring, especially during stability studies
Related substances	See Sterility	L		Acceptable	
Assay	See Sterility	L		Acceptable	
Appearance	See Sterility	L		Acceptable	
Leachable/extractable	See Sterility	L		Acceptable	
Osmolality	Formulation Raw materials Process Parameters	L		Acceptable	
pH	See Osmolality	L		Acceptable	
Deliverable volume	Container closure Process parameter Equipment	M	There is medium risk - the observed deliverable volumes range from (b) (4) mL with ≥ 20 ml/vial needed	Acceptable	Keep monitoring
Compatibility with diluent and infusion equipment	Diluent Equipment Time / Temperature	L	Compatibility demonstrated with 3 diluents and typical equipment; appropriate labeling statements	Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

Executive Summary Section

IV. Administrative**A. Reviewer's Signature**

Fuqiang Liu, Ph.D.

B. Endorsement Block

Stephen Miller, Ph.D., CMC Lead

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/s/

FUQIANG P LIU
08/19/2014

STEPHEN MILLER
08/19/2014

I concur; from the CMC perspective this NDA cannot be recommended for approval until inspectional issues have been resolved.

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **206-426**

2. DATES AND GOALS:

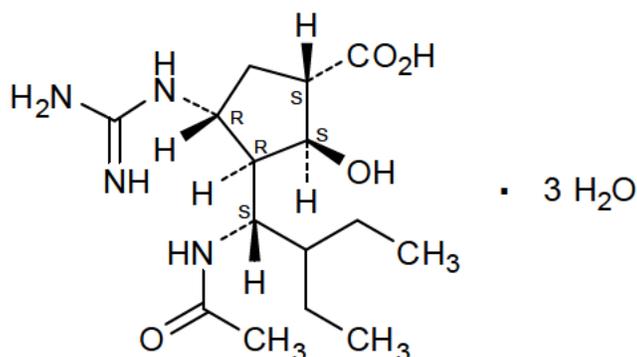
Letter Date:	Submission Received Date : Dec 23, 2013
PDUFA Goal Date: Dec 23, 2014	Sign-Off of Primary Review in DARRTS: Aug 23, 2014 (Office Director sign-off; PDUFA-V Standard Review)

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Rapivab
Established or Non-Proprietary Name (USAN):	Peramivir
Dosage Form:	Injection
Route of Administration	IV infusion
Strength/Potency	200 mg (20 mL vial)
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of acute uncomplicated influenza.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h):

Biocryst Pharmaceuticals

**ONDQA Initial Quality Assessment (IQA) and Filing Review, NDA 206426
CMC and Biopharmaceutics**

7. SUBMISSION PROPERTIES:

Review Priority:	Standard PDUFA V
Submission Classification (Chemical Classification Code):	Type 1 (New Molecular Entity)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAVP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation	X		New Molecular Entity
Environmental Assessment		X	
CDRH		X	
Other		X	

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
CMC Filing Issues:
1. None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
CMC Comments for 74-Day Letter:
1. Communicate prior to filing letter: 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.
2. Hold until data is assessed: The pH targets listed on the DP spec, in the description of the product in the application and in the labeling vary. Are these different ranges appropriate as described?
3. Hold until manufacturing process is evaluated: Is the target 10 mg/mL based on peramavir (b) (4)

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Biopharmaceutics Filing Issues:
1. None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Biopharmaceutics Comments for 74-Day Letter:
1. None

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Microbiology Filing Issues:
This NDA is fileable per Dr. Sweeney's Microbiology Filing Review in DARRTS (Jan 27, 2014).

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes	No
Suggested expertise for team:		
Fuqiang Liu (DS and DP)		
Banu Zolnik (Biopharmaceutics)		
Angelica Dorantes (Secondary Review Biopharmaceutics)		
Neal Sweeney (Prod Qual Micro)		
Rapti Madurawe (Secondary Review)		
Althea Cuff (ONDQA PM)		
David Araujo (DAVP PM)		

Summary of Critical Issues and Complexities

Drug Substance

The NDA lists two manufacturers of the drug substance (peramivir trihydrate):

- (b) (4) – made significant quantity of peramivir prior to 2009. Those supplies made after process validation will continue to be used. Once exhausted, (b) (4) will be removed from the NDA.
- (b) (4) – this will be the facility for future commercial manufacture; Batch analyses are provided on 17 commercial scale lots (b) (4) kg each) made between 2007-2009.

Stability data on 3 commercial batches of peramivir drug substance made at each of the 2 manufacturing facilities are supplied. This includes long-term data at 30°C/65%RH for 60 months, and 6 mo of accelerated data at 40°C/75%RH. Seems to be quite stable. A (b) (4) mo retest period is proposed when stored at (b) (4).

Drug Product

The drug product is a sterile solution in 0.9% sodium chloride with pH adjusted to (b) (4) (see draft comment). The peramavir at 10mg/mL (b) (4). It is supplied in a single-use 20 mL glass vial.

Studies at pH values of (b) (4) showed increased degradants on storage. The composition of the formulation has not changed throughout the clinical program with the exception of the addition of a pH adjustment by either (b) (4) Sodium Hydroxide or (b) (4) Hydrochloric Acid (b) (4). The pH adjustment was added during Phase 2, when it was noted that the pH shifted on stability from (b) (4) which was attributed to interaction with the glass vial surface.

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Phase 3 clinical supplies were manufactured at the intended commercial facility (b) (4) with the intended commercial formulation. A (b) (4) was added to the process for the Phase 3 supplies.

There is extensive batch experience using “commercial equipment” at (b) (4) scale. This supported the clinical studies, emergency INDs and stockpiling under an Emergency Use Authorization as part of influenza preparedness.

There is a slight overfill (b) (4) mL) to insure that the full 20 mL labeled volume can be withdrawn. Diluent compatibility studies are presented in Section 3.2.P.2.6. The DP is stated to be “compatible with the materials commonly used for administration such as polyvinylchloride bags and PVC free bags, polypropylene syringes, and polyethylene tubing” in that Section.

Leachable/extractable studies are presented in Section 3.2.P.2.4.4

Batch results are summarized on approximately 40 lots of DP.

Stability studies were conducted at 25°C/60%RH, 30°C/65%RH and accelerated at 40°C/75%RH (upright and inverted for all three conditions).

- Stability data out to 60 months are provided on 3 lots of DP made at (b) (4) scale from (b) (4) DS.
- Stability data of 48-60 month duration are provided on 3 lots of DP made at (b) (4) scale from (b) (4) DS.
- A 60-month expiration dating period is proposed

DMF (b) (4) (electronic) covers the (b) (4) where the DP is made (b) (4). This DMF was last evaluated by Min Tang (Compliance, OMPQ) in Aug 2013 for (b) (4) and found Adequate.

The Biopharmaceutics Reviewer, Dr. Banu Zolnik, asked whether the manufacturing processes are the same at the commercial (b) (4) facility compared to the (b) (4) facility where the clinical batches were made. In the Manufacturing Process Development section of Module 3 (3.2.P.2.3), this summary statement appears: (b) (4)

(b) (4)
This section also describes the (b) (4)

(b) (4) Given that the DP is a solution for injection, and in the context of Dr. Zolnik’s question (potential for impact on pharmacokinetic performance), I conclude that the formulations and manufacturing process at the (b) (4) facility were the same as the proposed commercial process at the (b) (4) facility.

Labeling

(b) (4)

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CMC and Biopharmaceutics**

Follow the steps below to prepare a diluted solution of RAPIVAE (b) (4) (b) (4)

[Redacted]

[Redacted] (b) (4)

RAPIVAB injection is compatible with materials commonly used for administration such as polyvinylchloride (PVC) bags and PVC-free bags, polypropylene syringes, and polyethylene tubing.

[Redacted] (b) (4)

Once a diluted solution of RAPIVAB has been prepared (b) (4) administer (b) (4) immediately or store (b) (4) under refrigerated conditions (2°C to 8°C or 36° to 46°F) for up to 24 hours.

[Redacted] (b) (4)

[Redacted] (b) (4)

Facilities

There is a OAI Alert (red) for the DP manufacturing site (b) (4) in EES.

Biopharmaceutics Initial Assessment

Submission:

NDA 206426 is an original 505(b)(1) submission. Peramivir is a selective inhibitor of influenza viral neuraminidase, with potent activity against a broad range of influenza A (b)(4) subtypes for the treatment of acute uncomplicated influenza in patients 18 years and older. The proposed peramivir dosing is 600 mg IV infusion for a minimum of 15 minutes. The proposed proprietary name Rapivab® was conditionally granted under IND 69038 on March 4, 2011.

Peramivir drug substance is sparingly soluble in water and 0.9% sodium chloride solution.

(b)(4)
Drug Product, peramivir injection is formulated as sterile, isotonic solution. The quantitative composition of peramivir for injection is provided in Appendix 1. According to the Applicant, a 10 mg/mL solution in 0.9% Sodium Chloride at neutral pH demonstrated the best stability; therefore, a pH of (b)(4) range was targeted for the proposed product. The proposed product is supplied in 20 mL/20 mm USP Type 1 Clear (b)(4) Glass.

The Applicant states that the composition of the formulation was not changed during the clinical program with the exception of the (b)(4) Sodium Hydroxide or (b)(4) HCL for pH adjustment. However, it should be noted that that Clinical (Batch CT0615, CT0627, CT0745) and Commercial Batches (7439, 7440, C0011, 7438, C0264, C0267, C0268, C0299, C0281, C0306, C0307) were manufactured at different sites, (b)(4) and (b)(4) respectively.

To support the approval of the proposed product, the Applicant conducted seventeen Phase 1 studies (single and multiple dose studies), four Phase 2 and six Phase 3 clinical studies to evaluate the efficacy and safety of peramivir in the treatment of influenza. The Applicant stated that Study 0722T0621 (aka Shionogi Study) and supporting studies BCX1812-211, BCX1812-212 and BCX1812-311 are conducted to support this NDA for the indication of acute uncomplicated influenza.

The Phase 2-3 safety and efficacy studies BCX1812-211, BCX1812-212, BCX1812-311 were conducted via the intramuscular route of administration of peramivir injections. Therefore, with the objective of leveraging the clinical information collected in these studies with intramuscular administration, the Applicant conducted study BCX1812-113, which is a bridging two-period crossover study assessing the bioequivalence between the intramuscular and the intravenous routes of administration.

Six batches (7438, 7439, 7440, C0011, C0264, C0267) of peramivir injection were placed on stability to support the registration and clinical studies.

Reviewer's Comments:

- *The Applicant used the to-be-marketed formulation for all the pivotal clinical studies with the exception of the addition of (b)(4) Sodium Hydroxide or (b)(4) HCl for pH adjustment and*

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CMC and Biopharmaceutics**

characterized the PK profile of the intended dose and therefore a biowaiver is not needed for this NDA. Note that all the PK studies, including BE study BCX1812-113 will be reviewed by OCP.

- *Although the Clinical and Commercial Batches were manufactured at [REDACTED] (b) (4) [REDACTED] and [REDACTED] (b) (4) [REDACTED] respectively, bridging studies comparing the two manufacturing sites are not required because the proposed product is an injectable solution and the formulation and manufacturing process are the same in both sites.*

Recommendation:

From Biopharmaceutics perspective, this NDA 206- 426 Peramivir Injection, 10 mg/mL is fileable.

Since there is no biopharmaceutics information to be reviewed in this NDA, no further action is warranted from ONDQA-Biopharmaceutics.

**ONDQA Initial Quality Assessment (IQA) and Filing Review, NDA 206426
CMC and Biopharmaceutics**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		IND 69,038 (IV solution) Extensive communication during IND, pre-EUA and EUA phases are documented in Module 1 Section 1.6

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

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	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

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	Parameter	Yes	No	Comment
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>		X	<p>Could not locate this statement. Clarification was requested twice (Jan 28 and Feb 13).</p> <p>In a Feb 20 amendment, Biocryst clarified that all sites other than the (b)(4) facility are ready for inspection (see cover letter). Biocryst also stated (Jan 29) that an external consulting group is assessing (b)(4) response to the (b)(4) FDA Warning Letter, and the facility is expected to be ready for re-inspection in (b)(4). After internal discussion, it was determined that an exception was appropriate in this case, partially in consideration that the facility delay is not related to this particular product, and also because an inspection of this site would not be scheduled before the end of (b)(4) in any case. Therefore, this should not prevent filing of the NDA, and adequacy of the (b)(4) facility will be evaluated during the review.</p>

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	<p>Has an environmental assessment or claim of categorical exclusion been provided?</p>	X		<p>21 CFR 25.30(b); (b)(4) but will be (b)(4) ppb</p>

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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		Attached below
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		A narrative description is included with a flow diagram. Executed batch records for 2 batches (b) (4) are included
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		Batch records; see Point 19, above.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		Attached below
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

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G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		Section 3.2.P.3.5

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	V			Oct 4, 2011	
	III			Oct 31, 2013	
				Oct 31, 2013	
	III			Oct 31, 2013	

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		Attached below

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?		x	NA
34.	Is the dissolution test part of the DP specifications?		x	NA

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35.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		x	NA
36.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
37.	Does the application include a biowaiver request?		x	The Applicant used the to-be-marketed formulation for all the clinical studies with the exception of the (b) (4)(D) Sodium Hydroxide or (u) (4) H ⁺ L for pH adjustment and characterized the PK profile of the intended dose; therefore, a biowaiver is no needed for the proposed product.
38.	Is there any information to support the approval of the lower strength(s)?		x	Only one strength is proposed for commercialization.
39.	Is information such as BCS classification mentioned, and supportive data provided?		x	NA
40.	Does the application include an IVIVC model?		x	NA
41.	Is there enough information to assess the extended release designation claim?		x	NA
42.	Does the application include information/data on in vitro alcohol dose-dumping potential?		x	NA
43.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		The Applicant conducted BE study BCX1812-113, which is a bridging two-period crossover study assessing the bioequivalence between the intramuscular and the intravenous routes of administration. This BE study will be evaluated by the Clinical Pharmacology Reviewer from OCP.

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44.	Is there any design space proposed using in vitro release as a response variable?		x	
45.	Are there any data supporting a manufacturing change?		x	The clinical (Batch CT0615, CT0627, CT0745) and Commercial Batches (7439, 7440, C0011, 7438, C0264, C0267, C0268, C0299, C0281, C0306, C0307) were manufactured at different sites, (b) (4) and (u) (4) respectively. However, a bridging study comparing the manufacturing sites is not needed because the proposed product is an injectable solution and the formulation and manufacturing process are the same in both sites.
46.	Is the control strategy related to in vitro drug release?		x	
K. FILING CONCLUSION				
	Parameter	Yes	No	Comment
47.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
48.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
49.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
50.	Are there any potential review issues identified?		X	
51.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	
52.	Are there any internal comments to other disciplines?	X		See Overall Filing Conclusions and Recommendations, CMC sub-section

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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

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Appendix 1. Composition of Drug Product

Component	Function	Reference to Quality Standards	Quantitative Composition (Amount/mL)	Amount per Vial (mg)
Peramivir	Active ingredient	In-house	10 mg	200 mg
Sodium Chloride	(b) (4)	USP	9 mg	180 mg
(b) (4) Hydrochloric Acid, (4)%	pH adjustment	USP	As required for pH adjustment	As required for pH adjustment
(b) (4) Sodium Hydroxide, (b) (4)N	pH adjustment	USP	As required for pH adjustment	As required for pH adjustment
Water for Injection	(b) (4)	USP	(b) (4)	

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Appendix 2. DP Specification

Test	Acceptance Criteria	Analytical Method
Description ^a	Clear colorless solution free from visible evidence of particulates	3.2.P.5.2.1
Identification - IR	Corresponds to reference spectrum or the spectrum of the reference standard	3.2.P.5.2.2
Identification - HPLC	Retention time of the major peak in the sample chromatogram corresponds to that of the major peak in the reference standard	3.2.P.5.2.3
Assay - HPLC ^a	(b) (4) 0% label claim	
Degradation Products ^a		
Each Specified Identified Degradant	≤ (b) (4)	
Any Unspecified Degradant	≤ (b) (4)	
Total Degradants	≤ (b) (4)	
pH ^a	5.5 – 8.5	3.2.P.5.2.4
Sterility ^a	Passes test (No evidence of microbial growth)	3.2.P.5.2.5
Bacterial Endotoxins ^a	≤ (b) (4) EU/mL	3.2.P.5.2.6
Particulate Matter ^a	≤ (b) (4) μm: ≤ (b) (4) particles/container	3.2.P.5.2.7
	≥ (b) (4) μm: ≤ (b) (4) particles/container	
Deliverable Volume	NLT ^b (b) (4) mL	3.2.P.5.2.8
Osmolality	290 – 350 mOsm/kg	3.2.P.5.2.9

(b) (4)

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Appendix 3. DS Specification

Test	Acceptance Criteria	Analytical Method
Description ^a	(b) (4)	3.2.S.4.2.1
Identification - IR	(b) (4)	3.2.S.4.2.2
Identification - HPLC	(b) (4)	3.2.S.4.2.3
Assay – HPLC ^a	(b) (4)	
Each Specified Identified Impurity ^{a, b}	NMT ^c (b) (4)	
Any Unspecified Impurity ^a	NMT (b) (4)	
Total Impurities ^a	NMT	3.2.S.4.2.4
Enantiomeric Purity	NMT (b) (4)	
Residual Solvent (b) (4)	NMT (b) (4) ppm	3.2.S.4.2.5
Residual Solvent (b) (4)	NMT (b) (4) ppm	
Residue on Ignition	NMT (b) (4)	3.2.S.4.2.6
Heavy Metals	NMT (b) (4) ppm	3.2.S.4.2.7
(b) (4)	NMT (b) (4) ppm	3.2.S.4.2.8
pH of Solution ^a	(b) (4)	3.2.S.4.2.9
Water Content ^a	(b) (4)	3.2.S.4.2.10
Bacterial Endotoxins	NMT (b) (4) EU/mg	3.2.S.4.2.11

Test	Acceptance Criteria	Analytical Method
Microbial Limits: Total aerobic microbial count: Total yeast and mold Count: Objectionable Organisms:	NMT (b) (4) cfu/g NMT (b) (4) cfu/g <i>Absence of E. Coli, Salmonella, Pseudomonas aeruginosa, Staphylococcus aureus</i>	3.2.S.4.2.12
(b) (4)	(b) (4)	

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Appendix 4. Container Labels

Vial Label



1.16"

3.4896"

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Label of Carton Containing 3 Vials

(b) (4)



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

/s/

STEPHEN MILLER

02/20/2014

NDA is fileable from the CMC and BP perspectives.

BANU S ZOLNIK

02/21/2014

ANGELICA DORANTES

02/21/2014

RAPTI D MADURAWAWE

02/24/2014