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RESEARCH**

APPLICATION NUMBER:

206426Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 206426
Product Name: RAPIVAB™ (peramivir injection) for intravenous use

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Study Completion:	<u>04/30/2018</u>
	Final Report Submission:	<u>12/31/2018</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies are completed and ready for approval. The review team met with the Pediatric Review Committee (PeRC) on August 13, 2014. The PeRC agreed with the Division to grant a deferral for pediatric patients aged birth to less than 18 years because the product is ready for approval in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The study is a deferred pediatric trial required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) 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. The Division has issued comments regarding the Applicant's overall pediatric plan.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A Phase 3 randomized, open label, active-controlled trial to evaluate the safety, pharmacokinetics and effectiveness of IV peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza ages birth to 18 years old.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

The resistance data from previous studies have been limited. It is unclear at this time what the impact of mixed populations of wild-type/resistant virus has on detection of resistance and the extent of cross-resistance to oseltamivir and zanamivir.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
The sponsor submitted only part of the resistance/cross-resistance data with the current NDA submission. The sponsor needs to submit the remainder of their data.

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 206426
Product Name: RAPIVAB™ (peramivir injection) for intravenous use

PMR/PMC Description: 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).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/30/2015</u>
	Study Completion:	<u>04/30/2016</u>
	Final Report Submission:	<u>10/31/2016</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The sponsor submitted only part of the cross-resistance data with the current NDA submission. The phenotype has been characterized for several amino acid substitutions. However, there are still several less frequently occurring amino acid substitutions that need to be characterized. The sponsor agreed at the pre-NDA meeting that the remainder of the cross-resistance data will be submitted as a PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The resistance data from previous studies have been limited. It is unclear at this time what the impact of mixed populations of wild-type/resistant virus has on detection of resistance and the extent of cross-resistance to oseltamivir and zanamivir. Additionally, resistance-associated substitutions in the HA have been identified. The impact of these substitutions on cross-resistance to oseltamivir and zanamivir need to be evaluated.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
The sponsor submitted only part of the resistance/cross-resistance data with the current NDA submission. The sponsor needs to submit the remainder of their data.
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 206426
Product Name: RAPIVAB™ (peramivir injection) for intravenous use

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2015</u>
	Study Completion:	<u>12/31/2018</u>
	Final Report Submission:	<u>06/30/2019</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
 Life-threatening condition
 Long-term data needed

- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Resistance-associated substitutions that emerge in the presence of peramivir map to the HA surface, which is the target of investigational mAbs and the influenza virus vaccine. Whether these substitutions have an impact on the influenza virus vaccine needs to be evaluated.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

All of the peramivir resistance-associated substitutions that emerged in H1N1 and H3N2 influenza virus populations led to changes in antigenic sites. Resistance-associated substitutions that emerge in the presence of peramivir map to the HA surface, which is the target of investigational mAbs and the influenza virus vaccine. The resistance-associated substitutions that emerged in the presence of peramivir in influenza B virus also map to the HA surface. Patients that use peramivir and fail treatment may be at risk of propagating influenza viruses that are not susceptible to the influenza virus vaccine

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

- 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
Nonclinical virology study; see description above
 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

The goal of the PMC is to collect clinical data from an adequate number of subjects to characterize the effectiveness of peramivir 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. Genotypic and phenotypic data should be collected to characterize resistance-associated substitutions specific to influenza B virus.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, controlled clinical trial(s) that includes a sufficient number of subjects with acute uncomplicated influenza B infection such that the effectiveness of peramivir IV administration in this population can be characterized.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
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- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
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- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 206426
Product Name: RAPIVAB™ (peramivir injection) for intravenous use

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2015</u>
	Trial Completion:	<u>04/30/2018</u>
	Final Report Submission:	<u>12/31/2018</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Phase 1 data suggest drug exposures and safety of peramivir are similar between healthy elderly and younger subjects; however, the registrational trials used to support approval of peramivir did not include a sufficient number of subjects aged of 65 years or older to properly characterize the safety and efficacy of peramivir in an elderly population with acute uncomplicated influenza. As elderly patients are at high risk of developing complications from influenza and may have particular reasons to benefit from a single-dose IV formulation (e.g., decreased mobility, decreased tolerance or ability to adhere to a multi-day oral regimen, residence in a long-term care facility), it is expected that use of IV peramivir will be considerable in this population. Therefore, a PMC is considered appropriate.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized controlled trial to evaluate the safety, PK and antiviral activity of IV peramivir in elderly subjects with acute uncomplicated influenza, aged 65 years or older. Subjects should be evaluated in a predominantly ambulatory setting, although it is recognized that some elderly subjects with influenza may be treated in a residential facility, a subacute skilled nursing facility, or even hospitalized setting.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 206426
Product Name: RAPIVAB™ (peramivir injection) for intravenous use

PMR/PMC Description: 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).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2015</u>
	Trial Completion:	<u>04/30/2018</u>
	Final Report Submission:	<u>12/31/2018</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The registrational trials used to support approval of peramivir did not include subjects at high risk of complications from influenza infection, as defined by the CDC. In the absence of adequate clinical data, therefore, there is a theoretical concern that peramivir might not be as safe or effective in this population. As use of the drug product is expected to be considerable in a high-risk patient population, a PMC is considered appropriate.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized controlled trial to evaluate the safety, PK, antiviral activity, and clinical benefit of IV peramivir in subjects at higher risk for influenza complications, as defined by the U.S. Centers for Disease Control and Prevention (CDC). Subjects should be evaluated in a predominantly ambulatory setting, although it is recognized that some high-risk subjects with influenza may require hospitalization.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

ELIZABETH G THOMPSON
12/18/2014

WILLIAM B TAUBER
12/18/2014

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

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

Memorandum

Date: November 12, 2014

To: Elizabeth Thompson
Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Kemi Asante, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 206426
RAPIVAB™ (peramivir injection), for intravenous use

In response to DAVP's February 3, 2014 consult request, OPDP has reviewed the proposed package insert (PI) and carton/container labeling for RAPIVAB™ (peramivir injection), for intravenous use.

Comments on the PI are provided below and are based on the version of the PI accessed from the following EDR link provided by DAVP via email on October 30, 2014: <\\CDSESUB1\evsprod\NDA206426\206426.enx>.

We have no comments on the draft carton/container labeling received by DAVP via email on November 12, 2014.

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at 301-796-7425 or Kemi.Asante@fda.hhs.gov.

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/s/

OLUWASEUN A ASANTE
11/12/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: November 7, 2014
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 206426
Product Name and Strength: Rapivab (peramivir) Injection,
200 mg/20 mL (10 mg/mL)
Submission Date: October 30, 2014
Applicant/Sponsor Name: Biocryst Pharmaceuticals
OSE RCM #: 2013-2842-1
DMEPA Primary Reviewer: James Schlick, RPh, MBA
DMEPA Team Leader: Vicky Borders-Hemphill, Pharm.D.

1 PURPOSE OF MEMO

The Division of Antiviral Products (DAVP) requested that we review the revised container label, carton labeling, and package insert labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container label, carton labeling, and package insert labeling are acceptable from a medication error perspective.

¹ Schlick J. Label and Labeling Review for Rapivab (NDA 206426). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 OCT 20. 12 p. OSE RCM No.: 2013-2842.

APPENDIX A. LABEL AND LABELING

Container Label: Submitted via email on November 5, 2014

Carton Labeling: Submitted via email on November 5, 2014

Package Insert Labeling: Submitted on October 30, 2014; No image

Container Label



Carton Labeling



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/s/

JAMES H SCHLICK
11/07/2014

BRENDA V BORDERS-HEMPHILL
11/07/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review: October 20, 2014
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 206426
Product Name and Strength: Rapivab (peramivir) Injection,
200 mg/20 mL (10 mg/mL)
Product Type: Single
Rx or OTC: Rx
Applicant/Sponsor Name: Biocryst Pharmaceuticals
Submission Date: December 21, 2013
OSE RCM #: 2013-2842
DMEPA Primary Reviewer: James Schlick, RPh, MBA
DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

Biocryst Pharmaceuticals submitted this NDA application for approval of peramivir injection for the treatment of acute uncomplicated influenza in patients 18 years and older. Thus, the Division of Anti-viral Products (DAVP) consulted DMEPA to evaluate the container labels, carton labeling, and insert labeling from a medication error perspective.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A B
Previous DMEPA Reviews	N/A C
Human Factors Study	N/A D
ISMP Newsletters	N/A E
Other	N/A F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The packaging configuration requires a health care practitioner to use 3 vials to make the recommended 600 mg dose. Multiple vials required to achieve a single dose have led to medication errors because of users making miscalculations.¹ Due to the late stage of product development, we will not recommend reconfiguring the vial sizes to get a 600 mg dose from a single vial. However, we will monitor Rapivab post approval to determine if these errors occur.

The proposed carton is designed to hold the exact number of vials (3) for the recommended full dose of 600 mg. This is the recommended dose, and we anticipate this will be the most likely used dose. Therefore, this packaging is appropriate for patients who will receive a dose of

¹ <http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm331808.htm> Safety Considerations for Product Design to Minimize Medication Errors. Draft Guidance for Industry, CDER Drug Safety, December 2012. Accessed on April 24, 2014.

600 mg. However, less volume or fewer vials are needed for reduced doses due to renal impairment. Thus, we considered whether the packaging may contribute to some patients receiving greater doses than needed. However, we believe this risk can be addressed through appropriate labeling. Additionally, we will monitor post approval to determine if these errors occur.

The Division of Antiviral Products (DAVP) is currently negotiating the labeling with Biocryst regarding dose reductions for renal impairment. At present, the only dosage and preparation information on the carton labeling reflects the 600 mg dose, which may be misleading given that other doses may be required. Thus, we provide a recommendation in Section 4 to address this.

Biocryst has included the strength of 600 mg on the carton when each vial contains only 200 mg. This is problematic because practitioners are accustomed to the presentation of the strength per vial, not per carton. Therefore a healthcare practitioner may misinterpret the strength of each vial as 600 mg, leading to an underdose. We provide recommendations to address this in Section 4.1 below.

Additionally, our review of the labels and labeling for this product identified additional areas of vulnerability that may be subject to confusion and can be further optimized. We provide recommendations to address these in Section 4.1 below.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling can be improved to increase the readability and prominence of important information on the label and add important information to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR BIOCRYST PHARMACEUTICALS

General Comments

1. Consider revising the proprietary name so it appears in title case (e.g. Tradename) to optimize the readability of the proprietary name.²
2. The abbreviation 'I.V.' which is listed on the Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations³ 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.

² <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.

³ Available at: www.ismp.org/tools/errorproneabbreviations.pdf. Accessed January 30, 2014.

Carton Labeling

1. Including dose and preparation information for one dose, but not all doses, may increase the risk for errors during preparation of the drug. Thus, (b) (4)

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

"Dosage: [REDACTED] (b) (4)

to read similar to

"Dosage: See accompanying package insert for complete product information."

3. 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.
4. 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)

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

6. 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 per 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.

4.2 RECOMMENDATIONS FOR THE DIVISION

Full Prescribing Information, Section 2.4

1. We recommend incorporating preparation instructions for additional renal impairment doses. Ensure the preparation instructions for each dose are easy to identify in the preparation section.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rapivab that Biocryst Pharmaceuticals submitted on December 21, 2013 and the September 12, 2014 working version of the prescribing information.

Table 2. Relevant Product Information for Rapivab	
Active Ingredient	Peramivir
Indication	Treatment of acute uncomplicated influenza in patients 18 years and older
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	200 mg/20 mL (10 mg/mL)
Dose and Frequency	<p><u>Applicant's Dose and Frequency Proposal</u></p> <p>One 600 mg dose via intravenous infusion over 15 minutes. (b) (4)</p> <p><u>Proposed Doses from September 12, 2014 Working Version</u></p> <p>One 600 mg dose via intravenous infusion over 15 minutes. Renal Impairment: Recommended dose for patients with creatinine clearance 30-49 mL/min is (b) (4) mg and the recommended dose for patients with creatinine clearance 10-29 mL/min is 100 mg. In patients with chronic renal impairment maintained on hemodialysis, RAPIVAB should be administered after dialysis.</p>
How Supplied/ Container Closure	Supplied in glass vials with flip-off cap. Three vials are packaged in a cardboard carton.
Storage	Store vials at room temperature - 20°C to 25°C (68 to 77°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁴ along with postmarket medication error data, we reviewed the following Rapivab labels and labeling submitted by Biocryst Pharmaceuticals on December 21, 2013.

- Container label
- Carton labeling
- Prescribing Information (working version as of September 12, 2014)

G.2 Label and Labeling Images

Container Label



⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JAMES H SCHLICK
10/20/2014

IRENE Z CHAN
10/20/2014

MEMORANDUM

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

DATE: August 1, 2014

TO: Debra Birnkrant M.D.
Director
Division of Anti-Viral Products (DAVP)
Office of Antimicrobial Products

FROM: Chase H. Bourke, Ph.D.
Pharmacologist, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Acting Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 206-426, Peramivir, 600 mg,
sponsored by Biocryst Pharmaceuticals Inc., USA

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4.	Final Site Classifications.....	4
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1. Summary

At the request of the Division of Antiviral Products (DAVP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected the following study:

BCX1812-113: "An Open Label, Randomized, Single Center, Two-Period Crossover Study to Evaluate the Relative Bioavailability and Safety of 600 mg Peramivir Administered Intramuscularly Versus 600 mg Peramivir Administered Intravenously in Healthy Adult Subjects"

Inspection of the clinical portion of the study was conducted at the following site:

ICON Development Solutions, San Antonio, TX

Inspection of the analytical portion of the study was conducted at the following site:

[REDACTED] (b) (4)

2. Recommendations

Following evaluation of the inspectional findings and the analytical site's response to Form FDA 483, the data generated by ICON Development Solutions (clinical site) and [REDACTED] (b) (4) [REDACTED] (analytical site) were found to be reliable. Therefore, this reviewer recommends that data generated at these sites should be accepted for Agency review.

3. Inspectional Findings by Site

3.1. ICON Development Solutions, San Antonio, TX

The inspection of the clinical portion of the study was conducted by Joel Martinez (ORA) during April 29 - May 2, 2014 at ICON Development Solutions, San Antonio, TX (ICON).

Following the inspection of the analytical site, Form FDA 483 was issued (**Attachment 5.1**). The response to Form FDA 483 was received on [REDACTED] (b) (4) (**Attachment 5.2**).

The Form FDA 483 observations, the firm's response to the Form FDA 483 observations, and our evaluation follow.

3.2.1. Failure to collect and retain reserve samples for the bioavailability study under protocol number BCX 1812-113.

In their response to Form FDA 483, ICON stated that they had already taken corrective action following the previous FDA inspection in [REDACTED] (b) (4). In response to a previous 483 observation, they had written an SOP detailing the procedures to follow regarding retention of bioavailability and bioequivalence samples. However, the current study audited was conducted prior to this corrective action. To prevent future recurrence of this problem ICON plans to conduct additional training of their pharmacy staff.

Because the test article and reference standard used in study **BCX 1812-113** differed in strength (10 mg/mL vs. 150 mg/mL), misidentification or inappropriate substitution of the reserve samples is unlikely. In the opinion of this reviewer, this observation has no effect on the study outcome.

3.2.2. Failure to keep accurate records to allow for the verification of the collection and processing of the PK samples under BCX 1812-113. Specifically, the B1113 "Sample for PK Analysis" records document times which are discrepant between the "Sample Into Lab" time and "Draw/Centrifuge" times.

In the response to Form FDA 483, the firm stated that the discrepancy was due to a procedural flaw and a QC failure. The firm has already amended their procedures so one staff member is responsible for the chain of custody. Additionally, the QC step will be performed on 100% of logging times.

In the opinion of this reviewer, the proposed corrective actions are acceptable. This observation has no effect on the study outcome.

3.2. [REDACTED] (b) (4)

Following the inspection of the analytical site by [REDACTED] (b) (4) (OSI) during [REDACTED] (b) (4) no objectionable conditions were observed and no Form FDA-483 was issued.

4. Final Site Classifications

VAI - ICON Development Solutions, San Antonio, TX
FEI: 3007158681

NAI - [REDACTED] (b) (4)
FEI: [REDACTED] (b) (4)

cc:
OSI/DBGLPC/Taylor/Haidar/Bonapace/Choi/Dasgupta/Skelly/Bourke
OSI/DBGLPC/Fenty-Stewart/Nkah/Dejernett/Johnson
OND/OAP/DAVP/Birnkrant/Thompson
OCP/DCP4/Reynolds/
ORA/DAL DO/Martinez
ORA/NOL DO/Dooley

Draft: CHB 7/14/2014
Edit: AD 7/14/2014
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ICON Development Solutions, San Antonio, TX/NDA 206-
426 Peramivir
Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Labora gram/Analytical
Sites/ [REDACTED] (b) (4) / NDA 206-
426 Pe
OSI FILE# BE6672; O:\BE\assigns\bio206426 bio per.doc
FACTS: 8751683

5. Attachments

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/s/

CHARLES R BONAPACE
08/01/2014

WILLIAM H TAYLOR
08/01/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 28, 2014

TO: Elizabeth Thompson, Regulatory Health Project Manager
Peter Miele, M.D., Medical Officer
Division of Antiviral Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., MPH
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206-426

APPLICANT: BioCryst Pharmaceutical, Inc.

DRUG: Peramivir

NME: No

THERAPEUTIC CLASSIFICATION: Standard review
INDICATION: Treatment of acute uncomplicated influenza in adults
CONSULTATION REQUEST DATE: February 14, 2014
DIVISION ACTION GOAL DATE: TBD
PDUFA DATE: December 23, 2014
INSPECTION SUMMARY DUE DATE: September 10, 2014

I. BACKGROUND:

The Applicant conducted two pivotal trials in support of approval of Peramivir for the treatment of acute uncomplicated influenza in adults.

The pivotal clinical Protocols BCX1812-211 and BCX1812-212 were selected to support the pending application.

Protocols: BCX 1812-211 entitled “A Phase II, Multicenter, Randomized, Double-Blind, Placebo- Controlled Study to Evaluate the Efficacy and Safety of Intramuscular Peramivir in Subjects with Uncomplicated Acute Influenza”, and

BCX 1812-212 entitled “A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Two Doses (300mg and 600mg) of Peramivir in Subjects with Uncomplicated Acute Influenza”.

Protocol BCX1812.211

The primary objective of this study was to evaluate the efficacy of peramivir administered intramuscularly compared to placebo in adult subjects with uncomplicated acute influenza.

The secondary objectives were: 1) to evaluate the safety and tolerability of peramivir compared to placebo in adults with uncomplicated acute influenza, and 2) to evaluate the effect on time to alleviation of symptoms, time to resumption of usual daily activities, incidence of influenza-related complications.

This protocol was a multi-national, randomized, double-blind, controlled study comparing the efficacy and safety of peramivir versus placebo administered intravenously once daily for 14 days in adults with uncomplicated acute influenza. Subjects with signs and symptoms compatible with acute influenza infection will be evaluated for participation. The study enrolled a total of 300 patients with confirmed influenza. Eligible subjects were randomized to receive intramuscularly peramivir for 14 days.

Protocol BCX1812-212

The objective of this trial was to evaluate the efficacy of peramivir administered intramuscularly compared to placebo on the time to alleviation of clinical symptoms in adult subjects with uncomplicated influenza.

The secondary and exploratory objectives of this study were: 1) to evaluate the safety and tolerability of peramivir administered intramuscularly; 2) to evaluate clinical outcomes in response to treatment; and 3) to assess changes in influenza viral susceptibility to neuraminidase inhibitors following treatment

The protocol was a multicenter, randomized, double-blind study to evaluate the efficacy and safety of single doses of peramivir (300 and 600mg) administered intramuscularly versus

placebo in adults with uncomplicated acute influenza. The study enrolled about 400 subjects into the study. Subject were assigned to treatment and stratified according to Rapid Antigen Test (RAT) results for influenza A or B and current smoking behavior. Subjects were centrally randomized via IVRS system in a 1:1:1ratio to receive one of the three treatment groups

The review division requested inspection of six clinical investigators for the pivotal studies noted above because data from the studies are considered essential to support the approval process. These sites were targeted for inspection due to 1) enrollment of a relatively large number of subjects with a treatment effect that was greater than average, 2) high screen failure rate (Site 60/Dr. Wise); high percentage of subjects meeting primary endpoint (100% Site 448/Dr. Kovacs and Site 405/Dr. Henry, and 3) the need to determine if sites conducted the trial ethically and were in compliance with GCP regulation.

II. RESULTS (by protocol/site):

Name of CI, location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
John M. Wise, M.D Bozeman Urgent Care 1006 W. Main St. Bozeman, MT 59715 Site #60	Protocol BCX1812-211 Number of subjects: 14	March 24-28, 2014	Pending (preliminary classification OAI/WL)
Mark Stich, M.D. Jacksonville Center for Clinical Research 810 Lane Ave. South Jacksonville, FL 32205 Site #55	Protocol BCX1812-211 Number of subjects: 13	April 14-16 and 22-23, 2014	NAI
David Damian, M.D. Discover Research, Inc. 2210 East 29th Street Byran, TX 77802 Site# 404	Protocol BCX1812-212 Number of subjects: 15	March 3-7, 2014	NAI
Stephen Kovacs, M.D. Urgent Care of Green County, PLLC 13616 East 103 Street N. Suite A Owasso, Ok 74055 Site #448	Protocol BCX1812-212 Number of subjects: 17	March 17-21, 2014	NAI
Dan Henry, M.D J. Lewis Research, Inc. Foothill Family Clinic	Protocol BCX 1812-212 Number of subjects:	June 17 - 20, 2014	Pending (preliminary classification)

Name of CI, location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
2295 Foothill Dr. Salt Lake City, UT 84109 Site #405	10		NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. John Wise, M.D
Bozeman, Mt 59715

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 206-426 and attempted to inspect Study Protocols BCX1812-211 and BCX 1812-212. For Study BCX1812-211, a total of 74 subjects were screened, 60 subjects were reported as screen failures, 14 subjects were randomized into the study, and 14 subjects completed the study according to the application. For study BCX1812-212, a total of six subjects were enrolled and all six completed the study.

The original medical records/source data for both studies BCX1812-211 and BCX 1812-311 were shredded on January 24, 2014. The clinical investigator stated that the study coordinator “mistakenly included the study files for both studies, along with business documents intended for shredding, and provided them to a mobile shredding company”. In the absence of source data, verification of the data submitted in support of the application could not be determined. However, a limited inspection of few records from study BCX 1812-212 revealed that the case report forms (CRFs) for at least five subjects were signed off by a sub-investigator who was not listed on the Form 1572 as a responsible individual. No other issues were noted from the limited inspection of study BCX1812-212.

- b. General Observations/Commentary:** At the conclusion of the inspection, a Form FDA 483 was issued to Dr. Wise. The inspectional finding included the clinical investigator failure to maintain and retain study records as required by FDA regulations. The failure to maintain and retain study source documents significantly compromises the validity and integrity of the data generated to support the pending application.
- c. Assessment of Data Integrity:** The OSI reviewer communicated the status of this inspection with the review division and an agreement was reached to exclude the site from their final assessment in support of safety and efficacy. Overall, the data

generated in support of the clinical efficacy and safety at Dr. Wise's site should not be considered reliable or acceptable in support of the pending application. OSI will classify the inspection as Official Action Indicated (OAI) and a Warning Letter (WL) will be issued to Dr. John Wise, M.D. More information will be available in the final WL once it is cleared by General Counsel and entered in DAARTS.

2. Mark Stich, M.D.
Jacksonville, FL 32205

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 206-426 and inspected Study Protocol BCX1812-211. At this site, a total of 16 subjects were screened, three subjects were reported as screen failures, and 13 subjects were randomized into the study and were properly followed according to the study protocol. Twelve (12) subjects completed the study and one subject was reported as lost to follow-up. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for all 13 subjects were reviewed. The medical records/source documents for seven enrolled subjects were reviewed in depth including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. A cursory review of the remaining six subjects was conducted. The field investigator compared the source documents/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Stich. However, our investigator noted and discussed with the clinical investigator minor protocol deviations such as an ECG not performed for one subject, body weight not obtained for three subjects, urine sample not done for one subject, and concomitant medications listed on the subjects' diary were not always transcribed to the concomitant medication list.

The clinical investigator acknowledged the inspectional findings in a written response dated May 7, 2014 in which he agreed with the observations and provided adequate explanation to include implementation of corrective actions to prevent the recurrence of the inspectional findings. OSI finds his response acceptable. In general, the medical records reviewed were found to be in order and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

- c. Assessment of Data Integrity:** Although minor deviations were noted at the above site, the findings appear to be isolated instances, and it is unlikely that these findings significantly impacted the outcome of the study. The data generated in support of the clinical efficacy and safety at Dr. Stich's site are considered reliable and may be used in support of the pending application.

**3. David Damian, M.D.
Byran, TX 77802**

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 206-426 and inspected Study Protocol BCX1812-212. At this site, a total of 32 subjects were screened, 17 subjects were reported as screen failures, 15 subjects were randomized into the study, and all 15 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 15 subjects enrolled were reviewed. The medical records/source documents for the majority of subjects were reviewed in depth, including drug accountability records, subjects diaries, study procedures, laboratory results, financial disclosures, vital signs, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents for all subjects were compared to data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Damian. The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** Overall, the study appears to have been conducted adequately, and the data generated/submitted in support of the clinical efficacy and safety from this site are considered reliable and appear acceptable in support of the pending application.

**4. Stephen Kovacs, M.D.
Owasso, OK 74055**

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 206-426 and inspected Study Protocol BCX1812-212. At this site, a total of 29 subjects were screened, 12 subjects were reported as screen failures, 17 subjects were randomized into the study, and 17 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment. However, four subjects did not sign the recent IRB approved version in a timely manner.

The medical records/source data for eight subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, laboratory results, study procedures, IRB records, sponsor correspondence, prior and current medications and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Kovacs. However, our investigator discussed with clinical investigator the delay in performing an EKG for one subject. In general, the medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated may be used to support the pending application.
- c. Assessment of Data Integrity:** With the exception of the delay in performing an EKG for one subject, the data generated in support of the clinical efficacy and safety at this site are considered reliable and acceptable in support of the pending application.

5. Dan Henry, M.D.
Salt Lake City, UT 84109

- a. What was Inspected:** This inspection was performed as a data audit for NDA 206-426 and inspected Study BCX1812-212. At this site, a total of 43 subjects were screened, 33 subjects were reported as screen failures, 10 subjects were randomized into the study, and all 10 subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for 10 subjects were reviewed for primary/secondary endpoints. The medical records reviewed included drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include adverse events and protocol deviations. No deficiencies were noted.

- c. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Henry. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- d. Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Henry's site is considered reliable and acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Five clinical investigator sites were inspected in support of this application. The inspection of the five clinical investigators listed above revealed one site (Dr. Wise) with significant regulatory violations and the pending classification is Official Action Indicated (OAI); we recommend that data from this site not be used. The pending classification for Dr. Henry's site is No Action Indicated (NAI) and the final

classification for Drs. Stich, Damian, and Kovacs sites are No Action Indicated (NAI). For the pending classification, a summary addendum will be generated if conclusions change upon receipt and review of the EIR. Overall, the data submitted from these four sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
(Acting Branch Chief for Kassa Ayalew, M.D. M.P.H.)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTOINE N EL HAGE
07/29/2014

SUSAN D THOMPSON
07/29/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206426

Application Type: New NME NDA

Name of Drug/Dosage Form: RAPIVAB (peramivir) solution for IV infusion

Applicant: BioCryst Pharmaceuticals, Inc.

Receipt Date: December 23, 2013

Goal Date: December 23, 2014

1. Regulatory History and Applicant's Main Proposals

BioCryst Pharmaceuticals, Inc. has submitted an original NDA (PDUFA V NME) that includes safety and efficacy data in support of an indication for the treatment of acute uncomplicated influenza in patients 18 years and older. The NDA is supported by studies conducted by BioCryst (IND 69038 and (b)(4)) and Shionogi and includes 17 Phase 1 studies, 4 Phase 2 studies and 6 Phase 3 studies. Seven influenza studies were conducted in patients with acute uncomplicated influenza and three studies were conducted in patients hospitalized with influenza.

In 2009, an Emergency Use Authorization for IV peramivir (under IND 69038) was authorized during the H1N1 pandemic.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an information request. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 23, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *No horizontal line separating TOC from FPI.*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is white space between HL heading and HL limitation statement. Also appears to be too much white space between HL limitation statement and product title.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment: Need to verify if applicant is calling the established name peramvir or peramivir injection; also note that product title is not displayed correctly (for intravenous use should be on same line).

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.
Comment: Fill in year of approval action

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.
Comment:
- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
Comment:
- N/A** 14. The BW must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” This statement should be centered immediately beneath the heading and appear in *italics*.
Comment:
- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “***See full prescribing information for complete boxed warning.***”).
Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage in Highlights

Selected Requirements of Prescribing Information

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Only one dosage form*

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *Needs phone number from manufacturer*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Needs to be updated with month/year of action*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment: *Need to change "See" to "see"*

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *Need to revise postapproval to post-approval*

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

ELIZABETH G THOMPSON
05/01/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 206426 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Rapivab (proposed trade name) Established/Proper Name: peramivir injection Dosage Form: injection Strengths: 200 mg (20 mL) vial (solution for IV infusion)		
Applicant: BioCryst Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: December 19, 2013 Date of Receipt: December 23, 2013 Date clock started after UN:		
PDUFA Goal Date: December 23, 2014	Action Goal Date (if different): TBD	
Filing Date: February 21, 2014	Date of Filing Meeting: January 29, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 (NME)		
Proposed indication(s)/Proposed change(s): treatment of acute uncomplicated influenza in patients 18 years and older		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" type="checkbox"/> Fast Track Designation (granted 1/5/2006) <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 69038, (b)(4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Proprietary: RAPIVAB Nonproprietary: Peramivir injection Dosage form: injection
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Attached; resubmitted on 2/20/14 to include that sites are ready for inspection (except (b) (4))
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients,</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Conditionally approved on March 4, 2011.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	RMP
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No PPI or MedGuide; OPDP did not want a consult
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult submitted
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult submitted
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

study report to QT Interdisciplinary Review Team)				
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): Type B EOP1 10-13-2006 Type A reg pathway 7-28-2009 <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Type B EOP2 meeting originally granted on but changed to Type C meeting once background pkg reviewed (3-17-2009 mtg date)
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): June 28, 2013 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 23, 2013

BLA/NDA/Supp #: 206426

PROPRIETARY NAME: RAPIVAB (proposed trade name)

ESTABLISHED/PROPER NAME: peramivir IV

DOSAGE FORM/STRENGTH: solution for IV infusion (200 mg in 20 mL vial)

APPLICANT: BioCryst Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of acute, uncomplicated influenza in patients 18 years of age and older

BACKGROUND: BioCryst submitted an original NDA application for RAPIVAB (peramivir injection) which provided safety and efficacy data to support a proposed indication for the treatment of acute uncomplicated influenza in patients 18 years and older.

The NDA is supported by studies conducted under INDs 69038 (IV) (b)(4). The NDA will be reviewed under PDUFA V NME (The Program) with a PDUFA date of December 23, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elizabeth Thomspson	Y
	CPMS/TL:	Elizabeth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Linda Lewis		Y
Clinical	Reviewer:	Peter Miele	Y
	TL:	Linda Lewis	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Takashi Komatsu	Y
	TL:	Jules O'Rear	Y
Clinical Pharmacology	Reviewer:	Leslie Chinn (clinical pharmacology and pharmacometrics)	Y
	TL:	Islam Younis Jeff Florian (PM)	Y Y
Biostatistics	Reviewer:	Tom Hammerstrom	Y
	TL:	Greg Soon	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kuei-Meng Wu	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:	Matthew Jackson	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Fuqiang Liu	Y
	TL:	Steve Miller	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Neal Sweeney	N
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:	Krishnakali Ghosh	Y
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	Y
	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:	Kelly Cao	Y

OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Tony El-Hage	Y
	TL:	Susan Leibenhaut (clinical) Sripal Mada (clin pharm)	N Y
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Danyal Chaudhry (OSE) Vikram Arya		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>Comments:</p> <ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES

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

<p>Comments:</p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: All sites ready for inspection except Jubilant Hollister Stier (OAI alert). BioCryst will announce when this site is ready for inspection.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Edward Cox, MD, MPH</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): May 19, 2014</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).

<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

ELIZABETH G THOMPSON
02/27/2014