CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206494Orig1s000

OTHER REVIEW(S)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 19, 2015

TO: Carmen DeBellas, Pharm.D., Regulatory Project Manager
Benjamin Lorenz M.D., Medical Officer, CDTL
Division of Anti-Infective Products

FROM: Janice Pohlman, M.D., M.P.H., Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections (Addendum)

NDA: 206494

APPLICANT: Cerexa, Inc. (a wholly owned subsidiary of Forest Laboratories, Inc.)
DRUG: Ceftazidime/avibactam
NME: Yes (avibactam component)
THERAPEUTIC CLASSIFICATION: Priority Review
INDICATIONS (proposed): Complicated Intra-abdominal Infections (cIAI)
Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP)
Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options

CONSULTATION REQUEST DATE: August 28, 2014
INSPECTION SUMMARY GOAL DATE: January 5, 2015
DIVISION ACTION GOAL DATE (proposed): February 11, 2015
PDUFA DATE: February 25, 2015

I. BACKGROUND:

This Clinical Inspection Summary (CIS) Addendum serves to update results of inspections conducted in support of this NDA. At the time the original CIS was entered into DARRTS, the clinical site inspection of Mayakonda Ramesh, M.D. in Bangalore, India who participated in Study NXL104 2002 was pending. This inspection has now been completed. For additional background and study details, see CIS from February 4, 2015 in DARRTS.

Study NXL104 2002 was a multicenter, double-blind, randomized, comparative study to designed to estimate the safety, tolerability, and efficacy of ceftazidime/NXL104 plus metronidazole vs. meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults. The study was conducted from March 2 – December 12, 2009, with 204 subjects randomized at 33 centers in 8 countries, with the majority of subjects outside the U.S.

II. RESULTS (by Site):

Name of CI	Protocol # and # of Subjects	Inspection Date	Final Classification
Site #400 Luis D. Gonzalez Patzan, M.D. Clinica De Enfermedades Infeciosas Centro Medico Militar, Finca El Palomar Actan, Santa Rosita, Zona 16 Guatemala	NXL104 2001 15 subjects	November 12 – 14, 2014	Pending Preliminary VAI
Site #113 Salahuddin Bibi, M.D. Modesto Clinical Research 1325 Melrose Ave., Suite C Modesto, CA 95350	NXL104 2001 6 subjects	January 6 – 13, 2015	Pending Preliminary VAI
Site #64 Mayakonda Ramesh, M.D. Victoria Hospital Room No. 140, Ground Floor Fort. Kamataka Bangalore, India 560002	NXL104 2002 26 subjects	February 2 – 6, 2015	Pending Preliminary NAI
Site #12 Christopher Lucasti, D.O. South Jersey Infectious Disease 730 Shore Road Somers Point, NJ 08244	NXL104 2002 10 subjects	October 3 – 16, 2014	Pending Preliminary NAI
Actavis P.L.C. (formerly Forest Laboratories, Inc./Cerexa subsidiary) Forest Research Institute Harborside Financial Center Plaza V, 20th Floor 185 Hudson St. Jersey City, NJ 07311	NXL104 2001 NXL104 2002	November 11 – 26, 2014	Pending Preliminary VAI

(b) (4)	NXL104 2002	(b) (4)	Pending Preliminary NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

III. INSPECTION OBSERVATIONS

Clinical Investigator: Mayakonda Ramesh, M.D.
Bangalore, India

a. What was inspected:
Data listings submitted to the NDA were verified against source data.

b. General observations/commentary:
Twenty eight subjects were screened and consented and 26 subjects were randomized and completed the study. Seventeen subject's records were reviewed. Primary efficacy endpoint data were verified and there was no under-reporting of adverse events.

c. Assessment of data integrity:
The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The preliminary classification of the inspection at Dr. Ramesh's clinical site for Study NXL1004 2002 is No Action Indicated (NAI).

The data generated by this site appear acceptable for use in support of the application.

For additional discussion of findings and recommendations, refer to the Clinical Inspection Summary in DARRTS, February 4, 2015.

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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

/s/

JANICE K POHLMAN
02/19/2015

KASSA AYALEW
02/20/2015

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 # 206494
Product Name: Avycaz

PMR Description: 2862-1: Conduct a randomized, multicenter, active-controlled trial to evaluate the safety and tolerability of AVYCAZ (ceftazidime-avibactam) in children from 3 months to less than 18 years of age with cUTI. The dose for this study will be determined upon review of the data to be submitted by June 2015 from a single-dose, multicenter, non-comparative study assessing the pharmacokinetics of ceftazidime-avibactam in pediatric patients from 3months to less than 18 years of age.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	06/2015
	Study/Trial Completion:	09/2017
	Final Report Submission:	09/2018

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

Infections such as cUTI caused by ceftazidime-resistant pathogens are potentially life-threatening and represent an urgent unmet need.

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."

Under PREA, AVYCAZ for the treatment of cUTI and cIAI needs to be evaluated in pediatric patients. This study will evaluate the pediatric dose that can be described in labeling.

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.

Under PREA, AVYCAZ for the treatment of cUTI and cIAI needs to be evaluated in pediatric patients. This study will evaluate the pediatric dose that can be described in labeling.

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 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 #	206494
Product Name:	Avycaz

PMR Description: 2862-2: Conduct a randomized, multicenter, active-controlled trial to evaluate the safety and tolerability of AVYCAZ ceftazidime-avibactam in children from3 months to less than 18 years of age with cIAI. The dose for this study will be determined upon review of the data to be submitted by June 2015 from a single-dose, multicenter, non-comparative study assessing the pharmacokinetics of AVYCAZ (ceftazidime-avibactam) in pediatric patients from birth to less than 18 years of age.

PMR Schedule Milestones:		
	Final Protocol Submission:	06/2015
	Study/Trial Completion:	09/2017
	Final Report Submission:	09/2018

6. 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

Infections such as cIAI caused by ceftazidime-resistant pathogens are potentially life-threatening and represent an urgent unmet need.

7. 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."

Under PREA, AVYCAZ for the treatment of cUTI and cIAI needs to be evaluated in pediatric patients. This study will evaluate the pediatric dose that can be described in labeling.

8. 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?

9. 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.

Under PREA, AVYCAZ for the treatment of cUTI and cIAI needs to be evaluated in pediatric patients. This study will evaluate the pediatric dose that can be described in labeling.

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

_____

10. 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)

APPEARS THIS WAY ON ORIGINAL

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 # 206494
Product Name: Avycaz

PMR Description: 2862-3: Conduct a trial to evaluate the pharmacokinetics, safety, and tolerability of AVYCAZ (ceftazidime-avibactam) in children from birth to less than 3 months of age with late-onset sepsis.

PMR Schedule Milestones:		
	Final Protocol Submission:	06/2018
	Study/Trial Completion:	12/2019
	Final Report Submission:	12/2020

11. 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

Infections such as sepsis caused by ceftazidime-resistant pathogens are potentially life-threatening and represent an urgent unmet need.

12. 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."

Under PREA, safety and effectiveness of AVYCAZ in the treatment of late onset sepsis needs to be evaluated. This study will evaluate the pediatric dose that needs to be used in safety and effectiveness studies

13. 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?

14. 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.

Under PREA, safety and effectiveness of AVYCAZ in the treatment of late onset sepsis needs to be evaluated. This study will evaluate the pediatric dose that needs to be used in safety and effectiveness
studies

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

_____

15. 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

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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)

APPEARS THIS WAY ON ORIGINAL

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 #	206494
Product Name:	Avycaz

PMR Description: 2862-5: Conduct a trial or submit data from the Phase 3 trial in cIAI to evaluate the pharmacokinetics, safety and clinical outcomes in adult patients with baseline renal impairment (creatinine clearance of 50 mL/min or less) receiving AVYCAZ (ceftazidime-avibactam) dosing regimen adjusted for renal function.

PMR Schedule Milestones:		
	Final Protocol Submission:	Submitted
	Trial Completion:	Completed
	Final Report Submission:	12/2015

16. During application review, explain why this issue is appropriate for a PMR 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

This study is needed in order to determine the appropriate dose to administer in patients with renal impairment with a creatinine clearance of 50mL/min or less.

17. 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."

A safety signal of increased mortality was observed in a subgroup of patients with baseline renal impairment; a biologically plausible reason for an adverse outcome was using a subtherapeutic dose of ceftazidime-avibactam in patients with baseline renal impairment. This study is needed in order to determine the appropriate dose to administer in patients with renal impairment with a creatinine clearance of 50mL/min or less.

18. 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?

19. 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.

Patients with baseline renal impairment with a creatinine clearance of 50mL/min or less will be studied.

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

_____

20. 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.*

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(signature line for BLAs)

APPEARS THIS WAY ON ORIGINAL

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 # 206494
Product Name: Avycaz

PMR/PMC Description: 2862-4: Conduct a prospective study over a five-year period after the introduction of AVYCAZ (ceftazidime-avibactam) to the market to determine if decreased susceptibility to AVYCAZ (ceftazidime-avibactam) is occurring in the target population of bacteria that are in the approved AVYCAZ (ceftazidime-avibactam) label.

Final protocol submission:	09/2015
First interim report:	05/2016
Second interim report:	05/2017
Third interim report:	05/2018
Fourth interim report:	05/2019
Fifth interim report:	05/2020
Sixth interim report:	02/2020
Study completion:	02/2020

21. 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

Long-term microbiologic surveillance data are needed to study development of bacterial resistance against AVYCAZ (ceftazidime-avibactam).

22. 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 required to determine if resistance to AVYCAZ (ceftazidime-avibactam) is occurring in the target population of bacteria specific to the indications in the label.
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23. 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?

24. 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 prospective study over a five-year period on the susceptibility of target bacteria to AVYCAZ (ceftazidime-avibactam).

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)

A study of the mechanisms of resistance to AVYCAZ (ceftazidime-avibactam) if such isolates are identified during the five-year surveillance study

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

25. 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

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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)

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

/s/

CARMEN L DEBELLAS
02/17/2015

JOSEPH G TOERNER
02/17/2015

505(b)(2) ASSESSMENT

Application Information		
NDA # 206494	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Avycaz Established/Proper Name: ceftazidime/avibactam Dosage Form: Injection Strengths: 2 grams ceftazidime and 0.5 grams avibactam		
Applicant: Forest Research Laboratories, Inc.		
Date of Receipt: June 25, 2014		
PDUFA Goal Date: February 25, 2014	Action Goal Date (if different):	
RPM: Carmen DeBellas		
Proposed Indication(s): Complicated Intra-abdominal Infections Complicated Urinary Tract Infections including Pyelonephritis Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

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

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 50578 Fortaz (GSK)	Previous findings of safety and effectiveness as presented n the Fortaz prescribing information for the following: Indications and Usage Contraindications Warnings and Precautions Drug Interactions Use in Specific Populations Overdosage Clinical Pharmacology

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

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Phase 1/2 and Phase 3 clinical formulations, ceftazidime and avibactam are presented as an aqueous solution at the point of administration and no excipients are present in these formulations to affect the solubility or pharmacokinetics of either active ingredient. The Phase 3 formulation is identical to the product intended for commercial use. The Phase 3 formulation was also used in one Phase 1 study (D4280C00012). The Phase 3 proposed commercial drug product have the same manufacturing process.

RELIANCE ON PUBLISHED LITERATURE

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

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

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

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

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

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

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

YES ☐ NO ☐

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

RELIANCE ON LISTED DRUG(S)

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

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

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Fortaz (ceftazidime)	50-578	Y

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☒

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

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

b) Approved by the DESI process?

YES ☐ NO ☒

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

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

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

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

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

d) Discontinued from marketing?

YES ☐ NO ☒

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

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

The listed drug is ceftazidime. This application provides for the use of ceftazidime in combination with another drug avibactam.

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

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

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

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

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

YES ☐ NO ☒

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

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

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

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

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

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

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

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s): U.S. Patent Nos. 7112592, 7612087, 8178554, 8471025

No patents listed ☐ *proceed to question #14*

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

YES ☒ NO ☐

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

Patent number(s): Expiry date(s):

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

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

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

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

Patent number(s):

(a)

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

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

Date(s):

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

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

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

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

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

/s/

CARMEN L DEBELLAS
02/05/2015

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 3, 2015

TO: Carmen DeBellas, Pharm.D., Regulatory Project Manager
Benjamin Lorenz M.D., Medical Officer, CDTL
Division of Anti-Infective Products

FROM: Janice Pohlman, M.D., M.P.H., Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206494

APPLICANT: Cerexa, Inc. (a wholly owned subsidiary of Forest Laboratories, Inc.)
DRUG: Ceftazidime/avibactam
NME: Yes (avibactam component)
THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS (proposed): Complicated Intra-abdominal Infections (cIAI)
Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP)
Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options

CONSULTATION REQUEST DATE: August 28, 2014
INSPECTION SUMMARY GOAL DATE: January 5, 2015
DIVISION ACTION GOAL DATE (proposed): February 11, 2015
PDUFA DATE: February 25, 2015

I. BACKGROUND:

Ceftazidime-avibactam is an antibiotic that is made up of ceftazidime, an injectable third-generation cephalosporin approved by FDA in 1985 and avibactam (formerly NXL104, AVE1330), a novel non-β-lactam β-lactamase inhibitor. Ceftazidime has activity against gram-positive and gram-negative bacteria mediated through binding to penicillin-binding proteins. Avibactam inactivates a wide variety of β-lactamases and protects ceftazidime from degradation and extends the spectrum of activity to include many gram-negative bacteria not normally susceptible to ceftazidime.

The sponsor is seeking approval of this NDA for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). A single Phase 2 study for each indication was submitted in support of this application. Study NXL104 2001 was a multicenter, investigator-blinded, randomized, comparative study conducted to evaluate the safety, efficacy, and tolerability of ceftazidime/NXL104 (ceftazidime/avibactam) vs. imipenem/cilastatin followed by appropriate oral therapy in the treatment of cUTI in hospitalized adults. The study was conducted from November 6, 2008 – June 15, 2010 with 137 subjects randomized at 26 centers in 5 countries, with the majority of subjects outside the U.S. Study NXL104 2002 was a multicenter, double-blind, randomized, comparative study to estimate the safety, tolerability, and efficacy of ceftazidime/NXL104 plus metronidazole vs. meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults. The study was conducted from March 2 – December 12, 2009, with 204 subjects randomized at 33 centers in 8 countries, with the majority of subjects outside the U.S.

Two clinical sites, one foreign and one domestic, were selected for routine inspection for each of the two clinical studies. An inspection of the sponsor, Cerexa, Inc. (a subsidiary of Forest Laboratories, Inc.) was also conducted.

The Clinical Study Report for Study NXL104 2002 included an Executive Summary describing the sponsor's efforts (AstraZeneca) to ensure accuracy of dosing administration records of investigational product through an extensive drug reconciliation program. This was necessary because problems with the interactive voice response system (IVRS) used to randomize and assign specific drug doses malfunctioned during the conduct of the trial. The Executive Summary included a third party audit report describing processes and practices at (b) (4), the contract research organization (CRO) responsible for providing the IVRS for this study. A decision was made by OSI to inspect (b) (4) because of the IVRS problem and to review processes related to their data management responsibilities for this study, as well as to assess whether corrective actions had been made to their procedures.

II. RESULTS (by Site):

Name of CI	Protocol # and # of Subjects	Inspection Date	Final Classification
Site #400 Luis D. Gonzalez Patzan, M.D. Clinica De Enfermedades Infeciosas Centro Medico Militar, Finca El Palomar Actan, Santa Rosita, Zona 16 Guatemala	NXL104 2001 15 subjects	November 12 – 14, 2014	Pending Preliminary VAI
Site #113 Salahuddin Bibi, M.D. Modesto Clinical Research 1325 Melrose Ave., Suite C Modesto, CA 95350	NXL104 2001 6 subjects	January 6 – 13, 2015	Pending Preliminary VAI
Site #64 Mayakonda Ramesh, M.D. Victoria Hospital Room No. 140, Ground Floor Fort. Kamataka Bangalore, India 560002	NXL104 2002 26 subjects	(Planned) February 2 – 6, 2015	PENDING
Site #12 Christopher Lucasti, D.O. South Jersey Infectious Disease 730 Shore Road Somers Point, NJ 08244	NXL104 2002 10 subjects	October 3 – 16, 2014	Pending Preliminary NAI
Actavis P.L.C. (formerly Forest Laboratories, Inc./Cerexa subsidiary) Forest Research Institute Harborside Financial Center Plaza V, 20th Floor 185 Hudson St. Jersey City, NJ 07311	NXL104 2001 NXL104 2002	November 11 – 26, 2014	Pending Preliminary VAI
(b) (4)	NXL104 2002	(b) (4)	Pending Preliminary NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

III. INSPECTION OBSERVATIONS

1. Luis Gonzalez Patzan, M.D.
Santa Rosita, Guatemala

a. What was inspected:
Individual subject records for all randomized subjects were reviewed for informed consent, eligibility criteria, primary efficacy endpoint, and adverse events.

b. General observations/commentary:
At this site, 28 subjects were screened, 15 subjects were randomized, and 15 subjects completed the study. All randomized subjects signed informed consent documents prior to study participation.

Source documents were compared with data listings provided by the sponsor to the NDA. There was isolated under-reporting of minor adverse events as described below on the Form FDA 483. The primary efficacy endpoint data were verifiable,

A three item Form FDA 483 was issued for:

i. The investigation was not performed in accordance with the investigational plan.
Three (3) of 15 subjects did not meet inclusion/exclusion criteria.
a) Subject 40008 was enrolled on 12/16/09 with gram negative bacilli in the urine. On 12/19/09, the urine culture showed growth of *Pseudomonas aeruginosa* that was resistant to imipenem. The subject was dosed with imipenem until 12/28/09. Another urine culture from 1/5/10 continued to show growth of *P. aeruginosa* resistant to imipenem. The subject's CRF indicates that the subject met all eligibility criteria.

OSI Reviewer Comment: In Dr. Gonzalez's written response to the 483 dated 12/23/2015, he provides a local microbiology laboratory report for a urine culture (baseline, dated 12/16/09) showing the P. aeruginosa isolate intermediate to imipenem by disk diffusion and

resistant to imipenem by MIC. The investigator was blinded to study treatment and observed that the subject experienced marked clinical improvement (decreased fever, absence of chills, and disappearance of flank and suprapubic pain), so the subject was continued on study therapy.

Although Exclusion Criterion #3 states that subjects with urine culture at admission known to contain a uropathogen resistant to one or both study drugs should not be included in the study, the protocol does not describe a procedure for subject withdrawal, particularly in cases where clinical improvement has been observed.

b) Subject 40020 was enrolled on 1/15/10 with gram negative bacilli in the urine. On 1/17/10, the urine culture showed no growth. The subject was continued on study medication until 1/20/10.

OSI Reviewer Comment: The protocol states that if the admission culture does not contain a recognized uropathogen in any amount the subject should be withdrawn from the study.

The eligibility and continued treatment were reported by the CI to the sponsor and the sponsor also reported this violation to the NDA.

c) Subject 40012 was enrolled into the study on 12/18/09. The subject was enrolled and started on study medication that day, however, baseline laboratory studies required as part of eligibility assessment were not performed or reviewed until 12/19/09.

OSI Reviewer Comment: Dr. Gonzalez provided documentation that laboratory studies were obtained, results received, and subject was appropriately randomized and treated.

ii. Failure to report to the sponsor adverse events that may be regarded as caused by, or reasonably caused by an investigational product.
a) On 5/11/10, Subject 40028 reported depression and facial edema on 5/10/10. These were not reported as adverse events to the sponsor.
b) On 4/25/10, Subject 40027 reported rash on 4/24/10. On 4/27/10, the subject reported headache follow infusion of study drug. These were not reported as adverse events to the sponsor.

iii. Failure to prepare or maintain accurate records with respect to observations and data pertinent to the investigation. For Subjects 40001, 40004, 40005, 40010, and 40015, the Oral Medication Log and chart worksheets were inconsistent in reporting the end date of administration, with discrepancies of one to two days.

OSI Reviewer Comment: Subjects 40001. 40004, and 40005 were treated with ceftazidime/avibactam and Subjects 40010 and 40015 were treated with imipenem. For all five of these subjects, based on NDA data listings, it appears that the Test of Cure urine culture specified by protocol to be obtained five to nine days after End of Therapy (both IV and oral) was obtained within one to two days after oral therapy was discontinued. The sponsor did report that Visit 5 (Test of Cure) was performed outside of the protocol required window. Although the sponsor excluded these subjects from the clinical and microbiologically evaluable populations, it appears that these subjects were included in the microbiological intent to treat population based on the data listings.

The review division (DAIP/Dr. Lorenz) was notified when this finding was discovered.

c. Assessment of data integrity:
GCP violations were noted at the site as described above. The data from the site appear to be reliable based on communications with the field investigator, the Form FDA 483, and the CI's written response to the 483. Based upon the review of this preliminary information and information contained in the data listing, it appears that the Test of Cure urine cultures were not obtained within the appropriate timeframe and the results of those cultures may have been potentially impacted by subjects' oral antibiotic regimen.

Observations for Dr. Gonzalez (Patzan) are based upon communications with the field investigator, the Form FDA 483, the clinical investigator's response to the 483, and the NDA data listings.

2. Salahuddin Bibi, M.D.
Modesto, CA

a. What was inspected:
Inspection included review of clinical investigator qualifications, 1572s, financial disclosure records, general protocol adherence, sponsor monitoring, IRB review and approvals, randomization procedures, and drug accountability. All six randomized subject source documents were reviewed for eligibility criteria, efficacy, adverse events, and protocol deviations. Spot checks of electronic CRFs were also performed.

b. General observations/commentary:
At this site, 37 subjects were screened, 6 subjects were randomized, and 2 subjects completed the study. Final disposition of those not completing the study were consistent with reporting in the NDA data listing.

A one item Form FDA 483 was issued for the investigation not being performed in accordance with the investigational plan. All six randomized subjects (Subjects 11301, 11302, 11303, 11304, 11305, and 11306) received a dose of another potentially effective systemic antibiotic after obtaining the urine culture for entry into the study, a violation of exclusion criterion #3. Additionally, Subjects 11301 and 11304 were enrolled prior to obtaining results of the urine gram stain (urine culture was pending at the time as expected).

OSI Reviewer Comment: In a written response to the Form FDA 483 dated January 26, 2015, Dr. Bibi acknowledged the protocol violations as described on the 483. In the response, Dr. Bibi noted that two key routine processes used by the hospital contradicted requirements of the protocol. The processes include cancellation of repeat urine cultures obtained within one hour of a prior urine culture by the laboratory to avoid duplication of assessments and the laboratory's practice of not routinely conducting urine gram stains at the site. Dr. Bibi's response to the 483 was adequate.

c. Assessment of data integrity:
While the reliability of data reported by this clinical site to the sponsor and subsequently by the sponsor to the NDA has been verified during inspection, the review division will need to determine whether receipt of a dose of potentially effective systemic antibiotic following collection of the baseline urine culture and prior to receipt of investigational drug product has significant impact on the overall assessment of efficacy (microbiological efficacy at the Test of Cure Visit 5-9 days after completion of therapy. The sponsor did report the failure to repeat the urine culture following a dose of antibiotic as a protocol deviation.

Observations for Dr. Bibi are based upon communications with the field investigator, the Form FDA 483, and the clinical investigator's response to the 483.

3. Mayakonda Ramesh, M.D.
Bangalore, India

INSPECTION PENDING (Planned February 2-6, 2015)

4. Christopher Lucasti, D.O.
Somers Point, NJ

a. What was inspected:
Inspection included review of clinical investigator qualifications, 1572s, financial disclosure records, general protocol adherence, sponsor monitoring, IRB review and approvals, randomization procedures, and drug accountability. Individual subject records including informed consent documents, subject source documents such as hospital records, firm derived data collection documents, eCRFs, and pharmacy drug preparation records/logs were reviewed. All 10 randomized subjects' records were reviewed.

b. General observations/commentary:
At this site, 21 subjects were screened, 10 subjects were randomized, and 10 subjects completed the study. All 10 subjects and/or their legally authorized representatives signed informed consent documents before study participation.

Primary efficacy endpoint data was verifiable at the study site.

There was no under-reporting of clinically significant adverse events. One subject (Subject 12007) required a second surgery (POD #7) for a "wound infection" (surgical note dated 7/30/09) although the CI noted that the re-operation was required because of a "drain that was stuck" and there was no pus or positive culture to support the finding of a wound infection. Three subjects (Subjects 12005, 12006, and 12008) were noted to have source documentation of pain at the IV site by the ORA investigator, but the clinical investigator, Dr. Lucasti, indicated that this pain was not considered to be an adverse event since he did not observe any swelling or tenderness at the IV site.

c. Assessment of data integrity:
The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Observations for Dr. Lucasti are based upon preliminary review of the EIR.

5. Actavis, P.L.C., (formerly Forest Research Institute, Inc., Cerexa, Inc. (subsidiary) Jersey City, NJ

a. What was inspected:
The inspection covered the historical course of development/change in ownership of the drug product (NXL104/ceftazidime, CAZ104, CAZ-AVI). The following elements were reviewed for both protocols (Protocol NXL104 2001 and NXL104 2002): human subject protection by IRB, organization and personnel, including contract research organizations responsible for conducting study processes, monitoring procedures and activities, FDA Form 1572s, financial disclosure forms, test article integrity and accountability, data collection and handling, adverse experience reporting, quality assurance, and annual reports.

b. General observations/commentary:

A three item Form FDA 483 was issued for:

i. Failure to retain records and reports for two years after marketing application approval. Specifically,
a) For Study NXL104 2002, not all drug shipment records were retained for clinical sites 40, 41, 42, 47, 50, 53, 55, 60, 72, 80, and 81.
b) Interim monitoring reports (four or 0.97% of total number of reports for Study NXL104 2001 and six or 2.0% of total number of reports for Study NXL104 2002) were not retained.

ii. Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as outlined in the IND. Specifically, the monitoring reports for three of eight clinical sites reviewed for Study NXL104 2001 and six of nine clinical sites reviewed for Study NXL 104 2002 were not signed within required timeframes.

OSI Reviewer Comment: Although the reports were not signed in accordance with plan-required timeframes, there did not appear to be any gross deviations from GCP as reported by the ORA investigator.

Most of the referenced monitoring reports were from the time period after problems with the IVRS had been noted. Two reports, one from July 2009 and one from August 2009, did not have any information to suggest the IVRS was problematic, however the study monitor was blinded to treatment assignment while the site pharmacist was not. Therefore, there were limited interactions/discussions between the monitor and pharmacist.

iii. Failure to ensure proper monitoring of the study. Specifically, the original sponsor of Study NXL104 2002 (Novexel) did not promptly identify study drug allocation deficiencies with the IVRS (over assignment and under assignment of number of vials to study subjects) at 28 of 33 clinical study sites.

OSI Reviewer Comment: As noted in the discussion for the previous observation, the study monitor was blinded while the site pharmacist was not. Specific items in the monitoring report referring to supply were discussed with the pharmacist, but the unblinded monitor was not permitted to assess accuracy of drug accountability records in the pharmacy.

Based on a (b) (4) *CAPA (Corrective and Preventative Action Plan) dated December 4, 2009,* (b) (4) *first became aware of problems with the IVRS in September 2009 (9/13/09). Problems identified in September – October 2009 included: double randomization (IVRS assigned a randomization number twice to the same subject, allowing for dispensing of twice the amount of designated investigational product to the subject. Each notification listed a different set of vials of the same (two subjects) OR different treatment (one subject) to be administered to a given subject.), site failed to receive a randomization confirmation (one subject), assignment of vials to subjects at one site when subjects were actually enrolled at a different site (20 vials), and site receipt of duplicate blinded randomization notices (ten of the same notices sent for one subject).*

Based upon the written response dated December 12, 2014, to the Form FDA 483 from Actavis, Novexel became aware of the initial double randomization

incident on September 25, 2009. Novexel was subsequently notified of additional problems in October. Novexel subsequently created and finalized a Drug Reconciliation Plan during November – December 2009. This plan included having unblinded monitors from INC and ClinServ (monitoring CROs) complete on-site drug accountability per the monitoring plan. Novexel then completed reconciliation of (b) (4) *IVRS with randomization schedule and site pharmacy dispensing logs. The findings from these efforts, along with a third party audit of* (b) (4)*, were summarized in a Study Drug Reconciliation Executive Summary, submitted with the CSR for Study NXL104 2002.*

The Study Drug Reconciliation Executive Summary contains a "Drug Dispensing Reconciliation Summary Report" which describes activities by two unblinded Novexel personnel to review treatment group assigned by IVRS during randomization to drug actually administered based on pharmacy records and to review the vial numbers assigned by IVRS to vial numbers actually dispensed to subjects again based on pharmacy records. Their report indicates that all subjects received treatment they were assigned to by IVRS on all days of treatment, and that there were an approximately equal number of patients assigned by stratum to each treatment group. In addition to problems reported by (b) (4)*, there were additional issues identified such as the IVRS stopping assignment of vials prior to a subject's discontinuation of treatment or sites not using vials assigned by IVRS. In general, the pharmacists were pulling the next vial in the same treatment arm and subjects received the correct medication.*

Database lock for this study and generation of SAS datasets occurred on June 18, 2010.

c. Assessment of data integrity:
This inspection identified deficiencies in study monitoring and minor instances of failure to retain study records likely resulting from change in sponsors for the product. The major deficiency identified, failure to detect and resolve problems with the IVRS system drug the conduct of the study, required the sponsor to conduct an extensive drug reconciliation program. Based upon review of the reconciliation report included as part of the CSR, it appears that the sponsor has identified the specific study drug received by subjects and there was no impact on efficacy or safety of subjects. The data as submitted by the sponsor appears to be acceptable for use in support of the indication.

Observations for Actavis (Forest/Cerexa) are based upon the Form FDA 483, preliminary review of the EIR, and written response by the sponsor (Actavis) to the 483.

6. (b) (4)

a. What was inspected:
Corporate history, current bioresearch development activities, roles and responsibilities

of current management officers, and roles and responsibilities of project team members responsible for the IVRS and data management processes for Study NXL104 2002 were reviewed. Review of issues related to operation of the IVRS and electronic data capture system used for the NXL104 2002 study (completed in 2009) and an ongoing (current) unrelated drug product study was also conducted.

b. General observations/commentary:
(b) (4) provided technical services for Study NXL104 2002's interactive voice response system (IVRS) that captured data related to subject randomization and supply management, and the electronic data capture system that integrated information from outside data sources (i.e. specialty and safety laboratory assessments including ECGs, and subjects diary information systems). No interviews of members of the management team responsible for Study NXL104 2002 were conducted as none are employed at (b) (4) at this time.

The functionality of the IVRS, particularly issues related to "double-randomization", was examined. The issues with "double-randomization" were limited in scope and appear to have been related to manual entry of incorrect information into a telephone line. Currently, (b) (4) computer systems incorporate Interactive Web Response Systems (IWRS) technology, rather than IVRS.

The data from the labs and electronic data capture (EDC) did not appear to have any major issues related to data integrity.

c. Assessment of data integrity:
Randomization and subsequent investigational drug product assignment using the (b) (4) IVRS were reported by the sponsor in the NDA. The sponsor has provided information detailing the problems at (b) (4) with a third party audit report and undertaken an extensive drug reconciliation effort (see discussion under the Actavis, Inc. inspection section). (b) (4) no longer uses IVRS technology and has modified their Standard Operating Procedures since the Study NXL104 2002 was conducted in 2009.

Notwithstanding the problems related to randomization and investigational product assignment (addressed by the sponsor's drug reconciliation effort), no problems with data integrity related to laboratory data and EDC were noted at this inspection.

Observations for (b) (4) are based upon communications with the field investigator.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites were inspected for each of two clinical studies submitted in support of the NDA. In addition, the sponsor and CRO responsible for IVRS and data management were inspected for this NDA.

For Study NXL104 2002 (cUTI), a domestic (Dr. Bibi) and foreign (Dr. Gonzalez) site were selected for inspection based upon enrollment numbers. The preliminary classification for both inspections is Voluntary Action Indicated (VAI). For Dr. Gonzalez, based upon my review of the preliminary information from inspection and information contained in the NDA data listings, it appears that the Test of Cure urine cultures at this site were not obtained within the appropriate timeframe and the results of those cultures may have been potentially impacted by subjects' oral antibiotic regimen. For Dr. Bibi, the ORA investigators noted that the all six subjects received a dose of potentially effective systemic antibiotic after the baseline urine culture was obtained and before the subject was randomized. The review division notes that this is a common problem in antibiotic studies and takes this into account during their review.

For Study NXL104 2002 (cIAI), a domestic (Dr. Lucasti) and a foreign (Dr. Ramesh) clinical site inspection were requested. The inspection of Dr. Ramesh in India is now scheduled to occur February 2-6, 2015 and results are pending. The preliminary classification for Dr. Lucasti's site is No Action Indicated (NAI).

Actavis P.L.C. was inspected as sponsor of this NDA. Preliminary classification is VAI, primarily related to monitoring practices during the course of the study. Problems with the IVRS randomization and assignment of study drug vials were not acted upon promptly. The sponsor did go through an extensive drug reconciliation process and appears to have ensured that subjects received appropriate study drug treatment. (b) (4), the CRO responsible for the malfunctioning IVRS was also inspected and preliminary classification for that inspection is NAI. Inspection of this CRO did not have much further impact on information for this NDA (the sponsor took actions to resolve drug accountability issues), but provides some assurance that they have modified procedures going forward with other drug development programs.

The inspection of Dr. Ramesh has not been completed/is ongoing, and the report is not available from the field. An inspection summary addendum will be generated after the inspection has been completed and the results have been evaluated by OSI. Inspection classifications will be finalized when the inspection correspondence is issued to the inspected entity.

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H., Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

JANICE K POHLMAN
02/03/2015

KASSA AYALEW
02/04/2015

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 206494

Application Type: New NDA

Name of Drug/Dosage Form: Avycaz (ceftazidime-avibactam)

Applicant: Cerexa/Forest Laboratories

Receipt Date: June 25, 2014

Goal Date: February 25, 2015

1. 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

No SRPI format deficiencies were identified in the review of this PI.

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

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 unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

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:

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

Comment:

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

Selected Requirements of Prescribing Information

• **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**.

Comment:

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:

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

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

YES 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:

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:

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

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

Comment:

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:

YES 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:

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:

YES 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:

N/A 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:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 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

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

Comment:

YES 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:

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]

----------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*

*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/

CARMEN L DEBELLAS
01/27/2015

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

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

Memorandum

Date: January 14, 2015

To: Carmen DeBellas, PharmD, Regulatory Health Project Manager
Division of Anti-Infective Products (DAIP)

From: Christine Corser, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA #206494
Avycaz (ceftazidime-avibactam) for Injection, for intravenous use
OPDP Labeling Comments

As requested in your consults dated July 29, 2014 and December 29, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the draft labeling for Avycaz (ceftazidime-avibactam) for Injection, for intravenous use (Avycaz).

OPDP's comments on the PI are based on the substantially complete clean WORD version of the labeling titled, "CAZAVI Working label.docx" which was received via email from DAIP on December 29, 2014. OPDP's comments on the PI are provided in the attached, clean version of the labeling.

Thank you for the opportunity to provide comments on this PI.

If you have any questions, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

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

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/s/

CHRISTINE G CORSER
01/14/2015

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:	January 8, 2015
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	NDA 206494
Product Name and Strength:	Avycaz (ceftazidime/avibactam) for injection 2.5 grams per vial
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Cerexa, Inc. (A Subsidiary of Forest Laboratories, Inc.)
Submission Date:	6/25/2014
OSE RCM #:	2014-1308
DMEPA Primary Reviewer:	Sevan Kolejian, PharmD
DMEPA Acting Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

This review evaluates the container label, carton labeling and Prescribing Information for Avycaz (ceftazidime/avibactam for injection), NDA 206494, submitted on June 25, 2014. The Division of Anti –Infective Products (DAIP) requested that DMEPA review the labels and labeling for areas of vulnerability that may lead to medication errors.

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)	B - N/A
Previous DMEPA Reviews	C - N/A
Human Factors Study	D - N/A
ISMP Newsletters	E -N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and Dosage and Administration and How Supplied Section of Prescribing Information to identify deficiencies that may lead to medication errors and areas for improvement.

Our review of the container labels and carton labeling identified areas of improvement to increase clarity, prominence, and readability of important information. We note that the proprietary name, Avycaz, granted on December 4, 2014 is not on the proposed container labels and carton labeling and provide recommendation to add the proprietary name (see Section 4.2).

Our review of the prescribing information identified error-prone abbreviations and symbols, expression of units of measure that may pose confusion to the prescriber and needed improvements in the Dosage and Administration (see section 4.1).

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability and prominence of important information to promote safe use of this product.

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA concludes that the proposed labeling is vulnerable to confusion which can lead to medication errors. We have revised the *Dosage and Administration* section of the Full Prescribing Information (See Appendix F) and have provided a detailed summary below for review and consideration by DAIP. We advise the following recommendations be implemented prior to approval:

A. Full Prescribing Information

a. All Sections

1. Revise the word "TRADENAME" to read "Avycaz".

b. Dosage and Administration Section

1. In Section 2.1 add statement that the dosing is based on the total of content ceftazidime plus avibactam.

2. In Section 2.2, table 2, the Presence of the error-prone symbols "≥" and "<" is dangerous because these symbols can be mistaken as the opposite of the intended meaning. We recommend replacing the error-prone symbols with the appropriate full meaning of "greater than or equal to" and "great than" respectively.[1]

3. In Section 2.2, table 2, use consistent dosing unit of measurement throughout the document for clarity. Delete [redacted] (b) (4) [redacted] " from the Renal Impairment table.

4. In Section 2.3, provide clarifying statements to show that the reconstituted solution must be further diluted.

5. In Section 2.3, Delete table [redacted] (b) (4) [redacted]

may contribute to dosing confusion and the remaining information will be redundant.

6. Revise the title of Subsection 2.4 from [redacted] (b) (4) to read "Compatibility". Relocate from Section 2.3 to Section 2.4 and revise the sentence that starts with TRADENAME at concentrations between 0.008 g/mL…" to read "Compatible infusion solutions include 0.9% sodium chloride injection USP and 5% dextrose injection." to improve readability and eliminate other confusing information.

4.2 RECOMMENDATIONS FOR THE CELEXA INC.

We recommend Cerexa, Inc. to submit these revisions below and include labels and labeling that includes approved proprietary name prior to approval of this NDA 206494.

a) Container Label

1. Revise the word "TRADENAME" to read "Avycaz" using title case letters to improve readability.

2. Ensure the established name at least ½ the size of the proprietary name (21 CFR 201.10 (g)(2).

3. Add parenthesis surrounding the established name "ceftazadime/avibactam". Revise the established name and dosage form to appear all on one line. Present the established name on the container labels separated by slashes. Relocate the strength presentation to appear under the established name and revise the strength presentation from 2.5 gram/vial to read "2.5 gram per vial" to appear as follows:

Avycaz (ceftazadime/avibactam) for injection 2.5 gram per vial

4. Revise the statement from "[redacted] (b) (4)" to read "Must be reconstituted then diluted. For Intravenous Infusion." to provide clarity of important product preparation and administration information.

5. Relocate the usual dose statement "See [redacted] (b) (4) …directions for use" from the principal display panel to appear on the side panel to reduce clutter and distraction from other important information. To make room on the side panel, consider revising the usual dose statement to read "See prescribing information".

6. Revise the word "Constitution" to read "Reconstitution" on the side panel for clarity of important information.

7. Revise the uncommon abbreviation "RT" to read "room temperature" on the side panel for clarity of important information.

B. Carton labeling

1. See A.1 above

2. See A.2 above

3. See A.3 above

4. Revise the statement from "[redacted (b) (4)]. Constituted solution must be further diluted for intravenous infusion" to read "Must be reconstituted then diluted. For Intravenous Infusion." to provide clarity of important product preparation and administration information.

5. See A.6 above

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ceftazidime/avibactam that Cerexa, Inc. (A Subsidiary of Forest Laboratories, Inc.) submitted on July 16, 2014.

Table 2. Relevant Product Information for ceftazidime/avibactam	
Initial Approval Date	N/A
Active Ingredient	ceftazidime-avibactam
Indication	Antibiotic for Complicated Intra-abdominal Infection, Complicated Urinary Tract Infection, and Acute Pyelonephritis Aerobic Gram-negative Infections.
Route of Administration	intravenous
Dosage Form	For Injection, [redacted (b) (4)] powder
Strength	2.5 g per vial

Dose and Frequency	2.5 g intravenously every 8 hours for 5 to 14 days
How Supplied	2.5 g individual vial (NDC# 0456-2700-01) and carton containing 10 vials (NDC# 0456-2700-10)
Storage	Unreconstituted vials should be stored at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) Protect from light.
Container Closure	(b) (4) clear, Type I glass vial with a (b) (4) rubber stopper with a (b) (4) aluminium flip-off overseal. The filled vials are packed in cartons.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS): N/A

APPENDIX C. PREVIOUS DMEPA REVIEWS: N/A

APPENDIX D. HUMAN FACTORS STUDY: N/A

APPENDIX E. ISMP NEWSLETTERS: N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

We reviewed the following ceftazidime/avibactam labels and labeling submitted by Cerexa, Inc. (A Subsidiary of Forest Laboratories, Inc.) on July 16, 2014.

- Container label
- Carton labeling

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

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/s/

SEVAN H KOLEJIAN
01/08/2015

BRENDA V BORDERS-HEMPHILL
01/08/2015

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 # 206494	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: CAZAVI Established/Proper Name: ceftazidime/avibactam Dosage Form: Injection		
Applicant: Cerexa Agent for Applicant (if applicable):		
Date of Application: June 25, 2014 Date of Receipt: June 25, 2014 Date clock started after UN:		
PDUFA Goal Date: February 25, 2014	Action Goal Date (if different): February 25, 2014	
Filing Date: August 24, 2014	Date of Filing Meeting: August 19, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1,4,P		
Proposed indication(s)/Proposed change(s): Complicated Intra-abdominal Infection Complicated Urinary Tract Infection, including pyelonephritits Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options		

Type of Original NDA: Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted

Resubmission after withdrawal? N/A	Resubmission after refuse to file? N/A
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): 101307

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	☒	☐		
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)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ 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?	☐	☒	☐	
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)].**	☐	☒	☐	
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)]?** ***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***	☐	☒	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 years + 5 for QIDP ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
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.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***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…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, 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.*	☒	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☒	☐	☐	A deferral has been requested and a pediatric plan has been submitted
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? ***If no, request in 74-day letter***	☐	☐	☒	
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)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☒	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** June 16, 2011 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** December 19, 2013 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 19, 2014

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: ceftazidime/avibactam

DOSAGE FORM/STRENGTH: 2.5 gram injection

APPLICANT: Cerexa

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):
The indications being sought for approval are:

- Complicated Intra-abdominal Infection (cIAI)
- Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP)
- Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options

BACKGROUND:

This application is being submitted for the use of ceftazidime-avibactam (CAZ-AVI)(ceftazidime-avibactam for injection) for intravenous (IV) administration, in accordance with Section 505(b)(2) of the Federal Food Drug and Cosmetics Act and Section 314.50 of the United States Code of Federal Regulations. The basis of the 505(b)(2) New Drug Application (NDA) is that the Sponsor is relying on the Agency's previous findings of safety and effectiveness for the listed drug FORTAZ® (ceftazidime for injection) NDA 50578 approved by FDA in July 1985. FORTAZ is approved for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases: Lower Respiratory Tract Infections, Skin and Skin-Structure Infections, Urinary Tract Infections, Bacterial Septicemia, Bone and Joint Infections, Gynecologic Infections, Intra-abdominal Infections, and Central Nervous System Infections.

The IND was submitted January 7, 2008. The End of Phase 2 meeting was held June 16, 2011. The application was granted QIDP and Fast Track designation for the indications of cIAI, cUTI, and hospital-acquired bacterial pneumonia (HABP) on March 11, 2013 and a Pre-NDA meeting was held December 19, 2013.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Carmen DeBellas Fariba Izadi	N Y
	CPMS/TL:	Frances LeSane	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Benjamin Lorenz	Y
	TL:	Shrimant Mishra	N
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Avery Goodwin	Y
	TL:	Kerry Snow	Y

Clinical Pharmacology	Reviewer:	Seong Jang	Y
	TL:	Kimberly Bergman	N
Biostatistics	Reviewer:	Margaret Gamalo	Y
	TL:	Thamban Valappil	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Armand Balboni	Y
	TL:	Wendelyn Schmidt	Y
Product Quality (CMC)	Reviewer:	Zhengfang Ge	Y
	TL:	Dorota Matecka	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Robert Mello	Y
	TL:	Bryan Riley	N
Biopharmaceutics	Reviewer:	Houda Mahanyi	Y
	TL:	Angelica Dorantes	N
Facility Review/Inspection	Reviewer:	Steven Hertz	N
OSE/DMEPA (proprietary name)	Reviewer:	Joyce Weaver	Y

Other attendees	Sumathi Nambiar Katherine Laessig Dionne Price Janice Pohlman Edward Cox	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**: IR Pending May be additional IRs	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: December 5, 2014- Packages Due Mid Oct. ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC) **Comments**: May have comments	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• 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?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days	None
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Sumathi Nambiar **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): October 27, 2014	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter.

	☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Priority Review
ACTIONS ITEMS	
☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • 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)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	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://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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

/s/

CARMEN L DEBELLAS
08/26/2014