

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206829Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 206829	NDA Supplement #: S- n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: ceftolozane/tazobactam Established/Proper Name: Zerbaxa Dosage Form: Powder for Injection Strengths: 1 g/0.5g		
Applicant: Cubist, Inc.		
Date of Receipt: April 21, 2014		
PDUFA Goal Date: December 21, 2014		Action Goal Date (if different): December 19, 2014
Proposed Indication(s): Treatment of complicated Intra-Abdominal Infections (cIAI); Treatment of complicated Urinary Tract Infections (cUTI) including pyelonephritis.		

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 or by reliance on published literature. *(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 referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 50-684, Zosyn (piperacillin/tazobactam) from Wyeth Pharmaceuticals, Inc.	Carcinogenicity, Genetic Toxicology and Reproductive and Developmental Toxicology data for tazobactam obtained from the Zosyn USPI, and literature sources.
Zosyn (NDA 50-684/RLD) Labeling	Tazobactam Carcinogenicity
Ohuchida <i>et al.</i>, J Toxicol Sci, 19, suppl II: 263-280, 1994).	Tazobactam Genetic Toxicology
Sato <i>et al.</i>, J Toxicol Sci, 19, Suppl II: 199-214, 1994.	Tazobactam Fertility:
Sato <i>et al.</i>, J Toxicol Sci, 19, Suppl II: 215-232, 1994.	Tazobactam Embryo-Fetal Toxicity
Sato <i>et al.</i>, J Toxicol Sci, 19, Suppl II: 233-247, 1994.	Tazobactam Pre- postnatal Toxicity
Zosyn (NDA 50-684/RLD) Labeling:	The following sections of the labeling from Zosyn USPI reference: *Drug Interactions *Use in Specific Populations/Pregnancy *Description *Clinical Pharmacology/PK/Distribution *Clinical Pharmacology/Microbiology *NonClinical Toxicology

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The human safety and efficacy data for tazobactam were provided in the application. A BA/BE study was not needed to support the reliance on the Zosyn labeling since the information relied upon (drug interactions, pregnancy, chemical structure, protein binding, and carcinogenicity) relate to the qualities of the molecule, rather than the actual product being administered. Use of this information is scientifically valid without having to compare the relative exposure of tazobactam between the two products.

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 without the published literature)?

YES X NO

If "NO," proceed to question #5.

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

YES NO X

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

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 referenced the 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 X NO

If "NO," proceed to question #10.

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

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Zosyn (piperacillin/tazobactam)	50-684	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 monograph?

YES NO

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

Name of drug(s) described in a 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 product is a combination of tazobactam with piperacillin. This application provides for the use of tazobactam in combination with another drug, ceftolozane.

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 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)).*

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?

YES NO

*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 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)?

YES NO

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.

(a) Listed drug/Patent number(s): **U.S. Patent Nos. 6,900,184; 7,915,229; 8,133,883**

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:

(b) Patent number(s): ***U.S. Patent Nos. 6,900,184; 7,915,229; 8,133,883***

(c) 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

***Submitted documentation to the NDA July 11, 2014
stating receipt was confirmed July 7, 2014.***

If “NO”, please contact the applicant and request the signed certification.

- (d) 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.

- (e) 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): **July 7, 2014**

- (f) 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

***Per Chuck Miller, Regulatory, at Cubist, and confirmed via submission dated 10.10.14 Cubist was not informed of any action, pursuant to 21 CFR 314.107(e)(2) within the 45-day period of receipt of the notification.**

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

/s/

MAUREEN P DILLON PARKER
12/19/2014

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 # 206829
Product Name: ZERBAXA

PMR/PMC Description: **2809-1:** Conduct A randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cUTI. The dose for this study will be determined upon review of the data to be submitted by December 2016 from a single-dose, multicenter, non-comparative study assessing the pharmacokinetics (PK) of ceftolozane/tazobactam in pediatric patients ages 0 to <18 years that was initiated in June 2014.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2017</u>
	Study/Trial Completion:	<u>09/2020</u>
	Final Report Submission:	<u>12/2020</u>

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

Pre-approval studies in pediatrics were not completed because safety and effectiveness results from adult trials were not available yet. Now that the drug is likely to be approved in the adult population, this approval should not be postponed until completion of pediatric studies as new therapeutic options for treatment of adult cUTI and cIAI are needed.

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, safety and effectiveness of ZERBAXA in the treatment of cUTI and cIAI needs to be evaluated. This study will evaluate the pediatric dose that needs to be used in safety and effectiveness studies.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

Analysis of spontaneous postmarketing adverse events?

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

Analysis using pharmacovigilance system?

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

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

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

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

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

A randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cIAI

Required

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

Continuation of Question 4

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

Agreed upon:

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

- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # 206829
Product Name: ZERBAXA

PMR/PMC Description: **2809-2:** A randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cIAI. The dose for this study will be determined upon the review of the data to be submitted by December 2016 from the a single- dose, multicenter, non-comparative study to assessing the PK pharmacokinetics (PK) of ceftolozane/tazobactam in pediatric patients ages 0 to <18 years that was initiated in June 2014.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2017</u>
	Study/Trial Completion:	<u>09/2020</u>
	Final Report Submission:	<u>12/2020</u>

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

Pre-approval studies in pediatrics were not completed because safety and effectiveness results from adult trials were not available yet. Now that the drug is likely to be approved in the adult population, this approval should not be postponed until completion of pediatric studies as new therapeutic options for treatment of adult cUTI and cIAI are needed.

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, safety and effectiveness of ZERBAXA in the treatment of cUTI and cIAI needs to be evaluated. This study will evaluate the safety and effectiveness of ZERBAXA for the treatment of cIAI in the pediatric population.

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.

A randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cIAI

Required

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

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 # 206829
Product Name: ZERBAXA

PMR/PMC Description: **2809-3:** Conduct a prospective study over a five-year period after the introduction of ceftolozane/tazobactam (ZERBAXA) to the market to determine if decreased susceptibility to ceftolozane/tazobactam (ZERBAXA) is occurring in the target population of bacteria that are in the approved (ZERBAXA) ceftolozane/tazobactam label.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/2015</u>
	Study/Trial Completion:	<u>12/2019</u>
	Final Report Submission:	<u>05/2020</u>
	Other: Interim Reports	May, 2015 (1 st)
		May, 2016 (2 nd)
		May, 2017 (3 rd)
		May, 2018 (4 th)
		May, 2019 (5 th)

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

Long-term microbiologic surveillance data are needed to study development of bacterial resistance against ceftolozane/tazobactam

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.”

The study is required to determine if resistance to ceftolozane/tazobactam (ZERBAXA) is occurring in the target population of bacteria specific to the indications in the label.

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.

A prospective study over a five-year period on the susceptibility of target bacteria to ceftolozane/tazobactam (ZERBAXA)

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 ceftolozane/tazobactam (ZERBAXA) 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
-

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

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/

SUSMITA SAMANTA
12/18/2014

JOSEPH G TOERNER
12/18/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: November 10, 2014

TO: Thomas Smith, Team Leader
Maria Allende, Medical Officer
Maureen Dillon-Parker, Regulatory Health Project Manager
Division of Anti-Infective Products

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 206829

APPLICANT: Cubist Pharmaceuticals

DRUG: ZERBAXA[®] (ceftolozane/tazobactam)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

PROTOCOLS:

CXA-cIAI-10-08 and CXA-cIAI-10-09: A Multicenter, Double-blind, Randomized, Phase 3 Study to Compare the Efficacy and Safety of Intravenous Ceftolozane/Tazobactam with that of Meropenem in Complicated Intra-abdominal Infections (cIAI)

INDICATION: Treatment of complicated intra-abdominal infections (cIAI)

Eligible Subjects: Eligible subjects were men and women, at least 18 years of age, with cIAI (with evidence of intraperitoneal infection) confirmed with a surgical intervention within 24 hours of (before or after) the first dose of study drug.

CXA-cUTI-10-04, CXA-cUTI-10-05: A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam and Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis

INDICATION: Treatment of Complicated Urinary Tract Infection, including pyelonephritis.

Eligible Subjects: Consenting males (practicing reliable birth control methods) or females (not of child-bearing potential or practicing reliable birth control methods) ≥ 18 years of age with clinical signs and/or symptoms of cUTI (either pyelonephritis or complicated lower UTI with a qualifying complication) and a urine microscopy demonstrating pyuria. In addition, a pretreatment baseline urine culture specimen was collected within 24 hours before the start of administration of the first dose of study drug. .

CONSULTATION REQUEST DATE:	June 2, 2014
INSPECTION SUMMARY GOAL DATE:	November 15, 2014
PDUFA DATE:	December 21, 2014
ACTION GOAL DATE:	December 19, 2014

I. BACKGROUND:

Cubist Pharmaceuticals, Inc. (Cubist) submits NDA 206829 for ceftolozane/tazobactam intravenous infusion for the proposed treatment of two complicated bacterial infections (intra-abdominal and urinary tract). The active drug consists of ceftolozane, a novel cephalosporin, and tazobactam, a well-established β -lactamase inhibitor for the treatment of serious bacterial infections.

Two individual protocols were used for each indication. The decision to pool the data across the studies was made prior to completion of the studies, in agreement with the FDA and EMA's Committee for Medicinal Products for Human Use (CHMP). The two protocols were identical in all aspects of study conduct, and the treatment effects in the two individual studies were consistent and no statistically significant result was noted between studies.

A brief overview of the four pivotal studies is given below.

CXA-cIAI-10-08 and CXA-cIAI-10-09: A Multicenter, Double-blind, Randomized, Phase 3 Study to Compare the Efficacy and Safety of Intravenous Ceftolozane/Tazobactam with that of Meropenem in Complicated Intra-abdominal Infections

These were Phase 3, multicenter, prospective, randomized, double-blind studies of CXA-201 intravenous (IV) infusions (1500 mg every 8 hours [q8h]) and metronidazole (500 mg q8h) IV infusion vs. meropenem IV (1000 mg q8h) in the treatment of cIAI in adult subjects requiring surgical intervention. The primary goals of these studies were to establish non-inferiority of CXA-201 plus metronidazole to meropenem with respect to the proportion of subjects in the Microbiological Intent-to-Treat (MITT) population who achieve clinical cure at the Test-of-Cure (TOC) visit 26 to 30 days after the initiation of study drug administration.

The MITT population consisted of all randomized subjects who had IAI as evidenced by identification of at least one baseline intra-abdominal pathogen, regardless of susceptibility to study drug. There were six daily infusions (six active infusions in the ceftolozane/tazobactam plus metronidazole treatment arm or three active infusions and three dummy saline infusions in the meropenem treatment arm) for subjects in each randomized treatment arm.

Primary Efficacy Endpoint: Clinical cure rate at the TOC visit in the primary MITT population

A total planned sample size of 988 subjects (494 per treatment arm) when the 2 studies (CXA-cIAI-10-08 and CXA-cIAI-10-09) were combined was expected to result in approximately 395 MITT subjects per treatment arm.

CXA-cUTI-10-04, CXA-cUTI-10-05: A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam and Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis

These were multicenter, prospective, randomized, double-blind, double-dummy Phase 3 studies of ceftolozane/tazobactam (1.5 g every 8 hours) administered as a 1-hour intravenous (IV) infusion versus levofloxacin (750 mg once daily) administered as a 1.5-hour IV infusion in the treatment of adult subjects with cUTI, including pyelonephritis.

The **primary efficacy variable** was the composite microbiological eradication and clinical cure rate in the Microbiological Modified Intent-to-Treat (mMITT) population at the TOC visit. The mMITT population was a subset of all randomized subjects who received any amount of study drug that included subjects who had at least one qualified uropathogen from a study-qualifying pretreatment baseline urine specimen.

A total of 1083 subjects were randomized into the studies (543 to the ceftolozane/tazobactam arm and 540 to the levofloxacin arm) to achieve the target mMITT-evaluable sample size of approximately 800 subjects in the pooled studies. The majority of subjects (~75%) were enrolled in Eastern Europe. Approximately 95% of subjects in both treatment arms completed the study (513 in the ceftolozane/tazobactam arm and 515 in the levofloxacin arm).

Reasons for Site Selection: All sites chosen for inspection had high enrollment and/or a high treatment effect favoring the active drug arm.

II. Results

Name of CI/Site #	Protocol # and # of Subjects	Inspection Dates	Final Classification
Gintaras Cesnauskas Site 6380 Lithuania	CXA-cIAI-10-09 28 subjects	September 8 – 12, 2014	Preliminary VAI
Michal Nowicki Site 5801 Poland	CXA-cUTI-10-05 26 subjects	September 1 – 5, 2014	Preliminary VAI
Anca-Ileana Ruxanda Site 4720 Romania	CXA-cIAI-10-08 30 subjects	September 1 – 9, 2014	Preliminary NAI
Gregorio Sanchez-Vallejo Site 7404 Colombia, Latin America	CXA-cUTI-10-04 27 subjects	September 8 – 12, 2014	Preliminary VAI
Andres Tein Site 6275 Estonia	CXA-cIAI-10-09 44 subjects	September 11 – 17, 2014	Preliminary NAI
Egils Vjaters Site 6602 Latvia	CXA-cUTI-10-04 28 subjects	September 22- 26, 2014	Preliminary NAI
Cubist Pharmaceuticals, Inc. Lexington, MA	Sponsor inspection	August 19 – September 4, 2014	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.

1. Gintaras Cesnauskas (Site #6380)
Hipodromo str. 13
Kaunas, LT-45130
Lithuania

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The inspection audited Protocol CXA- cIAC-10-09. Dr. Cesnauskas has (b) (4) no prior FDA inspections. This site was chosen to inspect because of high enrollment and high treatment effect size.

The site screened 29 subjects and enrolled 28 subjects. Subject #4 withdrew consent during the study. A total of 27 subjects completed the study.

The inspection reviewed the following: Informed Consent Documents for all enrolled subjects; clinical cure rate assessment at the End of Treatment (EOT) visit, microbiology results at Test of Cure (TOC, primary efficacy endpoints) visit, and last follow-up (LFU) visit for 27 subjects; inclusion and exclusion criteria for three subjects; baseline visit requirements for three subjects; randomization records, infusion records, adverse events and protocol deviations for seven subjects; and test article accountability records.

- b. General observations/commentary:** No deficiencies were observed in review of Informed Consent Documents. There was no under-reporting of adverse events, and the primary efficacy endpoint data at the TOC visit was verifiable (for all subjects).

The inspection found minor issues relating to study drug infusions. The name of the person who performed study drug infusions was not documented, and exact infusion times were not documented. Infusion times were recorded as beginning at the top of the hour and lasting for exactly 1 hour. The person who completed the study drug infusion was not always the same person who began the infusion, and this was not documented.

The inspection found that some study nurses who performed test article administration were not documented on the Site Signature and Duty Delegation Log. Some nurses did not have protocol training documented until after starting study participation. In his September 25, 2014 response letter Dr. Cesnauskas provided the Site Signature and Duty Delegation Log which included names of all study nurses. He also provided a Note to File (NTF) that included a training date of April 16, 2013.

The inspection observed that 5 of 27 subjects were randomized incorrectly. This occurred because some sub-investigators considered the appendix site of infection to be part of the bowel, and so those subjects were mis-stratified to “bowel” instead of “other site of IAI”. This issue was identified during monitoring, and subsequent training provided at the site. Following subsequent training, this issue did not reoccur.

At the conclusion of the inspection, a Form FDA 483 was issued for **failure to follow the investigational plan**. Dr. Cesnauskas responded to the FDA 483 by letter dated September 25, 2014. His response is considered acceptable.

- c. Assessment of data integrity:** Minor regulatory violations were noted which should not impact data integrity or subject safety. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Cesnauskas was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

2. **Michal Nowicki (Site #5801)**
Oddzial Kliniczny
Nefrologii, Hipertensjologii i
Transplantologii Nerek,
ulica Kopcinskiego 22
Lódz, Poland

- a. **What was inspected:** The inspection was conducted using Compliance Program 7348.811. Dr. Nowicki (b) (4). His last inspection in (b) (4).

Twenty-six subjects were randomized and 24 subjects completed the study. One subject was discontinued due to an adverse event of rash, and another subject was discontinued due to *Staphylococcus epidermidis* infection in the baseline urine culture.

The inspection reviewed 100% of Informed Consent Documents. Four subject records were reviewed for inclusion and exclusion criteria, and to confirm baseline visit requirements including local laboratory microbiology results. The inspection reviewed Day 1-7 infusion dates and times, the TOC primary efficacy endpoint, microbiology results, local laboratory TOC microbiology results, adverse events, and protocol deviations for seven subjects. Subject records were reviewed for alkaline phosphatase testing at the screening or baseline visit, and for three subjects with a diagnosis of pyelonephritis, the inspection verified that the baseline blood culture was drawn. Test article accountability records were audited.

- b. **General observations/commentary:** The inspection observed that the site screening log was incomplete. It was unclear how many subjects were screened for the study. No deficiencies were observed in the review of Informed Consent Documents. There was no under-reporting of adverse events. The inspection reported that the primary efficacy endpoint was the microbiological results of the 'central' laboratory at the Test of Cure (TOC) visit. The site did not receive reports of the microbiology results from the 'central' laboratory. The data listings provided microbiology test results at the TOC visit from the local laboratory. The local laboratory results at the site were compared against the data listing for four subjects, and no deviations were noted.

At the conclusion of the inspection, a one observational Form FDA 483 was issued for:

An investigation not conducted in accordance with the signed statement of investigator and investigational plan. Specifically,

- a) For 25 subjects, the site did not test for alkaline phosphatase, as required by the protocol.

Comments: The site did perform other liver function tests such as ALT, AST, and bilirubin, so OSI does not consider this issue as significant, and it will not importantly impact overall results of the study.

- b) For subjects who were diagnosed with pyelonephritis the inspection found that site did not always have blood cultures taken at baseline, as required by the protocol.
 - c) Subjects who upon receipt of the local laboratory urine culture results did not meet the study inclusion criteria were not always discontinued from study drug in a timely manner, as per the protocol requirements. Because of high and rapid site enrollment, these subjects were often not discovered to have a non-qualifying UTI until several months later, at which time they were discontinued.
 - d) The blind was potentially broken for Subject 01. The last infusion of study drug did not include a second IV bag to mimic the infusion of non-randomized drug product. The two drugs had different infusion times, such that one could conceivably guess which drug was being administered.
 - e) The site did not maintain an accurate screening log, and did not have training documented for all personnel prior to study involvement.
- c. **Assessment of data integrity:** Although regulatory issues were found, they are unlikely to significantly impact the results of the study. The data is acceptable in support of the respective indication.

Note: The final EIR for Dr. Nowicki was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

3. **Anca-Ileana Ruxanda (Site #4720)**
Strada Tabaci Numar 1
Craiova, DOLJ 200642
ROU Eastern Europe

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Ruxanda has (b) (4) no prior FDA inspections. This site was chosen to inspect because of relatively high enrollment, and high treatment effect size.

A total of 30 subjects were enrolled, and 29 subjects completed the study. Enrollment took place between January and July 2013. Subject 4720-001 died prior to completion of the treatment protocol.

The inspection reviewed the inclusion and exclusion criteria for 23 subjects. The data listings in the assignment were corroborated with source medical records for 23 of the 30 subjects. The following data was corroborated: adverse events, microbiology test results at

the TOC visit, treatment assignment in the ITT population, central laboratory hematology results, and other microbiology data results.

The investigational product (IP) records including receipt, storage, medication administration and final disposition of IP were reviewed. The IP storage area was observed. The monitoring log was reviewed for site visits, and the personnel training log reviewed.

- b. General observations/commentary:** Records were organized and were in hard copy format. No protocol violations were reported relating to the I/E criteria and none were identified during the inspection. Review of source document medical records and medication administration records revealed that only subject 4720-001 experienced a Severe Adverse Event. This was confirmed by the data listings. No other Serious Adverse Events (SAE) or Adverse Events (AEs) were reported and review of the other 22 subject records at the site confirmed that no other SAEs or AEs occurred throughout the study.

Cubist contracted with a Clinical Research Organization (CRO), [REDACTED] (b) (4) [REDACTED] to provide monitoring activities for the site. Site visits provided training on clinical study procedures.

No significant findings were found, and no Form FDA 483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Ruxanda was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

- 4. Gregorio Sanchez-Vallejo (Site #7404)**
Cra 14 Cl 17N, Avenida Bolivar Hospital Juan de Dios
Pisa Sexto Oficina de Medicina Interna
Armenia, Colombia
Latin America

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Sanchez-Vallejo has [REDACTED] (b) (4) no prior inspections. The site conducted Study protocol CXA-cUTI-10-04. A total of 27 subjects were enrolled and 27 subjects completed the study at this site.

The inspection reviewed the following items: Informed Consent Document for all subjects; corroboration of data listings to source records for the primary and secondary efficacy endpoints, adverse events and serious adverse events, randomization, allocation of study drug, concomitant medications, protocol deviations, and clinical laboratory data (local and

central laboratory) for 13 subjects. The inspection also reviewed other documentation including administrative files, correspondences, randomization schedule, and screening log.

- b. General observations/commentary:** The clinical investigator followed the protocol with respect to: number of subjects enrolled, randomization, blinding procedures, required evaluations, and administration of the investigational product. No unreported out-of-window visits were noted. The source documents appeared well-organized, complete, and legible. The clinical data were predominately progress notes and lab reports. Documentation of protocol-required activities was found sufficient.

The inspection issued a one observational FDA 483 for **failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.** The protocol required that all prescription and Over-the-Counter (OTC) medications from 7 days prior to the first dose of study medication be reported to the CRF. For 9 of 13 subject records reviewed, the inspection found that concomitant medications were not listed in the Case Report Form. For example:

- 1) Patient #1 was administered Diprona IV and Boscapina IV from September 30, 2012 through October 2, 2012. The date of randomization was October 2, 2012. Diprona IV and Boscapina IV were not listed in the CRF.
- 2) Patient #12 was administered Tramal IV on January 17, 2013, and was randomized on January 18, 2013. Tramal IV was not reported to the CRF.

Dr. Sanchez-Vallejo's written response dated September 25, 2014 provided detail of corrective action to capture the patient's pre-study medication.

- c. Assessment of data integrity:** Although deficiencies were found for failure to report some concomitant medications, they are unlikely to importantly impact the outcome of the study. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Sanchez-Vallejo was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

5. Andres Tein (Site #6275)
L. Puusepa 8
Tartu, 51014
Estonia

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The inspection audited Protocol CXA-cIAI-10-09. Dr. Tein has (b) (4) no prior FDA inspections. This site was chosen to inspect because of high enrollment and high treatment effect

size.

The site enrollment period was from October 2012 through September 2013. The site screened 50 subjects, and enrolled 44 subjects. A total of 43 subjects completed the study. One subject 6275-019, died during the study. The cause of death was reported as unknown. The family declined to have an autopsy performed.

The inspection reviewed inclusion and exclusion criteria for six subjects that were screen failures, and for 29 of 44 enrolled subjects. Two deviations relating to the inclusion and exclusion criteria were reported and reviewed. Source data was corroborated with the data listings for 29 subjects for serology test results, anatomic site of infection, primary diagnosis, primary and key secondary efficacy variables at Test of Cure (TOC) visit, protocol deviations, Serious Adverse Events (SAEs) and Adverse Events (AEs), subject discontinuations, concomitant medications, and central laboratory hematology and microbiology data. Test article accountability records were verified for receipt, storage, administration, and final disposition. The site monitoring log was reviewed, as were activities performed during monitoring visits.

- b. General observations/commentary:** This study appeared to be well-conducted. Study records were well-organized, and in hard copy format. Clinical study data was included within the medical records for each subject. Drug accountability records were well organized. The Sponsor contracted with (b) (4) whose corporate headquarters are in (b) (4) to provide monitoring and training activities at the site. Monitoring and training appeared adequate.

There were no significant findings and a Form FDA 483 was not issued.

- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Tein was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

**6. Egils Vjaters (Site #6602)
Pilsonu str. 13
Riga, LV-1002
Latvia**

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The inspection was conducted between September 22 and 25, 2014. The site screened 38 subjects, and enrolled 38 subjects. Twelve subjects were withdrawn within five days due to confirmation of a non-qualifying UTI microorganism. Their status was considered completed because they attended the TOC visit and LFU visit. Per protocol, subjects were allowed to begin on trial and be withdrawn pending urine microbiology results showing targeted microorganisms. A total of 37 subjects completed study procedures, including the 12 subjects withdrawn from treatment.

Records for all 38 enrolled subjects were reviewed. This included the ICD verification, inclusion and exclusion criteria, reporting of adverse events, and the primary efficacy endpoint data.

- b. General observations/commentary:** This study appeared to be well-conducted. Study records were well-organized, and in hard copy format. Clinical study data was included within the medical records for each subject. Drug accountability records were well organized, making evaluation of drug accountability easy.

A FDA 483 was issued for **failure to include risk information on the Informed Consent Document**. Specifically, the ICD failed to let subjects know that their UTI may not be cured by the study medication, not because it was a study medication but because the subject was enrolled prior to having microbiology results, and might be withdrawn from the study if not having the targeted organism. Twelve subjects were administered study medication for between two and five days, and then withdrawn for not having the targeted microbiology.

Medical Reviewer's Comment: Since empiric treatment of a UTI pending cultures would occur whether or not the subject was enrolled in a study, this "risk" is not study specific; subjects will receive appropriate treatment after culture results are received. Therefore, failure to include this in an ICD is not a regulatory violation.

- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

7. Cubist Pharmaceuticals (Sponsor)
65 Hayden Avenue
Lexington, MA 02421

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.810. The inspection audited the four protocols associated with the NDA: CXA-cIAI-10-08 and CXA-cIAI-10-09 (complicated intra-abdominal infection) and CXA-cUTI-10-04 and CXA-cUTI-10-05 (complicated urinary tract infections). This was the first BIMO inspection of Cubist Pharmaceuticals. Prior inspections included a (b) (4)

The final classification from that inspection is pending.

The current inspection focused on the six clinical investigator sites where BIMO inspections were conducted:

- Site #7404, Sanchez-Vallejo (CXA-cUTI-10-04)
- Site #6602, Vjaters (CXA-cUTI-10-04)
- Site #5801, Nowicki (CXA-cUTI-10-05)
- Site #4720, Ruxanda (CXA-cIAI-10-08)
- Site #6380, Cesnauskas (CXA-cIAI-10-09)
- Site #6275, Tein (CXA-cIAI-10-09)

The inspection covered sponsor responsibilities of investigational drug; organizational charts, transfer of obligations and responsibilities of study vendors; standard operating procedures for activities such as reporting of protocol deviations, and identifying issues of clinical investigator non-compliance; selection and monitoring of clinical investigators; monitoring reports; data management plans; quality assurance plans; case report forms; investigator agreements; financial disclosure statements; drug accountability records; and Serious Adverse Event (SAE) reports. The inspection reviewed monitoring activities and reports at the sites listed above. All IND safety reports for all four studies were reviewed

- b. General observations/commentary:** A non-compliant site was identified during the inspection. The monitor ^{(b) (4)} noted issues of serious non-compliance and potential fraud at Site #4227, Dr. Silvio Lazzeri in Argentina. This issue was escalated to Cubist who investigated and terminated the site due to data falsification. The investigation found that Cubist had reported the site's termination to the FDA.

In general, monitoring appeared adequate. Due to high, rapid enrollment at some sites, the CRAs could not perform 100% source data verification at all visits. This led to some repeat study site protocol deviations that were not detected until later monitoring visits. For example, Site #5801 (Nowicki) had five subjects, with non-qualifying cultures at baseline, who were not withdrawn from the study. These subjects continued to receive study drug until an interim monitoring visit occurring between four and seven months later. No adverse events occurred related to study drug for any of these five subjects, and all five subjects were excluded from the efficacy analysis of the study, and included in the safety analysis.

Other issues that occurred at Site #5801 included: blood cultures not being taken per protocol, improper study drug dose adjustments, and ten subjects who did not fully meet inclusion and exclusion criteria in that they did not have alkaline phosphatase levels drawn locally. However, all other liver function tests (AST, ALT and bilirubin) had been done for these ten subjects. These issues were identified during later monitoring visits.

The inspection observed that Cubist provided training at sites where issues were identified during monitoring. Protocol deviation forms were completed and submitted by the sites in a timely manner. All IND safety reports were sent to FDA on time. No significant deficiencies were observed during the sponsor site inspection, and no FDA 483 was issued.

- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Six clinical investigator site inspections and a Sponsor site inspection were conducted in support of NDA 206829. No regulatory violations were found during the inspections of Dr. Ruxanda (Site 4720, Romania) and Dr. Tein (Site 6275, Estonia). Both inspections were classified as preliminary NAI. Minor regulatory violations were found during the inspections of Dr. Cesnauskas (Site 6380, Lithuania), Dr. Nowicki (Site 5801, Poland), and Dr. Sanchez-Vallejo (Site 7404, Latin America), and a one observational Form FDA 483 was issued for

failure to follow the investigational plan (Cesnauskas, and Nowicki), and failure to maintain accurate records (Sanchez-Vallejo). A one observational Form FDA 483 was issued for failure to include risk information in the ICD for Dr. Vjaters (Site 6602, Latvia); however, review by OSI does not confirm this as a regulatory violation. No regulatory violations were found during the inspection at the sponsor site. The sponsor inspection was classified as NAI.

The regulatory violations noted during inspections at Dr. Cesnauskas, Nowicki, and Sanchez-Vallejo are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable.

Note: The final EIRs for Drs. Nowicki, Ruxanda, Sanchez-Vallejo, Tein, and Vjaters were not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
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/s/

SHARON K GERSHON
11/10/2014

SUSAN D THOMPSON
11/10/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: November 25, 2014
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 206829
Product Name and Strength: Zerbaxa (Ceftolozane and Tazobactam) for injection
1g/0.5 g
Submission Date: November 7, 2014
Applicant/Sponsor Name: Cubist Pharmaceuticals
OSE RCM #: 2014-946
DMEPA Primary Reviewer: Jacqueline Sheppard, PharmD
DMEPA Acting Team Leader: Vicky Borders-Hemphill, PharmD
DMEPA Associate Director: Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised vial label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised vial label and carton labeling is acceptable from a medication error perspective.

¹ Winiarski A. Label and Labeling Review for Zerbaxa (NDA 206829). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Aug 7. 8 p. OSE RCM No.: 2014-946.

APPENDIX A. LABEL AND LABELING SUBMITTED ON NOVEMBER 7, 2014

Vial Label



Carton Labeling



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/s/

JACQUELINE E SHEPPARD
11/25/2014

LUBNA A MERCHANT
11/25/2014

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND or NDA	NDA 206829
Brand Name	Zerbaxa
Generic Name	Ceftolozane/tazobactam IV
Sponsor	Cubist Pharmaceuticals, Inc.
Indication	For the treatment of Complicated Urinary Tract Infections (cUTI) including Pyelonephritis and Complicated Intra-abdominal Infections (cIAI).
Dosage Form	IV infusion
Drug Class	Antibacterial combination product consisting of the cephalosporin antibacterial ceftolozane sulfate and the beta-lactamase inhibitor tazobactam sodium
Therapeutic Dosing Regimen	CXA-101/tazobactam 1000/500 mg
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	MTD has not been established. The maximum single and multiple doses studies were safe and well tolerated.
Submission Number and Date	SDN 002; 21 Apr 2014
Review Division	DAIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of CXA-101/tazobactam (1000/500 mg and 3000/1500 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between CXA-101/tazobactam (1000/500 mg and 3000/1500 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcI}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, double-blinded, double-dummy, four-period crossover study, 52 healthy subjects received CXA-101/tazobactam 1000/500 mg, CXA-101/tazobactam 3000/1500 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for CXA-101/tazobactam (1000/500 mg and 3000/1500 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
CXA-101/tazobactam 1000/500 mg	1	1.2	(-0.9, 3.3)
CXA-101/tazobactam 3000/1500 mg	1	4.0	(1.9, 6.1)
Moxifloxacin 400 mg*	2.5	11.7	(9.0, 14.5)

* Multiple endpoint adjustment of 3 time points was applied. Similar results also showed at 4.5 hour.

The suprathreshold dose (CXA-101/tazobactam 3000/1500 mg) produces mean C_{max} values ~3.0-fold the mean C_{max} for the therapeutic dose (CXA-101/tazobactam 1000/500 mg) for each of the two drugs CXA-101 and tazobactam and major tazobactam metabolite M1 (mean C_{max} of 66.5 and 198.5 $\mu\text{g/mL}$ for CXA-101 for 1000 mg and 3000 mg dose respectively, and mean C_{max} of 18.6 and 51.2 $\mu\text{g/mL}$ for tazobactam for 500 mg and 1500 mg dose respectively). There is dose proportionality in C_{max} concentrations for both the drugs CXA-101 and tazobactam within these doses. It is expected from organ impairment studies that CXA-101 and tazobactam mean C_{max} can be as much as 1.3-, 2.5-, and 4- to 5-fold for CXA-101 and approximately 1.3-, 2-, and 1.5- to 2-fold for tazobactam in subjects with mild, moderate, and severe renal impairment compared to that in healthy subjects with normal renal function. A 50% and 75% dose reduction in the therapeutic dose of these drugs has been recommended in patients with moderate and severe renal impairment, respectively, to ensure that exposure is within the limit of what has been found safe in clinical setting. Because of this, the concentrations with the suprathreshold doses tested here would be above those for the possible worst case scenario (moderate/severe renal impairment scenarios) encountered with the recommended reduced therapeutic dose. At the concentrations achieved with the suprathreshold dose level, there are no detectable prolongations of the QT-interval.

2 PROPOSED LABEL

Following proposed labeling information is provided by the sponsor related to cardiac Electrophysiology:

12.2 Pharmacodynamics

(b) (4)

Source: Section 12.2 (Pharmacodynamics) in Sponsor's proposed label

2.1 QT-IRT RECOMMENDATIONS

Our recommendations are suggestions only. We defer final labeling decisions to the review division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of ZERBAXA™ on the QTc interval was evaluated in a double-blind, randomized, moxifloxacin and placebo controlled, crossover study in 51 healthy subjects. At a dose 3 times the maximum recommended dose, ZERBAXA™ did not prolong the QT interval to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

CXA-101 is a parenteral broad-spectrum cephalosporin with excellent in vitro activity against *Pseudomonas aeruginosa*. CXA-101 shares the antibacterial mode of action of other β -lactams by targeting penicillin-binding proteins to inhibit the biosynthesis of the bacterial cell wall and to stop bacterial replication.

3.2 MARKET APPROVAL STATUS

CXA-101 is not approved for marketing in any country.

Tazobactam is a β -lactamase inhibitor that is a component of the currently marketed drug piperacillin/tazobactam.

3.3 PRECLINICAL INFORMATION

The in vitro effect of CXA-101 on the hERG channel current was examined. The median inhibitory concentration (IC50) value for CXA-101 inhibition of the hERG potassium current was not determined since hERG inhibition was <1% and similar to that induced by the vehicle control. In summary, CXA-101 had no significant inhibition of the hERG potassium current.

No changes in QT or QTc intervals were observed in telemetered dogs at maximum plasma concentration (Cmax) exposures of approximately 3 times greater than the human therapeutic dose. Furthermore, CXA-101 did not have neuropharmacological, cardiovascular, or respiratory effects in mice, rats, or dogs. Based on data from preclinical toxicology studies CXA-101 has low potential for cardiovascular toxicity. CXA-101 had no significant inhibition of the human hERG potassium current. No changes in QT or QTc intervals were observed in telemetered dogs at maximum plasma concentration (Cmax) exposures of approximately 3 times greater than the human therapeutic dose. Based on data from preclinical toxicology studies CXA-101 has low potential for cardiovascular toxicity.

Source: Sponsor's cardiac safety report, Page 10

3.4 PREVIOUS CLINICAL EXPERIENCE

(b) (4)

Source: Section 6.1 (Clinical Trial Experience) in Sponsor's proposed label

Reviewer's comments: No syncope, seizures or sudden cardiac death were reported. No clinically relevant ECG changes were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clinical pharmacology of ZERBAXA™ (CXA-101/tazobactam).

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report CXA-QT-10-02 for CXA-101/tazobactam, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A double-blind, double-dummy, randomized, moxifloxacin and placebo controlled, four-way crossover study of the effects of a single intravenous supra-therapeutic dose and a single intravenous therapeutic dose of CXA-101/tazobactam on the QT/QTc intervals in healthy subjects

4.2.2 Protocol Number

CXA-QT-10-02

4.2.3 Study Dates

02 Jun 2010 -- 09 Jul 2010

4.2.4 Objectives

The primary objectives of this study were to:

- Evaluate the effect of a single intravenous (IV) supra-therapeutic dose of CXA-101/tazobactam on ventricular repolarization as measured by QTc interval in healthy subjects compared to baseline-adjusted, time-matched placebo.
- Evaluate the change from the period specific pre-dose baseline of QT/QTc interval corrected by QTcI (Individual Correction subject-specific formula) across all dose groups.

The secondary objectives of this study were to:

- Evaluate the change from the pre-dose baseline of QT/QTc interval corrected by the QTcF (Fridericia's method) and QTcB (Bazett's method).
- Characterize concentration-response relationship for QT/QTc intervals.
- Obtain pharmacokinetic (PK) information for CXA-101/tazobactam in healthy subjects.
- Provide safety information for CXA-101/tazobactam.
- Validate study sensitivity by inclusion of a positive control treatment, moxifloxacin.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 4-sequence, crossover design with four dosing occasions. Each dosing occasion will be followed by a 3-day washout period.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were overencapsulated.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 4 treatments:

Group A: Therapeutic Dose:

Single IV dose of CXA-101/tazobactam 1000/500 mg (administered over 60 ± 2 minutes) plus an oral over-encapsulated moxifloxacin placebo tablet administered at the start of the infusion.

Group B: Supra-Therapeutic Dose:

Single IV dose of CXA-101/tazobactam 3000/1500 mg (administered over 60 ± 2 minutes) plus an oral over-encapsulated moxifloxacin placebo tablet administered at the start of the infusion.

Group C: Placebo Dose (CXA-101/TAZOBACTAM Placebo/Moxifloxacin Placebo):

Single IV dose of CXA-101/tazobactam placebo (sterile 0.9% NaCl solution, administered over 60 ± 2 minutes) plus an oral over-encapsulated moxifloxacin placebo tablet administered at the start of the infusion.

Group D: Moxifloxacin Dose:

Single IV dose of CXA-101/tazobactam placebo (sterile 0.9% NaCl solution, administered over 60 ± 2 minutes) plus an oral over-encapsulated moxifloxacin 400 mg tablet administered at the start of the infusion.

4.2.6.2 Sponsor's Justification for Doses

Based on the available human PK, PK/pharmacodynamic (PD) data in animal infection models, and desired PK/PD target attainment in humans, the 1000/500 mg dose of CXA-101/tazobactam is the projected efficacious dose for evaluation in Phase 3 studies. Therefore the dose of 1000/500 mg was assessed as the therapeutic dose in this TQT study.

In order to account for clinical circumstances where concentrations of CXA-101/tazobactam can be increased beyond the projected exposure, cardiac safety at concentrations 3 times higher than those achieved following the anticipated therapeutic doses were also explored. Thus, the proposed supra-therapeutic dose for this study was a single IV dose of 3000 mg CXA-101 with 1500 mg tazobactam.

Moxifloxacin at a dose of 400 mg is known to prolong the mean QT/QTc interval by approximately 5 msec (the threshold of regulatory concern); therefore, it acted as a positive control to establish assay sensitivity.

In study CXA-201-01 following multiple dose administration of CXA-101/tazobactam for 10 days in healthy subjects, the elimination half-life of CXA-101 and tazobactam was similar to those calculated following a single-dose. In addition, no accumulation was observed for CXA-101 and tazobactam following repeated q8h and q12h dosing of CXA-101 alone, tazobactam alone, and CXA-101/tazobactam as a mixture solution for 8 days. Slight accumulation of the metabolite M-1 was observed, as expected with a half-life of about 3-4.5 hr, following repeated q8h and q12h dosing for 8 days. Pharmacokinetic parameters were very similar between Day 1 and Day 10.

Considering the short half-lives of both CXA-101 (~2.5 hr) and tazobactam (~1 hr), absence of active metabolites of CXA-101, and lack of accumulation of CXA-101 and tazobactam following multiple doses, a single dose TQT study was considered appropriate to assess the effect of CXA-101/tazobactam on QT/QTc intervals. The slight observed accumulation of tazobactam metabolite M-1 is not clinically relevant as the metabolite lacks pharmacological and antibacterial activity. In addition, the accumulation of the M-1 metabolite observed following multiple doses is less than that expected from a single supra-therapeutic dose used for this study.

Source: section 9.4.4 in sponsor's clinical study report and section 4.3 in sponsor's cardiac safety report

Reviewer's Comment: The supratherapeutic dose (CXA-101/tazobactam 3000/1500 mg) produces mean C_{max} values ~3.0-fold the mean C_{max} for the therapeutic dose (CXA-101/tazobactam 1000/500 mg) for each of the two drugs CXA-101 and tazobactam and major tazobactam metabolite M1. It is expected from organ impairment studies that CXA-101 and tazobactam mean C_{max} can be as much as 1.3-, 2.5-, and 4- to 5-fold for CXA-101 and approximately 1.3-, 2-, and 1.5- to 2-fold for tazobactam in subjects with mild, moderate, and severe renal impairment compared to that in healthy subjects with normal renal function. A 50% and 75% dose reduction in the therapeutic dose of these drugs has been recommended in patients with moderate and severe renal impairment, respectively, to ensure that exposure is within the limit of what has been found safe in clinical setting. Because of this, the concentrations with the supratherapeutic doses tested here would be above those for the possible worst case scenario (moderate/severe renal impairment scenarios) encountered with the recommended reduced therapeutic dose. Thus the proposed supratherapeutic dose seems to be reasonable.

4.2.6.3 Instructions with Regard to Meals

Not applicable as an IV drug.

Reviewer's Comment: There is no necessity of instructions with regard to meals, since the drug is to be administered intravenously over 60 minutes.

4.2.6.4 ECG and PK Assessments

ECG Assessments:

The Study Electrocardiograms that were included in the final endpoint statistical analysis were acquired from a 24-hour Holter recording.

On the day prior to dosing (Day -1) and on dosing days (Days 1, 5, 9, and 13), the Holter recorders were placed on the subjects and started 90 minutes prior to the dosing time. The Holter recorders were removed about 23.0 hours after the placement of the recorders.

Twelve-lead, 10-seconds ECGs, were extracted in triplicate (approximately 3 minutes apart) from these Holter recordings. The extractions were made where the heart rate was stable for approximately two minutes and the tracings were void of artifact, baseline wandering or irregular heart rhythm. Each subject's individual QT-HR relationship was established by analysis of the data on Day -1 for the computation of an individual exponent for QT correction for HR (QTcI.)

Baseline values were the time-matched values from Day -1 for each individual subject.

Definitive treatment ECG data was obtained by 12-lead Holter monitoring on Study Days 1, 5, 9 and 13, within a 10-minute time window at each of the following nominal time points: -60, -30, and -15 minutes prior to start of infusion (period-specific baseline); and 30 and 55 minutes, and 1.5, 2.0, 2.5, 3.0, 3.5, 4.5, 6.5, 8.5, 12.5, 16.5, and 22.5 hours after the start of the infusion.

PK Assessments:

Blood was drawn on dosing days immediately after each of the designated ECG observations for the determination of PK parameters for CXA-101/tazobactam, M-1 metabolite, and for moxifloxacin if needed.

Nominal PK sample time points are: 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 6.5, 8.5, 12.5, 16.5, 22.5 hours after dosing.

Source: Sponsor's cardiac safety report, section 6.1

Reviewer's Comment: ECG measurements were done continuously and in close proximity to T_{max} for the drugs ($T_{max} \sim 0.667$ hours) and the metabolite (median $T_{max} \sim 3.67$ hours). Thus, the sampling for ECG was appropriate from the perspective of capturing immediate effect related to C_{max} .

4.2.6.5 Baseline

The average of predose QT/QTc values on Day 1 of each period was used as baseline for that period.

4.2.7 ECG Collection

Twelve-lead, 10-seconds ECGs, were extracted in triplicate (approximately 3 minutes apart) from the Holter recordings. Definitive treatment ECG data was obtained by 12-lead Holter monitoring on Study Days 1, 5, 9 and 13, within a 10-minute time window at each

of the following nominal time points: -60, -30, and -15 minutes prior to start of infusion (period-specific baseline); and 30 and 55 minutes, and 1.5, 2.0, 2.5, 3.0, 3.5, 4.5, 6.5, 8.5, 12.5, 16.5, and 22.5 hours after the start of the infusion.

Source: Sponsor's cardiac safety report, section 6.1

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 52 subjects were randomized into the study, including 13 subjects into each of the 4 sequence groups. All 52 subjects received at least 1 of the study drugs and are included in the Safety population. The majority of subjects (50 of 52, 96.2%) completed the study. Two subjects withdrew from study treatment and the study prematurely: Subject 001-0035 in sequence group BACD withdrew due to an AE (pyrexia) and Subject 001-0030 in sequence group DCAB, withdrew consent to participate. Subject 001-0035 withdrew after receiving both the therapeutic and supra-therapeutic doses of CXA-101/tazobactam and Subject 001-0030 withdrew after receiving only moxifloxacin.

Source: Section 10.1 in sponsor's clinical study report

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor used repeated measures mixed effects linear model for the primary analysis. The sponsor's results are displayed in Table 2. The sponsor concluded that this was a negative thorough QT Study with no findings indicating an effect of CXA-101/tazobactam on cardiac repolarization.

Table 2: Primary and Secondary Endpoints - Mean CXA-101/tazobactam Differences from Placebo in Change from Predose Baseline and 95% One-sided Upper Confidence Bounds (Sponsor's Results)

Dose	ddQTcI (msec)				ddQTcF (msec)				ddQTcB (msec)			
	CXA-101/ tazobactam 1000/500 mg		CXA-101/ tazobactam 3000/1500 mg		CXA-101/ tazobactam 1000/500 mg		CXA-101/ tazobactam 3000/1500 mg		CXA-101/ tazobactam 1000/500 mg		CXA-101/ tazobactam 3000/1500 mg	
Hour	diff	ucb	diff	ucb	diff	ucb	diff	ucb	diff	ucb	diff	ucb
0.5	0.24	2.34	3.28	5.37	1.00	2.92	3.25	5.17	0.97	3.47	5.23	7.73
1	1.31	3.41	4.16	6.25	1.08	2.99	3.83	5.74	1.70	4.20	5.09	7.59
1.5	-0.73	1.36	0.82	2.92	-0.50	1.41	1.46	3.38	-0.73	1.77	-0.52	1.99
2	0.01	2.11	1.75	3.85	0.49	2.41	1.44	3.35	-0.20	2.30	1.39	3.89
2.5	0.79	2.88	2.57	4.67	0.17	2.09	2.62	4.54	1.44	3.95	2.22	4.72
3	-0.44	1.66	-0.18	1.92	-0.72	1.19	-0.61	1.31	-0.06	2.44	-0.85	1.65
3.5	0.81	2.90	-1.16	0.94	0.03	1.95	-1.63	0.29	1.32	3.83	-2.73	-0.22
4.5	-0.48	1.62	-0.38	1.71	-0.72	1.20	-0.68	1.23	0.44	2.94	0.55	3.05
6.5	-1.77	0.32	-1.37	0.72	-2.26	-0.35	-1.55	0.37	-1.75	0.75	-0.47	2.03
8.5	-1.42	0.69	-0.99	1.12	-0.87	1.06	-0.59	1.33	-1.91	0.61	-0.69	1.83
12.5	-1.51	0.59	-0.97	1.13	-0.80	1.12	-0.98	0.93	-0.59	1.92	-1.34	1.16
16.5	-1.40	0.69	0.79	2.89	-0.88	1.03	0.80	2.71	-1.82	0.68	-0.02	2.48
22.5	-1.12	0.99	0.92	3.02	0.35	2.27	0.77	2.69	-0.77	1.75	0.37	2.87

Reviewer's Comments: please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

The assay sensitivity of the study was assessed by placing a one-sided lower 95% confidence bound on the differences from baseline between moxifloxacin and placebo (ddQTcI) at 2, 3, and 3.5 hours postdose. The lower bound was above 5 msec at each of these designated times. Further, the time course of the moxifloxacin response was as expected. These criteria demonstrate that the study had assay sensitivity.

A summary of the sponsor's assay sensitivity analysis is shown in Table 3.

Table 3: Assay Sensitivity - Mean Moxifloxacin Differences from Placebo in Change from Predose Baseline and 95% One-sided Lower Confidence Bounds (Sponsor's Results)

ddQTcI (msec)		
Dose Moxifloxacin 400 mg		
Hour	diff	lcb
0.5	3.37	
1	7.49	
1.5	7.90	
2	11.04	8.94
2.5	11.92	
3	10.26	8.16
3.5	11.87	9.77
4.5	11.99	
6.5	4.82	
8.5	6.83	
12.5	6.00	
16.5	6.91	
22.5	3.74	

Reviewer's Comments: please see the reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

No subject had a QTcI interval > 450 msec. Only one subject had values of QTcF >450 msec and these were following the 3000/1500 mg dose. That subject's baseline QTcF for that day (Day 13) was 445 msec and the 3 postdose values ranged from 451 to 453 msec at 0.5, 1.0, and 16.5 hours postdose. Four subjects had one or more QTcB intervals >450 msec following the 1000/500 mg dose, three had one or more QTcB intervals >450 msec following the 3000/1500 mg dose, and two had such a result following placebo. No subject ever had a QTc interval > 480 msec.

No subject ever had an increase in QTcI or QTcF >30 msec, while one, two, and two subjects each had one or more increases in QTcB >30 msec following the 1000/500 mg dose, the 3000/1500 mg dose, and placebo, respectively. No subject ever had an increase from baseline in QTc > 60 msec.

4.2.8.3 Safety Analysis

Single therapeutic (1000/500 mg) and supra-therapeutic (3000/1500 mg) doses of CXA-101/tazobactam were safe and well tolerated in healthy male and female subjects. All adverse events reported during the study were mild to moderate in severity. No events of severe intensity were reported and no SAEs occurred during the study. The most common TEAE was headache. Infusion site reactions, mild in severity, occurred more often following the CXA-101/tazobactam 3000/1000 mg dose; however all reports were

mild in intensity. None of the subjects had treatment-emergent PCS findings for hematology, chemistry, or urinalysis laboratory assessments or for vital signs parameters and there were no clinically significant findings on 12-lead ECGs read locally by the Investigator.

Source: Section 12.6 in sponsor's clinical study report

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for CXA-101, tazobactam and tazobactam metabolite M1 are presented in Table 4. C_{max} and AUC values of CXA-101 and tazobactam and tazobactam metabolite M1 in the thorough QT study were tripled or proportionally higher following administration of 3000/1500 mg dose of CXA-101/tazobactam (supratherapeutic dose) compared with 1000/500 mg CXA-101/tazobactam, the intended therapeutic clinical dose. The mean concentration-time profiles are shown in **Figure 1**.

Table 4: Sponsor's Results for Pharmacokinetic Parameters for CXA-101, tazobactam and tazobactam metabolite M1 after administration of therapeutic (1000/500 mg) and supra-therapeutic (3000/1500 mg) doses of CXA-101/tazobactam in healthy subjects

CXA-101

PK Parameter	CXA-101 1000 mg N=51	CXA-101 3000 mg N=51
AUC _{0-last} (µg•h/mL)	184.0 (18.4)	559.5 (17.5)
AUC _{0-∞} (µg•h/mL)	185.5 (18.3)	561.6 (17.4)
C _{max} (µg/mL)	66.50 (18.6)	198.5(19.4)
T _{max} (h) ^a	0.667 (0.667, 1.17)	0.667 (0.667, 1.18)
t _{1/2} (h)	2.294 (15.2)	2.719 (20.5)
CL (L/h)	5.565 (17.9)	5.500 (17.2)
V _{ss} (L)	13.50 (20.6)	13.67 (20.4)
CL/WT (L/h/kg)	0.08096 (12.5)	0.08017 (12.9)
V _{ss} /WT (L/kg)	0.1954 (11.7)	0.1980 (11.2)

a Median (minimum, maximum)

Tazobactam

PK Parameter	Tazobactam	Tazobactam
	500 mg N=51	1500 mg N=51
AUC _{0-last} (µg•h/mL)	23.5 (23.6)	73.1 (18.9)
AUC _{0-∞} (µg•h/mL)	23.8 (23.5)	73.4 (18.8)
C _{max} (µg/mL)	18.6 (23.2)	51.2(20.7)
T _{max} (h) ^a	0.667 (0.667-1.17)	0.667 (0.667, 1.17)
t _{1/2} (h)	0.870 (18.4)	1.05 (17.0)
CL (L/h)	22.1 (21.0)	21.2 (19.2)
V _{ss} (L)	18.2 (24.5)	19.3 (22.0)
CL/WT (L/h/kg)	0.322 (19.3)	0.309 (17.2)
V _{ss} /WT (L/kg)	0.264 (19.2)	0.280 (15.5)

a Median (minimum, maximum)

Tazobactam Metabolite M1

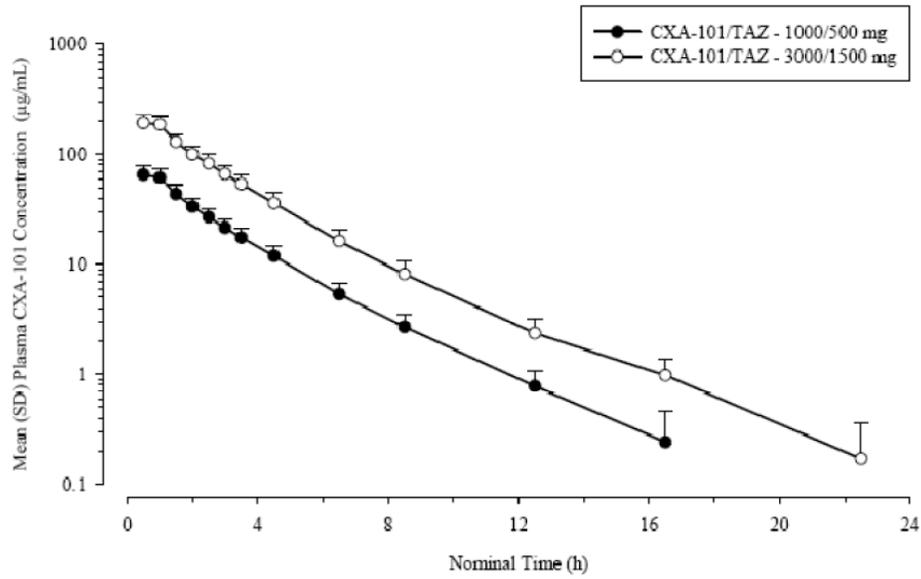
Parameters	Plasma Metabolite M-1 Mean (CV%)	
	Therapeutic Dose	Supra-Therapeutic Dose
	N=51	N=51
AUC _{0-last} (µg•h/mL)	7.54 (49.2)	22.8 (26.3)
AUC _{0-∞} (µg•h/mL)	7.92 (47.1)	23.4 (25.9)
C _{max} (µg/mL)	1.02 (53.5)	2.96 (35.6)
T _{max} (h) ^a	3.67 (2.67 - 4.67)	3.67 (1.17 - 6.67)
t _{1/2} (h)	3.24 (28.5)	3.61 (20.4)
CL/F _m (L/h)	58.5 (29.4)	57.2 (31.3)
V _{ss} /F _m (L)	352 (30.4)	359 (32.4)
CL/F _m /Weight (L/h/kg)	0.858 (30.1)	0.846 (38.1)
V _{ss} /F _m /Weight (L/kg)	5.15 (29.9)	5.25 (36.3)

^aMedian (Min-Max)

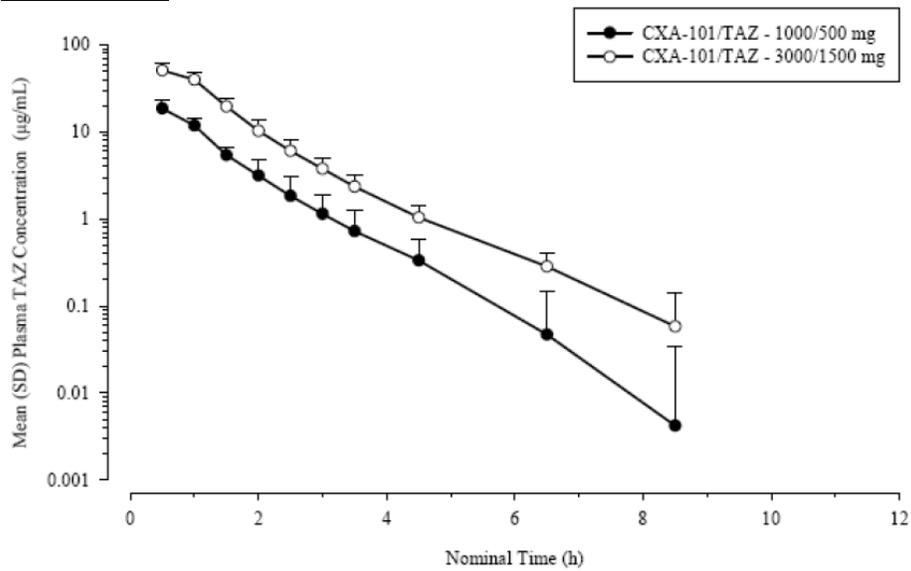
Source: Tables 11-3, 11-4 in sponsor's clinical study report and Table 12 in sponsor's Pharmacokinetic Report CUBI-RAS-006

Figure 1: Mean CXA-101, tazobactam and tazobactam metabolite M1 plasma concentration-time profiles after administration of therapeutic (1000/500 mg) and supra-therapeutic (3000/1500 mg) doses of CXA-101/tazobactam in healthy subjects

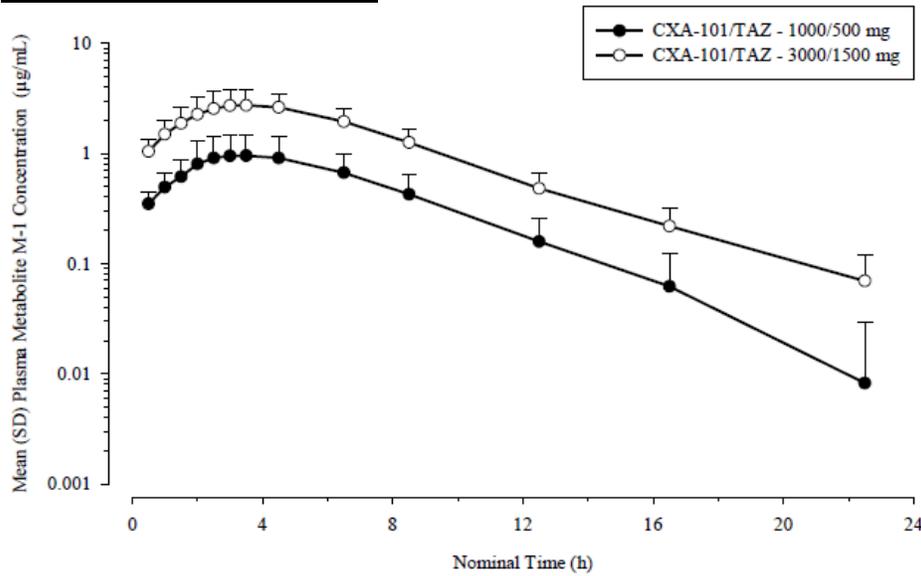
CXA-101



Tazobactam



Tazobactam Metabolite M1



Source: Figures 11-1, 11-2 in sponsor's clinical study report and Figure 3 in sponsor's Pharmacokinetic Report CUBI-RAS-006

4.2.8.4.2 Exposure-Response Analysis

The sponsor employed a linear mixed effects model with analysis with time-matched placebo-subtracted differences in changes from predose baseline in QTcI intervals ($\Delta\Delta\text{QTcI}$) as the dependent variable and the corresponding time-matched log₁₀ CXA-101, tazobactam and tazobactam metabolite M1 concentrations as three separate independent variables.

The resulting slopes and p-values were as follows: CXA-101 slope= 1.08 (p=0.101), tazobactam slope = 1.30 (p=0.035), and tazobactam metabolite M1 slope = 0.69 (p=0.390). Thus a small positive slope was observed for each relationship. Estimated mean differences from placebo from each model, along with their one-sided upper 95% confidence bounds, for the lowest and highest observed concentrations, and the 20th, 40th, 60th, and 80th percentile concentrations are shown in Table 5. All the upper confidence bounds were < 5 ms.

Table 5: Estimated mean $\Delta\Delta\text{QTcI}$ at various concentrations of CXA-101, tazobactam and tazobactam metabolite M1

A) CXA-101

Concentration (mcg/mL)	Mean Difference (msec)	Upper 95% CB (msec)
0.3	-2.64	-0.97
3.3	-1.44	-0.48
18.1	-0.65	0.50
42.4	-0.25	1.15
79.4	0.04	1.67
297.0	0.66	2.81

B) Tazobactam

Concentration (mcg/mL)	Mean Difference (msec)	Upper 95% CB (msec)
0.10	-2.25	-0.61
0.71	-1.14	-0.11
2.15	-0.52	0.40
5.47	0.01	1.02
16.20	0.62	1.90
75.40	1.48	3.30

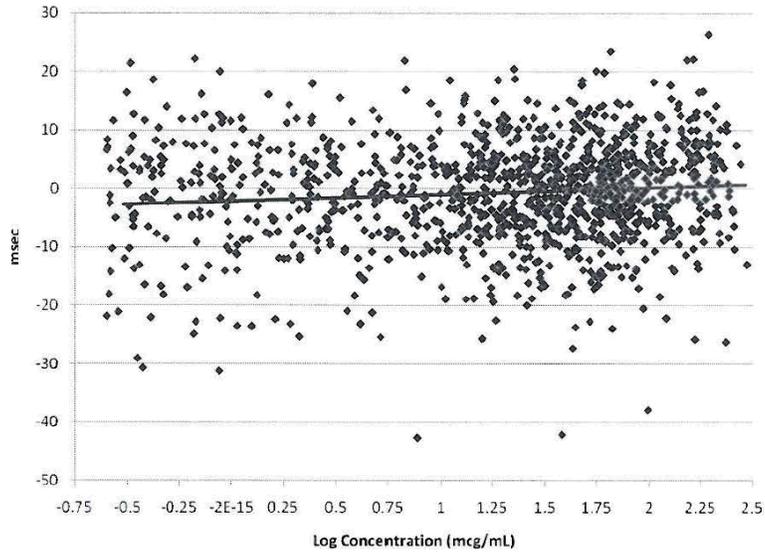
C) Tazobactam Metabolite M1

Concentration (mcg/mL)	Mean Difference (msec)	Upper 95% CB (msec)
0.051	-1.38	0.53
0.351	-0.81	0.37
0.623	-0.64	0.46
1.100	-0.47	0.64
1.860	-0.31	0.89
6.430	0.07	1.72

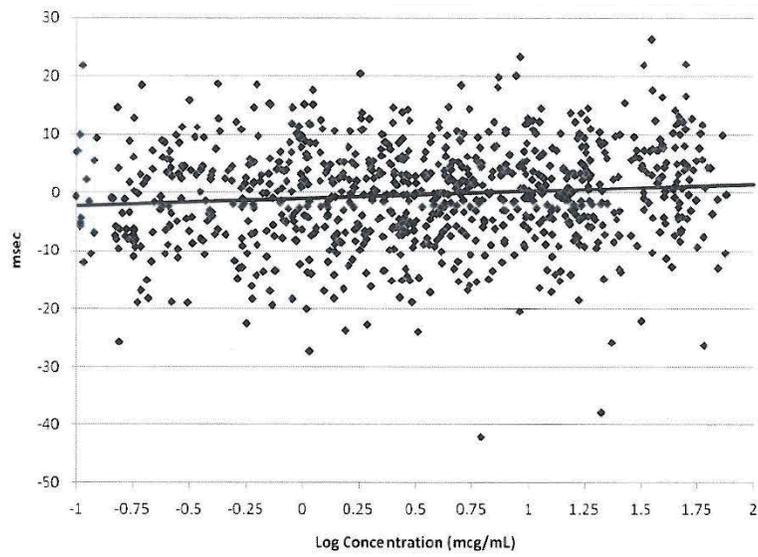
Sponsor's $\Delta\Delta Q T c I$ vs. log of CXA-101, tazobactam or tazobactam metabolite M1 plasma concentrations are shown in **Figure 2**.

Figure 2: Sponsor's Concentration- $\Delta\Delta Q T c I$ relationship for A) CXA-101, B) tazobactam and C) tazobactam metabolite M1. Logarithm of concentrations is plotted on x-axis and $\Delta\Delta Q T c I$ on y-axis

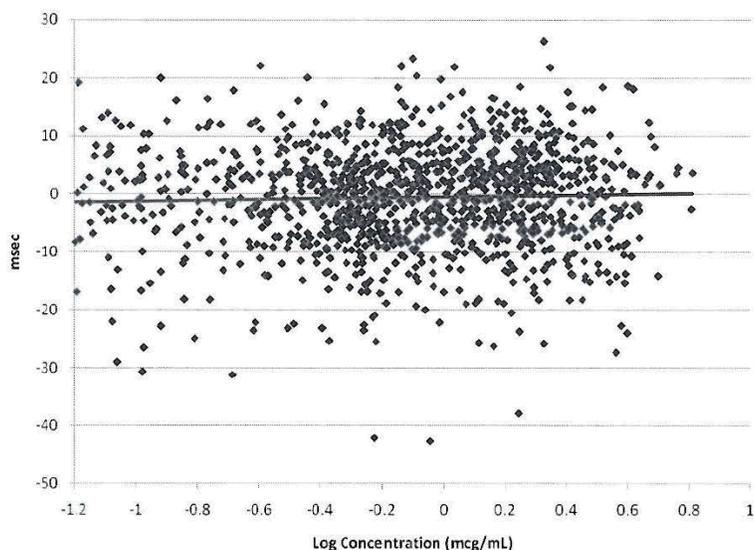
A) CXA-101



B) Tazobactam



C) Tazobactam Metabolite M1



Source: Figure 1, 2 and 3 in sponsor's Cardiac Safety Report Addendum for Concentration/QT analysis

Reviewer's Comments: For relationships of $\Delta\Delta QTcI$ vs. log of drug or metabolite concentrations evaluated by the sponsor, only the slope with tazobactam log concentrations had $p < 0.05$. But the one-sided upper 95% confidence bound for even the highest observed concentrations was below 5 ms.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcB, QTcF, and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

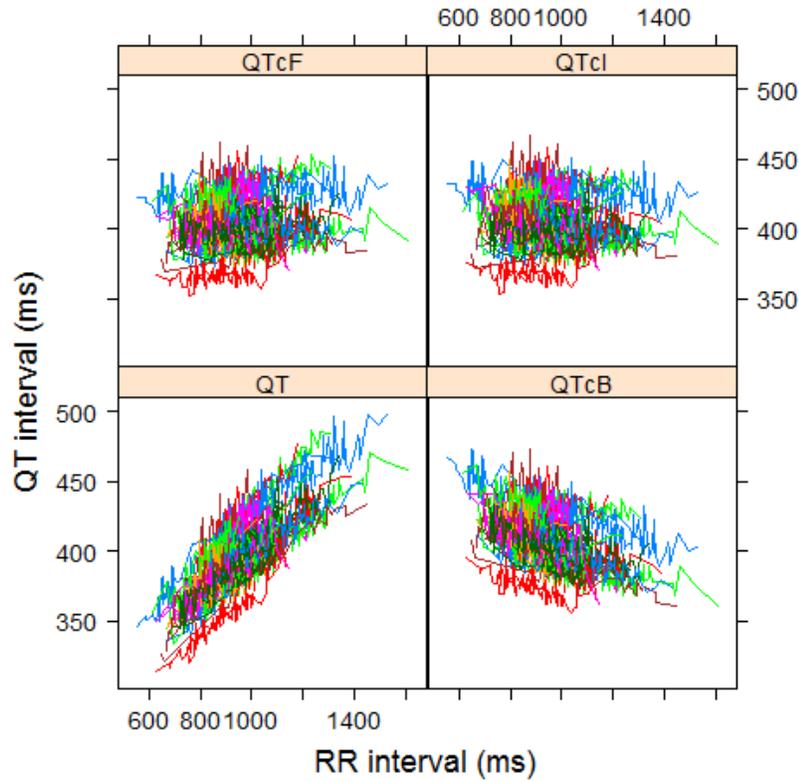
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Placebo	50	0.00328	50	0.00182	50	0.00144
Moxifloxacin 400 mg	51	0.00398	51	0.00234	51	0.00171
CXA-101/tazobactam 1000/500 mg	51	0.00320	51	0.00155	51	0.00122
CXA-101/tazobactam 3000/1500 mg	51	0.00330	51	0.00298	51	0.00213
All	52	0.00342	52	0.00096	52	0.00075

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for CXA-101/tazobactam

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The model includes treatment, sequence, period, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 7: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group = A:
CXA-101/tazobactam 1000/500 mg**

Time (hour)	ΔQTcI (ms) CXA-101/tazobactam 1000/500 mg	ΔQTcI (ms) Placebo	$\Delta\Delta$QTcI (ms) CXA-101/tazobactam 1000/500 mg	
	LSmean	LSmean	LSmean	90% CI
0.5	-1.0	-0.5	0.1	(-2.0, 2.3)
1	1.3	0.6	1.2	(-0.9, 3.3)
1.5	-0.6	0.8	-0.8	(-3.0, 1.3)
2	-2.6	-1.9	-0.1	(-2.2, 2.0)
2.5	-1.1	-1.2	0.7	(-1.4, 2.8)
3	-1.2	-0.1	-0.5	(-2.7, 1.6)
3.5	-1.0	-1.1	0.7	(-1.4, 2.8)
4.5	-1.8	-0.6	-0.6	(-2.7, 1.5)
6.5	-5.4	-3.0	-1.9	(-4.0, 0.2)
8.5	-8.2	-6.1	-1.5	(-3.7, 0.6)
12.5	-6.4	-4.2	-1.6	(-3.7, 0.5)
16.5	4.8	6.9	-1.5	(-3.6, 0.6)
22.5	-1.9	-0.2	-1.3	(-3.4, 0.8)

**Table 8: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group = B:
CXA-101/tazobactam 3000/1500 mg**

Time (hour)	Δ QTcI (ms) CXA-101/tazobactam 3000/1500 mg	Δ QTcI (ms) Placebo	$\Delta\Delta$ QTcI (ms) CXA-101/tazobactam 3000/1500 mg	
	LSmean	LSmean	LSmean	90% CI
0.5	1.9	-0.5	3.1	(1.0, 5.3)
1	3.9	0.6	4.0	(1.9, 6.1)
1.5	0.8	0.8	0.7	(-1.4, 2.8)
2	-1.0	-1.9	1.6	(-0.5, 3.7)
2.5	0.5	-1.2	2.4	(0.3, 4.6)
3	-1.1	-0.1	-0.3	(-2.4, 1.8)
3.5	-3.2	-1.1	-1.3	(-3.4, 0.8)
4.5	-1.9	-0.6	-0.5	(-2.6, 1.6)
6.5	-5.2	-3.0	-1.5	(-3.6, 0.6)
8.5	-8.0	-6.1	-1.1	(-3.3, 1.0)
12.5	-6.0	-4.2	-1.1	(-3.2, 1.0)
16.5	6.9	6.9	0.6	(-1.5, 2.8)
22.5	-0.1	-0.2	0.8	(-1.3, 2.9)

The largest upper bounds of the 2-sided 90% CI for the mean differences between CXA-101/tazobactam 1000/500 mg and placebo, and between CXA-101/tazobactam 3000/1500 mg and placebo were 3.3 ms and 6.1 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval was 9.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 9.0 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group =D: Moxifloxacin 400 mg

Time (hour)	Δ QTcI (ms) Moxifloxacin 400 mg	Δ QTcI (ms) Placebo	$\Delta\Delta$ QTcI (ms) Moxifloxacin 400 mg		
	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
0.5	1.7	-0.5	3.2	(1.1, 5.3)	(0.4, 5.9)
1	7.0	0.6	7.3	(5.2, 9.4)	(4.5, 10.1)
1.5	7.5	0.8	7.7	(5.6, 9.8)	(5.0, 10.5)
2	8.0	-1.9	10.8	(8.7, 13.0)	(8.1, 13.6)
2.5	9.6	-1.2	11.7	(9.6, 13.9)	(9.0, 14.5)
3	9.0	-0.1	10.1	(7.9, 12.2)	(7.3, 12.8)
3.5	9.6	-1.1	11.7	(9.6, 13.8)	(8.9, 14.4)
4.5	10.2	-0.6	11.8	(9.7, 13.9)	(9.0, 14.6)
6.5	0.7	-3.0	4.6	(2.5, 6.8)	(1.9, 7.4)
8.5	-0.5	-6.1	6.6	(4.5, 8.8)	(3.9, 9.4)
12.5	0.7	-4.2	5.7	(3.6, 7.9)	(2.9, 8.5)
16.5	12.7	6.9	6.7	(4.6, 8.9)	(3.9, 9.5)
22.5	2.5	-0.2	3.4	(1.3, 5.6)	(0.7, 6.2)

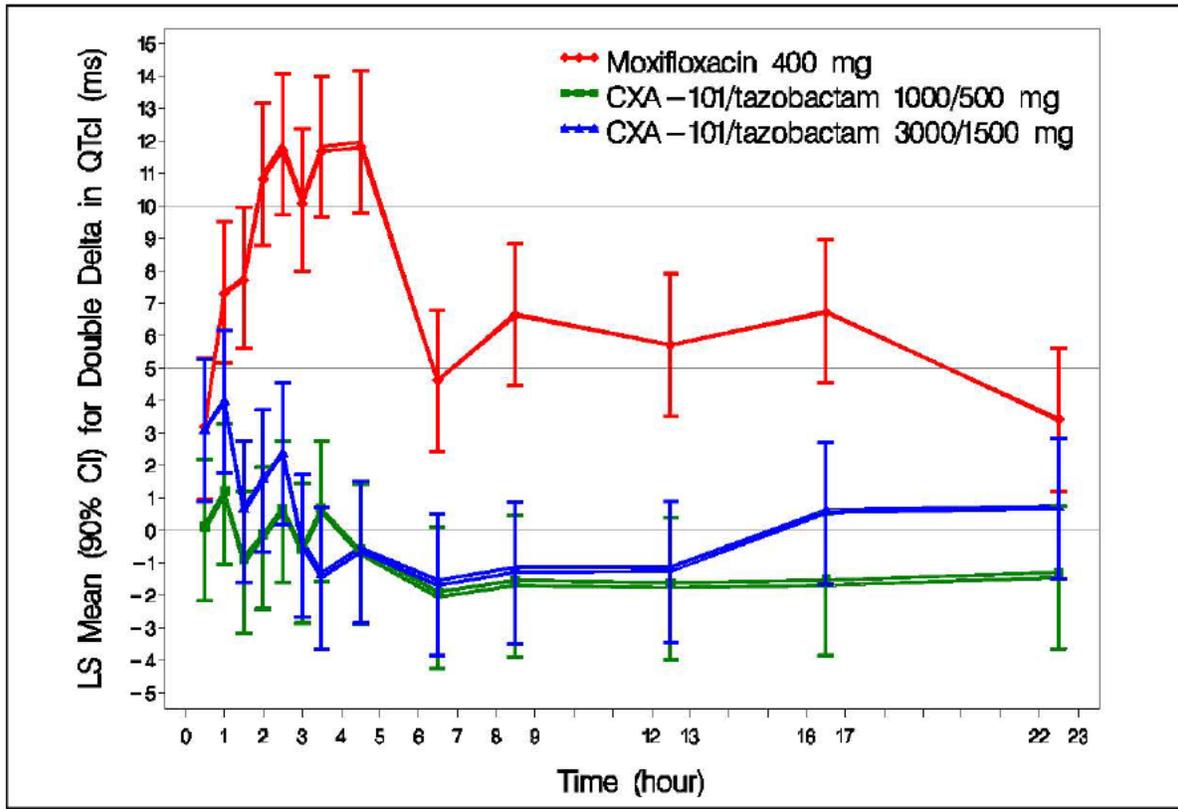
* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcI for different treatment groups.

(Note: CIs are all unadjusted including moxifloxacin)

Figure 4: Mean and 90% CI $\Delta\Delta$ QTcI Timecourse



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcI values were ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

Table 10: Categorical Analysis for QTcI

Treatment Group	Total N		QTcI \leq 450 ms		450<QTcI \leq 480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	52	203	52 (100%)	203 (100%)	0 (0.0%)	0 (0.0%)
Placebo	50	649	49 (98.0%)	648 (99.8%)	1 (2.0%)	1 (0.2%)
Moxifloxacin 400 mg	51	658	47 (92.2%)	647 (98.3%)	4 (7.8%)	11 (1.7%)
CXA-101/tazobactam 1000/500 mg	51	661	51 (100%)	661 (100%)	0 (0.0%)	0 (0.0%)
CXA-101/tazobactam 3000/1500 mg	51	662	51 (100%)	662 (100%)	0 (0.0%)	0 (0.0%)

*The difference from the sponsor's claim in placebo group came from rounding.

Table 11 lists the categorical analysis results for Δ QTcI. No subject's change from baseline in QTcI was above 60 ms.

Table 11: Categorical Analysis of Δ QTcI

Treatment Group	Total N		Δ QTcI \leq 30 ms		30< Δ QTcI \leq 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	50	649	50 (100%)	649 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	51	658	47 (92.2%)	654 (99.4%)	4 (7.8%)	4 (0.6%)
CXA-101/tazobactam 1000/500 mg	51	661	51 (100%)	661 (100%)	0 (0.0%)	0 (0.0%)
CXA-101/tazobactam 3000/1500 mg	51	662	51 (100%)	662 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the HR mean differences between CXA-101/tazobactam 1000/500 mg and placebo, and between CXA-101/tazobactam 3000/1500 mg and placebo were 2.5 bpm and 3.1 bpm, respectively.

The outlier analysis results for HR are presented in Table 13.

Table 12: Analysis Results of Δ HR and $\Delta\Delta$ HR

Time (hour)	CXA-101/tazobactam 1000/500 mg			CXA-101/tazobactam 3000/1500 mg		
	Δ HR LSmean (bpm)	Δ HR LSmean Placebo (bpm)	$\Delta\Delta$ HR LSmean (90% CI) (bpm)	Δ HR LSmean (bpm)	Δ HR LSmean Placebo (bpm)	$\Delta\Delta$ HR LSmean (90% CI) (bpm)
0.5	-1.0	-0.3	-0.4 (-1.9, 1.2)	1.3	-0.3	1.5 (-0.0, 3.1)
1	0.7	0.8	0.3 (-1.3, 1.8)	1.6	0.8	0.8 (-0.7, 2.3)
1.5	1.3	2.2	-0.6 (-2.1, 1.0)	-0.0	2.2	-2.3 (-3.9, -0.8)
2	-1.1	0.1	-0.9 (-2.4, 0.7)	-0.3	0.1	-0.4 (-2.0, 1.1)
2.5	0.6	-0.1	1.0 (-0.6, 2.5)	-0.8	-0.1	-0.8 (-2.3, 0.8)
3	0.5	0.5	0.3 (-1.3, 1.8)	-0.1	0.5	-0.6 (-2.2, 0.9)
3.5	0.6	0.0	0.9 (-0.7, 2.4)	-1.2	0.0	-1.3 (-2.9, 0.2)
4.5	0.9	0.6	0.6 (-0.9, 2.2)	1.2	0.6	0.6 (-1.0, 2.1)
6.5	8.8	8.8	0.2 (-1.3, 1.8)	9.7	8.8	0.8 (-0.7, 2.4)
8.5	3.1	4.6	-1.2 (-2.7, 0.4)	4.3	4.6	-0.4 (-1.9, 1.2)
12.5	4.8	5.1	-0.2 (-1.8, 1.3)	4.4	5.1	-0.8 (-2.3, 0.8)
16.5	-2.9	-1.5	-1.2 (-2.7, 0.4)	-2.5	-1.5	-1.1 (-2.7, 0.4)
22.5	-1.7	-0.1	-1.2 (-2.8, 0.3)	-0.8	-0.1	-0.7 (-2.3, 0.8)

Table 13: Categorical Analysis for HR

	Total N	HR≤100 bpm	HR>100 bpm	HR>45 bpm	HR≤45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	52	52 (100%)	0 (0.0%)	51 (98.1%)	1 (1.9%)
Placebo	50	50 (100%)	0 (0.0%)	45 (90.0%)	5 (10.0%)
Moxifloxacin 400 mg	51	51 (100%)	0 (0.0%)	48 (94.1%)	3 (5.9%)
CXA-101/tazobactam 1000/500 mg	51	50 (98.0%)	1 (2.0%)	48 (94.1%)	3 (5.9%)
CXA-101/tazobactam 3000/1500 mg	51	51 (100%)	0 (0.0%)	46 (90.2%)	5 (9.8%)

5.2.3 PR Analysis

Similar statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI for the PR mean differences between CXA-101/tazobactam 1000/500 mg and placebo, and between CXA-101/tazobactam 3000/1500 mg and placebo were 3.9 ms and 3.5 ms, respectively.

The outlier analysis results for PR are presented in Table 15. The PR>200 ms observations all came from one same subject.

Table 14: Analysis Results of ΔPR and ΔΔPR

Time (hour)	CXA-101/tazobactam 1000/500 mg			CXA-101/tazobactam 3000/1500 mg		
	ΔPR LSmean (ms)	ΔPR LSmean Placebo (ms)	ΔΔ PR LSmean (90% CI) (ms)	ΔPR LSmean (ms)	ΔPR LSmean Placebo (ms)	ΔΔ PR LSmean (90% CI) (ms)
0.5	0.6	0.4	0.2 (-1.7, 2.2)	1.4	0.4	1.1 (-0.9, 3.1)
1	-0.8	-0.1	-0.5 (-2.5, 1.5)	0.1	-0.1	0.3 (-1.6, 2.3)
1.5	-1.0	-0.9	0.0 (-1.9, 2.0)	-2.0	-0.9	-0.9 (-2.8, 1.1)
2	-0.9	-0.0	-0.8 (-2.7, 1.2)	-0.1	-0.0	0.0 (-1.9, 2.0)
2.5	-1.7	-0.8	-0.8 (-2.8, 1.1)	-1.0	-0.8	-0.1 (-2.1, 1.8)
3	-1.9	-1.1	-0.7 (-2.7, 1.3)	-0.8	-1.1	0.4 (-1.6, 2.4)
3.5	-1.3	-3.1	1.9 (-0.1, 3.9)	-1.6	-3.1	1.6 (-0.4, 3.5)
4.5	-1.1	-1.3	0.3 (-1.6, 2.3)	-1.6	-1.3	-0.1 (-2.1, 1.8)
6.5	-5.0	-3.9	-1.0 (-3.0, 1.0)	-4.5	-3.9	-0.5 (-2.4, 1.5)
8.5	-5.2	-3.2	-1.9 (-3.9, 0.1)	-4.6	-3.2	-1.3 (-3.3, 0.7)
12.5	-3.5	-2.1	-1.2 (-3.2, 0.7)	-3.2	-2.1	-1.0 (-3.0, 0.9)
16.5	1.6	2.0	-0.2 (-2.2, 1.7)	2.1	2.0	0.2 (-1.7, 2.2)
22.5	-1.5	-0.9	-0.6 (-2.5, 1.4)	-0.4	-0.9	0.6 (-1.4, 2.5)

Table 15: Categorical Analysis for PR

Treatment Group	Total N		PR≤200 ms		PR>200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	52	203	51 (98.1%)	199 (98.0%)	1 (1.9%)	4 (2.0%)
Placebo	50	649	49 (98.0%)	636 (98.0%)	1 (2.0%)	13 (2.0%)
Moxifloxacin 400 mg	51	658	50 (98.0%)	647 (98.3%)	1 (2.0%)	11 (1.7%)
CXA101/tazobactam 1000/500 mg	51	661	50 (98.0%)	648 (98.0%)	1 (2.0%)	13 (2.0%)
CXA-101/tazobactam 3000/1500 mg	51	662	50 (98.0%)	649 (98.0%)	1 (2.0%)	13 (2.0%)

5.2.4 QRS Analysis

Similar statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the QRS mean differences between between CXA-101/tazobactam 1000/500 mg and placebo, and between CXA-101/tazobactam 3000/1500 mg and placebo were 1.0 ms and 0.8 ms, respectively.

The outlier analysis results for QRS are presented in Table 17.

Table 16: Analysis Results of Δ QRS and $\Delta\Delta$ QRS

Time (hour)	CXA-101/tazobactam 1000/500 mg			CXA-101/tazobactam 3000/1500 mg		
	Δ QRS LSmean (ms)	Δ QRS LSmean Placebo (ms)	$\Delta\Delta$ QRS LSmean (90% CI) (ms)	Δ QRS LSmean (ms)	Δ QRS LSmean Placebo (ms)	$\Delta\Delta$ QRS LSmean (90% CI) (ms)
0.5	0.1	0.1	-0.0 (-0.7, 0.7)	0.1	0.1	0.1 (-0.6, 0.8)
1	0.0	-0.1	0.1 (-0.6, 0.8)	-0.9	-0.1	-0.8 (-1.5, -0.1)
1.5	-0.1	-0.3	0.2 (-0.5, 0.9)	-0.6	-0.3	-0.3 (-1.0, 0.4)
2	0.0	-0.3	0.3 (-0.4, 1.0)	-1.0	-0.3	-0.7 (-1.4, -0.0)
2.5	-0.2	-0.5	0.3 (-0.4, 1.0)	-0.5	-0.5	0.0 (-0.7, 0.7)
3	-0.1	-0.3	0.1 (-0.5, 0.8)	-0.4	-0.3	-0.1 (-0.8, 0.5)
3.5	-0.3	-0.5	0.2 (-0.5, 0.9)	-0.8	-0.5	-0.3 (-1.0, 0.4)
4.5	0.0	-0.2	0.2 (-0.5, 0.9)	-0.7	-0.2	-0.5 (-1.2, 0.2)
6.5	0.2	1.0	-0.9 (-1.5, -0.2)	-0.3	1.0	-1.4 (-2.1, -0.7)
8.5	-0.5	-0.4	-0.1 (-0.8, 0.6)	-1.0	-0.4	-0.6 (-1.3, 0.1)
12.5	0.0	-0.0	-0.0 (-0.7, 0.7)	-1.2	-0.0	-1.2 (-1.9, -0.5)
16.5	0.5	0.8	-0.3 (-1.0, 0.4)	0.5	0.8	-0.3 (-1.0, 0.4)
22.5	0.2	0.2	-0.0 (-0.7, 0.7)	0.1	0.2	-0.2 (-0.8, 0.5)

Table 17: Categorical Analysis for QRS

Treatment Group	Total N		QRS≤110 ms		QRS>110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	52	203	50 (96.2%)	198 (97.5%)	2 (3.8%)	5 (2.5%)
Placebo	50	649	48 (96.0%)	632 (97.4%)	2 (4.0%)	17 (2.6%)
Moxifloxacin 400 mg	51	658	50 (98.0%)	653 (99.2%)	1 (2.0%)	5 (0.8%)
CXA-101/tazobactam 1000/500 mg	51	661	49 (96.1%)	643 (97.3%)	2 (3.9%)	18 (2.7%)
CXA-101/tazobactam 3000/1500 mg	51	662	48 (94.1%)	644 (97.3%)	3 (5.9%)	18 (2.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug (CXA-101 and tazobactam) and metabolite (tazobactam metabolite M1) concentration-time profiles are illustrated in Figure 1 above.

The relationship between $\Delta\Delta\text{QTcI}$ and CXA-101, tazobactam or tazobactam metabolite M1 concentrations was investigated by linear mixed-effects modeling. The following three linear models were considered:

- Model 1 is a linear model with an intercept
- Model 2 is a linear model with mean intercept fixed to 0 (with variability)
- Model 3 is a linear model with no intercept

Model 1, a linear model with intercept, was used for further analysis since this model was found to fit the data best for both drugs individually. Table 18 summarizes the results of the CXA-101 - $\Delta\Delta\text{QTcI}$ and tazobactam - $\Delta\Delta\text{QTcI}$ analyses. There was no relationship between $\Delta\Delta\text{QTcI}$ and tazobactam metabolite M1 as suggested by the regression trend and statistically insignificant slope parameter for the linear model.

Table 18: Exposure-Response Analysis of CXA-101 or Tazobactam Associated $\Delta\Delta\text{QTcI}$ changes

Parameter	Estimate	P-value	Inter-individual Variability (%)
$\Delta\Delta\text{QTcI} = \text{Intercept} + \text{slope} * \text{CXA-101 concentration}$			
Intercept (ms)	-1.75 (-2.76; -0.74)	0.0055	3.76
Slope (ms per ng/mL)	0.0225 (0.0136; 0.0313)	<0.0001	0.02
Residual Variability (ms)	7.42		

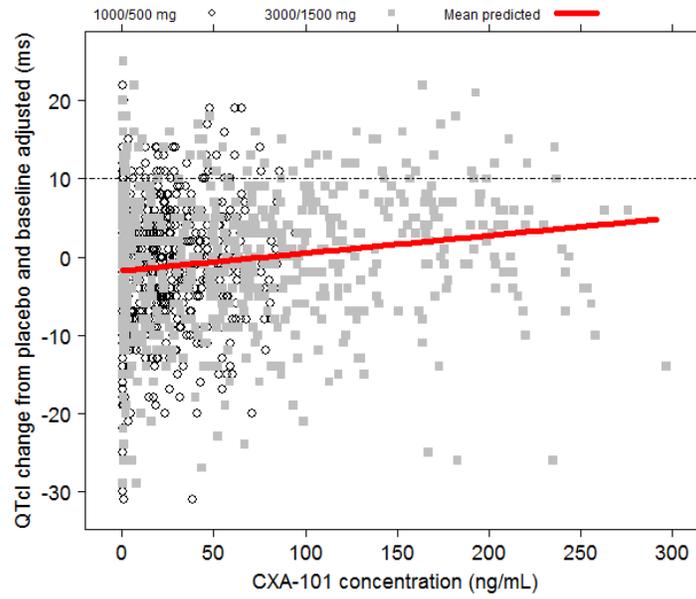
Parameter	Estimate	P-value	Inter-individual Variability (%)
$\Delta\Delta\text{QTcI} = \text{Intercept} + \text{slope} * \text{Tazobactam concentration}$			
Intercept (ms)	-1.06 (-2.15; 0.02)	0.1077	4.06
Slope (ms per ng/mL)	0.077 (0.0406; 0.114)	0.0009	0.09
Residual Variability (ms)	7.33		

The relationship between $\Delta\Delta\text{QTcI}$ and CXA-101 or tazobactam concentrations is visualized in

Figure 5. The relationship between $\Delta\Delta\text{QTcI}$ and tazobactam metabolite M1 concentrations is visualized in Figure 6.

Figure 5: $\Delta\Delta\text{QTcI}$ vs. CXA-101 (panel A) or Tazobactam (panel B) Concentration together with the Population Predictions (solid red line)

A)



B)

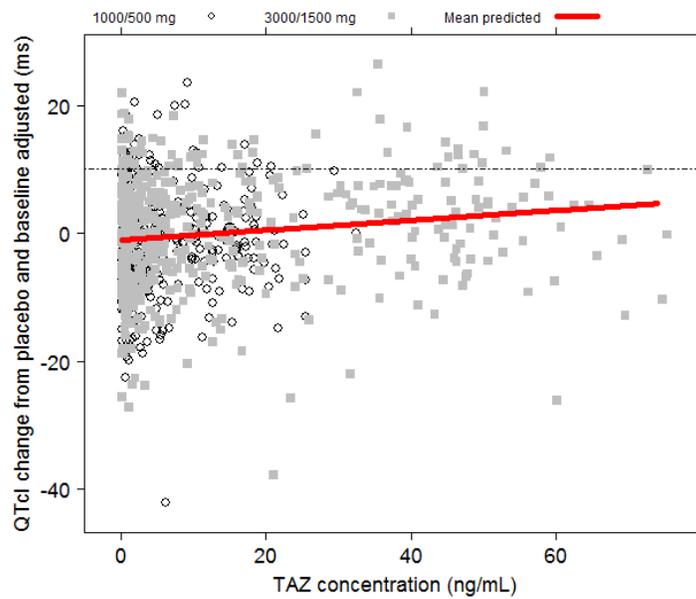
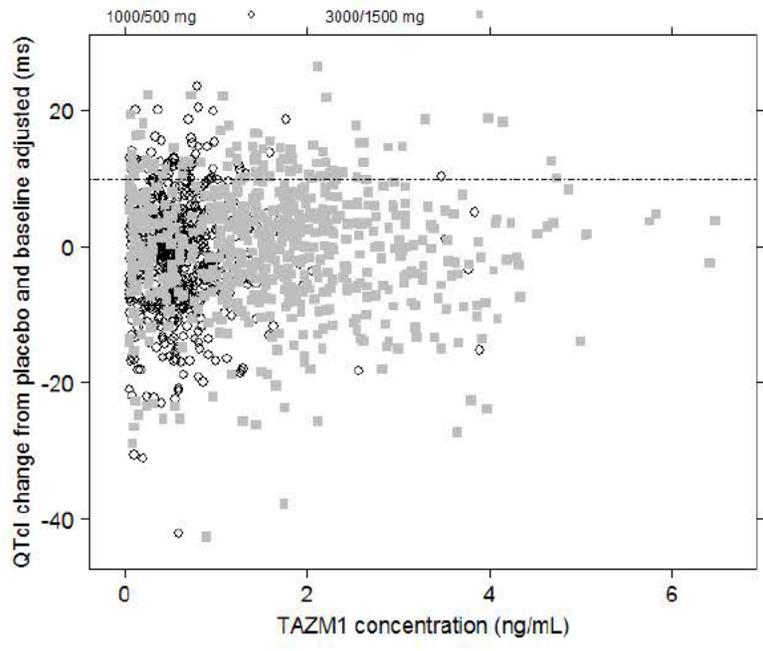


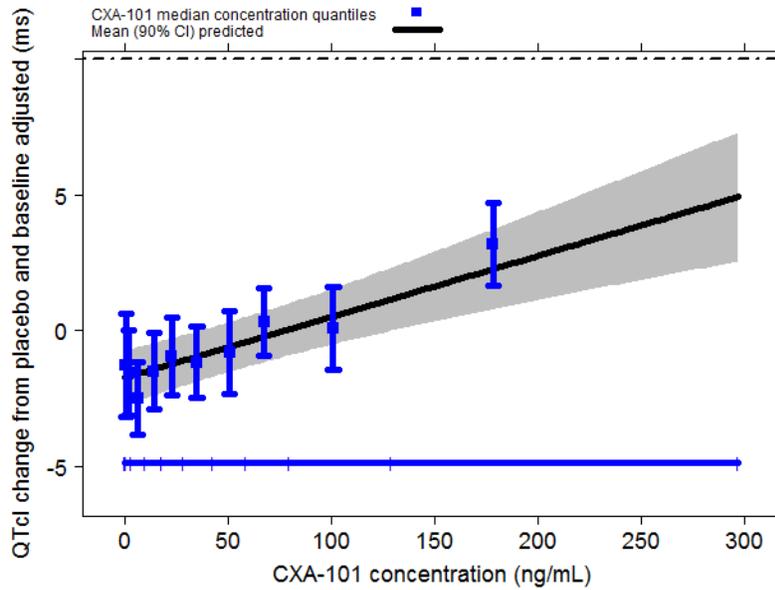
Figure 6: $\Delta\Delta$ QTcI vs. Tazobactam Metabolite M1 Concentration



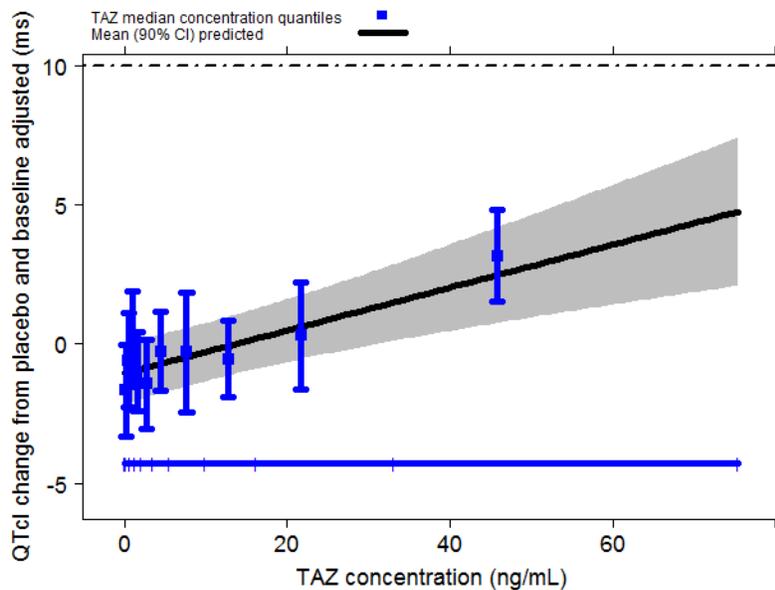
The goodness-of-fit plots in Figure 7 show the observed median-quantile CXA-101 concentrations or tazobactam concentrations and associated mean (90% CI) $\Delta\Delta\text{QTcI}$ together with the mean (90% CI) predicted $\Delta\Delta\text{QTcI}$.

Figure 7: Observed Median-Quantile CXA-101 Concentrations (panel A) or Tazobactam Concentrations (panel B) and Associated Mean (90% CI) $\Delta\Delta\text{QTcI}$ (colored dots) together with the Mean (90% CI) Predicted $\Delta\Delta\text{QTcI}$ (black line with shaded grey area)

A)



B)



There is a positive, statistically significant slope in exposure-response relationship for $\Delta\Delta\text{QTcI}$ with CXA-101 and with tazobactam exposures individually. But the slopes are relatively flat and the predicted $\Delta\Delta\text{QTcI}$ at the average C_{max} of supratherapeutic dose or at the highest quantile of exposures of both CXA-101 and tazobactam was less than 5 ms.

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There was no clinically significant effect on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	1 g ceftolozane / 0.5 g tazobactam	
Maximum tolerated dose	MTD has not been established. The maximum single and multiple doses studies were safe and well tolerated.	
Principal adverse events	In the Phase 3 program, the most common identified treatment-related adverse events with ceftolozane/tazobactam were nausea (1.7%), diarrhea (1.6%), headache (1.4%), and transaminase increases (1.0%). No dose limiting adverse events were identified.	
Maximum dose tested	Single Dose (Study CXA-QT-10-02)	3 g ceftolozane / 1.5 g tazobactam
	Multiple Dose (Study CXA-MD-11-07)	2 g ceftolozane / 1 g tazobactam every 8 hr for 10 days
Exposures Achieved at Maximum Tested Dose	Single Dose	<p><u>Ceftolozane:</u> Mean (%CV) C_{max}: 199 (19) $\mu\text{g/mL}$ Mean (%CV) AUC_{∞}: 562 (17) $\mu\text{g}\cdot\text{hr/mL}$</p> <p><u>Tazobactam:</u> Mean (%CV) C_{max}: 51.2 (21) $\mu\text{g/mL}$ Mean (%CV) AUC_{∞}: 73.4 (19) $\mu\text{g}\cdot\text{hr/mL}$</p> <p><u>Tazobactam MI:</u> Mean (%CV) C_{max}: 2.96 (36) $\mu\text{g/mL}$ Mean (%CV) AUC_{∞}: 23.4 (26) $\mu\text{g}\cdot\text{hr/mL}$</p>
	Multiple Dose	<p><u>Ceftolozane:</u> Mean (%CV) C_{max}: 112 (13) $\mu\text{g/mL}$ Mean (%CV) $AUC_{\tau,ss}$: 300 (10) $\mu\text{g}\cdot\text{hr/mL}$</p> <p><u>Tazobactam:</u> Mean (%CV) C_{max}: 25.8 (15) $\mu\text{g/mL}$ Mean (%CV) $AUC_{\tau,ss}$: 40.5 (13) $\mu\text{g}\cdot\text{hr/mL}$</p> <p><u>Tazobactam MI:</u> Mean (%CV) C_{max}: 1.8 (20) $\mu\text{g/mL}$ Mean (%CV) $AUC_{last,ss}$: 11.9 (19) $\mu\text{g}\cdot\text{hr/mL}$</p>

Therapeutic dose	1 g ceftolozane / 0.5 g tazobactam	
Range of linear PK	<p><u>Ceftolozane:</u> 250 mg to 3 g in single dose studies 500 mg every 8 hr to 2 g every 8 hr in multiple dose studies</p> <p><u>Tazobactam:</u> 500 mg to 1.5 g in single dose studies 500 mg every 8 hr to 1 g every 8 hr in multiple dose studies</p>	
Accumulation at steady state	<p><u>Ceftolozane:</u> Mean (%CV): 1.14 (6); 1 g ceftolozane / 500 mg tazobactam every 8 hr</p> <p><u>Tazobactam:</u> Mean (%CV): 0.93 (33); 1 g ceftolozane / 500 mg tazobactam every 8 hr</p> <p><u>Tazobactam M1:</u> Mean (%CV): 1.69 (14); 1 g ceftolozane / 500 mg tazobactam every 8 hr</p>	
Metabolites	<p>Ceftolozane is not metabolized</p> <p>Tazobactam undergoes hydrolysis to form tazobactam M1 that is pharmacologically inactive.</p>	
Absorption	Absolute/Relative Bioavailability	Not applicable, as given via IV route only
	T _{max}	<p><u>Ceftolozane/tazobactam:</u> T_{max} occurs at the end of infusion (~1 hr) for ceftolozane/tazobactam</p> <p><u>Tazobactam M1:</u> T_{max} Median (range): 3.67 (2.67-4.67) hr</p>

Therapeutic dose	1 g ceftolozane / 0.5 g tazobactam	
Distribution	V _{ss}	<u>Ceftolozane:</u> Mean (%CV): 13.5 (21) L <u>Tazobactam:</u> Mean (%CV): 18.2 (25) L
	% bound	<u>Ceftolozane:</u> 16 to 21% <u>Tazobactam:</u> 30%
Elimination	Route	<ul style="list-style-type: none"> • renal <u>Ceftolozane:</u> Mean (%CV): 98.8 (17) % of the administered dose as the unchanged parent drug in the urine <u>Tazobactam and tazobactam M1:</u> Mean (%CV): 88.2 (22) % of the administered dose as the unchanged parent drug and remaining as tazobactam M1 in the urine
	Terminal t _{1/2}	<u>Ceftolozane:</u> Mean (%CV): 2.29 (15) hr <u>Tazobactam:</u> Mean (%CV): 0.870 (18) hr <u>Tazobactam M1:</u> Mean (%CV): 3.24 (29) hr
	CL	<u>Ceftolozane:</u> Mean (%CV): 5.57 (18) L/hr <u>Tazobactam:</u> Mean (%CV): 22.1 (21) L/hr

Therapeutic dose	1 g ceftolozane / 0.5 g tazobactam	
Intrinsic Factors	Age	A population pharmacokinetic analysis was performed to evaluate the impact of age as a continuous covariate on the pharmacokinetics of ceftolozane. Age alone was not found to influence exposure and thus no dose adjustment of based on age alone is recommended.
	Sex	A population pharmacokinetic analysis was performed to evaluate the impact of sex on the pharmacokinetics. Sex was not found to influence exposure and thus no dose adjustment is recommended based on sex.
	Race	A population pharmacokinetic analysis was performed to evaluate the impact of race on the pharmacokinetics. Race was not found to influence exposure and thus no dose adjustment is recommended based on race.
	Hepatic & Renal Impairment	<p>Ceftolozane/tazobactam is not cleared by hepatic pathways so no hepatic impairment study conducted.</p> <p>Ceftolozane/tazobactam is eliminated in the urine and thus renal impairment increases exposure.</p> <p><u>Ceftolozane:</u></p> <p>Ceftolozane dose normalized geometric mean AUC was 1.3-fold, 2.5-fold, and 4 to 5-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to that in healthy subjects with normal renal function, while dose normalized geometric mean C_{max} was approximately 1.3-fold, 2.5-fold, and 4 to 5-fold of that in healthy subjects with normal renal function.</p> <p><u>Tazobactam:</u></p> <p>Tazobactam dose normalized geometric mean AUC was 1.3-fold, 2-fold, and 3 to 4-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to that healthy subjects with normal renal function, while dose normalized geometric mean C_{max} was approximately 1.3-fold, 2-fold, and 1.5 to 2-fold of that in healthy subjects with normal renal function.</p>

Therapeutic dose	1 g ceftolozane / 0.5 g tazobactam	
Intrinsic Factors, continued		<u>Tazobactam M1:</u> Tazobactam dose normalized geometric mean AUC was 1.4-fold, 4.7-fold, and 12 to 13.5-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to that in healthy subjects with normal renal function, while dose normalized geometric mean Cmax was approximately 1.5-fold, 2.8-fold, and 4 to 5.6 fold of that in healthy subjects with normal renal function.
Extrinsic Factors	Drug interactions	Drug interactions potential was evaluated in <i>in vitro</i> studies and in a clinical study (CXA-DDI-12-10). No significant drug-drug interactions were identified between ceftolozane/tazobactam and substrates, inhibitors, and inducers of cytochrome P450 enzymes (CYPs). While co-administration of ceftolozane/tazobactam with drugs that inhibit OAT1 and/or OAT3 (e.g., probenecid) may increase tazobactam plasma concentrations, tazobactam as a part of an approved marketed drug, Zosyn, has been prescribed safely for more than 20 years. No other significant drug-drug interactions involving membrane transporters were identified.
	Food Effects	Not applicable as an IV drug
Expected High Clinical Exposure Scenario	No covariates other than renal impairment increased exposure in a clinically relevant manner. Accordingly, in patients with moderate and severe renal impairment, a 2-fold and 4-fold dose reduction, respectively, is recommended to ensure that exposure is within the limit of what has been found safe in a clinical setting.	

Therapeutic dose	1 g ceftolozane / 0.5 g tazobactam
Preclinical Cardiac Safety	<p><u>Ceftolozane:</u></p> <p>Ceftolozane demonstrated no effect on the human ether-à-go-go related gene (hERG) channel up to a maximum concentration of 667 µg/mL, approximately 12-fold greater than the mean clinical C_{max} of 57 µg/mL. No significant effects upon cardiovascular functioning were seen in male rats or dogs following IV administration of ceftolozane at 100 mg/kg. Bolus IV administration of ceftolozane to rats at 320 mg/kg produced a slight but statistically significant decrease in heart rate (11%) as compared to predose values.</p> <p>A statistically significant decrease in heart rate (22%) and mean blood pressure (27%) as compared to predose values was observed at 1000 mg/kg. Following IV administration to dogs, ceftolozane produced a transient 37% increase in heart rate in one animal in the 300 mg/kg dose group with no effects upon ECGs. Together, these effects occurred at doses with estimated associated C_{max} values of 728 to 2028 µg/mL for male rats and 793 µg/mL for male dogs. These C_{max} values are approximately 13- to 36-fold greater than the mean clinical C_{max} of 57 µg/mL.</p> <p><u>Tazobactam:</u></p> <p>No cardiovascular safety pharmacology studies were conducted by the Sponsor with tazobactam because tazobactam is a well-established β-lactamase inhibitor that is a component of the currently marketed drug piperacillin/tazobactam with a long history of safe use in humans.</p> <p><u>Ceftolozane/Tazobactam:</u></p> <p>No cardiovascular safety pharmacology studies were conducted by the Sponsor with ceftolozane/tazobactam. The pharmacokinetics of ceftolozane and tazobactam are not altered when administered in combination and therefore, the potential for ceftolozane/tazobactam to affect cardiovascular function is not anticipated to be altered as compared to the individual compounds. Moreover, in accordance with the Guidance for Industry document “M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals”, combination safety pharmacology studies are generally not recommended to support clinical trials or marketing.</p>
Clinical Cardiac Safety	Cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths) are summarized below in Table 2.

Note: AUC_∞ - area under plasma concentration-time curve from time zero to infinity, AUC_{τ,ss} - area under plasma concentration-time curve for a dosing interval (8 hr) at steady-state, AUC_{last,ss} - area under plasma concentration-time curve from time zero to last measurable plasma concentration at steady-state, C_{max} - maximum (peak) plasma concentration, T_{max} - time to reach maximum (peak) plasma concentration following drug administration, V_{ss} - apparent volume of distribution at steady state after intravenous administration, NA - not applicable

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/s/

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10/01/2014

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

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

Memorandum

Date: September 16, 2014

To: Maureen Dillon-Parker, Chief Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

Maria Allende, MD, Clinical Reviewer
DAIP

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

Subject: **NDA #206829
ZERBAXA (ceftolozane/tazobactam) for injection, for
intravenous use**

As requested in your consult dated June 12, 2014, OPDP has reviewed the proposed draft labeling for ZERBAXA (ceftolozane/tazobacatam) for injection, for intravenous use (Zerbaxa).

OPDP's comments on the PI are based on the substantially complete version of the labeling titled, "WORKING COPY.doc," which was received via email from DAIP on September 15, 2014.

OPDP's comments on the PI are provided in the attached, clean version of the labeling.

OPDP has also reviewed the proposed carton and vial labels that were submitted to FDA on July 9, 2014. OPDP notes that the PI refers to Zerbaxa as ceftolozane/tazobacatam 1.0 g/0.5 g. For clarity and consistency with the PI, OPDP recommends revising the 1.5 g strength on the carton and vial labels to 1.0 g/0.5g.

Thank you for the opportunity to review and provide comments on the proposed PI and carton/container labeling. If you have any questions about OPDP's comments, please contact Christine Corser at 6-2653 or Christine.corser@fda.hhs.gov.

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

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CHRISTINE G CORSER
09/16/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review: August 7, 2014
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 206829
Product Name and Strength: Zerbaxa (Ceftolozane and Tazobactam) for Injection,
1.5 g per vial
Product Type: Multi-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Cubist
Submission Date: April 21, 2014
OSE RCM #: 2014-312
DMEPA Primary Reviewer: Aleksander Winiarski, PharmD
DMEPA Acting Team Leader: Tingting Gao, PharmD

1 REASON FOR REVIEW

Cubist submitted Zerbaxa (Ceftolozane/Tazobactam) for injection, 1.5 g per vial, for review under NDA 206829. This is a multi-ingredient product which includes one new molecular entity (Ceftolozane) and one previously approved molecular entity (Tazobactam).

The Division of Anti-Infective Products (DAIP) requested that we review the submitted Zerbaxa 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
Human Factors Study	D - N/A
ISMP Newsletters	E - N/A
Other	F - N/A
Proposed Labels and Labeling	G

N/A = Not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the submitted Zerbaxa prescribing information (PI) labeling and identified that the PI labeling contains potentially confusing dose preparation instructions in section 2.3, "Preparation of Solutions", which may lead to dosing errors.

The concentration of the product in the vial after reconstitution is listed as (b) (4)

This may be confusing to the end user and may lead to dosing errors due to recalculations. Additionally we identified one error in section 2.3 which instructs the user to (b) (4)

(b) (4)

We have shared the potential for these errors with DAIP, the Office for New Drug Quality Assessment (ONDQA), and Cubist via mid-cycle communication. Although Cubist proposed (b) (4) we are in discussion with our FDA colleagues and Cubist on potential strategies to mitigate this risk, including changing the initial volume of the diluent, for example, (b) (4)

Revising the concentration to (b) (4) would allow easier dose calculation and measurement of the intended doses. Additional strategies to minimize the risk for these errors include any lessons learned from the clinical trials (we are currently awaiting this information from Cubist) and to improve labeling to clearly communicate the correct post-reconstitution concentration and dose preparation instructions.

Also, in our review we identified the use of symbols such as ' \leq ', '>', ' \geq ', and 'IV' ¹, in the Dosage and Administrations sections of the PI labeling, which should be replaced with the corresponding words.

Our review of the container labels and carton labeling identified some potential readability issues and lack of prominence of important use and prescribing information (e.g. strength, storage, NDC number, and post-reconstitution concentration information).

We provide specific recommendations in sections 4.1 and 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

The submitted labels and labeling for Zerbaxa may be improved to communicate important use information and to improve prominence of product information. We recommend the following revisions be implemented prior to approval of the NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for the Division's consideration

A. Dosage and Administration Sections, Highlights of Prescribing Information and Full Prescribing Information

¹ FDA Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*.

1. We note the use of symbols, such as: ‘≤’, ‘>’, ‘≥’, and ‘IV’¹, in the Dosage and Administrations sections of the PI labeling. Consider replacing the symbols with the corresponding words, such as ‘≤’ with “less than or equal to”, ‘>’ with “greater than”, ‘≥’ with “greater than or equal to”, and ‘IV’ with “intravenous”, for clarity.
2. If it is determined that the volume of diluent may be revised to yield a concentration of (b) (4) in the vial, then ensure that the volumes needed to be withdrawn from the vial to prepare the infusion solutions are appropriately recalculated for each corresponding dose in Section 2.3, “Preparation of Solutions”.
3. To improve readability in Section 2.3, “Preparation of Solutions”, consider listing the doses and volumes needed to be withdrawn from the vial to prepare the infusion solutions in a table format. For example:

Dose	Volume to Withdraw from Vial
1.5 g	xx mL
750 mg	xx mL
375 mg	xx mL
150 mg	xx mL

4. If it is determined that the volume of diluent cannot be revised, ensure that Cubist lists an exact concentration (for example (b) (4)) and the exact volumes needed to be withdrawn from the vial to prepare each infusion dose in Section 2.3, “Preparation of Solutions”, rounded to the nearest tenth (one decimal place) whenever appropriate to minimize the risk for recalculation errors.

4.2 RECOMMENDATIONS FOR CUBIST

DMEPA recommends the following revisions prior to approval of the NDA:

A. Vial Label

1. To improve readability and for consistency with the carton labeling, consider relocating the strength statement (b) (4) directly under the established name.

2. The strength statement lacks adequate prominence compared to some of the other use information on the label. To improve readability and promote adequate prominence of the strength, increase the font size of the statement [REDACTED] (b) (4) [REDACTED]
3. The vial label of one unit and the carton labeling of 10 units should have different NDC numbers. Consider revising the NDC numbers so that the carton labeling and vial label NDC numbers are different for these two package configurations.
4. To reduce the potential for recalculation/dosing errors, on the side panel add the statement “Post-reconstitution concentration: xx mg/mL” (final mg/mL concentration to be determined). If additional space is needed to accommodate the above revision, consider decreasing the font size of current text on the side panel.

B. Carton Labeling

1. See A2 and A3 above
2. Product refrigeration and light sensitivity are important storage information and may be inadvertently overlooked on the side panel. Consider including a statement similar to “refrigerate and keep vials in carton until use” on the Principal Display Panel (PDP), below the “For Intravenous Infusion” statement.
3. Instructions for reconstituting the product and the resultant concentration should be included on side panel. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zerbaxa from the submitted insert labeling on July 9, 2014.

Table 2. Relevant Product Information for Zerbaxa	
Active Ingredient	Ceftolozane/Tazobactam
Indication	Complicated urinary tract infections caused by <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , (b) (4) and <i>Proteus mirabilis</i> Complicated intra-abdominal infections (used in combination with metronidazole) caused by <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus mirabilis</i> , <i>Bacteroides fragilis</i> , and <i>Streptococcus spp.</i>
Route of Administration	Intravenous Infusion
Dosage Form	Powder for injection
Strengths	1.5 g per vial
Dose and Frequency	<ul style="list-style-type: none">1.5 g intravenous infusion over 1 hour every 8 hours for 4 to 14 days; requires renal dose adjustment to 750 mg, 375 mg or 150 mg every 8 hours depending on severity of renal insufficiency
How Supplied	Zerbaxa is supplied in single-use vials, packaged in carton containing 10 vials
Storage	Refrigerate and protect from light
Container Closure	Glass vial

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:drive on August 4, 2014 using the terms Zerbaxa or Ceftolozane or Tazobactam to identify reviews previously performed by DMEPA.

C.2 Results

Our search did not identify any relevant labeling reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Zerbaxa labels and labeling submitted by Cubist June 13, 2014 and July 9, 2014.

G.2 Label and Labeling Images

Vial Label



Carton Labeling

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



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/s/

ALEKSANDER P WINIARSKI
08/07/2014

TINGTING N GAO
08/07/2014

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Application: NDA 206829

Application Type: New NDA

Name of Drug/Dosage Form: Zerbaxa (ceftolozane/tazobactam) Injection

Applicant: Cubist Pharmaceuticals, Inc.

Receipt Date: 4/21/14

Goal Date: 12/21/14 [12/19/14; Friday]

1. Regulatory History and Applicant's Main Proposals

NDA 206829 was submitted on 4/21/14. The indications the applicant is seeking are cUTI and cIAI.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

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:

Selected Requirements of Prescribing Information

- 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:

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

Comment: *Horizontal line must be added.*

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

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

Selected Requirements of Prescribing Information

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,

Selected Requirements of Prescribing Information

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

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

Comment: *Only one dosage form; Intravenous.*

Contraindications in Highlights

- N/A** 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"

Selected Requirements of Prescribing Information

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

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

Comment:

Revision Date in Highlights

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

Comment:

Contents: Table of Contents (TOC)

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

- NO** 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:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment:

- NO** 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:

Selected Requirements of Prescribing Information

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- NO** 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: *Font needs to match.*

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

- N/A** 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

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

Selected Requirements of Prescribing Information

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

MAUREEN P DILLON PARKER
06/19/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 206829 BLA#	NDA Supplement #:S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Zerbaxa Established/Proper Name: ceftolozane/tazobactam Dosage Form: Injection for Intravenous (IV) Use Strengths: 1.5g		
Applicant: Cubist Pharmaceuticals, Inc. Agent for Applicant (if applicable): n/a		
Date of Application: April 19, 2014 Date of Receipt: April 21, 2014 [Rolling Review; first piece received 2/14/14; last piece 4/21/14] Date clock started after UN: n/a		
PDUFA Goal Date: December 21, 2014	Action Goal Date (if different): n/a	
Filing Date: June 20, 2014	Date of Filing Meeting: June 12, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s): Complicated Intra-abdominal infections; Complicated Urinary Tract Infections including pyelonephritis.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<p>X Fast Track Designation</p> <p><input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i></p> <p><input type="checkbox"/> Rolling Review</p> <p><input type="checkbox"/> Orphan Designation</p> <p><input type="checkbox"/> Rx-to-OTC switch, Full</p> <p><input type="checkbox"/> Rx-to-OTC switch, Partial</p> <p><input type="checkbox"/> Direct-to-OTC</p> <p>Other: Qualified Infectious Disease Product (QIDP)</p>	<p><input type="checkbox"/> PMC response</p> <p><input type="checkbox"/> PMR response:</p> <p><input type="checkbox"/> FDAAA [505(o)]</p> <p><input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]</p> <p><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)</p> <p><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)</p>			
Collaborative Review Division (if OTC product): n/a				
List referenced IND Number(s): 104,490				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p>X Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p>X Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p>X</p>	<p><input type="checkbox"/></p>																	
<p>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)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p>X</p>																	
<p>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)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p>X</p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p>X</p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>	<p><input type="checkbox"/></p>	<p>X</p>																		

<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5 years plus 5 years for QIDP/GAIN</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	Sponsor commented on fixed dose combination issue for exclusivity.
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p>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)?</p> <p><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	

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

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

X Legible X English (or translated into English) X Pagination X Navigable hyperlinks (electronic submissions only)				
If no, explain.				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	

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? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	electronic
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)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>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.</i>	X	<input type="checkbox"/>		Notified PeRC RPM 6/12/14 via email. PeRC scheduled for 10/22/14.
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	X	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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

<i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only):	<input type="checkbox"/>	X		
Is this submission a complete response to a pediatric Written Request?				
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	X	<input type="checkbox"/>	<input type="checkbox"/>	Reviewed and found acceptable.
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	X	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	X	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	X	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	X	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	Consult issued 06.12.14 in DARRTs
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	X	No MedGuide, PPI, IFU; no consult

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

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	<input type="checkbox"/>	<input type="checkbox"/>	Consult issued 06.12.14 in DARRTs
OTC Labeling	X Not Applicable			
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	QT IRT; Consult sent 06.19.14
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 12/6/2010 meeting cancelled after receiving comments; March 7, 2011 <i>If yes, distribute minutes before filing meeting</i>	X	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 01-14-14 (CMC); 02-10-14 <i>If yes, distribute minutes before filing meeting</i>	X	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): n/a <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 6/12/14

BLA/NDA/Supp #: 206829

PROPRIETARY NAME: Zerbaxa

ESTABLISHED/PROPER NAME: ceftolozane/tazobactam

DOSAGE FORM/STRENGTH: Intravenous, 1.5g

APPLICANT: Cubist Pharmaceuticals, Inc.

PROPOSED INDICATION(S): Complicated Urinary Tract Infection with pyelonephritis;
Complicated Intra-abdominal Infections.

BACKGROUND: This NDA was developed under IND 104490. This is a rolling review NDA, first piece received 2/14/14 and final piece 4/21/14, with both Fast Track and Qualified Infectious Disease Product designations. Several meetings were held with the sponsor prior to the NDA submission and several late submission components were agreed to. The NDA is a PDUFA V submission with a due date of 12/21/14.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Maureen Dillon-Parker	Y
	CPMS/TL:	same	n/a
Cross-Discipline Team Leader (CDTL)	Thomas Smith, MD		Y
Clinical	Reviewer:	Maria Allende, MD	Y
	TL:	Thomas Smith, MD	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Avery Goodwin, PhD	Y
	TL:	Kerry Snow, MS	Y
Clinical Pharmacology	Reviewer:	Ryan Owen, PhD	Y
	TL:	Kim Bergman, PharmD	Y
Biostatistics	Reviewer:	Daniel Rubin, PhD [cUTI]	Y
		Christopher Kadoorie [cIAI]	Y
	TL	Thamban Valappil	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jim Wild, PhD	Y
	TL:	Wendy Schmidt, PhD	Y*
Product Quality (CMC)	Reviewer:	Shrikant Pagay, PhD	Y
	TL:	Dorota Matecka, PhD	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Erika Pfeiler, PhD	Y*
	TL:	Stephen Langille	N
Facility Review/Inspection	Reviewer:	Steven Hertz	Y*
	TL:	Mahesh Ramanadham Vipul Dholakia (covering)	N Y
OSE/DMEPA (proprietary name)	Reviewer:	Aleksander Winiarski PM /Karen Townsend	N Y*
	TL:	Kellie Taylor	N
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver/Risk Mgmt Analyst [safety]	Y
	TL:	Ron Wassel, PharmD Safety Evaluator	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	N
	TL:	Susan Thompson Susan Leibenhaut (covering)	N Y
Other reviewers	ONDQA Biopharm Minerva Hughes /Reviewer Angelica Dorantes / TL		
Other attendees	Susmita Samanta, MD, Safety RPM Katherine Laessig, MD, Dep Dir, DAIP* Sumati Nambiar, MD, Director, DAIP Ed Cox, MD, Director, OAP		Y Y Y Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES X NO
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<ul style="list-style-type: none"> ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO n/a
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain: n/a</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: n/a</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: n/a</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: n/a</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments: n/a</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i><u>the application did not raise significant safety or efficacy issues</u></i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: No significant safety or efficacy issues
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments: n/a</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

health significance? Comments: n/a	
CLINICAL MICROBIOLOGY Comments: n/a	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments: n/a	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIostatISTICS Comments: n/a	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: n/a	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: n/a	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments: n/a	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: n/a</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: Agreement made for [REDACTED] (b) (4)</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: no comments</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	<p>Pending submission of facility readiness for inspection information, sterility validation package, and stability update. Reminder included in 60/74-day letter</p>

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Edward Cox, Office Director, OAP</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 7/25/14</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments: <i>See attached.</i></p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> X No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review X Priority Review
ACTIONS ITEMS	
Done	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).
N/A	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

N/A	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.
N/A	BLA/BLA supplements: If filed, send 60-day filing letter
Done	If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) notify OMPQ (so facility inspections can be scheduled earlier)
Done	Send review issues/no review issues by day 74
Done	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
Pending	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
N/A	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

SUMMARY COMMENTS:

- Two indications submitted; cUTI and cIAI
- Seven Facilities /Only one in U.S.
- No review needed from ONDQA Biopharm
- Information Request to be sent for Methods & Criteria from Quality Micro; 2 DMFs for Sterile drug substance.
- Pharm/Tox may need a pre-/post natal study as post-marketing as a rabbit embryo fetal study was not conducted. Impurities appear to have been qualified.
- Clinical noted that there is a minority population in the U.S. (3%), and that highest enrollers are in Russia and the UK (Eastern Europe).
- Revisions to labeling in Contraindications may be necessary for hypersensitivity.
- The cIAI study numbers are low and a sensitivity analysis will be completed.
- Consult to QT/IRT needed for study included in submission.
- A date for PeRC will be requested – Post-meeting note: PeRC scheduled for 10/22/14
- Mid-cycle/Late Cycle and Labeling/PMC-PMR meetings to be scheduled
- 74-day letter to issue with 60-day priority review letter as there are no filing issues.
- 505(b)(2) form will need to be submitted to the IO by 2-months prior to action

ATTACHMENT – Milestone and other project dates

KEY DATES for NDA 206829 Zerbaxa (ceftolozane/tazobactam):

Received: 04/21/14

Filing Reviews due in DARRTS: 06/19/14

60-day Filing Day: 06/20/14; 74-day Letter Due: 07/04/14

Mid-Cycle Day: 7/20/14 -- ***Mid-Cycle Meeting Date: 7/25/14***

Mid-Cycle Communication: send by 08/04/14

Labeling Meetings to be held between 07/28/14 to 09/10/14

Labeling to OPDP and DMPP: 09/10/14

Primary Reviews Due/Signed-off in DARRTS: 09/23/14

PMC/PMR/Labeling to Sponsor: by 09/25/14

Secondary Reviews Due/Signed-off in DARRTS: 09/26/14

DR Letters to issue by: 09/25/14

Pre-Meeting for Late-Cycle Meeting: by 09/24/14

Begin Labeling Discussion with Sponsor: 09/30/14

Send Sponsor LCM Briefing Package: 10/11/14

Send 505(b)(2) form to IO: NLT 10/21/14

PeRC date: 10/22/14

Late-Cycle Meeting: by 10/22/14

Hold Wrap-Up Meeting: by 11/15/14

CDTL Review Due: 11/26/14

Circulate Letter/Action Package: starting 12/01/14

Div Director Review: by 12/11/14

Office Director Review: by 12/19/14

NDA Due Date: 12/19/14 [actual due date 12/21/14, is a Sunday]

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

/s/

MAUREEN P DILLON PARKER
06/19/2014
RPM Filing Review/NDA 206829