CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206829 SUPPL # n/a DIVISION: Anti-Infective Products

Trade Name ZERBAXA (ceftolozane/tazobactam) Injection for IV Use

Generic Name ceftolozane/tazobactam

Applicant Name Cubist Pharmaceuticals

Approval Date, If Known December 19, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

n/a

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

n/a

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5-years + 5-years [Qualified Infectious Disease Product designation]

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

YES ☐ **NO** ☒

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

n/a

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

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

YES ☐ **NO** ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA# 50-684 Zosyn (piperacillin/tazobactam)

NDA#

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

NDA 206829 contains ceftolozane, a new chemical entity, in combination with tazobactam, a previously approved active moiety. Under the Agency’s new interpretation described in the Agency’s Guidance for Industry, New Chemical Entity Exclusivity for Certain Fixed-Combination Drug Products, a drug substance is eligible for 5-year exclusivity, provided it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product or in a fixed-combination with another drug substance that contains no previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety. This NDA is thus eligible for 5-year new chemical entity exclusivity pursuant to the new interpretation.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

a) For each investigation identified in response to question 3(c): if the investigation was

carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

YES ☐ NO ☐

Investigation #2

YES ☐ NO ☐

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Maureen Dillon-Parker
Title: Chief, Project Management Staff, Division of Anti-Infective Products
Date: 12/19/14

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH
Title: Director, Division of Anti-Infective Products
Date: 12/19/14

ATTACHMENT: GAIN EXCLUSIVITY

Form OGD-011347

GAIN Exclusivity Summary

Application Number	206829
Product Name/Generic/Dosage Form	ZERBAXA (ceftolozane/tazobactam) for Injection, for intravenous use
Sponsor	Cubist Pharmaceuticals, Inc.

1. Does this product have Qualified Infectious Disease Product (QIDP) designation?

YES	NO
X	

2. Is the indication(s) approved in this NDA or supplement the same as the indication(s) identified in the QIDP designation letter?

YES	NO
X	

3. Has this product or any product containing these drugs previously received a 5-year GAIN exclusivity extension?

YES	NO
	X

We note that ZERBAXA is a combination of two drugs, ceftolozane and tazobactam, the latter of which is contained in a previously approved product, ZOSYN (piperacillin/tazobactam) for injection (NDA# 050684). The new combination represented by ZERBAXA does not fall within the limitations to GAIN exclusivity set forth in Section 505E(c)(2) of the FD&C Act (providing that GAIN exclusivity does not apply to a "subsequent application filed with respect to a product approved under section 505 that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength.")

Name of person completing form: Maureen Dillon-Parker

Title: Chief, Project Management Staff, Regulatory Project Manager

Date: *<see electronic signature>*

Name of Division Director signing form: Sumathi Nambiar, MD, MPH

Title: Director, Division of Anti-Infective Products

Date: *<see electronic signature>*

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

SUMATHI NAMBIAR
12/19/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **206829**	NDA Supplement # n/a	If NDA, Efficacy Supplement Type: **n/a** *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: **ZERBAXA** Established/Proper Name: **ceftolozane/tazobactam** Dosage Form: **Injection, for IV infusion**		Applicant: Cubist Pharmaceuticals Agent for Applicant (if applicable): **n/a**
RPM: **Maureen Dillon-Parker**		Division: of Anti-Infective Products

NDA Application Type: ☐ 505(b)(1) **X 505(b)(2)**

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

X No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 12/19/14

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

✓ Actions	
• Proposed action • User Fee Goal Date is **12/21/14; Action Taken 12/19/14**	**X AP** ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? n/a Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Application Characteristics[3]	

Review priority: ☐ Standard **X Priority**
Chemical classification (new NDAs only): **1, 4**
(confirm chemical classification at time of approval)

X Fast Track
X Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
X Qualified Infectious Disease Product designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
X REMS not required

Comments: **QIDP**

❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	**X Yes** ☐ No
• Indicate what types (if any) of information were issued	☐ None **X** FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	**X No** ☐ Yes n/a
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**X Verified** ☐ Not applicable because drug is an old antibiotic.

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

CONTENTS OF ACTION PACKAGE

Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) **APPROVAL/12/19/14**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	X Included
• Original applicant-proposed labeling	X Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling X None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	X Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	**06-02-14** **05-28-14**
❖ Labeling reviews *(indicate dates of reviews)*	RPM: **06-19-14** DMEPA: **08-07-14; 11-25-14** DMPP/PLT (DRISK): **09-19-14** OPDP: **09-16-14** SEALD: X None CSS: X None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	**06-19-14** ☐ Not a (b)(2) **12/11/14** Assessment included.
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes **X No**
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes **X No** ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC **10-22-14** If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes **considered important** to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	**Enclosed**
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	**Enclosed**
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	X N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg **2-10-14**
• EOP2 meeting *(indicate date of mtg)*	X No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A **08-04-14**
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A **10-22-14**
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	**01-24-13; 01/14/14 Manufacturing/facilities**
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	n/a
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None **12/19/14**
Division Director Summary Review *(indicate date for each review)*	☐ None **12/19/14**
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None **11/26/14**
PMR/PMC Development Templates *(indicate total number)*	☐ None **12/18/14**
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	**X No separate review/ Also see CDTL Review**
• Clinical review(s) *(indicate date for each review)*	**10/22/14**
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**Clinical Review, Page 20** n/a

Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	n/a n/a X None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	**11/18/14**
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	X No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	**09/26/14**
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	**10/04/14**
Statistical Team Leader Review(s) *(indicate date for each review)*	X No separate review
Statistical Review(s) *(indicate date for each review)*	**06/11/14; 06/16/14; 10/04/14; 11/10/14**
Clinical Pharmacology ☐ None	
Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	X No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	X No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	**06/13/14; 10/24/14**
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	X None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• AD P/T Review(s) *(indicate date for each review)*	**11/03/14**
• Supervisory Review(s) *(indicate date for each review)*	X No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**06/19/14; 10/23/14**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	X None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	X None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	X No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	X No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None CMC -**06/19/14 [filing]; 09/23/14 [primary]; 12/18/14 [addendum 1]; 12/19/14 [CMC addendum 2] 06/20/14[Biopharm];**
❖ Microbiology Reviews X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)*	**06/02/14 & 09/15/14**
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**Chemistry Review, Page 102**
☐ Review & FONSI *(indicate date of review)*	n/a
☐ Review & Environmental Impact Statement *(indicate date of each review)*	n/a
❖ Facilities Review/Inspection	
X NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: **X Acceptable** ☐ Withhold recommendation ☐ Not applicable
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed **X** Requested **11/07/14** ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	**X** No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	**X** Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by secure email	**X** Done 12/19/14; receipt confirmed via email.
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	**X** Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	**X** Done
❖ Ensure Pediatric Record is accurate	**X** Done
❖ Send approval email within one business day to CDER-APPROVALS	**X** Done 12/19/14

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

GAIN Exclusivity

Cubist Pharmaceuticals, Inc.
Attention: Charles A. Miller
Senior Director, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZERBAXA (ceftolozane/tazobactam) Injection, for Intravenous Use, for the treatment of complicated Urinary Tract Infections (cUTI) and complicated Intra-Abdominal Infections (cIAI). We also refer to the letter dated December 19, 2014, granting approval of this NDA.

We also refer to our correspondences to your Investigational New Drug (IND) application 104490, dated December 5, 2012, and February 20, 2013, in which we granted Qualified Infectious Disease Product (QIDP) designation for Ceftolozane/Tazobactam Injection for the treatment of cIAI and cUTI, respectively.

This letter is to inform you that your application meets the criteria for the 5-year exclusivity extension under section 505E(a) of the Act. Five years of additional exclusivity will be added to any applicable exclusivity periods described in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of section 505 of the Act; clauses (iii) and (iv) of subsection (c)(3)(E) and clauses (iii) and (iv) of subsection (j)(5)(F) of section 505 of the Act; or section 527 of the Act that are otherwise associated with the approval of this NDA.

If you have any questions, call Maureen Dillon-Parker, Chief, Project Management Staff, at (301) 796-0706.

Sincerely yours,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

SUMATHI NAMBIAR
12/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

METHODS VALIDATION MATERIALS RECEIVED

Cubist Pharmaceuticals
Attention: Charles Miller
65 Hayden Avenue
Lexington, MA 02421

Dear Charles Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zerbaxa (Ceftolozane/Tazobactam for Injection) and to our November 7, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 3, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

REQUEST FOR METHODS VALIDATION MATERIALS

Cubist Pharmaceuticals
Attention: Charles Miller
65 Hayden Avenue
Lexington, MA 02421
Charles.Miller@cubist.com

Dear Charles Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zerbaxa (Ceftolozane/Tazobactam for injection) 1.0/0.5g.

We will be performing methods validation studies on Zerbaxa (Ceftolozane/Tazobactam for injection) 1.0/0.5g, as described in NDA 206829.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Drug Substance

Assay and Related Substances by HPLC for Ceftolozane sulfate

(b) (4)

Drug Product

Assay and related substances by HPLC for Zerbaxa

Samples and Reference Standards

1 g Ceftolozane sulfate drug substance
2 x 500 mg Ceftolozane sulfate drug reference standard
200 mg Tazobactam reference standard
100 mg (b) (4)
25 vials Zerbaxa (Ceftolozane/Tazobactam for injection) 1.0/0.5g
20 mg (b) (4)
20 mg

Equipment

1 Develosil ODS-UG-5, 5 µm, 250 mm x 4.6 mm column
1 Develosil ODS-UG-5, 5 µm, 10 mm x 4.6 mm guard column
1 Metrosep A Supp, 5, 4.0 x 150 mm column
1 Fused silica, 25 m x 0.25 mm id with stationary phase CP-SIL 5CB 1.2 µm

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
11/07/2014

PeRC PREA Subcommittee Meeting Minutes
October 22, 2014

PeRC Members Attending:
Wiley Chambers
George Greeley
Rosemary Addy (Did not review Zerbaxa and (b) (4))
Melissa Tassinari
Robert "Skip" Nelson
Tom Smith
Karen Davis-Bruno (Did not review (b) (4))
Kevin Krudys
Olivia Ziolkowski
Barbara Buch
Julia Pinto (Did not review (b) (4))
Dionna Green
Michelle Roth-Cline
Freda Cooner
Daiva Shetty
Diane Murphy

PREA

10:10	NDA	206829	Zerbaxa Deferral/Plan	Treatment of cUTI and cIAI in pediatric patients

(b) (4)

[redacted]

Zerbexa Deferral/Plan

- Proposed Indication: Treatment of cUTI and cIAI in pediatric patients
- This application triggered PREA as a new: indication, dosage form, dosing regimen, route of administration.
- The PDUFA goal date is December 19, 2014
- *PeRC Recommendations*:
    - The PeRC agreed with the deferral in patients ages birth to less than 17 years because the product is ready for approval in adults.

(b) (4)

[redacted]

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/s/

GEORGE E GREELEY
11/05/2014

From:	Chuck Miller
To:	Dillon Parker, Maureen P
Cc:	Karen Terry
Subject:	Re: Request for NDA 206829
Date:	Wednesday, October 29, 2014 5:45:45 PM

Hi Maureen

We will query our colleagues for the information and get back to you.

Best regards

Chuck

On Oct 29, 2014, at 5:12 PM, "Dillon Parker, Maureen P" <Maureen.DillonParker@fda.hhs.gov> wrote:

> Hi Karen and Chuck,
>
> I received this request from the Clinical Reviewer. If you could provide this information that would be great.
>
> We have the Protocol Submission, Study Initiation Date and Final Report Submission dates but need the **Study Completion Date** for each of the (b) (4) pediatric studies.
>
> Thanks very much.
> Maureen

Maureen P. Dillon-Parker | Chief, Project Management Staff | Division of Anti-Infective Products | Office of Antimicrobial Products | Center for Drug Evaluation and Research |
ph: 301.796.0706 | fax: 301.796.9882 |
Email: **maureen.dillonparker@fda.hhs.gov**
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/s/

MAUREEN P DILLON PARKER
11/03/2014

From: Karen Terry
To: Dillon Parker, Maureen P; Chuck Miller
Subject: RE: NDA 206829/Microbiology Information Request
Date: Friday, October 24, 2014 1:46:56 PM

Hi Maureen,

I just wanted to confirm that we've received the request from the micro team.

Thanks,
Karen

From: Dillon Parker, Maureen P [mailto:Maureen.DillonParker@fda.hhs.gov]
Sent: Friday, October 24, 2014 1:42 PM
To: Chuck Miller; Karen Terry
Cc: Dillon Parker, Maureen P
Subject: NDA 206829/Microbiology Information Request

Hi Chuck and Karen,

Today I received the following request for information from the Microbiology team.

Clinical Microbiology:
We have found the scatterplots included in Study CXA.061.MC, used to correlate MIC and disc diffusion zone diameter data for the purposes of determining disc diffusion interpretive criteria, very difficult to read and analyze. Please resubmit the scatterplot figures included in that report, in a format that is more clear and legible.

Please also include line listings of baseline isolates used to compile those scatterplots, in separate files presented in sortable format (e.g. XPT file).

Finally, in cases where you have proposed disc diffusion interpretive criteria that include errors that exceed the limits suggested in the discussion of Error-Bounding Analysis included in CLSI M23-A3 (particularly Very Major and Major Errors), please provide your rationale for those proposals.

Please let me know if you need any clarifications on this request.

Regards,
Maureen

Maureen P. Dillon-Parker | Chief, Project Management Staff |
Division of Anti-Infective Products | Office of Antimicrobial Products |
Center for Drug Evaluation and Research |
ph: 301.796.0706 | fax: 301.796.9882 |
Email: **maureen.dillonparker@fda.hhs.gov**

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/s/

MAUREEN P DILLON PARKER
11/03/2014

From:	Chuck Miller
To:	Dillon Parker, Maureen P
Cc:	Karen Terry
Subject:	Re: NDA 206829: Label sections and Carton and Container Labels /edits
Date:	Thursday, September 25, 2014 9:45:14 PM

Good evening Maureen,

Just confirming that we received this. Thanks to you and the team and have a nice evening.

Best regards

Chuck

On Sep 25, 2014, at 9:30 PM, "Dillon Parker, Maureen P" <Maureen.DillonParker@fda.hhs.gov> wrote:

> Hello Karen and Chuck,
>
> In follow-up to our letter of June 12, 2014, where we communicated our target date of September 25, 2014, for communicating labeling changes, attached please find edits to the following sections of the draft labeling: 5, 7, 8 (except 8.5), 10, 11, 13, 15, 16 and 17, as well as edits to the Carton/Container labeling for Zerbaxa [NDA 206829].
>
> Edits to the remainder of the labeling will be provided shortly.
>
> Please let me know that you receive this communication.
>
> Kind Regards,
>
> Maureen

Maureen P. Dillon-Parker | Chief, Project Management Staff |
Division of Anti-Infective Products | Office of Antimicrobial Products |
Center for Drug Evaluation and Research |
ph: 301.796.0706 | fax: 301.796.9882 |
Email: **maureen.dillonparker@fda.hhs.gov**
Please consider the environment before printing this e-mail

<Vial Label for Sponsor 09.25.14.pdf>

<Vial Carton for Sponsor 09.25.14.pdf>

<Sections for Sponsor 09.25.14.pdf>

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

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/s/

MAUREEN P DILLON PARKER
09/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

MID-CYCLE COMMUNICATION

Cubist Pharmaceuticals, Inc.
Attention: Charles A. Miller
Senior Director, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zerbaxa (ceftolozane/tazobactam) Injection.

We also refer to the teleconference between representatives of your firm and the FDA on August 4, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please call me at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 4, 2014

Application Number: NDA 206829
Product Name: Zerbaxa (ceftolozane/tazobactam) for Injection
Indications: Complicated Intra-Abdominal Infections (cIAI)
Complicated Urinary Tract Infections (cUTI)
Applicant Name: Cubist Pharmaceuticals

Meeting Chair: Thomas Smith, MD
Meeting Recorder: Maureen Dillon-Parker

FDA ATTENDEES

Division of Anti-Infective Products
Maria Allende, MD, Clinical Reviewer
Maureen Dillon-Parker, Chief, Project Management Staff
Kerian Grande Roche, PhD, Microbiology Reviewer
Christopher Kadoorie, PhD, Statistical Reviewer
Katherine Laessig, MD, Deputy Director
Hannah Mak, Pharmacy Intern, ONDQA
Sumathi Nambiar, MD, MPH, Director
Daniel Rubin, PhD, Statistical Reviewer
Thomas Smith, MD, Clinical Team Leader
James Wild, PhD, Pharmacology/Toxicology Reviewer
Thamban Valappil, PhD, Statistical Team Leader

Office of Antimicrobial Products
John Farley, MD, MPH, Deputy Director
David Roeder, MS, Associate Director for Regulatory Affairs

Office of Scientific Investigations
Good Clinical Practice Assessment Branch
Sharon Gershon, PharmD, Pharmacologist

Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Division of Risk Management
Joyce Weaver, PharmD, BCPS, Senior Drug Risk Management Analyst

Division of Epidemiology
Veronica Sansing, Safety Evaluator

Division of Medication Error Prevention and Analysis (DMEPA)
Aleksander Winiarski, PharmD

Eastern Research Group, Inc.
Christopher Sese, Independent Contractor

APPLICANT ATTENDEES
Cubist Pharmaceuticals
Sylva Collins, PhD, Vice President, Biomedical Data Sciences and Informatics
Ellie Hershberger, PharmD, Senior Medical Director, Clinical Research
Maria Iacovelli, Director, Regulatory Affairs, CMC
Jennifer Jackson, PhD, Senior Vice President, Regulatory Affairs
Chuck Miller, Senior Director, Regulatory Affairs
Robert Pawliuk, PhD, Senior Director, Regulatory Nonclinical Development
Judith Steenberen, PhD, Director, Clinical Microbiology
Karen Terry, RAC, Manager, Regulatory Affairs
Obi Umeh, MD, M.Sc., Vice President, Global Medical Sciences

INTRODUCTION

After introductions, the FDA Clinical Team Leader conveyed the following information [unless noted otherwise]:

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

1. Significant Review Issues

There are no issues to report at this time.

2. Information Requests

Several IRs were sent to Cubist from the Clinical and Statistical Reviewers in July, 2014.

Prior to the meeting Cubist provided an update of the status of the response. FDA acknowledged receiving the update(s) as follows:

Request from Compliance Group on cIAI Site Closures (received 25 July 2014)
Cubist's response to the request regarding the closure of Sites 4227 and 4024 in CXA-cIAI-10-08/09 is being submitted to the NDA today (Sequence No. 0014) [8/4/14].

Two Requests RE: cIAI Prior Antibiotic Therapy and Surgeries (received 2 July and 16 July 2014) -Due to the related topics of the two requests from the Clinical/Statistical reviewers received 2 July and 16 July, Cubist will respond to both in a single response document. Submission of this **response is planned for next week**.

Additionally, FDA mentioned the Microbiology request for information sent to Cubist today [8/4/14] as follows:

Clinical Microbiology:

1. We notice that quality control ranges for ceftolozane-tazobactam were published in the 2014 version of CLSI M100 (S24), and that the information presented there does not agree with the quality control ranges in your proposed labeling. Please explain the discrepancy.

2. Each value of the MIC quality control (QC) ranges for ceftolozane-tazobactam is presented by CLSI (M100-S24) in the form of two numbers, one for ceftolozane and one for tazobactam (i.e. E. coli ATCC® 25922 QC range for MIC is 0.12/4-0.5/4 mcg/ml). It seems that the MIC quality control ranges for tazobactam were not represented in your susceptibility test interpretive criteria or quality control tables (Tables 1 and 2). Please explain.

****Additionally, there may be future information requests as the review cycle continues.****

3. Major Safety Concerns:

The FDA reviewer from DMEPA commented that there are potential concerns for confusion with dosing, specifically with the reconstitution volume. The Division commented that there may be confusion introduced when using 'approximate' wording in the labeling given some might re-calculate the dose. The specifics of this issue will be provided to Cubist following this discussion.

Post-Meeting Note: Following the meeting the below text was communicated to Cubist via email August 4, 2014.

Potential for use/dosing errors

From a use perspective, the concentration of the product in the vial after reconstitution (b) (4) and specified volume estimations to be withdrawn in preparation of the infusion may be confusing to the end user and difficult to withdraw.

The following volume (b) (4) to be withdrawn to yield a 150 mg dose appears to be an error (section 2.3 of the full prescribing information). The volume approximating (b) (4) to be withdrawn at the current concentration of approximately (b) (4) yields a dose approximating 150 mg. Accurate withdrawal of (b) (4) from a vial using syringes may be difficult and inaccurate. Please provide a mitigation plan to minimize the chance for this kind of preparation/dosing error.

Use of "approximate" concentrations and volumes in the preparation instructions (section 2.3 of the full prescribing information) may lead to confusion and may lead the end user to recalculate exact volumes and doses. Please clarify the rationale for selecting 10 mL as the initial diluent volume to achieve a final concentration of 1.5 g /11.4 mL in the vial (or approximately (b) (4)). Additionally, please indicate if consideration has been made to increase the volume of the diluent (b) (4) which would allow for easier dose calculation and measurement of the intended doses? Please provide your thoughts on this potential issue.

If available, please provide further information or strategies from the clinical trials which may minimize the potential for these types of preparation/dosing errors.

4. Risk Management Update

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology has not conclusively determined whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. A final determination on the need for a REMS will be made during the review of your application.

5. Advisory Committee Meeting Plans

At this time the Division does not plan to present this NDA at an FDA Advisory Committee Meeting.

6. Proposed Dates for Late-Cycle Meeting/Other Projected Milestones

***September 25, 2014*:** The Division will be conveying preliminary, proposed revisions to the product labeling to Cubist electronically by this date.

Be advised that these revisions may be limited to a certain section (or sections) of the label and provided to you in stepwise fashion so that issues can be resolved throughout the labeling negotiations.

In addition, we will communicate with you regarding any preliminary assessment(s) as to whether or not there will be post marketing commitments (PMC) and/or requirements (PMR).

***October 22, 2014*:** This will be the date of your Late Cycle Review Meeting. You may elect to have this meeting by teleconference or in person with the review team at the White Oak Campus. We will provide a briefing document for this meeting to you electronically on or about October 11, 2014. Topics of discussion at the meeting include, but are not limited to, substantive review issues, additional applicant data (e.g., to be submitted in response to any pending information request or at the Sponsor's discretion), REMS or other risk management actions [as applicable], potential PMRs/PMCs and major labeling issues (if applicable).

***December 19, 2014*:** DAIP will take an action on your application on or prior to this date.

7. CONCLUSIONS:

- Cubist confirmed they are on target for submitting the final facility acceptability information [work at the site has been completed] and the media fill data the week of August 18th. Submission of this information following NDA submission was agreed to at the pre-NDA meeting [no later than August 25th was the agreed to timeframe].
- Cubist inquired if it was known when their facility would be inspected. The FDA communicated that the field inspector will be in contact with them and that the inspection will occur within the next several weeks.
- Both parties agreed to provide a list of attendees at the teleconference following the discussion.
- Meeting minutes will be issued to Cubist within 30-days of the meeting.

There were no further questions/clarifications and the teleconference ended amicably.

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/s/

MAUREEN P DILLON PARKER
09/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

INFORMATION REQUEST

Cubist Pharmaceuticals, Inc.
Attention: Karen R. Terry
RAC Manager, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Ms. Terry:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zerbaxa (ceftolozane/tazobactam) for injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by August 27, 2014, in order to continue our evaluation of your NDA.

Ceftolozane Sulfate Drug Substance

1. The proposed acceptance criterion for (b) (4) a specified identified impurity in one of the proposed starting materials (b) (4) is NMT (b) (4) Data provided for 42 batches of (b) (4) varied from as low as (b) (4) to (b) (4) (reported for one batch B13001C), with the majority of batches containing less than (b) (4) of (b) (4) Considering the proximity of (b) (4) to the drug substance in the proposed manufacturing process, please (b) (4) the acceptance criterion for (b) (4) to (b) (4)

2. Please clarify if the proposed analytical procedure for related substances in the ceftolozane sulfate drug substance described in Section 3.2.S.4.2 is capable of detecting the starting materials and isolated intermediates not currently included as impurities in the proposed drug substance specification.

3. The stability information to support the proposed retest period of (b) (4) for (b) (4) provided in Section 4.1.4.5 (Report CXA.017QC) includes 12 month long term stability results for only one batch of (b) (4) Please provide stability data for additional batches of (b) (4) to support the proposed retest period.

4. It has been demonstrated in the application that the ceftolozane sulfate drug substance process can control the structurally related genotoxic impurities (b) (4) and (b) (4) to levels well below (b) (4) Although a test for (b) (4) and (b) (4) is not currently proposed in the drug substance specification, please include testing for these impurities as part of the release testing for the drug substance validation lots.

5. The specification for ceftolozane sulfate drug substance includes attributes such as (b) (4) Please provide mass balance calculations to explain and further justify the proposed acceptance criteria proposed for (b) (4) Also, propose an upper limit for (b) (4)

6. The differences in the stability results for potency between the three primary stability batches and the two supportive batches have been attributed to the test method. Please clarify if different test methods were used for testing of the primary and supportive stability batches and outline the differences, if applicable.

7. The stability section 3.2.S.7.2.2 includes a statement that the stability protocol outlined in Table 1 will be used for any *significant* manufacturing changes for the drug substance. Please revise this statement to indicate that the protocol in Table 1 will be used for any manufacturing changes made to the drug substance that could potentially impact and would require testing of the drug substance stability.

Drug Product

8. Your application describes sterility testing performed using methods described in USP <71>. Provide a more thorough description of the test method that you use for the drug product. For example, is the test performed by (b) (4)

9. Your application describes endotoxin testing performed using methods described in USP <85>. What is the maximum valid dilution for endotoxin testing, and what dilution is used in routine product testing?

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

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

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/s/

DOROTA M MATECKA
08/15/2014

From: Karen Terry
To: Dillon Parker, Maureen P
Subject: Re: MidCycle Follow-up/reconstitution dosing issue
Date: Monday, August 04, 2014 6:25:48 PM

Hi Maureen,

I confirm receipt of this email, thanks so much for the quick follow up on this topic!

Best,
Karen

On Aug 4, 2014, at 5:38 PM, "Dillon Parker, Maureen P" <Maureen.DillonParker@fda.hhs.gov> wrote:

> Hi Karen,
>
> In follow-up to the mid-cycle communication meeting this afternoon, please find comments below related to the concerns regarding potential dosing errors.
>
> **Potential for use/dosing errors**
> From a use perspective, the concentration of the product in the vial after reconstitution (b) (4) and specified volume estimations to be withdrawn in preparation of the infusion may be confusing to the end user and difficult to withdraw.
>
> The following volume (b) (4) to be withdrawn to yield a 150 mg dose appears to be an error (section 2.3 of the full prescribing information). The volume approximating (b) (4) to be withdrawn at the current concentration of approximately (b) (4) yields a dose approximating 150 mg. Accurate withdrawal of (b) (4) from a vial using syringes may be difficult and inaccurate. Please provide a mitigation plan to minimize the chance for this kind of preparation/dosing error.
>
> Use of "approximate" concentrations and volumes in the preparation instructions (section 2.3 of the full prescribing information) may lead to confusion and may lead the end user to recalculate exact volumes and doses. Please clarify the rationale for selecting 10 mL as the initial diluent volume to achieve a final concentration of 1.5 g /11.4 mL in the vial (or approximately (b) (4)). Additionally, please indicate if consideration has been made to increase the volume of the diluent (b) (4) which would allow for easier dose calculation and measurement of the intended doses? Please provide your thoughts on this potential issue.
>
> If available, please provide further information or strategies from the clinical trials which may minimize the potential for these types of preparation/dosing

errors?

When you have a moment, please let me know that you receive this email.

Again, we very much appreciated your time today.

Regards,
Maureen

Maureen P. Dillon-Parker | Chief, Project Management Staff |
Division of Anti-Infective Products | Office of Antimicrobial Products |
Center for Drug Evaluation and Research |
ph: 301.796.0706 | fax: 301.796.9882 |
Email: **maureen.dillonparker@fda.hhs.gov**
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/s/

MAUREEN P DILLON PARKER
08/04/2014

From: Karen Terry
To: Dillon Parker, Maureen P
Subject: RE: NDA 206829 - - Site Information Request
Date: Friday, July 25, 2014 8:15:46 PM

Hi Maureen,

I have received your request and we'll get this information together for the two sites you list below.

Best,
Karen

From: Dillon Parker, Maureen P [mailto:Maureen.DillonParker@fda.hhs.gov]
Sent: Friday, July 25, 2014 5:27 PM
To: Karen Terry
Subject: RE: NDA 206829 - - Site Information Request

Hi Karen,

I recently received this request from our compliance group.

Would you be able to provide us with the following information for Sites 1009-4227 (Argentina) and 1008-4024 (U.S.).

1. Please provide specifics of the GCP violations resulting in site closure
2. For each site, provide the number of subjects enrolled, screened, and completing the study. How many of these subjects were included in the final analyses in the CSR If some subjects were included in the NDA, please provide the justification for including them.
3. How were the GCP violations identified?

Please let me know that you receive this request and if this information can be provided.

Thanks very much.
Maureen

Maureen P. Dillon-Parker | Chief, Project Management Staff |
Division of Anti-Infective Products | Office of Antimicrobial Products |
Center for Drug Evaluation and Research |
ph: 301.796.0706 | fax: 301.796.9882 |
Email: **maureen.dillonparker@fda.hhs.gov**
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/s/

MAUREEN P DILLON PARKER
08/04/2014

From: Karen Terry
To: Dillon Parker, Maureen P
Subject: RE: NDA 206829 - Request for Information/Microbiology
Date: Monday, August 04, 2014 2:21:18 PM

Hi Maureen,

I just wanted to confirm receipt of these clinical microbiology questions.

Talk to you soon,
Karen

From: Dillon Parker, Maureen P [mailto:Maureen.DillonParker@fda.hhs.gov]
Sent: Monday, August 04, 2014 11:04 AM
To: Karen Terry
Subject: RE: NDA 206829 - Request for Information/Microbiology

Hi Karen,

I am just back from being out last week and received the following request from the reviewing microbiologist. If you can please share with your team.

Clinical Microbiology:

1. We notice that quality control ranges for ceftolozane-tazobactam were published in the 2014 version of CLSI M100 (S24), and that the information presented there does not agree with the quality control ranges in your proposed labeling. Please explain the discrepancy.

2. Each value of the MIC quality control (QC) ranges for ceftolozane-tazobactam is presented by CLSI (M100-S24) in the form of two numbers, one for ceftolozane and one for tazobactam (i.e. *E. coli* ATCC® 25922 QC range for MIC is 0.12/4-0.5/4 mcg/ml). It seems that the MIC quality control ranges for tazobactam were not represented in your susceptibility test interpretive criteria or quality control tables (Tables 1 and 2). Please explain.

Regards,
Maureen

Maureen P. Dillon-Parker | Chief, Project Management Staff |
Division of Anti-Infective Products | Office of Antimicrobial Products |
Center for Drug Evaluation and Research |
ph: 301.796.0706 | fax: 301.796.9882 |
Email: **maureen.dillonparker@fda.hhs.gov**
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/s/

MAUREEN P DILLON PARKER
08/04/2014

From: Karen Terry
To: Dillon Parker, Maureen P
Subject: RE: NDA 206829 - - Clinical/Statistical Requests for information
Date: Wednesday, July 16, 2014 6:12:13 PM

Hi Maureen,

I've received the new clinical/statistical request for information and we'll begin working on it.

Also – a head's up that the OSI/BIMO data will be submitted tomorrow morning.

Regards,
Karen

Karen R. Terry, RAC
Manager, Regulatory Affairs

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421
Phone: (781) 860-8326
Fax: (781) 240-5522
Karen.Terry@cubist.com
www.cubist.com

From: Dillon Parker, Maureen P [mailto:Maureen.DillonParker@fda.hhs.gov]
Sent: Wednesday, July 16, 2014 4:56 PM
To: Karen Terry
Subject: NDA 206829 - - Clinical/Statistical Requests for information

Hi Karen,

Below please find requests for information from the clinical/statistical team regarding cIAI and cUTI.

For the cIAI indication:

Please provide a listing of subjects who received any second and/or third surgery. In the listing, also include variables to indicate the following: the planned treatment arm, analysis population, whether the surgery occurred before or after 72 hours of enrollment, and reason for the surgery, including whether the surgery was considered to be 'a persisting or recurrent infection within the abdomen requiring additional intervention to cure the infection. Please also provide the clinical outcome (TOC visit) assigned to each of these patients.

Provide primary analysis results using region and primary site of infection as recorded in IVRS/IWRS as stratification factors. Also provide the stratum weights (i.e. Minimum Risk weights) and verify that statistical assumptions are met (e.g weights are greater than 0 and sum up to one).

Please provide a listing of subjects who had concomitant antibacterial treatment to treat distal infections, including type of infection and name of antibacterial agent, with the clinical outcome (TOC visit) assigned to those patients.

For the cUTI indication:

Please provide the Sample Informed Consent forms for CXA-cUTI-10-04 and CXA-cUTI-10-05.

Please let me know that you receive this request and if you have any questions.

Regards,

Maureen

Maureen P. Dillon-Parker | Chief, Project Management Staff |
Division of Anti-Infective Products | Office of Antimicrobial Products |
Center for Drug Evaluation and Research |
ph: 301.796.0706 | fax: 301.796.9882 |
Email: **maureen.dillonparker@fda.hhs.gov**
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MAUREEN P DILLON PARKER
07/18/2014

From: Bhandari, Navdeep
To: "Maria Iacovelli"
Subject: NDA 206829 Information Request Quick Turnaround
Date: Friday, July 11, 2014 10:15:00 AM
Importance: High

Hello Maria,

We acknowledge your 08 July information request response to the quality microbiology reviewer's questions. Unfortunately, the information request sent on 26 June was incomplete. We have provided the complete list below, and acknowledge your responses to questions 1-8. Please provide a response to questions 9-12 by 25 July so that we may continue review of your application.

Sterile Ceftolozane Drug Substance

1. Your application describes the manufacturing process for the sterile ceftolozane drug substance, and states that a commercial filling batch size will be (b) (4) Provide a description of the planned manufacturing campaign for the drug substance, including the maximum campaign duration.

2. Your application provides stability information for the non-sterile ceftolozane drug substance, but does not provide information for the sterile drug substance. Provide a stability summary, post-approval stability protocol and commitment, and stability data for the sterile ceftolozane drug substance.

Drug Product

3. Your application describes microbiological spiking studies to support post-dilution hold time of the drug product in 0.9% saline or D5W. The study methods that you describe are adequate; however, the study duration of your 2-8°C samples is 14 days to support a (b) (4) post-dilution hold period. Typical hold time studies use a hold time that is 2-3 times longer than the proposed holding period listed on the product label. You may wish to repeat the 2-8°C hold study for a minimum of 20 days; alternatively, your labeling should state a maximum holding time of 7 days. Please note that this comment only applies to the product held at 2-8°C.

4. A description of the requalification studies for the (b) (4) (b) (4) was provided in your application, and states that the expiration date for one set of biological indicators was August 2013, when the study was performed in October 2013 (Section 5.3.4.4). Clarify the expiration date of your biological indicators.

5. Your application describes the (b) (4) Provide a list of equipment used for (b) (4) List the location of each piece of equipment in your facility.

6. Your application states that the [redacted] Typically, requalification is performed on an annual basis. Provide a rationale for your schedule of requalification for this equipment.

7. Your application describes a requalification study for the [redacted] Provide the date on which this study was conducted.

8. Your application describes media fill simulations that use [redacted] Provide a description of how equipment used in media fill simulations is different from equipment used to fill drug product.

9. Your application describes methods for media fill simulations, but you do not state your planned requalification schedule. Provide your proposed schedule of media fill simulations.

10. The description of your facility's media fills states that acceptance criteria are considered to be met if the number of contaminated units in [redacted] is in agreement with limits listed in Table 68 (Section 5.4.2). This criterion is unacceptable, [redacted] You should revise your media fill acceptance criteria to account for all filled and incubated vials.

11. You perform growth promotion testing as a part of your media fill simulations. Confirm that this testing is performed at the same incubation temperature as used for media fill test vials.

12. We acknowledge that you plan to submit data from media fills to qualify [redacted] no later than August 25, 2014. Further, we acknowledge the summaries of previous media fill activities that you provided in your application. Provide a summary description of the media fill study that you plan to conduct following completion of the [redacted]. Include the number of fills, the duration of fills, a summary of proposed interventions, and proposed acceptance criteria.

Navi

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/s/

NAVDEEP BHANDARI
07/11/2014

From: Karen Terry
To: Dillon Parker, Maureen P
Subject: RE: NDA 206829 - Zerbaxa request for clinical/statistical information
Date: Wednesday, July 02, 2014 11:53:44 AM

Hi Maureen,

I have received your clinical/statistical request and we'll get to work on it.

The Clinical Pharmacology and Cardiac Safety table information for the QT-IRT request along with the ECG analysis dataset is close to final and we plan to submit that information early next week.

Best,
Karen

Karen R. Terry, RAC
Manager, Regulatory Affairs

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421
Phone: (781) 860-8326
Fax: (781) 240-5522
Karen.Terry@cubist.com
www.cubist.com

From: Dillon Parker, Maureen P [mailto:Maureen.DillonParker@fda.hhs.gov]
Sent: Wednesday, July 02, 2014 11:42 AM
To: Karen Terry
Subject: NDA 206829 - Zerbaxa request for clinical/statistical information

Hi Karen,

The Clinical/Statistical review team asked that I convey the following request to you:

Please provide the following analyses for the Phase 3 complicated intra-abdominal infection study (Protocol CXA-cIAI-10-08 and CXA-cIAI-10-09) both overall and by treatment arm.

The proportion of patients who received prior antibiotic therapy before and after the first abdominal procedure by duration of therapy (24 hours only, 48-hours only, more than 48 hours) and by dose (single versus multiple).
The primary outcome for those who received prior therapy and those who do not receive prior therapy, both overall and stratified by time relative to surgery (before and after surgery).
Number of subjects who needed a second surgery after 72 hours of enrollment.
Distribution of prior therapy received by duration of therapy in days and by dose (single vs.

multiple).
Number of subjects with prior effective antibiotic treatment and duration of treatment

Please let me know you received this communication when you get a moment.

Additionally, can you let me know when the response to the request for ECG analysis dataset information will be available. The consulting group asked that I check.

Thanks very much,
Maureen

Maureen P. Dillon-Parker | Chief, Project Management Staff |
Division of Anti-Infective Products | Office of Antimicrobial Products |
Center for Drug Evaluation and Research |
ph: 301.796.0706 | fax: 301.796.9882 |
Email: **maureen.dillonparker@fda.hhs.gov**
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/s/

MAUREEN P DILLON PARKER
07/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829 **INFORMATION REQUEST**

Cubist Pharmaceuticals, Inc.
Attention: Charles A. Miller
Senior Director, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zerbaxa (ceftolozane/tazobactam) Injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by July 10, 2014 in order to continue our evaluation of your NDA.

Sterile Ceftolozane Drug Substance

1. Your application describes the manufacturing process for the sterile ceftolozane drug substance, and states that a commercial filling batch size will be (b) (4) Provide a description of the planned manufacturing campaign for the drug substance, including the maximum campaign duration.

2. Your application provides stability information for the non-sterile ceftolozane drug substance, but does not provide information for the sterile drug substance. Provide a stability summary, post-approval stability protocol and commitment, and stability data for the sterile ceftolozane drug substance.

Drug Product

3. Your application describes microbiological spiking studies to support post-dilution hold time of the drug product in 0.9% saline or D5W. The study methods that you describe are adequate; however, the study duration of your 2-8°C samples is 14 days to support a (b) (4) post-dilution hold period. Typical hold time studies use a hold time that is 2-3 times longer than the proposed holding period listed on the product label. You may wish to repeat the 2-8°C hold study for a minimum of 20 days; alternatively, your labeling should state a maximum holding time of 7 days. Please note that this comment only applies to the product held at 2-8°C.

4. A description of the requalification studies for the [redacted] was provided in your application, and states that the expiration date for one set of biological indicators was August 2013, when the study was performed in October 2013 (Section 5.3.4.4). Clarify the expiration date of your biological indicators.

5. Your application describes the [redacted] Provide a list of equipment used for [redacted] List the location of each piece of equipment in your facility.

6. Your application states that the [redacted], are requalified once every three years. Typically, requalification is performed on an annual basis. Provide a rationale for your schedule of requalification for this equipment.

7. Your application describes a requalification study for the [redacted] Provide the date on which this study was conducted.

8. Your application describes media fill simulations that use [redacted] Provide a description of how equipment used in media fill simulations is different from equipment used to fill drug product.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

{See appended electronic signature page}

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

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/s/

RAPTI D MADURAWE
06/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Cubist Pharmaceuticals, Inc.
Attention: Karen R. Terry, RAC
Manager, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Ms. Terry:

Please refer to your New Drug Application (NDA) dated April 21, 2014, received April 21, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zerbaxa (ceftolozane/tazobactam) Injection.

We also refer to your submission dated February 12, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is December 21, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 25, 2014. In addition, the planned date for our internal mid-cycle review meeting is July 25, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We remind you of the agreements made at the pre-submission meetings:

- Submission of additional stability data (9-month) no later than 60 days after NDA submission.
- Submission by the targeted date of July 30, 2014, and no later than August 25, 2014, of the remaining portions to complete the sterility assurance validation package (facility requalification, including three media fills, etc.) and a statement that the Steri-Pharma facility is ready for pre-approval inspection.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

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

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

HIGHLIGHTS (HL) GENERAL FORMAT

1. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
2. 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.
3. 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.
4. The TOC should be in a two-column format.

FULL PRESCRIBING INFORMATION (FPI) Heading

5. 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)*]".
6. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 11, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Maureen Dillon-Parker, Regulatory Project Manager, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
06/12/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206829

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

ATTENTION: Karen R. Terry, RAC
Manager Regulatory Affairs

Dear Ms. Terry:

Please refer to your New Drug Application (NDA) dated February 13, 2104, received February 14, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ceftolozane/Tazobactam for Injection, 1.5 gram.

We also refer to your correspondence, dated and received, May 16, 2014, requesting review of your proposed proprietary name, Zerbaxa.

We have completed our review of the proposed proprietary name, Zerbaxa and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your May 16, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301)796-5413. For any other information regarding this application, contact Maureen Dillon Parker, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

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

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/s/

KELLIE A TAYLOR
06/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

NDA ACKNOWLEDGMENT

Cubist Pharmaceuticals, Inc.
Attention: Charles A. Miller
Senior Director, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Mr. Miller:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ZERBAXA (ceftolozane/tazobactam) Injection for Intravenous (IV) Use

Date of Application: April 19, 2014

Date of Receipt: April 21, 2014

Our Reference Number: NDA 206829

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 20, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
05/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104,490

MEETING MINUTES

Cubist Pharmaceuticals, Inc.
Attention: Karen Terry, RAC
Senior Manager, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Ms. Terry:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ceftolozane/Tazobactam (CXA-201) Intravenous.

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on February 10, 2014.

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

If you have any questions, call Maureen Dillon-Parker, Chief Project Management Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	February 10, 2014/2:00pm-3:00pm
Meeting Location:	White Oak 22/Room 1415
Application Number:	IND 104,490 [PreNDA 206829]
Product Name:	Ceftolozane/Tazobactam Intravenous
Indications:	complicated Urinary Tract Infections (cUTI)/ complicated Intra-abdominal Infections (cIAI)
Sponsor/Applicant Name:	Cubist Pharmaceuticals, Inc.
Meeting Chair:	Sumathi Nambiar, MD, MPH
Meeting Recorder:	Maureen Dillon-Parker

FDA ATTENDEES

Office of Antimicrobial Products

Edward Cox, MD, MPH, Director
John Farley, MD, MPH, Deputy Director
David Roeder, MS, Associate Director for Regulatory Affairs

Division of Anti-Infective Products

Maria Allende, MD, Medical Officer
Amy Ellis, PhD, Acting Pharmacology/Toxicology Team Leader
Maureen Dillon-Parker, Chief, Project Management Staff
Katherine Laessig, MD, Deputy Director
Christopher Kadoorie, PhD, Statistical Reviewer
Dorota Matecka, PhD, CMC Lead
Sumathi Nambiar, MD, MPH, Director
Ryan Owen, PhD, Clinical Pharmacology Reviewer
Shrikant (Suresh) Pagay, Ph.D. Chemistry Reviewer
Diane Raccasi, Microbiologist, Compliance, OMPQ [by phone]
Thomas Smith, MD, Clinical Team Leader
Kerry Snow, MS, Clinical Microbiology Team Leader [by phone]
Joseph Toerner, MD, MPH, Deputy Director for Safety [acting]
Edward Weinstein, MD, Medical Officer
James Wild, PhD, Pharmacology/Toxicology Reviewer [by phone]

Kunyi Wu, PhD, Clinical Pharmacology Reviewer
Thamban Valappil, PhD, Statistical Team Leader

EASTERN RESEARCH GROUP / FDA
Christopher Sese, Independent Assessor

SPONSOR ATTENDEES – Cubist Pharmaceuticals (Cubist)
Sylva Collins, PhD, Vice President, Biomedical Data Sciences & Informatics
Barry Eisenstein, MD, Senior Vice President, Scientific Affairs
Ian Friedland, MD, Vice President, Clinical Development
Steven Gilman, PhD, Executive Vice President, Research and Development/CSO
Ellie Hershberger, PharmD, Senior Medical Director, Clinical Research
Jennifer Huntington, PharmD, Senior Clinical Research Scientist
Maria Iacovelli, Senior Manager, Regulatory Affairs, CMC
Jennifer Jackson, PhD, Senior Vice President, Regulatory Affairs
Valdas Jurkauskas, PhD, Senior Manager, Manufacturing Process Chemistry
Timothy Keutzer, Senior Director, Project Management
Christopher Masterson, Vice President, Quality
Lorianne Masuoka, MD, Senior Vice President, Clinical Development/CMO
Charles A. Miller, Senior Director, Regulatory Affairs
Robert Pawlink, PhD, Senior Director, Regulatory Nonclinical
Judith Steenbergen, PhD, Director, Clinical Microbiology
Karen Terry, RAC, Manager, Regulatory Affairs
Obi Umeh, MD, MSc, Senior Director, Clinical Research
Jacqueline Walsh, Program Manager, Quality Control
Michael Young, Director, Drug Product Manufacturing
Guojun Yuan, PhD, Director, Biostatistics

BACKGROUND

This product is a cephalosporin beta-lactamase inhibitor combination being submitted as NDA 206829 for the indications of complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI).

On December 06, 2013, the Division received a Type B, pre-NDA meeting request to discuss all remaining outstanding, discipline specific issues prior to submitting the NDA, granted rolling review on January 31, 2014.

In addition to the scheduled pre-NDA meeting, the Division also met with Cubist on January 14, 2014, to discuss specific manufacturing issues regarding the facility (dedicated facility) built to manufacture ceftolozane/tazobactam. Following the meeting the Division agreed to address any remaining CMC issues at the February 10, 2014, pre-NDA meeting.

Preliminary comments were provided to Cubist on February 6, 2014, via email. Cubist submitted, on February 10, 2014, slides and a revised Agenda for the meeting. [copy attached]

DISCUSSION

- After opening introductions, the Division reviewed some issues pertinent to the PDUFA V program that would be applicable to the NDA.
  - All agreements for a limited number of minor application components for submission after the NDA is submitted must be discussed/agreed to.
  - Discussion of need for Risk Evaluation and Mitigation Strategies (REMS) and other risk management actions. The Division noted that, as communicated in the preliminary comments, no REMS are expected with this application at this time.
  - Reminder that the application must contain a comprehensive list of all Clinical and Manufacturing facilities.
  - Any issues regarding the pediatric assessment required for submission in the NDA.
- Cubist commented that the responses to most of the questions were acceptable, and therefore, the focus of the discussion would be on the one (1) clinical question regarding (b) (4) and the two (2) chemistry questions on starting materials and pre-operational visit.
- Cubist presented and discussed the information on the slides as follows:

6.3.6 Topline Phase 3 Data

Question 17 – (b) (4) in Study CXA-cUTI-10-04/05

- Cubist presented the information on slide 4, "Composite Microbiological and Clinical Response Rate at Test-of-Cure (TOC) Visit by Population", concluding that ceftolozane/tazobactam (b) (4)
- The Division commented that having only one cUTI trial to support a (b) (4) is a review issue. The Division reiterated that as noted in a previous communication, a (b) (4)
- Cubist was encouraged to submit their position/conclusions in the NDA and the Division will review.

5.1 Quality / CMC Questions

Question 1 – Ceftolozane Sulfate Starting Materials

- The Division did not agree in the preliminary responses that (b) (4) is an appropriate starting material due to potential contamination that would not be detected by routine analysis and which could be present if (b) (4) is manufactured in a non-GMP environment.
- Cubist presented an overview of the quality aspects in place for (b) (4) manufactured at (b) (4) See Slides 6 and 7.
- Cubist stated that the (b) (4) facility is GMP compliant, has been FDA inspected and is an approved API manufacturer. Additionally, Cubist stated that they conduct their own oversight as part of routine GMP audits for supplier qualifications. Further, they have master batch record and change control approval processes and other quality systems in place.

- Cubist also stated that the (b) (4) manufacturing process is a proprietary process owned by the Sponsor. All release methods in the (b) (4) specification have been validated and additional qualified characterization methods also exist such as (b) (4) etc. More than 30 batches have been manufactured and tested for release and characterization at (b) (4)
- Cubist then displayed the (b) (4) scheme for the (b) (4) starting material [Slide 8]. The Division questioned why they [Cubist] are not beginning with one of the (b) (4) as the starting material since (b) (4) is manufactured at the GMP facility.
- The Division expressed concern that since (b) (4) is introduced in the (b) (4) step of the drug substance synthesis, unforeseen raw material impurities may not be detected by routine analytical methods. This will be of particular concern when manufacturers are switched and changes are made in (b) (4) synthesis. At this time there are no real concerns with (b) (4) The Division stated that this will be a review issue and they [Division] continue to recommend that an (b) (4) in the (b) (4) manufacturing process be selected.
- When asked how Cubist will qualify a supply change, Cubist responded that they have a supplier certification program and they must meet Cubist's rigorous qualification process. Cubist wants the same quality from all of the suppliers.
- The Division's overall recommendation to Cubist was to (b) (4) to better control the process and quality of the drug substance. The Division stated that there was not enough time to review information provided in the slides as it was submitted very late in the process and more details would be needed to continue the discussion. This information is usually available and discussed at the end of Phase 2. Cubist commented that this was because the facility issues took priority.
- Cubist understands, but plans to submit the data in the NDA as they believe it is acceptable and fully qualified.
- The Division reiterated that they [Cubist] use one of the intermediates in the synthesis of (b) (4) as a starting material, however, Cubist can submit their proposal and all supporting information in the NDA.

Question 2 – Pre-Operational Facility Visit

- The Office of Manufacturing and Product Quality (OMPQ) supports conducting a pre-operational visit. It was clarified that this is not an inspection; the inspection will be scheduled and conducted separately.
- The Division requested that Cubist provide a timeline for the visit so that the OMPQ reviewer can start making site visit arrangements.
- Cubist clarified that Steripharma will be inspection ready and has quality systems in place. This facility has been FDA inspected and is in compliance. Some (b) (4) is ongoing but this will be completed by June.
- It was recommended that the site visit occur prior to the prior approval inspection (PAI). The Division noted that a facility (b) (4) will not be compliant as (b) (4) activities would be needed and corrective actions may be needed such as (b) (4) studies.

- Cubist stated that by mid-June a process validation will occur, (b) (4) studies will be conducted and there will be three media fills. Cubist stated that there is a sound plan in place post (b) (4) and that there will be no changes in the facility.
- Cubist stated that this is the normal process for (b) (4) (b) (4)

Additional Discussion

- The Division asked about enrollment in the hospital acquired/ventilator associated bacterial pneumonia (HABP/VABP) trial. Cubist stated that the trial was discontinued. (b) (4)
- Regarding pediatric studies, the initial Pediatric Study Plan (iPSP) was agreed to and Cubist stated that (b) (4) This pediatric information, with agreed to submission dates, will be submitted in the NDA to address the pediatric component of the application.
- A proprietary name has been submitted and has a due date of March. The name will again be requested in the NDA.
- (b) (4)

CONCLUSIONS

- The timeframe for the facility pre-operational visit will be summarized and sent to the Division for review so that all parties are aware of what is expected and no additional time is lost.
- With regard to the facility and the pre-approval inspection, the Division requested that Cubist populate the 356h with the facilities and the timeframe(s) for inspection readiness and the Division will work with the Office of Compliance and render an acceptability decision to Cubist.
- The Division reiterated that there are concerns regarding the use of (b) (4) as the proposed drug substance starting material versus one of the intermediates in the (b) (4) synthesis. Cubist agreed to provide the information on both the proposed starting material (b) (4) and intermediate materials in the synthesis of (b) (4), both have been reviewed.
- This application will be reviewed as discussed under PDUFA V, as a program application. Therefore, all agreements for minor components must be captured in the meeting record. Cubist and the Division agreed that the additional stability data (9-months) will be provided 30-60 days after the last piece of the NDA has been submitted [anticipated for late April]. This agreement is being made because this information will not materially affect the ability of the review team to begin the review of the application.

- Cubist will slightly modify the submission timeline to allow for submission of the stability data in the set timeframe (30-60 days post last piece of the NDA submission/clock start). Therefore, the last portion of the application will be submitted in late April.
- Issue with the scheduling of the PAI remains pending until additional information on the timeline is provided.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- A preliminary discussion on the need for a REMS was held, and it was concluded that that REMS are not needed at this time.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30-60 calendar days after the submission of the original application:

  Stability data [9-months] after the last piece is submitted that starts the review clock per the agreement in the rolling review.

Post-Meeting Note:

As discussed during the March 10, 2014, teleconference the Division agrees to allow Cubist to submit the majority of the sterility assurance validation package in the April submission. All of the remaining information associated with the facility requalification, including the three media fills, will be submitted in a subsequent amendment that will complete the sterility assurance validation package. This amendment will be targeted for July 30, 2014, but will be submitted no later than August 25, 2014. Additionally, it was agreed that the submission will also include a statement that the facility, Steri-Pharma, is ready for pre-approval inspection.

The pre-approval inspection will be initiated after (b) (4) associated qualification studies have been completed.

The Division communicated that because the submission will be received after the review clock has commenced, Cubist's adherence to the agreed-to timeframe is critical. FDA is initiating the review and inspection activities very late in the review cycle in order to accommodate the timeframes needed by Cubist and Steri-Pharma to complete all (b) (4) and associated activities. Any extensions to the above dates will likely impact the first-cycle review action for the application.

- **Prominently identify the submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:**

  NDA 206829: LATE COMPONENT – QUALITY / QUALITY MICROBIOLOGY

NDA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a chemistry pre-submission meeting was held on January 14, 2014. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

ISSUES REQUIRING FURTHER DISCUSSION

Timeline for facility inspections will be an ongoing discussion until resolved.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	Division	Within 30-days of meeting
Submit facilities list on 356h with anticipated readiness for inspection dates identified.	Cubist	In planned April submission.

ATTACHMENTS AND HANDOUTS
-Preliminary comments sent to Cubist via email February 6, 2014
-Cubist slides presented at the meeting

IND 104,490/Cubist
Ceftolozane/Tazobactam (CXA-201)
Questions/Preliminary Responses
for Pre-NDA Meeting Scheduled for February 10, 2014
2:00pm – 3:00pm, WO22, Room 1415

6.1 Regulatory

1. Cubist intends on requesting a Priority Review based on the positive clinical trial data and the QIDP designation granted for cIAI and cUTI by the Division on 05 December 2012 and 20 February 2013, respectively. Does the Agency agree with Cubist's expectation of a Priority Review NDA for ceftolozane/tazobactam based on QIDP designation for cUTI and cIAI indications, as outlined in Section 7.1?

DAIP RESPONSE: Yes, we agree.

2. Does the Agency agree with the reporting period and submission timing for the 4-Month Safety Update, as described in Section 7.2?

DAIP RESPONSE: Yes, we agree.

3. As stated in Section 7.3, Cubist would like to engage the Agency in discussion regarding the process by which exclusivity determination is made. Who at the Agency would be appropriate to engage for discussion regarding this process?

DAIP RESPONSE: Cubist should request the 5-year additional GAIN exclusivity at the time of NDA submission; no additional information needs to be provided to the FDA at that time. The exclusivity determination is made at the time of approval of the application. If Cubist has specific questions about the GAIN exclusivity provisions, or the exclusivity provisions in general, these questions should be directed to DAIP.

4. Does the Agency agree with Cubist's plan to included relevant sections of the prescribing information (e.g., nonclinical toxicology) specific to tazobactam from the approved Zosyn® package insert in the draft ceftolozane/tazobactam package insert, as outlined in Section 7.4?

DAIP RESPONSE: Yes, we agree.

5. Would the Agency comment on the potential for an Anti-Infective Drugs Advisory Committee meeting to be held for ceftolozane/tazobactam (as described in Section 7.5) and if planned, what the timing of a meeting may be?

DAIP RESPONSE: Our preliminary impression is that an Advisory Committee meeting will not be necessary for ceftolozane/tazobactam. A final decision will be made following the NDA submission.

6. Considering the global nature of the Phase 3 pivotal trials, would the Agency comment on the potential timing of clinical trial inspections (Section 7.6)?

DAIP RESPONSE: The inspections will be scheduled as soon as possible after submission of the NDA. All sites must be ready for inspection at the time of NDA submission.

6.2 Nonclinical

7. As detailed in the Request for Submissions of Portions of an Application, submitted on 06 December 2013 (Sequence No. 158), Reviewable Unit 1 is planned for submission on 31 January 2014 and will be available for review at the Agency at the time of the Pre-NDA Meeting. Assuming agreement with the submission timetable, does the Division agree that the set of nonclinical studies that were submitted in the first reviewable unit of the NDA are sufficient to support the continued review of the NDA?

DAIP RESPONSE: Evaluation of Reviewable Unit 1 will be required before this question can be answered.

6.3. CLINICAL

6.3.1 Clinical Pharmacology

8. Does the Agency agree with the content and format of the Summary of Clinical Pharmacology – eCTD Module 2.7.2, including the inclusion of exposure response and renal impairment dosing data, as described in Section 8.2, support the filing of the NDA?

DAIP RESPONSE: The proposed content and format of the clinical pharmacology section appear appropriate.

6.3.2 Clinical Efficacy

9. Does the Agency agree that the proposed content and format of the Summary of Clinical Efficacy – eCTD Module 2.7.3, as outlined in Section 8.3, support the filing of the NDA?

DAIP RESPONSE: We agree.

10. Does the Agency agree with the proposed presentation of Surgical Review Panel (SRP) outcome assessments and sensitivity analysis, as outlined in Section 8.3.5?

DAIP RESPONSE: Sensitivity analyses exploring the concordance/discordance of assessments by investigators and by the SRP should also be performed.

6.3.3 Clinical Microbiology

11. Does the Agency agree that the data summarized in Section 8.4.2 are adequate to support breakpoint discussions?

DAIP RESPONSE: The proposed data to be submitted appear to be adequate to support breakpoint discussions.

12. Does the Agency agree that the summary of the central microbiology laboratory quality control (QC) data, as described in Section 8.4.3, is adequate to support the validity of the central microbiology laboratory susceptibility data?

DAIP RESPONSE: We agree that the summary of the central microbiology laboratory QC data appears to be adequate.

6.3.4 Clinical Safety

13. Does the Agency agree that the proposed content and format of the Summary of Clinical Safety – eCTD Module 2.7.4, as outlined in Section 8.5, supports the filing of the NDA?

DAIP RESPONSE: Yes, we agree.

14. Does the Agency agree, as outlined in Section 8.5.5 based on the data available at the time of the Pre-NDA Meeting, Risk Evaluation and Mitigation Strategies (REMS) and Medication Guide are not necessary to include with the ceftolozane/tazobactam NDA?

DAIP RESPONSE: Yes, we agree.

6.3.5 Clinical Dataset Format and Supporting Documents

15. Does the Agency agree with the planned format of clinical datasets and supporting documents in the NDA, as outlined in Section 8.6?

    a. In the Type C (WRO) Meeting Agency Comments received on 24 May 2013 (see Appendix A), the Agency agreed with the planned dataset format for data from clinical studies to be included in the NDA. Does the Agency agree with the planned dataset format for the ISS and ISM as described in Section 8.6.1?

DAIP RESPONSE: Yes, we agree with the planned dataset format.

    b. Does the Agency agree with the plan for inclusion of Data Definition Documents, blank CRF, and reviewers guide for tabulation and analysis datasets, as outlined in Section 8.6.2?

DAIP RESPONSE: Yes, we agree.

    c. Does the Agency agree with the proposed plan for inclusion of SAS codes for analysis datasets, as outlined in Section 8.6.3?

DAIP RESPONSE: The proposed plan is acceptable. We also recommend that a brief algorithm be provided which describes the steps involved in generating primary and secondary analysis findings (e.g., the datasets and variables used).

6.3.6 Topline Phase 3 Data

16. Does the Agency agree that the ceftolozane/tazobactam clinical development program, including the topline results from pivotal studies CXA-cUTI-10-04/05 and CXA-cIAI-10-08/09 (summarized in Section 9, Appendix H and Appendix I) supports the filing of the ceftolozane/tazobactam NDA for cUTI and cIAI indications?

DAIP RESPONSE: Yes, we agree.

17. Does the Agency agree [redacted]

DAIP RESPONSE: No, we do not agree. [redacted]

18. Does the Agency agree that the lack of treatment interaction and similar treatment effect seen in the 2 trials within each indication, as described in Section 9.3, supports the pooled analysis as proposed in the Type C (WRO) Meeting Information Package (Sequence No. 113; submitted 11 March 2013) and as agreed by the Agency in comments dated 24 May 2013?

DAIP RESPONSE: To confirm the appropriateness of the pooling of the two trials is a review issue which would rely upon more extensive analyses exploring factors that could potentially modify the treatment difference (e.g., imbalances with respect to differences in baseline characteristics, standard of care, prognostic factors, and other co-morbid conditions).

ADDENDUM to Information Package/Submission dated January 24, 2014

5. ADDITIONAL QUESTIONS FOR THE AGENCY

5.1 Quality / CMC Questions

1. Does the Agency agree the information provided in IND Quality Information Amendment submitted 24 January 2014, Sequence No. 0166 demonstrates the appropriateness of the regulatory starting materials for ceftolozane sulfate drug substance?

DAIP RESPONSE: The Agency agrees to designate [redacted] and [redacted] as starting materials.

With regard to [redacted] the Agency does not agree that this is an appropriate starting material, given its use [redacted] of the synthesis. In particular, we have concerns about potential contamination that would not be detected by routine analysis and which could be present if [redacted] is manufactured in a non-GMP environment.

We recommend that you select an [redacted] in the [redacted] manufacturing process.

Alternatively, a late stage starting material such as [redacted] could be considered if advanced analytical methods are used. NDA submission should then describe the manufacturing process for [redacted] including information on the starting materials, reagents, and intermediates in the [redacted] manufacturing process. The NDA should also discuss the possibility that unexpected contaminants may be present, the capability of the advanced analytical method to detect such contaminants, and the adequacy of your vendor qualification program (particularly if it includes knowledge of the vendor's cleaning techniques).

2. Does the Agency agree to the proposal for a pre-operational manufacturing facility visit, as described in Section 6.2?

DAIP RESPONSE: We are working with our colleagues in the Office of Compliance to generate a response to your question regarding a pre-operational manufacturing facility visit. However, at the time that we are sending our preliminary responses, we are unable to respond. We will either have a response at the face-to-face meeting, or provide it in the meeting minutes.

3. Does the Agency agree with Cubist's proposal to include 6-months stability in the initial NDA submission, followed by 9 months of data during the review (b) (4) as discussed in Section 6.3?

DAIP RESPONSE: ONDQA's baseline expectation as discussed in the January 14th, 2014 meeting is 12 months of stability data on three primary stability batches. Although you may submit the NDA with the amount of stability data you have proposed to include in the initial filing (as per the January 27th, 2014 submission), please note that the shelf life granted will be dependent on the extent of the stability data provided. As per our previous commitment, we will accept any additional data within the first 30 days, but no later than 60 days, for a priority review.

Additional CMC Comment*:*

We note from your response on starting materials (submission no.174 dated1/24/2014) that all the impurities from the starting materials, intermediates and ceftolozane are designated with acronyms and peak numbers. Please use the assigned names, as applicable. Include all the chemical structures and the assigned names in a tabulated form.

9 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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

/s/

SUMATHI NAMBIAR
03/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104,490

MEETING MINUTES

Cubist Pharmaceuticals, Inc.
Attention: Maria Iacovelli
Senior Manager, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Ms. Iacovelli:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ceftolozane/Tazobactam (1000mg/500mg)[CXA-201].

We also refer to the Type A meeting held between representatives of your firm and the FDA on January 14, 2014. The purpose of the meeting was to discuss the issues regarding manufacturing the product in designated facilities.

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

If you have any questions, please contact Maureen Dillon-Parker, Chief, Project Management Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	Guidance/Chemistry, Manufacturing & Controls (CMC)
Meeting Date and Time:	January 14, 2014/3:00pm-4:00pm
Meeting Location:	10903 New Hampshire Avenue White Oak, Building 22, Room 1311 Silver Spring, MD 20993
Application Number:	IND 104,490
Product Name:	Ceftolozane/Tazobactam [CX-201]
Indication:	Complicated Urinary Tract Infections (cUTI) and Complicated Intra-Abdominal Infections (cIAI)
Sponsor Name:	Cubist Pharmaceuticals, Inc.
Meeting Chair:	Rapti Madurawe, PhD, Branch Chief, CMC, ONDQA
Meeting Recorder:	Maureen Dillon-Parker, Chief, Project Management Staff

FDA ATTENDEES - Division of Anti-Infective Products and Office of Compliance (Division) [* by phone]

Maria Allende, MD, Clinical Reviewer
Maureen Dillon-Parker, Chief, Project Management Staff
Rick L. Friedman, Associate Director, Office of Manufacturing & Product Quality (OMPQ)
Katherine Laessig, MD, Deputy Director
Shrikant (Suresh) Pagay, PhD, Chemistry Reviewer
Dorota Matecka, PhD, CMC Lead), Branch V
Rapti Madurawe, PhD, Branch Chief, CMC, ONDQA
Diane Raccasi, Microbiologist, OMPQ
Thomas Smith, MD, Clinical Team Leader
James Wild, PhD, Non-Clinical Reviewer*
Wendelyn Schmidt, PhD, Non-Clinical Team Leader

SPONSOR ATTENDEES – Cubist Pharmaceuticals (Cubist)

Nicole Damour, M.A., Process Engineer II, Process Development
Ehab Hamed, PhD, Director, Drug Product Technology
Maria Iacovelli, Senior Manager, Regulatory Affairs, CMC
Jennifer Jackson, PhD, Senior Vice President, Regulatory Affairs
Valdas Jurkauskas, PhD, Senior Manager, Manufacturing Process Chemistry
Timothy Keutzer, Program Leader, Program and Portfolio Management
Carlos Lopez, PhD, Senior Director, Process Development
Christopher Masterson, Vice President, Quality
Charles A. Miller, Senior Director, Regulatory Affairs
Prabu Nambiar, PhD, Consultant to Cubist, Regulatory CMC
Joseph Terracciano, PhD, Director, CMC Technical Operations
Jacqueline Walsh, Program Manager, Quality Control
Michael Young, Director, Drug Product Manufacturing

BACKGROUND

This product is a cephalosporin beta-lactamase inhibitor combination being developed for the treatment of serious and life-threatening bacterial infections including complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI) (b) (4)

On January 24, 2013, Cubist met with the Division to discuss manufacturing issues regarding the need for (b) (4) manufacturing facility to process Ceftolozane/Tazobactam.

On November 18, 2013, the Division received a Type A meeting request from Cubist to discuss the manufacturing plans in follow-up to the 2013 meeting.

Preliminary comments were provided to Cubist on January 10, 2014, via email. Cubist then submitted, on January 14, 2014, slides for the meeting.

DISCUSSION

- After opening introductions, Cubist commented that the responses to Questions 3 and 4 were acceptable, and that the focus of the meeting would be on Questions 1 and 2.
- Cubist presented and discussed the information on the slides (copy attached).
- Cubist stated that information on the starting materials will be submitted to the Agency as soon as possible. Highlights of the discussion regarding the materials presented are as follows:
    - The product will be a single, co-filled vial presentation so that it is easy to use in the pharmacy and designed to prevent medical errors.
    - Between February and August, a global site search was conducted and Steripharma, located in Syracuse New York, was selected as the manufacturer. Registration lots began in September 2013, and the product will be manufactured in a fully dedicated line.
    - Phase 3 (b) (4) data is available and this information will be provided in the Pre-NDA meeting package.
    - Anticipated NDA filing is April 2014 and rolling review is requested.

Question 1, Manufacturing Segregation

- Cubist stated that the product will be manufactured in a completely segregated facility with completely separated (b) (4) (ceftolozane/tazobactam line). (b) (4)
- (b) (4) .
- (D) (4) classifications will be complete prior to process validation.
- Environmental requalification will take 1-2 months. All clean rooms will be at correct microbial limits and all protocols will be in place for the air and surface materials.

- [redacted]
- With regards to the modifications to [redacted], Cubist clarified that the equipment is the same but that the [redacted].
- Cubist will clarify the status of the [redacted]
- Cubist commented that the test methods for quality have not changed. Additionally, Cubist stated that employees [redacted] to assure there is no risk for contamination. The Division reminded Cubist that procedures need to be in place for [redacted]. Cubist stated that a lot of work has been done since last year's meeting and these assurances have been made so that all of these requirements will be in place.
- Microbiology tests will be conducted.
- Regarding the facility and its readiness for inspection, Cubist stated that the facility will be ready for inspection. They anticipate [redacted].
  [*Post Meeting Comment from the Office of Compliance: This approach is acceptable if the production is to occur* [redacted]
- The Division commented that [redacted] and that they (Cubist) will need to ensure that the line has been adequately cleaned.
- The Division recommended that Cubist consider all the [redacted] and equipment changes and conduct a risk assessment evaluating their ability to manufacture in an aseptic environment.
- The [redacted] should be completed June 14, 2014, although they (Cubist) would like to submit the final piece of the NDA in April 2014. The Division asked how the facility could be ready for inspection [redacted]
  They have Standard Operating Procedures (SOPs) in place, the records, and the data integrity files available.
- The Division recommended that Cubist submit a proposal for a pre-operational site visit at the drug product manufacturing site so that the Division can discuss the inspectional issues fully with District office.
- The Division recommended that all qualifications be completed prior to a Pre-Approval Inspection (PAI) to alleviate any concerns.
- Cubist agreed to submit a GANTT chart for the facility qualifications to the Division.

- The Division also outlined several areas where the inspection will be critical and recommended that they (Cubist) conduct their own audit prior to the Agency inspection:
  - Sterility
  - Fill issues
  - Weights (powder fills)
  - Moisture control/hydrolysis
  - Relative humidity in the rooms
  - Environmental control records (accurate)

Question 2 – Drug Product Stability

- Cubist stated that ceftolozane drug substance is (b) (4)
- The lyophilized ceftolozane DPI is (b) (4) and so far no development failures have been observed. Cubist stated that (b) (4) The container/closure and product composition is the same between the to-be-marketed product and the one in development.
- Cubist stated that (b) (4) The proposed storage condition for the commercial drug product is (b) (4)
- The registration batches are approximately (b) (4) vials, and process validation approximately (b) (4) vials, with a commercial lot anticipated to be about (b) (4) vials. The current development size ranges from (b) (4)

Stability Data

- Cubist proposed to submit 6-months of stability data on three registration batches in the NDA (b) (4) The Division recommended 9 months of primary drug product stability data in the initial NDA [minimally], (b) (4) data would be accepted during the NDA review, preferably within the first 30 days but not later than 60 days. The Division re-iterated that the current requirement is 12 months of stability data on three primary batches in the initial NDA submission per ICHQ1A(R2).
- The Division Agency expressed concern about the lack of stability data and the timing of the submission since the (b) (4) has not been completed [anticipated for June]. If the NDA submission is anticipated for April [final component per rolling review request] then the facility must be ready for inspection at that time unless an agreement is made in advance.
- The Division commented that for an NME PDUFA V application, the review clock is already tight and completing the CMC without all the necessary data may result in additional review cycles for the product. Cubist should consider this potential risk.

- Cubist asked if there were exceptions to the stability requirement, for example with breakthrough therapies. The Agency stated that in such cases there may be exceptions granted and noted that this product, while a QIDP, is not breakthrough therapy.
- Cubist asked if the oncology products were viewed as more important than antimicrobial products, to which the Division answered no, clarifying that each product is looked at individually and on a global basis.

CONCLUSION(S):

- Cubist and the Agency will continue discussions regarding the facility inspection(s) and the adequacy of 6-months stability data.
- The Agency agreed to further discuss, however, Cubist was reminded that this is an NME application with high visibility and that the review period for the primary reviewer's is really only 4 months so submitting an NDA with 6 months of stability data is problematic and may impact a first cycle approval action. The Division recommended submitting the NDA with no less than 9-months of stability data on three registration batches.
- The Division acknowledged that the rolling submission is pending and that if agreeable, the first piece would need to accompany the user fee and the last piece would start the review. [*Post-meeting Note: Rolling Review Granted January 31, 2014]*.
- The Agency requested that Cubist submit all the information available on the starting material prior to the Pre-NDA meeting.*[Post-meeting Note: Information submitted to the IND January 24, 2014]*.
- The Division will further discuss the inspection issues with the District once the proposal for the pre-operational site visit is received. *[Post-meeting Note: This information was submitted January 27, 2014, and this issue will be further discussed at the Pre-NDA meeting]*.
- The Pre-NDA meeting is scheduled for February 10, 2014.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Minutes of discussion within 30-days	Agency	February 13, 2014
Division discussion with District office regarding pre-operational inspection	Cubist/Agency	Once material is submitted/reviewed

ATTACHMENTS AND HANDOUTS

- **January 10, 2014 – FDA Preliminary Comments sent to Cubist**
- **January 14, 2014 – Slide Presentation (Cubist)**

IND 104,490 – Ceftolozane/Tazobactam
Sponsor Meeting January 14, 2014 @ 3:00pm WO 22

Sponsor Questions/FDA Response:

1. **Does the Agency agree the permanent plans for manufacture of commercial ceftolozane/tazobactam drug product are aligned with expectations as detailed in the April 2013 guidance, *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination* as discussed in Section 4.1?**

FDA RESPONSE:

We concur with your decision to separate the manufacturing of ceftolozane/tazobactam drug product in the Steri-Pharma facility. In your meeting and background materials dated November 18, 2013, (b) (4) provide adequate controls necessary to prevent contamination as stated under 211 CFR 211.42(c). We concur that your meeting and background materials have considered several critical cross-contamination controls at the Steri-Pharma facility. It is the FDA's policy that the final determination of acceptability will be evaluated on a pre-approval inspection. Note that all sites should be ready for inspection at the time of NDA submission.

2. **Does the Agency agree with Cubist's proposal for the expiry of the ceftolozane/tazobactam drug product, the stability data to be included in the initial NDA and the proposal to update during the course of review as discussed in Section 4.2?**

FDA RESPONSE:

The stability data package for (b) (4) is acceptable. However, we do not agree with your proposal to submit (b) (4)

ONDQA's baseline expectation is that 12 months of stability data on three primary stability batches will be included in the initial NDA submission as per ICHQ1A(R2) guidance. Based on the information provided in the meeting package, we will accept 9 months of primary DP stability data at initial NDA submission if the 12 month update is submitted, preferably within the next 30 days, but no later than 60 days if a priority review is requested (or by the mid-point for a standard review cycle). Note that this agreement is based on the assumption that the registration stability batches are per ICH Q1A(R2) with respect to formulation, container-closure (proposed marketing configuration), manufacturing process and scale.

Table 8 of the briefing package lists the lot numbers of the ceftolozane drug substance batches used in the drug product primary stability batches. It is unclear if these are different batches of cetolozane drug substance or sublots. Drug product primary batches should be manufactured using different batches of the drug substance.

Note that the expiration date granted will be based on the quality and quantity of data provided.

3. Does the Agency agree with Cubist's plan to demonstrate pharmaceutical equivalence between ceftolozane/tazobactam drug product evaluated in Phase 3 clinical studies and the proposed commercial drug product as discussed in Section 4.3?

FDA RESPONSE:

The proposal to demonstrate pharmaceutical equivalence appears reasonable with the inclusion of the following additional data.

- A side-by-side comparison of the detailed impurity profile of all batches (clinical, registration stability, available commercial-site batches). If any new impurity appears in the commercial batches, the impurity should be qualified and information included in the NDA.
- A side-by-side comparison of the "in-use stability" data for the above drug product batches after reconstitution.

4. Elements of the ceftolozane sulfate drug substance control strategy, including:

a. Does the Agency agree with our designation of (b) (4) as starting materials for the preparation of ceftolozane sulfate drug substance as discussed in Section 4.4?

FDA RESPONSE:

Information provided on the proposed starting materials is insufficient to determine the appropriateness of the proposed starting materials at this time. Please provide the following information to continue our evaluation.

i. Batch analysis data for the drug substance lots made using the proposed starting materials from the proposed manufacturers. The complete impurity profile should also be included. We understand that the same starting materials were used in the manufacture of the clinical material.
ii. Proposed in-process specifications for isolated intermediates.
iii. Batch data on the isolated intermediates. In the impurity data provided, clearly identify individual carryover impurities and level present.
iv. Discussion on impurities arising from the starting material that are or likely to be present in the drug substance. Please include a discussion of the stages/steps where these impurities are cleared, purging capability for each of those impurities and supporting data from spiking studies.
v. Include in the specification proposed for each starting material acceptance criteria for the total impurities and total unspecified impurities. Additionally, the (b) (4) starting material should include a control/specification for stereochemistry. Provide updated batch data with the added test attributes.
vi. Proposed specification for Ceftolozane sulfate drug substance.
vii. Please clarify the following:
    - Difference between the purity and assay for the batch analysis data on the starting materials (Tables 14, 18 and 21 in the submission). How are these calculated?
    - Cumulative purging factor listed in Table 24. How is that calculated?

b. Does the Agency agree with our strategy for controlling potential genotoxic impurities derived from [redacted] (b) (4) and our proposal not to include this as a drug substance release test as discussed in Section 4.5?

FDA RESPONSE:

Although you have provided [redacted] (b) (4) data on existing batches, you have not articulated the control strategy used for controlling these two genotoxic impurities to levels below [redacted] (b) (4) Include in the NDA control procedures undertaken to consistently assure that the [redacted] (b) (4) levels in the drug substance are below [redacted] (b) (4) and include available batch data and test methods used. Data from commercial batches would be particularly useful. Whether or not [redacted] (b) (4) need to be included in the drug substance release test, and appropriate thresholds for these impurities will be assessed at the time of NDA review.

c. Does the Agency agree with Cubist's approach for the assignment of the absolute stereochemistry of ceftolozane sulfate drug substance, and with Cubist's proposal to use optical rotation as the release test for control of stereochemistry as discussed in Section 4.6?

FDA RESPONSE:

Cubist's approach for the assignment of the absolute stereochemistry of ceftolozane sulfate drug substance and the proposal to use optical rotation as the release test for control of stereochemistry appear reasonable. All information will be reviewed at the NDA stage for acceptability, including the test method and specification for stereochemistry.

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/s/

SUMATHI NAMBIAR
02/13/2014
Signed on behalf of Dr. Laessig.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104,490

MEETING MINUTES

Cubist Pharmaceuticals, Inc.
Attention: Jeffrey P. Bourque
Director, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Mr. Bourque:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ceftolozane/Tazobactam (1000mg/500mg)[CXA-201].

We also refer to the Type A meeting held between representatives of your firm and the FDA on January 24, 2013. The purpose of the meeting was to discuss the issues regarding manufacturing the product in designated facilities.

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

If you have any questions, please contact Maureen Dillon-Parker, Chief, Project Management Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

John J. Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	Guidance
Meeting Date and Time:	January 24, 2013/4:00pm-5:00pm
Meeting Location:	10903 New Hampshire Avenue White Oak, Building 22, Room 1309 Silver Spring, MD 20993
Application Number:	IND 104,490
Product Name:	Ceftolozane/Tazobactam [CX-201]
Indication:	Complicated Urinary Tract Infections (cUTI) and Complicated Intra-Abdominal Infections (cIAI)
Sponsor Name:	Cubist Pharmaceuticals, Inc.
Meeting Chair:	John Farley, MD, MPH, Acting Division Director
Meeting Recorder:	Maureen Dillon-Parker, Chief, Project Management Staff

FDA ATTENDEES - Division of Anti-Infective Products (Division) and Office of Compliance (Agency)

Maria Allende, MD, Clinical Reviewer
Maureen Dillon-Parker, Chief, Project Management Staff
John Farley, MD, MPH, Acting Director
Tara Gooen, LCDR, Acting Branch Chief, Office of Compliance, Drug Manufacturing
Katherine Laessig, MD, Deputy Director
Shrikant (Suresh) Pagay, PhD, Chemistry Reviewer
Sumati Nambiar, MD, Deputy Director for Safety
Dorota Matecka, PhD, Pharmaceutical Assessment Lead (CMC), Branch V
Rapti Madurawe, PhD, Branch Chief, CMC
Diane Raccasi, Consumer Safety Officer, Office of Manufacturing and Product Quality
Thomas Smith, MD, Clinical Team Leader

SPONSOR ATTENDEES – Cubist Pharmaceuticals (Cubist)

Jeffrey P. Bourque, Director, Regulatory Affairs, CMC
Jennifer Jackson, PhD, Senior Vice President, Regulatory Affairs
Timothy Keutzer, Senior Director, Project Management
Carlos Lopez, Senior director, Process Development
Christopher Masterson, Senior Director, Quality Technical Operations Management
Charles A. Miller, Senior Director, Regulatory Affairs
Dawn Spooner, Senior Manager, Regulatory Affairs, CMC
Joseph Terracciano, PhD, Director, CMC Process Development

BACKGROUND

This product is a cephalosporin beta-lactamase inhibitor combination being developed for the treatment of serious and life-threatening bacterial infections including complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI) [redacted] (b) (4)

On August 29, 2012, Cubist submitted a position paper to the Agency and requested feedback (response to three questions) on the classification of beta-lactam antibiotics and the implications for manufacturing their product ceftolozane/tazobactam. The three questions listed in the package are as follows:

1. Given the information provided in this position paper, does the Agency agree that Tazobactam is not a sensitizing agent?

2. Does the Agency agree the beta-lactamase inhibitor, Tazobactam, does not need to be considered a separate class from cephalosporins (Ceftolozane) for the purposes of processing and commercial manufacturing of the drug product?

3. Does the Agency agree with our proposed manufacturing plan for Ceftolozane/Tazobactam and that Tazobactam could be processed on a dedicated cephalosporin line in order to produce the Ceftolozane/Tazobactam drug product?

On December 20, 2012, the Division received a Type A meeting request from Cubist to discuss the manufacturing proposal outlined in the position paper. Cubist stated that a decision on the manufacturing has become critical as Cubist anticipates that the Phase 3 studies for cUTI and cIAI will be completed in mid-2013, and they anticipate an NDA submission near the end of 2013. Therefore, commercial product and stability batches need to be manufactured. Further, Cubist stated that [redacted] (b) (4)

Cubist would like to resolve the manufacturing issue(s) [redacted] (b) (4)

On January 15, 2013, via email, the Division provided Cubist with preliminary comments on the manufacturing proposal. This communication conveyed that manufacturing ceftolozane/ tazobactam in [redacted] (b) (4) would not be optimal based on the lack of information provided. This Type A meeting was held to further discuss this issue.

1. DISCUSSION

- After opening introductions, Cubist commented that they believe they are in compliance regarding manufacturing, yet from the comments received on January 15, 2013, they conclude that the Agency is suggesting that they [redacted] (b) (4)

- [redacted]
- The Agency clarified that the [redacted].
- Cubist stated that they had explored [redacted] input from regulatory authorities from other nations prior to submitting the August inquiry. Based on the information gathered, the review of global regulatory guidelines, and in looking at risk assessments, Cubist formulated their (potential) [redacted] approach to manufacturing provided in the August submission.
- Cubist analyzed the chemical structure, synthetic process, degradation pathway(s) and literature and concluded that the potential for a hypersensitivity reaction to tazobactam remains low. [redacted].
- Cubist stated that a dedicated facility for manufacturing commercial product is being [redacted] Cubist is using a Contract Manufacturing Organization (CMO) to manufacture its clinical trial material and this CMO [redacted]
- The Agency informed Cubist that this issue is still under Agency discussion and that today's meeting will not likely result in a decision regarding a path forward.
- The Agency noted that lack of evidence of sensitizing activity of tazobactam is not sufficient to conclude that it is not a sensitizer.
- The Agency commented that an assessment of low risk for manufacturing may be different than a health assessment. Cubist was questioned as to whether there were any animal data, cleaning validation data, records of people placement (movement), human factors, and any other additional data available for review as the position paper supplied reads as a conclusion document and lacks details. The Agency requested additional information, if available, for review, and indicated that some of these factors may be covered during an on-site inspection.
- Cubist stated that they understand the issues regarding cross-contamination and that they work closely with their contract manufacturers to assure that appropriate controls are in place. Cubist also mentioned that tazobactam has previously been used in combination

with other products, such as piperacillin, and these combination products are manufactured in penicillin dedicated facilities per previous Agency agreements/guidances.

- At this point the Agency is not able to conclude that there is no risk, and the issue regarding the classification of this product, potentially as a new beta-lactam antibacterial class, is not discussed in any available guidances.
- The Agency acknowledged that this development program is important, having recently received Qualified Infectious Disease Product (QIDP) designation, and that the drug would potentially have the ability to address unmet medical needs.
- Cubist stated that this is a real challenge as (b) (4)
- (b) (4) This option will be explored further.
- Cubist proposed to continue the clinical supply production with strict controls in place for monitoring and cleaning with regular audits since the manufacture of this product has been underway since (b) (4).
- (b) (4)
- (b) (4).
- The Agency stated that paper reviews are not typical, and that on-site evaluations of the manufacturing facilities are the standard.
- Cubist inquired as to what else they can provide to give the Agency confidence. The Agency responded that a facility inspection would be needed and a full assessment done during the inspection, further commenting that the manufacture is at their (Cubist) risk. Cubist stated that they are trying to follow the guidance and are asking the Agency to help them (Cubist) understand. The Agency reiterated that the current draft guidance does not specifically address beta-lactamase inhibitors.
- The Agency asked about the drug powder for clinical supply. Cubist stated that (b) (4) (b) (4).

- [redacted] (b) (4)

2. CONCLUSION(S):

- Cubist requested that the Agency allow for continued manufacturing with appropriate controls, at the current facility so that the Phase 3 studies can continue and asked what additional information they can provide to the Agency. The Agency reiterated the need for cleaning validation, residual testing, detection methods, types or reagents, contact vs non-contact information, etc.
- The Agency reiterated that any potential risks or issues regarding cross-contamination will require a full assessment, noting that Cubist should decide on controls based on scientific data.
- The Division commented that understanding Cubist's position was helpful and reiterated the commitment to continue to work in an expeditious fashion to resolve the issue, noting the product's QIDP designation and potential ability to treat serious and life-threatening infections.
- Cubist requested that an interim solution be achieved sooner rather than later and reiterated that they are committed to working with the Agency to resolve this issue; [redacted] (b) (4)
- The Agency commented that Cubist might want to explore the use of experts in the field as consultants.
- The Agency summarized stating that this issue cannot be resolved during this discussion but agreed to review any additional information Cubist can provide as discussed. Additionally, the Agency agreed to discuss this issue with the Office of Pharmaceutical Sciences (OPS)/Office of Compliance (OC), and if necessary the Antibacterial Drug Development Task Force. This is new ground and this issue will require the involvement of others above the review division level.

3. ISSUES REQUIRING FURTHER DISCUSSION

The issue of the [redacted] (b) (4) remains outstanding. Internal follow-up discussions are necessary with others at the Agency. Additional communication with Cubist is also warranted.

4. ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Minutes of discussion within 30-days	Agency	February 22, 2013
Follow-up discussion with the OC/OPS/ATF.	Agency	As soon as possible.
Follow-up discussion with Cubist	Agency	As soon as information is available.

5. ATTACHMENTS AND HANDOUTS

- **Correspondence(s) from FDA to Cubist:**
  - **January 15, 2013, via email; Preliminary Comments**

RE: IND 104490, Serial No. 0102

Submission dated 12/20/12

Ceftolazone/Tazobactam

Type A Meeting Request: Chemistry, Manufacturing, and Controls

Preliminary Comments

Thank you for your Type A meeting request dated December 20, 2012, and background package. We provide the following preliminary comments and a request for additional information to be discussed at our meeting.

We have discussed your submission with personnel from the Office of New Drug Quality Assessment and an Allergist. While we agree that there are not literature reports of hypersensitivity attributed to tazobactam, we cannot conclude that there is no risk of hypersensitivity from cross-contamination. From a clinical perspective, we consider tazobactam to be a separate class of beta-lactam from cephalosporins. We recommend that the section of the facility dedicated to manufacturing your finished drug product should be isolated (i.e. completely and comprehensively separated) from areas in the facility in which cephalosporins are manufactured.

We note that you intend to use a (b) (4) It would be helpful if you could provide additional information tracing the lifecycle of tazobactam within the facility so that other possible opportunities for cross-contamination can be assessed. For example, (b) (4)

(b) (4)

We look forward to meeting with you and apologize for the delay in responding.

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/s/

JOHN J FARLEY
02/22/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

LATE-CYCLE MEETING MINUTES

Cubist Pharmaceuticals, Inc.
Attention: Charles A. Miller
Senior Director, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated April 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zerbaxa (ceftolozane/tazobactam) Injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 22, 2014.

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

If you have any questions, call Maureen Dillon-Parker, Regulatory Project Manager, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Thomas Smith, MD
Cross-Discipline Team Leader / Clinical Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: October 22, 2014 12:00noon-12:20pm
Meeting Type: Teleconference

Application Number: 206829
Product Name: Zerbaxa (ceftolozane/tazobactam)
Applicant Name: Cubist Pharmaceuticals Inc.
Meeting Chair: Thomas Smith, MD
Meeting Recorder: Maureen Dillon-Parker

FDA ATTENDEES

Division of Anti-Infective Products
Maria Allende, MD, Clinical Reviewer
Kimberly Bergman, PharmD, Clinical Pharmacology Team Leader
Maureen Dillon-Parker, Chief, Project Management Staff
Kerian Grande Roche, PhD, Microbiology Reviewer
Christopher Kadoorie, PhD, Statistical Reviewer
Sumathi Nambiar, MD, MPH, Director
Shrikant Pagay, PhD, Chemistry Reviewer
Daniel Rubin, PhD, Statistical Reviewer
Wendelyn Schmidt, PhD, Pharmacology/Toxicology Team Leader
Hala Shamsuddin, MD, Clinical Reviewer
Thomas Smith, MD, Clinical Team Leader
Kerry Snow, MS, Clinical Microbiology Team Leader
James Wild, PhD, Pharmacology/Toxicology Reviewer
Jeff Florian, Acting Pharmacometrics Team Leader, OCP, DPM

Office of Antimicrobial Products
John Farley, MD, MPH, Deputy Director
David Roeder, MS, Associate Director for Regulatory Affairs
Joseph Toerner, MD, MPH, Lead Medical Officer

Office of Scientific Investigations/Division of Good Clinical Practice Branch 2
Sharon Gershon, Pharmacologist

Office of Compliance
Steven B. Hertz, Lead Compliance Facility Reviewer

Office of Surveillance and Epidemiology
Division of Risk Management
Joyce Weaver, Risk Management Analyst

Division of Epidemiology
Veronica Sansing, Safety Evaluator/Epidemiologist

Division of Pharmacovigilance
Ronald Wassel, PharmD, Safety Evaluator

Division of Medication Error Prevention and Analysis (DMEPA)
Aleksander Winiarski, PharmD, Safety Evaluator

Eastern Research Group, Inc.
Christopher Sese, Independent Contractor [PDUFA V applications]

APPLICANT ATTENDEES - Cubist Pharmaceuticals
Chuck Miller, Sr. Director, Regulatory Affairs Anti-Infectives
Judith Steenbergen, Director, Clinical Microbiology
Barry Eisenstein, Senior Vice President, Scientific Affairs
Karen Terry, Manager, Regulatory Affairs
Maria Iacovelli, Director, Regulatory Affairs CMC
Rob Pawliuk, Senior Director, Regulatory Nonclinical
Obi Umeh, Vice President, Global Medical Sciences
Patricia Bernardo, Principal Biostatistician
Ellie Hershberger, Senior Medical Director, Clinical Research
Timothy Keutzer, Vice President, Program Management
Sylva Collins, Vice President, Biometrics

BACKGROUND

NDA 206829 was submitted on April 21, 2014, for ZERBAXA (ceftolozane/tazobactam) for Injection for intravenous use.

Proposed indication(s): Complicated Urinary Tract Infections (cUTI) and Complicated Intra-abdominal Infections (cIAI)

PDUFA goal date: December 21, 2014

FDA issued a Background Package in preparation for this meeting on October 8, 2014.

DISCUSSION

1. Introductory Comments

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

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

Discussion: *There was no further discussion.*

2. Substantive Review Issues

Discussion: *None at this time.*

3. Minor Review Issues

a. Complicated Intra-Abdominal Infections

Subgroup analyses showed a trend toward less favorable efficacy outcomes in the ceftolozane/tazobactam + metronidazole arm in patients with higher risk profiles at baseline (e.g., age ≥ 65 years, region of North America/Western Europe/Rest of World, primary site of infection of bowel, anatomic site of infection of non-appendix, prior antibiotic use, APACHE II Score > 10, creatinine clearance < 50 mL/min., or multiple abscesses).

Discussion: *There was no further discussion of this issue. The sponsor provided a response on October 21, 2014, to the Division's request of October 2, 2014; see #4 below.*

b. Complicated Urinary Tract Infections (cUTI)

We have no review issues at this time. However, we do not agree with your assessment that (b) (4) has been demonstrated.

Discussion: *There was no further discussion of this issue.*

c. Microbiology

Susceptibility test interpretive criteria are still under review. Our preliminary assessment is that the proposed criteria will need to be revised.

Discussion: *Cubist will await the Division's proposal for the Microbiology subsection of the labeling. The Division commented that a request for additional information regarding the scatterplots and disc diffusion interpretive criteria will be sent by the end of the week.*

4. Information Requests

The following request from the statistical review team was communicated to Cubist on October 2, 2014, via email:

Complicated Intra-Abdominal Infections:

Please provide a multivariate logistic regression analysis of the primary outcome (cure vs. indeterminates/failure) using the MITT population, adjusting for the covariates including treatment groups, Age-group (<65, >=65), Prior Antibiotic Use (Y/N), Renal function, CrCl (< 50 mL/min, ≥ 50 mL/min), Infection Type (Bowel vs. other), Baseline APACHE II Score (<10, ≥10), Number of Abscesses Present (<=1, >1), Peritonitis Present (Local peritonitis, Diffuse peritonitis, No peritonitis), Appendix (Y/N) and Region. Please repeat the analysis without the region and discuss the findings.

Discussion: *The Division will review the response to this request received from Cubist October 21, 2014, and provide additional comments to Cubist as applicable.*

5. Postmarketing Requirements/Postmarketing Commitments

Resistance

Conduct US surveillance studies for five years from the date of marketing Zerbaxa to determine if resistance to ceftolozane/tazobactam has developed in those organisms specific to the indication in the label for cUTI and cIAI.

PREA

(b) (4)

Study 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 cUTI	
Estimated Protocol Submission Date:	April 2017
Estimated Study Initiation Date:	June 2017
Estimated Final Study Report Submission Date:	December 2020
Study 3: 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	
Estimated Protocol Submission Date:	April 2017
Estimated Study Initiation Date:	June 2017
Estimated Final Study Report Submission Date:	December 2020

Discussion: *Cubist found these proposals acceptable as the PREA timelines were negotiated under the IND 104,490 and the surveillance study is standard for new antimicrobial products.*

6. Review Plans

- Finalize the chemistry inspections

  Discussion: *The Division and Cubist are aware that the facility inspections have been completed. The final report/recommendation has not been completed at this time.*

- Finalize the labeling and complete final reviews.

  Discussion: *The Division and Cubist agreed to continue working on the labeling; Cubist was informed that the reviews are being completed and that the application is on schedule.*

- Reach agreement on the PMC/PMRs and timeframes for submission.

  Discussion: *See #5 above.*

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL), and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

THOMAS D SMITH
11/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829

LATE CYCLE MEETING
BACKGROUND PACKAGE

Cubist Pharmaceuticals, Inc.
Attention: Charles A. Miller
Senior Director, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zerbaxa (ceftolozane/tazobactam) Injection.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 22, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Maureen Dillon-Parker, Regulatory Project Manager, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	October 22, 2014; 12:00pm-1:00pm
Meeting Location:	White Oak, Building 22, Room 1415 10903 New Hampshire Avenue Silver Spring, MD 20993
Application Number:	NDA 206829
Product Name:	Zerbaxa (ceftolozane/tazobactam) IV
Indications:	Complicated Urinary Tract Infections including pyelonephritis; Complicated Intra-abdominal Infections
Sponsor/Applicant Name:	CUBIST Pharmaceuticals Inc.

INTRODUCTION

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

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

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

No Advisory Committee meeting is planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LATE-CYCLE MEETING AGENDA

1. Introductory Comments – 5 minutes

Welcome/Introductions; Ground rules; Objectives of the meeting

2. Discussion of Substantive Review Issues:

None at this time.

3. Discussion of Minor Review Issues – 10 minutes

a. Complicated Intra-Abdominal Infections

Subgroup analyses showed a trend towards less favorable efficacy outcomes in ceftolozane/tazobactam + metronidazole arm in patients with higher risk profiles at baseline (e.g. age ≥ 65 years, region of North America/Western Europe/Rest of World, primary site of infection of bowel, anatomic site of infection of non-appendix, prior antibiotic use, APACHE II Score > 10, creatinine clearance < 50 mL/min. or multiple abscesses).

b. Complicated Urinary Tract Infections (cUTI)

We have no review issues at this time. However, we do not agree with your assessment that [redacted] (b) (4) has been demonstrated.

c. Microbiology

Susceptibility test interpretive criteria are still under review. Our preliminary assessment is that the proposed criteria will need to be revised.

4. Information Requests – 10 minutes

The following request from the statistical review team was communicated to you on October 2, 2014, via email:

Complicated Intra-Abdominal Infections:

Please provide a multivariate logistic regression analysis of the primary outcome (cure vs. indeterminates/failure) using the MITT population, adjusting for the covariates including treatment groups, Age-group (<65, >=65), Prior Antibiotic Use (Y/N), Renal function, CrCl (< 50 mL/min, ≥ 50 mL/min), Infection Type (Bowel vs. other), Baseline APACHE II Score (<10, ≥10), Number of Abscesses Present (<=1, >1), Peritonitis Present (Local peritonitis, Diffuse peritonitis, No peritonitis), Appendix (Y/N) and Region. Please repeat the analysis without the region and discuss the findings.

5. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

Resistance

Conduct US surveillance studies for five years from the date of marketing Zerbaxa to determine if resistance to ceftolozane/tazobactam has developed in those organisms specific to the indication in the label for cUTI and cIAI.

PREA

(b) (4)

Study 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 cUTI	
Estimated Protocol Submission Date:	April 2017
Estimated Study Initiation Date:	June 2017
Estimated Final Study Report Submission Date:	December 2020
Study 3: 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	
Estimated Protocol Submission Date:	April 2017
Estimated Study Initiation Date:	June 2017
Estimated Final Study Report Submission Date:	December 2020

6. Major labeling issues –

None.

7. Review Plans – 5 minutes

- Finalize the chemistry inspections
- Finalize the labeling and complete final reviews.
- Reach agreement on the PMC/PMRs and timeframes for submission.

8. Wrap-up and Action Items – 10 minutes

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

/s/

SUMATHI NAMBIAR
10/08/2014