CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205436Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205436 HFD # 520

Trade Name Sivextro 200 mg Injection

Generic Name tedizolid phosphate

Applicant Name Cubist Pharmaceuticals, Inc.

Approval Date, If Known June 20, 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)(1)

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

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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

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).

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NDA# N/A

NDA# N/A

NDA# N/A

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# N/A

NDA# N/A

NDA# N/A

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.

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

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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 ☐

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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 ☐

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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 ! !

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !

IND # YES ☐ ! NO ☐
! Explain:

(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?

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Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(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:

==========

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

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GAIN Exclusivity Summary

NDA#: 205436

Product Name: Silvextro (tedizolid phosphate) for injection

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 this drug previously received a 5-year GAIN exclusivity extension?

YES	NO
	X

There are no currently approved products containing tedizolid phosphate and no products containing tedizolid phosphate that have received an exclusivity extension under GAIN. However, we note that a new drug application (NDA) for another product containing tedizolid phosphate from the same sponsor (NDA # 205435 for Silvextro (tedizolid phosphate) Tablets) was submitted simultaneously with this NDA and is expected to be approved on the same day. Regardless of the order of approval of NDA # 205435 and NDA # 205436 on that day, neither NDA will be considered a "subsequent application filed with respect to a product approved under section 505" for the purposes of section 505E(c)(2) of the FD&C Act.

Name of person completing form: Carmen DeBellas, PharmD, RPh

Title: Senior Regulatory Project Manager

Date: *<see electronic signature>*

Name of Office/Division Director signing form: Edward Cox, MD, MPH

Title: Director

Office of Antimicrobial 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/

CARMEN L DEBELLAS
06/20/2014

EDWARD M COX
06/20/2014

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 205435 & 205436 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _

Division Name: Division of Anti-Infective Products PDUFA Goal Date: June 21, 2014 Stamp Date: 10/21/2013

Proprietary Name: Sivextro Tablets and Injection

Established/Generic Name: tediazolid Dosage

Form: Tablets & Injection

Applicant/Sponsor: Cubist Pharmaceuticals, Inc

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Acute Bacterial Skins and Skin Structure Infections

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☒	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☒	☐	☐	☒
	Date studies are due (mm/dd/yy): 05/31/19						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

CARMEN L DEBELLAS
04/21/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # NDA 205436	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Sivextro Injection Established/Proper Name: tedizolid phosphate Dosage Form: 200 mg		Applicant: Cubist Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Carmen DeBellas		Division: Division of Anti-Infective Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

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)**

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

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 June 20, 2014 • User Fee Goal Date is June 21, 2014	☒ AP
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? 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
❖ Application Characteristics[3]	

[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, (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).
[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.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): 1P
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy 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
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ 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	☒ No
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

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)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Reference ID: 3529752

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	June 20, 2014
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)*	☒ Included
• Original applicant-proposed labeling	☒ 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 ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	N/A
• Original applicant-proposed labeling	N/A
❖ 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	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	December 19, 2013 December 18, 2013
Labeling reviews *(indicate dates of reviews)*	RPM: March 24, 2014 DMEPA: May 2, 2014 DMPP/PLT (DRISK): ☒ None OPDP: May 12, 2104 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	January 29, 2014 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☒ No

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

Reference ID: 3529752

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☒ No ☒ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC May 7, 204 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) *(do not include previous action letters, as these are located elsewhere in package)*	Letters Included Emails Included
❖ 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)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	May 13, 2013
• EOP2 meeting *(indicate date of mtg)*	October 19, 2009
• Mid-cycle Communication *(indicate date of mtg)*	March 6, 2014
• Late-cycle Meeting *(indicate date of mtg)*	March 14, 2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	
• Date(s) of Meeting(s)	March 30, 2104
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	June 20, 2014
Division Director Summary Review *(indicate date for each review)*	June 13, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	June 9, 2014
PMR/PMC Development Templates *(indicate total number)*	6
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	June 10, 2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ 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)*	See Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A

Reference ID: 3529752

❖ 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 May 6, 2014
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Letters April 29, 2014 (2) June 4, 2014 Reviews March 11, 2014 May 20, 2014
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	May 9, 2014
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	May 8, 2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)* *Pharmacometirc Review*	March 24, 2014 (both) June 18, 2014 (Label Review)
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	May 27, 2014
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	May 28, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Reference ID: 3529752

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	March 17, 2014 May 22, 2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	January 8, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	March 17, 2014
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ 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: **See CMC Review** ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ 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.

Reference ID: 3529752

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ 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	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Reference ID: 3529752

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/s/

CARMEN L DEBELLAS
06/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug
Administration Silver Spring
MD 20993

NDA 205436

GAIN Exclusivity

Cubist Pharmaceuticals, Inc.
Attention: Mary Celine Scott, PhD, MBA
Senior Director, Regulatory Affairs
6310 Nancy Ridge Dr., Suite 105
San Diego, CA 92121

Dear Dr. Scott:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SIVEXTRO (tedizolid phosphate) Injection for the treatment of Acute Bacterial Skin and Skin Structure Infections. We also refer to the letter, dated June 20, 2014, granting approval of this NDA.

We also refer to our correspondence dated January 3, 2013 to your Investigational New Drug (IND) Application 106307 in which we granted Qualified Infectious Disease Product (QIDP) designation for SIVEXTRO (tedizolid phosphate) Injection for the treatment of Acute Bacterial Skin and Skin Structure Infections.

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 Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely yours,

{See appended electronic signature page}

Edward Cox, MD MPH
Office Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

EDWARD M COX
06/20/2014

From:Mary Celine Scott <MaryCeline.Scott@cubist.com>
Sent:Friday, June 20, 2014 1:49 PM
To:DeBellas, Carmen
Subject:RE: Comment needing agreement

Thanks Carmen! Cubist appreciates the FDA Laboratory assessment of Ted ate method AP-010. We will investigate reducing the injection volume from (b) (4) Cubist will provide an update to FDA upon completion of this assessment.

Kind regards,
Mary Celine Scott, PhD, MBA

From: DeBellas, Carmen [mailto:Carmen.DeBellas@fda.hhs.gov]
Sent: Friday, June 20, 2014 6:16 AM
To: Mary Celine Scott
Subject: Comment needing agreement

Hi Mary,

The Methods Validation review has the following comment. I have been asked to send to you.

Based on the evaluation of the method by FDA labs, we recommend reducing the injection volume in the HPLC method (AP-010.0)for assay, identity and impurities from (b) (4).

Carmen

This e-mail and any attachments are meant for the intended recipient only and may contain information belonging to Cubist Pharmaceuticals, Inc. that is privileged, confidential, proprietary, and/or otherwise protected or prohibited from disclosure. If you have received this message in error, are not the intended recipient, or are uncertain about its proper handling, please notify the sender as soon as possible and immediately delete the e-mail and any attachments from your computer system. Cubist Pharmaceuticals, Inc., 65 Hayden Avenue, Lexington, Massachusetts, 02421, U.S.A. 781-860-8660 www.cubist.com

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/s/

CARMEN L DEBELLAS
06/20/2014

From: DeBellas, Carmen
Sent: Friday, June 20, 2014 9:16 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Comment needing agreement

Hi Mary,

The Methods Validation review has the following comment. I have been asked to send to you.

Based on the evaluation of the method by FDA labs, we recommend reducing the injection volume in the HPLC method (AP-010.0)for assay, identity and impurities from (b) (4)

Carmen

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/s/

CARMEN L DEBELLAS
06/20/2014

From: DeBellas, Carmen
Sent: Friday, June 20, 2014 7:23 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Sorry more label edits

Sorry Mary,

One last checker has input.

1. There were a few minor labeling edits still noted. I have placed them in the label with attached comments (look at the comments made by **MS**). The sponsor may have already submitted a label to DARRTS but hopefully we can turn this back to them quickly and then have them resubmit. I have attached the label

Almost finalized label.docx

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/s/

CARMEN L DEBELLAS
06/20/2014

From: DeBellas, Carmen
Sent: Friday, June 20, 2014 8:13 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Submission question

Hi Mary,

Can you check and see if there is a statement in your original NDA submission for this if not can you add it to the letter with the final label today.

1. According to CFR 312.120(b)(6), there needs to be a statement somewhere in the application that attests that there was a committee that reviewed/certified the foreign IRB's participating in these studies and found them to be acceptable.

Thanks,

Carmen

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/s/

CARMEN L DEBELLAS
06/20/2014

NDAs 205435 and 205436

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

A Phase 1, Single-Dose Safety and Pharmacokinetic Study of Oral and IV SIVEXTRO in Pediatric Patients Under Two Years Old

Final Protocol Submission: April 2016
StudyCompletion: MM/YY
Final Report Submission: July 2019

A Phase 1, Single-Dose Safety and Pharmacokinetic Study of Oral and IV SIVEXTRO in Patients 2 to <12 Years of Age

Final Protocol Submission: December 2014
StudyCompletion: MM/YY
Final Report Submission: April 2017

Randomized Single-Blind, Multicenter Safety and Efficacy Study of Intravenous to Oral SIVEXTRO and Intravenous to Oral Comparator for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged 12 to <18 Years

Final Protocol Submission: November 2014
StudyCompletion: MM/YY
Final Report Submission: June 2017

Randomized, Single-Blind, Multicenter Safety and Efficacy Study of Intravenous to Oral SIVEXTRO and IV to Oral Comparator for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged >3 Months to < 12 years.

Final Protocol Submission: January 2016
StudyCompletion: MM/YY
Final Report Submission: May 2019

Open-Label, Multicenter Study of 10-14 days IV SIVEXTRO for hospital-acquired late onset sepsis in full term and preterm neonates and infants aged 5 days to ≤ 3 months.

Final Protocol Submission: July 2018
StudyCompletion: MM/YY
Final Report Submission: February 2020

The following study is required based on section 505(o)(3) of the FDCA authorizing FDA to require holders of approved drug applications to conduct postmarketing studies and clinical trials for certain purposes.

Conduct US surveillance studies for five years from the date of marketing SIVEXTRO to determine if resistance to tedizolid has developed in those organisms specific to the indication in the label for ABSSSI.

Final protocol submission:	MM/YY
First interim report:	MM/YY
Second interim report:	MM/YY
Third interim report:	MM/YY
Fourth interim report:	MM/YY
Fifth interim report:	MM/YY
Study completion date:	MM/YY
Final report submission:	MM/YY

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/s/

CARMEN L DEBELLAS
06/06/2014

From: DeBellas, Carmen
Sent: Thursday, May 15, 2014 7:59 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Clinical IR

Hi Mary Celine,

Sorry response times are sort of shortening.

For all cases of adverse events classified as abscess and/or cellulitis, please reclassify the primary and secondary endpoints as follows:

Classify each of these events as a failure (in both arms) according to the study time period in which they occurred. For example, if a subject had an adverse event of abscess/cellulitis prior to/at the 48-72 hr. visit, he/she should be classified as a failure for the 48-72 hr. visit (primary endpoint). Similarly, if a subject had such an event between the 48-72 hr. and/at the EOT visit, then they should be classified as a failure at the EOT visit. Adverse events that occurred after the late follow up visit can be ignored. Based on these reclassifications, please resubmit the results for:

1. *The primary endpoint- 48 to 72 hr. visit using the study 113 definition (≥20% reduction in lesion size for responders)*
2. *The secondary endpoint- EOT visit (programmatic definition for sustained clinical response at EOT with failures not being carried forward; for study 112, this analysis can be done with and without the pain component being included).*
3. *The secondary endpoint- PTE (Investigator assessment of clinical success at PTE)*
4. *Other endpoints- LFU visit (Investigator assessment of clinical relapse)*

If possible, we would like to see the results by Friday, May 16th, 2014.

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/s/

CARMEN L DEBELLAS
05/15/2014

From:DeBellas, Carmen
Sent:Tuesday, May 06, 2014 3:41 PM
To:Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject:NDA 205435 & 436 Carton & Container labels

Hi Mary Celine,

Please find the Agency recommendations for your carton and container labels.

A. Oral Tablet Blister Label

1. To improve readability, revise the letter case of the proprietary name SIVEXTRO from all capital letters to title case, to read: Sivextro.1 Additionally, ensure that the established name is at least half the size of the proprietary name per 21CFR
201.10(g)(2). The established name, which includes the dosage from, should appear in one font type and color.

2. To improve readability, consider using the same font size and boldness for the entire strength presentation “200 mg per tablet”.

B. Oral Tablet Blister Carton Labeling

1. See A1, A2 above.

2. The graphic design located to the left of the proprietary name is prominent and may be misinterpreted as part of the proprietary name. On all panels, delete this graphic, or reduce the size of the graphic design and relocate away from the proprietary name.1

C. Oral Tablet Bottle Label

1. See A1, A2 and B2 above.

2. The cubist logo on the Principal Display Panel (PDP) draws attention to the eye and competes for prominence with important prescribing information, such as the established name and strength. Decrease the prominence of the logo by significantly reducing its size or consider removing the logo.

D. Intravenous Vial Label

1. See A1, B2 and C2 above.

2. The Principal Display Panel (PDP) contains the IV abbreviation which should be replaced with the corresponding words “intravenous”, as per FDA Guidance for Industry titled: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, which states that “The route of administration should be described without abbreviation”. Replace the IV abbreviation with the word “Intravenous” for clarity.

3. To improve readability, revise the letter case of the use statement from all capitals to title case, to read: “For Intravenous Infusion”.

4. Please revise the dosage form statement to “for injection”, for consistency with the prescribing information labeling and in accordance with the nomenclature definitions listed in the United States Pharmacopeia (USP) General Chapter 1: Injections.

5. To improve readability, consider using the same font size and boldness for the entire strength presentation: 200 mg per vial.

E. Intravenous Individual Carton
Labeling

1. See A1, B2, D3, D4 and D5 above.

2. Ensure that the proprietary name, established name and strength statements are the most prominent information on all panels where they appear, by increasing their size.

3. Revise the boxed warning statement for consistency with the insert labeling by replacing the negative portion of the statement “do not use …” with an affirmative statement “incompatible with …”

We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word “not” can be overlooked and misinterpret the warning as an affirmative action.2

Additionally, relocate this statement to the side or back panel and revise from all capital letters to title case to improve readability.

F. Intravenous Carton Labeling Containing 10 vials

1. See A1, B2, D3, D4, D5 and E3 above.

1 Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.
Food and Drug Administration. 2013. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM349009.pdf.

2 Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

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/s/

CARMEN L DEBELLAS
05/06/2014

From: DeBellas, Carmen
Sent: Monday, May 05, 2014 8:02 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: NDA 205435 & 436 Clinical Info Request #2

Good morning, As promised the second Clinical Information request. We will need this by May 9, 2014.

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

Information Request: Analyses of Liver Toxicity

1. Please complete the following tables for both Phase 2 and Phase 3 trials.
2. Please clearly state definitions used for normal and ULN for each laboratory parameter described in the tables.
3. Where actual results of laboratory values are requested, please report in U.S. Conventional Units.
4. Please submit eCRFs for patients with ALT, AST, ALP, and TB with results ≥2x, 3x, 5x, and ≥10x ULN.
5. Given time constraints, please submit these tables by **May 8, 2014**. If analyses for the Phase 3 trials are completed before then, please submit in advance.

	Table 1: Liver Functions Tests Elevations in Phase 3 trials			
	Tedizolid Phosphate N =		Comparator N =	
	Subject Count	% of Subjects	Subject Count	% of Subjects
ALT ≥ ULN				
2x ULN				
3x ULN				
5x ULN				
10x ULN				
AST ≥ ULN				
2x ULN				
3x ULN				
5x ULN				
ALP ≥ ULN				
2x ULN				
3x ULN				
5x ULN				

	Table 1: Liver Functions Tests Elevations in Phase 3 trials			
	Tedizolid Phosphate N =		Comparator N =	
TB ≥ ULN				
1.5x ULN				
2x ULN				
3x ULN				
All measurements are post-baseline but subjects may have abnormal baseline levels. ALP – alkaline phosphatase; TB – total bilirubin				

Table 1: Selected Baseline Liver Diseases in Phase 3 Trials						
	TR701-112		TR701-113		Total	
	Tedizolid phosphate N= n (%)	Comparator N= n (%)	Tedizolid phosphate N= n (%)	Comparator N= n (%)	Tedizolid phosphate N= n (%)	Comparator N= n (%)
Events Total						
Subjects Total						
Hepatitis C						
Alcohol abuse						
Hepatic insufficiency						
Hepatitis B						
Others						
Please note subjects who may have more than one problem						

Table 3: Post- Dose Alanine Aminotransferase Elevations in Subjects with Normal Baseline Transaminase Levels in Tedizolid Phosphate Trials				
	TR701-112 & 113		All Phase 2&3 Trials	
	Tedizolid phosphate N=	Comparator N=	Tedizolid phosphate N=	Comparator N=
> 3x ULN – 5 ULN				
> 5x ULN – 10x ULN				
> 10x ULN				
Total n (%)				
N - baseline ALT < the upper limit of normal; Subjects are counted once Please state when these measurements were obtained. For example, “For trials xxxx the measurements are obtained on Day x and End of Treatment visits (Day xx-xx); for other trials (xxxx) measurements are obtained through the Post Therapy Evaluation Visit (xxx days following the completion of study medication).”				

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/s/

CARMEN L DEBELLAS
05/05/2014

From: DeBellas, Carmen
Sent: Friday, May 02, 2014 10:13 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: NDA 205435 & 436 Clinical Information Request #1

Hi Mary Celine, Please find information request. We are in need of a quick turn around on this May 8, 2014. There will another request coming to you on Monday.

To the Sponsor

We are seeking information regarding the following issues:

1. *We noted that in both Studies 112 and 113 several subjects were reported as having adverse events of "cellulitis" and "abscess." The vast majority of these subjects were not judged to be failures at any time point (48-72 hrs., EOT, PTE, or LFU). We are currently seeking more information about each subject. This can be submitted in tabular format. Specifically, we would like the Unique Subject ID, planned treatment, number of actual doses received of treatment, clinical syndrome, important background demographic and medical history including age/sex/race/BMI /whether the patient had a history or recent or current IV drug use, location of primary lesion, whether secondary lesions were present at baseline, baseline pathogen, time of onset of AE, whether AE represented worsening of a primary (or nearby) or secondary lesion, surgical or drug treatment received (if drug treatment received, please give the name of the drug) and day received, and the assessed clinical response at the 48-72 hr., End of Treatment, PTE, and LFU time points. Please submit the CRF's for each of these subjects if not done so already.*

   The CRFs we have on file for such cases are as follows:

TR701-112-101-099
TR701-112-101-138
TR701-112-103-326
TR701-112-101-303
TR701-112-103-645
TR701-112-105-205
TR701-112-128-179
TR701-112-101-235
TR701-112-102-292
TR701-112-103-131
TR701-112-103-379
TR701-112-103-550
TR701-112-104-192
TR701-112-104-496
TR701-112-105-070
TR701-112-105-110
TR701-112-105-113

TR701-112-105-119
TR701-112-105-264
TR701-112-105-400
TR701-112-118-201
TR701-112-126-076
TR701-112-126-090
TR701-112-101-208
TR701-112-101-449
TR701-112-102-223
TR701-112-113-562
TR701-112-128-040
TR701-112-101-004
TR701-112-101-007
TR701-112-101-212
TR701-112-103-061
TR701-112-103-123
TR701-112-103-302
TR701-112-103-411
TR701-112-103-586
TR701-112-104-117
TR701-112-105-091
TR701-112-105-096
TR701-112-105-116
TR701-112-105-390
TR701-112-105-405
TR701-112-105-424
TR701-112-105-460
TR701-112-105-548
TR701-112-118-108
TR701-112-118-440
TR701-112-126-153
TR701-112-128-373
TR701-112-128-557

TR701-113-101-021
TR701-113-101-026
TR701-113-101-100
TR701-113-103-007
TR701-113-103-064
TR701-113-103-066
TR701-113-103-096
TR701-113-103-120
TR701-113-103-137

TR701-113-103-189
TR701-113-105-027
TR701-113-105-060
TR701-113-105-073
TR701-113-105-107
TR701-113-105-126
TR701-113-105-165
TR701-113-105-171
TR701-113-141-111
TR701-113-143-092
TR701-113-143-094
TR701-113-143-098
TR701-113-143-119
TR701-113-143-125
TR701-113-143-160
TR701-113-143-170
TR701-113-143-215
TR701-113-143-220
TR701-113-143-359
TR701-113-143-415
TR701-113-144-510
TR701-113-157-412
TR701-113-159-268
TR701-113-160-453
TR701-113-160-521
TR701-113-160-522
TR701-113-160-583
TR701-113-160-605
TR701-113-286-417
TR701-113-358-326

2. *Please perform sensitivity analyses for the primary and secondary endpoints (programmatic determination at EOT, investigator assessment at PTE, assessment of relapse at LFU) where (1) all of the above cases are considered failures in both treatment groups and (2) where all cases are considered failures for tedizolid phosphate and successes for linezolid*

   For the ITT population in studies 112 and 113:

3. *Please clarify the number of subjects noted to have Staph. aureus, MRSA, and MSSA at baseline in both phase 3 studies. We have tried to confirm your numbers and are unable to do so.*
4. *Please clarify the difference between Derived Investigator Assessment of Clinical Response at PTE and Investigator Assessment of Clinical Response at PTE. What is the difference in how these assessments were made?*

We would like to have these by May 8, 2014.

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
05/02/2014

From:DeBellas, Carmen
Sent:Wednesday, April 30, 2014 7:12 AM
To:Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject:Sivextro NDC numbers?

Hi Mary Celine,

I am sort of confused. We seem to have different NDC numbers for one or both products in the PI and Carton and Container label. Can you please verify all numbers and when amending the PI and Carton and Container labels make sure the numbers are consistent.

I should have carton and container labels comments in the near future. I have comment below. Don't amend carton and container until I see if there are more comments coming from the review.

Please change the dosage form (b) (4) to "for injection" on their primary and secondary containers and amend the application with the new colored mock ups.

Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
04/30/2014

From: Corey Chong
To: Bhandari, Navdeep
Cc: David Lust; Jeffrey Bourque
Subject: RE: NDA 205436 Agency Guidance and Telecon Meeting Request
Date: Friday, April 18, 2014 3:23:23 PM

Hello Navi,

Unfortunately there is a delay in sending the additional information to you. Our CMO is in the process of providing us with additional detail and facility schematics to be included in the meeting request. I will keep you updated if there is a prolonged delay.

Regards,
Corey

From: Corey Chong
Sent: Tuesday, April 15, 2014 10:14 AM
To: 'Bhandari, Navdeep'
Cc: David Lust; Jeffrey Bourque
Subject: RE: NDA 205436 Agency Guidance and Telecon Meeting Request

Good Morning Navi,

We'll provide more information as requested in a formal meeting request that will be submitted this week.

Regards,
Corey

From: Bhandari, Navdeep [mailto:Navdeep.Bhandari@fda.hhs.gov]
Sent: Monday, April 14, 2014 7:50 AM
To: Corey Chong
Subject: NDA 205436 Agency Guidance and Telecon Meeting Request
Importance: High

Good morning Corey,

My team has asked that you provide the following information:

"supply us with a more detailed list of exactly what changes will be made (b) (4)
(b) (4)

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815

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/s/

NAVDEEP BHANDARI
04/21/2014

Tedizolid (Sivextro) proposed clinical microbiology label.

FDA's version of the Tedizolid label:

12.4 Microbiology

Mechanism of Action

The antibacterial activity of tedizolid is mediated by binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis. (b) (4)

(b) (4)

Mechanism of Resistance

(b) (4)

Frequency of Resistance

Spontaneous mutations conferring reduced susceptibility to tedizolid occur *in vitro* at a frequency rate of approximately 10^{-10}. (b) (4)

(b) (4)

Interaction with Other Antimicrobials

In vitro drug combination studies with tedizolid and aztreonam, ceftriaxone, ceftazidime, imipenem, rifampin, trimethoprim/sulfamethoxazole, minocycline, clindamycin, ciprofloxacin, daptomycin, vancomycin, gentamicin, amphotericin B, ketoconazole, and terbinafine demonstrate neither synergy nor antagonism.

Spectrum of Activity

Tedizolid has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections, as described in (b) (4) *Indications and Usage (1)* (b) (4).

Aerobic and Facultative Gram-positive Microorganisms

- *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates)

(b) (4)

- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* Group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*)
- *Enterococcus faecalis* (b) (4)

The following *in vitro* data are available, but their clinical significance has not been established. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the (b) (4) for tedizolid. However, the safety and effectiveness of TRADENAME in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and Facultative Anaerobic Gram-positive Microorganisms

- *Staphylococcus epidermidis* (including methicillin-susceptible and methicillin-resistant strains)
- (b) (4)
- *Enterococcus faecium* (b) (4)

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure based on dilution methods (broth, agar, or microdilution)[1,3] or equivalent using standardized inoculum and concentrations of tedizolid. The MIC values should be interpreted according to the criteria provided in Table 1.

Table 1 Susceptibility Interpretive Criteria for TRADENAME

Pathogen	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤0.5	1	≥2	≥19	16-18	≤15
(b) (4)						
Streptococcus pyogenes	≤0.5	-	-	≥18	-	-
Streptococcus agalactiae	≤0.5	-	-	≥18	-	-
Streptococcus anginosus Group*	≤0.25	-	-	≥17	-	-
Enterococcus faecalis	≤0.5	-	-	≥19	-	-

S=susceptible, I=intermediate, R=resistant
*Includes *S. anginosus*, *S. intermedius*, *S. constellatus*

Diffusion techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 20 µg tedizolid to test the susceptibility of microorganisms to tedizolid. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 20 µg tedizolid disk should be interpreted according to the criteria in Table 1.

A report of "Susceptible" indicates that the (b) (4) is likely to inhibit growth of the pathogen if the antimicrobial (b) (4) reaches the concentration (b) (4) (b) (4). A report of "Intermediate" indicates that the result should be considered equivocal, and if the (b) (4) is not fully susceptible to alternative (b) (4) drugs, the test should be repeated. This category implies possible clinical (b) (4) in body sites where the drug is physiologically concentrated. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing

major discrepancies in interpretation. A report of "Resistant" indicates that the (b) (4) is not likely to inhibit growth of the pathogen if the (b) (4) reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.[1, 2, 3] Standardized tedizolid powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 20 µg tedizolid disk, results within the ranges specified in Table 2 should be observed.

Table 2 Acceptable Quality Control Ranges for Susceptibility Testing

Quality Control Organism	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (zone diameter in mm)
Staphylococcus aureus ATCC 29213	0.25 - 1	Not Applicable
Staphylococcus aureus ATCC 25923	Not Applicable	22 - 29
Enterococcus faecalis ATCC 29212	0.25 - 1	Not Applicable
Streptococcus pneumoniae ATCC 49619	0.12 - 0.5	24 - 30

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – 9th ed., CLSI document M7 A9. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved Standard – 11th ed. CLSI document M2 A11 (ISBN 1-56238-781-2 [Print]; ISBN 1-56238-782-0 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2012.
3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing – 24th Informational Supplement. CLSI document M100 S24 (ISBN 1-56238-865-7 [Print]; ISBN 1-56238-866-5 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2014.

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/s/

CARMEN L DEBELLAS
04/01/2014

From: DeBellas, Carmen
Sent: Monday, March 24, 2014 4:59 PM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Information Request Micro/CliniPharm

Hi Mary,

Please find our Information Request regarding the granulocyte-mediated effect on tedizolid activity.

In the mouse thigh infection model, it was shown that treatment with tedizolid phosphate resulted in a significant increase in the antistaphylococcal killing activity in the presence of granulocytes relative to granulocytopenic animals. In granulocytopenic mice, bacterial stasis was achieved at a human-equivalent dose of approximately 2000 mg/day; whereas, in non- granulocytopenic animals, stasis was achieved at a human-equivalent dose of approximately 100 mg/day. We noted that patients with neutropenia were excluded from Phase 3 studies where the 200 mg/day dose was used. What are your plans for the use of tedizolid in patients with neutropenia given this nonclinical finding and the exclusion of patients with neutropenia in your phase 3 studies?

Can we have this submitted by Wednesday?

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
03/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205435
NDA 205436

MID-CYCLE COMMUNICATION

Cubist Pharmaceuticals, Inc.
Attention: Mary Celine Scott, PhD, MBA
Senior Director, Regulatory Affairs
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121

Dear Dr. Scott:

Please refer to your New Drug Application (NDA) dated DATE, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

NDA 205435 Sivextro (tedizolid phosphate) Tablets
NDA 205436 Sivextro (tedizolid phosphate) Injection

We also refer to the teleconference between representatives of your firm and the FDA on March 6, 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, call Carmen DeBellas, Regulatory Project Manager at (301) 796-1203.

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:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date: March 6, 2014

Application Number: **NDA 205435**
NDA 205436

Product Name: **Sivextro (tedizolid phosphate) Tablets**
Sivextro (tedizolid phosphate) Injection

Indication: **Acute Bacterial Skin and Skin Structure Infections**
Applicant Name: **Cubist Therapeutics, Inc.**

FDA ATTENDEES

Division of Anti-Infective Products and Office of Antimicrobial Products*

Dr. Sumathi Nambiar	Director
Dr. Katherine Laessig	Deputy Director
Dr. Shrimant Mishra	Cross-Discipline Team Leader
Dr. Sheral Patel	Clinical Reviewer
Dr. Benjamin Lorenz	Acting Clinical Team Leader
Dr. Margaret Gamalo	Statistical Reviewer
Dr. Thamban Valappil	Statistical Team Leader
Mr. David Roeder	Associate Director Regulatory Affairs*
Ms. Frances LeSane	Chief Project Manager
Ms. Mona Atkinson	Project Manger

APPLICANT ATTENDEES

Dr. Philippe Prokocimer	Chief Medical Officer
	(b) (4)
Dr. Carissa De Anda	Vice President, Clinical Research
Dr. Shawn Flanagan	Executive Director, Clinical Pharmacology
Dr. Mary Celine Scott	Senior Director, Regulatory Affairs
Dr. Janet Herrington	Global Head, Global Regulatory Affairs Primary Care, Bayer Healthcare
Mr. Michael Monahan	Director, Regulatory Affairs Strategy, Cubist Pharmaceuticals
Ms. Carol Waldo	Senior Director, Regulatory Affairs Strategy, Cubist

1.0 INTRODUCTION

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.

2.0 SIGNIFICANT ISSUES

No issues to report at this time.

3.0 INFORMATION REQUESTS

Safety: Submission of CRF TR701-104-001-025 is pending (clinical).
Meeting Discussion: The Applicant stated that the response would be submitted March 6, 2014.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have 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. A final determination on the need for a REMS will be made during the review of your application.

5.0 ADVISORY COMMITTEE MEETING

NDA 205435 and NDA 205436 will be taken to the Anti-Infective Drugs Advisory Committee on the morning of March 31, 2014. The Sponsor was asked to continue to work with Jennifer Shepherd, RPh, Designated Federal Officer for the Anti-Infective Drugs Advisory Committee, for specific details regarding deliverables and due dates.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

March 30, 2014: The Division will be conveying preliminary, proposed revisions to the product labeling to you electronically.

Reference ID: 3474937

Be advised that these revisions may be limited to a certain section (or sections) of the label in stepwise fashion, as reviews are ongoing and the outcome of the Advisory Committee Meeting may necessitate additional labeling discussion. 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).

March 14, 2014: Late Cycle Review Meeting. You may elect to have this meeting by teleconference or in person with the review team. We will provide a briefing document for this meeting to you electronically on or about March 10, 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 applicant's discretion), REMS or other risk management actions, potential PMRs/PMCs and major labeling issues (if applicable).

June 20, 2014: PDUFA goal date. The Sponsor asked if there might be an early action. The Agency replied that the NDAs were on schedule for a June 20, 2014 action date.

The Division confirmed with the Sponsor that the information conveyed at the meeting would be documented in meeting minutes. There were no further questions/clarifications.

Reference ID: 3474937

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/s/

SUMATHI NAMBIAR
03/21/2014

From: DeBellas, Carmen
Sent: Wednesday, March 19, 2014 11:07 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Information Request -Clinical Pharmacology

Hi Mary, Please find a request from our Clinical Pharmacology Group.

Clinical Pharmacology Information Request:
Please submit information on tedizolid sample stability in different matrices under short-term storage (bench top, room temperature) and freeze-thaw conditions as recommended in the FDA Guidance for Industry - Bioanalytical Method Validation (or provide the location, submission date/number, etc. if previously submitted).

Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
03/19/2014

From: DeBellas, Carmen
Sent: Tuesday, March 18, 2014 8:09 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Information Request Statistics

Hi Mary,

Please find another IR.

1. Please provide the responder rates of patients with at least one NSAID, steroids, antipyretics, or pain medications through the 48-72 Hour Visit and after the 48-72 hour visit through the EOT Visit at the ECE and EOT visits, respectively.
2. Please provide SAS code for the result.

   Can you respond to this one by the end of the week?

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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CARMEN L DEBELLAS
03/18/2014

From:DeBellas, Carmen
Sent:Friday, March 14, 2014 12:03 PM
To:'Mary Celine Scott'
Subject:RE: CMC IR Clarification Request

Hi Mary,

Please find Agency response. Carmen

No, the Agency does not agree with a NMT (b) (4) acceptance criterion for (b) (4) (versus NMT (b) (4)). Per ICH Q3A (revision 2, 2008), "Below 1.0 percent, the results should be reported to two decimal places (e.g., 0.06 percent, 0.13 percent); at and above 1.0 percent, the
results should be reported to one decimal place (e.g., 1.3 percent)". Please report all the
impurities per ICH and update both NDAs with the amended specification sheet.

From: Mary Celine Scott [mailto:MaryCeline.Scott@cubist.com]
Sent: Thursday, March 13, 2014 1:06 PM
To: Bhandari, Navdeep; DeBellas, Carmen
Subject: CMC IR Clarification Request
Importance: High

Good afternoon, gentlemen,

Our CMC team would like to ask for clarification on the following item from the 11 March 2014 OR:

Drug Substance
Specifications:
Revise the drug substance specification as follows and update both NDAs with the amended specification sheet
a. Tighten the acceptance criterion of (b) (4) at release and during stability.

We would appreciate clarification on the reviewer's request for a NMT (b) (4) acceptance criterion for (b) (4). Our current specified identified impurities are reported to one decimal place (e.g. NMT (b) (4)). (b) (4) is qualified at a level of (b) (4) in a 28-day rat intravenous toxicology study so the change from NMT (b) (4) to NMT (b) (4) should not be a safety concern.

Does Agency agree with a NMT (b) (4)% acceptance criterion for (b) (4) (versus NMT (b) (4))?

Thanks for your help!

Kind regards,

Mary

Mary Celine Scott, PhD, MBA
Senior Director, Regulatory Affairs
TRIUS THERAPEUTICS,
a CUBIST COMPANY
6310 Nancy Ridge Dr, Suite 105
San Diego, CA 92121

858 452-0370 X-312 (office)
858 452-0412 (fax)
(b) (6)
Please note new email: MaryCeline.Scott@Cubist.com

www.cubist.com

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CARMEN L DEBELLAS
03/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205435/205436 **INFORMATION REQUEST**

Trius Therapeutics, Inc.
Attention: Mary Celine Scott, Senior Director, Regulatory Affairs
6310 Nancy Ridge Drive
Suite 105
San Diego, CA 92121

Dear Ms. Scott:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sivextro® Tablets and Sivextro® 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 March 20, 2014, in order to continue our evaluation of your NDA.

1. **Drug Substance:**

Specifications:

Revise the drug substance specification as follows and update both NDAs with the amended specification sheet.

a. Tighten the acceptance criterion of Rx600024 to 0.20% at release and during stability.
b. Include a test and acceptance criterion for "Optical rotation" at release.

2. **Drug Product (Tablet):**

Manufacturing:

A complete description of the commercial scale drug product manufacturing process is required. Include all Critical Process Parameter and process parameter targets and ranges that are in the batch manufacturing instruction for the production of drug product provided. Also include the acceptance criteria for the in-process tests. We also noted that there is (b) (4) for Batch GNFG (b) (4) as compared to (b) (4) batch GNFH. Please explain.

3. Drug Product (Injection):

You have indicated that [redacted] (b) (4). Provide the amount of sodium hydroxide [redacted] (b) (4).

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
03/11/2014

From: DeBellas, Carmen
Sent: Tuesday, March 04, 2014 2:36 PM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Information Request

Hi Mary Celine,

Please find another Information request for NDAs 205435 & 436.

1.) Please submit the following CRFs:
    a. TR701-104-001-025
    b. TR701-112-115-453
    c. TR701-112-114-625

2.) Please provide a date when a response can be expected for the Information Request sent 2/14/2014 and 2/25/2014:
    ISS ADEX - Drug Exposure:
    a. Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADEX) used for 'Linezolid 13-16 doses, Linezolid 17-20 doses, Linezolid >20 doses' as illustrated in Table 11 of the ISS.
    b. Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADEX) used for 'Number of doses of active drug' as illustrated in Table 11 of the ISS.

3.) Please provide a date when a response can be expected for the Information Request sent 2/11/2014, 2/12/2014 and 2/25/2014:
    Snellen Visual Acuity: Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADSN) used for 'Worst Post Baseline, category change from baseline' as illustrated in Table 67 of the ISS.

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
03/04/2014

From:DeBellas, Carmen
Sent:Tuesday, February 25, 2014 3:06 PM
To:Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject:Tedizolid Information Request New

Hi,

Please find an information request below:

1.)Please provide details on the analyses used to develop Table 3 of the proposed label.
a.“Percent of patients who experienced at least one potentially clinically significant laboratory value.” Please provide the names of the specific variables and specific datasets used for the analyses.
b.“All values less than the lower limit of the normal range through the last dose of active drug in the pooled Phase 3 ABSSSI clinical trials.” Please provide the names of the specific variables and specific datasets used for the analyses.

2.)Please provide details on the analyses used to develop Table 41 “Incidence of abnormal ANC, hemoglobin values and platelet counts (all patients)” in the ISS. Please provide the names of the specific variables and specific datasets used for the analysis.

3.)Please submit CRF TR701-113-289-370.

4.)Please provide a date when a response can be expected for the Information Request sent 2/14/2014:
ISS ADEX - Drug Exposure:
a.Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADEX) used for ‘Linezolid 13-16 doses, Linezolid 17-20 doses, Linezolid >20 doses’ as illustrated in Table 11 of the ISS.
b.Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADEX) used for ‘Number of doses of active drug’ as illustrated in Table 11 of the ISS.

5.)Please provide a date when a response can be expected for the Information Request sent 2/11/2014 and 2/12/2014:
Snellen Visual Acuity: Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADSN) used for ‘Worst Post Baseline, category change from baseline’ as illustrated in Table 67 of the ISS.

Thanks,
Carmen

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/s/

CARMEN L DEBELLAS
02/25/2014

From:DeBellas, Carmen
Sent:Friday, February 14, 2014 1:43 PM
To:Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject:information request

Hi Mary Celine,

Please find a new information request.

1.)ISS ADEX - Drug Exposure:
a.Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADEX) used for 'Linezolid 13-16 doses, Linezolid 17-20 doses, Linezolid >20 doses' as illustrated in Table 11 of the ISS.
b.Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADEX) used for 'Number of doses of active drug' as illustrated in Table 11 of the ISS.

2.)ISS ADLB – Laboratory Results:
In addition to the prior requests regarding this dataset, please provide Baseline Value and Change from Baseline in US Conventional Units. Furthermore, any metric provided in SI Units, should also be submitted in US Conventional Units.

Request sent 1/24/2014.
We would like to confirm whether the ISS has laboratory results in US Conventional Units. We would like to request the inclusion of the laboratory results also in US Conventional units and Conventional Normal Range variables Upper Limit and Lower Limit in the ISS datasets. This would be consistent with the individual studies submitted. The individual studies, however use different dataset variables for the laboratory results in conventional units, and we would like this resolved in the ISS ADLB dataset.

Request sent 2/11/2014
a.Please provide us an update on when the revised ISS ADLB datasets will be submitted (Note: received 2/12/2014).
b.Also we request that the SAS Label for the Data Sets and variables are free of special characters. We appreciate, as is expected, useful simple descriptive text in the SAS Label fields – free of any special characters (including 'or ").
c.Please provide a list of normal laboratory ranges in Conventional Units used for safety analyses.

3.)CRF: Please provide the following CRF, or confirm if it has been previously submitted.
a.TR701-113-143-606

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
02/14/2014

A. Provide the following analysis to give a consistent measure of efficacy between the two trials:

    1. ECE at 48-72 hours (a composite endpoint of cessation of spread, **with/without** fever component, no rescue antibiotic medication, and death)

    2. ≥ 20% reduction in size of baseline lesion at 48-72 hours, with/without fever component, no rescue antibiotic medication, and death

    3. Sustained clinical response at EOT with clinical success as defined in the TR 701-113 protocol and with clinical success defined as

        a. complete resolution of all signs and symptoms (e.g. Purulent Drainage/Discharge, Erythema, Fluctuance, Heat/Localized Warmth, Swelling/induration, Pain, Tenderness to palpation)
        b. absence of systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal WBC count), if present at baseline
        c. no new signs, symptoms, or complications attributable to the ABSSSI so no further antibiotic therapy is required for the treatment of the primary lesion

    4. Investigator's assessment of clinical success at the PTE Visit in the ITT and CE-PTE Analysis Sets using definition of clinical success in the TR-701-113 protocol and with clinical success defined in #A-3.

B. Provide reason for patients considered failure or indeterminate at 48-72 hours (cessation and reduction but without fever component), EOT and PTE.

C. Provide concordance/discordance for the outcomes listed above at 48-72 hours, End-of-Therapy (EOT), and PTE visits, i.e, concordance/discordance between outcomes listed in #A-1, #A-3, #A-4 using both definitions of clinical success and concordance/discordance between outcomes listed in #A-2, #A-3, #A-4 using also both definitions of clinical success.

D. Provide concordance/discordance for ECE at 48-72 hours (as stated in #A-1 and #A-2) and Investigator assessment of Clinical Response at PTE defined as

    a. complete resolution of all signs and symptoms as defined in #A-3
    b. Residual lesion size compared to baseline not more than 5% or 10%).

E. Provide a list of patients who used additional systemic antibiotics from start of study drug to 48-72 hours, from start of study drug to EOT and from start of study drug to PTE (include the treatment arm, the systemic antibiotic(s) used and the relative study

day initiated, reason(s) for systemic antibiotics use, region, infection type, clinical outcome)

F. Provide a list of patients who had secondary infections sites and the outcome of these infections sites. Were their surface area added to the surface area of the primary anatomical site of infection?

It is possible that some of these analyses have been submitted in your original NDA submission. Our intent here is to look at the side by side comparison of TR 701-112 and 113 using a common efficacy endpoint. Furthermore, to facilitate future inquiry, please provide the streamlined dataset used for the analysis of the endpoints described above.

SAFETY

1.) **Laboratory (ISS ADLB) Dataset**: (Request sent 1/24/2014.)

We would like to confirm whether the ISS has laboratory results in US Conventional Units.

We would like to request the inclusion of the laboratory results also in US Conventional units and Conventional Normal Range variables Upper Limit and Lower Limit in the ISS datasets. This would be consistent with the individual studies submitted. The individual studies, however use different dataset variables for the laboratory results in conventional units, and we would like this resolved in the ISS ADLB dataset.

Addendum (02/10/2014)

a. Please provide us an update on when the revised ISS ADLB datasets will be submitted.

b. Also we request that the SAS Label for the Data Sets and variables are free of special characters. We appreciate, as is expected, useful simple descriptive text in the SAS Label fields – free of any special characters (including 'or ").

c.Please provide a list of normal laboratory ranges in Conventional Units used for safety analyses.

2.) **Snellen Visual Acuity**: *Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADSN) used for 'Worst Post Baseline, category change from baseline' as illustrated in Table 67 of the ISS.*

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/s/

CARMEN L DEBELLAS
02/12/2014

A. Provide the following analysis to give a consistent measure of efficacy between the two trials:

   1. ECE at 48-72 hours (a composite endpoint of cessation of spread, **with/without** fever component, no rescue antibiotic medication, and death)

   2. ≥ 20% reduction in size of baseline lesion at 48-72 hours, with/without fever component, no rescue antibiotic medication, and death

   3. Sustained clinical response at EOT with clinical success as defined in the TR 701-113 protocol and with clinical success defined as

      a. complete resolution of all signs and symptoms (e.g. Purulent Drainage/Discharge, Erythema, Fluctuance, Heat/Localized Warmth, Swelling/induration, Pain, Tenderness to palpation)
      b. absence of systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal WBC count), if present at baseline
      c. no new signs, symptoms, or complications attributable to the ABSSSI so no further antibiotic therapy is required for the treatment of the primary lesion

   4. Investigator's assessment of clinical success at the PTE Visit in the ITT and CE-PTE Analysis Sets using definition of clinical success in the TR-701-113 protocol and with clinical success defined in #A-3.

B. Provide reason for patients considered failure or indeterminate at 48-72 hours (cessation and reduction but without fever component), EOT and PTE.

C. Provide concordance/discordance for the outcomes listed above at 48-72 hours, End-of-Therapy (EOT), and PTE visits, i.e, concordance/discordance between outcomes listed in #A-1, #A-3, #A-4 using both definitions of clinical success and concordance/discordance between outcomes listed in #A-2, #A-3, #A-4 using also both definitions of clinical success.

D. Provide concordance/discordance for ECE at 48-72 hours (as stated in #A-1 and #A-2) and Investigator assessment of Clinical Response at PTE defined as

   a. complete resolution of all signs and symptoms as defined in #A-3
   b. Residual lesion size compared to baseline not more than 5% or 10%).

E. Provide a list of patients who used additional systemic antibiotics from start of study drug to 48-72 hours, from start of study drug to EOT and from start of study drug to PTE (include the treatment arm, the systemic antibiotic(s) used and the relative study

day initiated, reason(s) for systemic antibiotics use, region, infection type, clinical outcome)

F. Provide a list of patients who had secondary infections sites and the outcome of these infections sites. Were their surface area added to the surface area of the primary anatomical site of infection?

It is possible that some of these analyses have been submitted in your original NDA submission. Our intent here is to look at the side by side comparison of TR 701-112 and 113 using a common efficacy endpoint. Furthermore, to facilitate future inquiry, please provide the streamlined dataset used for the analysis of the endpoints described above.

SAFETY

1.) **Laboratory (ISS ADLB) Dataset**: (Request sent 1/24/2014.)

We would like to confirm whether the ISS has laboratory results in US Conventional Units.

We would like to request the inclusion of the laboratory results also in US Conventional units and Conventional Normal Range variables Upper Limit and Lower Limit in the ISS datasets. This would be consistent with the individual studies submitted. The individual studies, however use different dataset variables for the laboratory results in conventional units, and we would like this resolved in the ISS ADLB dataset.

Addendum (02/10/2014)

a. Please provide us an update on when the revised ISS ADLB datasets will be submitted.

b. Also we request that the SAS Label for the Data Sets and variables are free of special characters. We appreciate, as is expected, useful simple descriptive text in the SAS Label fields – free of any special characters (including 'or ").

c.Please provide a list of normal laboratory ranges in Conventional Units used for safety analyses.

2.) **Snellen Visual Acuity**: *Please provide the name and location of the variables in the ISS Analysis Dataset (ISS ADSN) used for 'Worst Post Baseline, category change from baseline' as illustrated in Table 67 of the ISS.*

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/s/

CARMEN L DEBELLAS
02/11/2014

From: DeBellas, Carmen
Sent: Wednesday, February 05, 2014 9:20 AM
To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: CMC question

Good morning,

Please find question from our CMC reviewer.

Could you please ask the applicant about the status of their 6 months additional stability data on Injection dosage form (NDA 205436). There was some agreement that they would submit the data during the review cycle.

Thanks,
Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
02/05/2014

From: DeBellas, Carmen
Sent: Monday, February 03, 2014 9:29 AM
To: Jennifer Grodberg (Jennifer.Grodberg@cubist.com); Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject: Information Request

Hi,

Reference is made to your letter dated January 14, 2014. In that letter you have described issues with 3 sites that have raised concerns during the auditing of TR701-112. Please provide the audit report for the audit that occurred [redacted] (b) (4) and the more focused audit report from [redacted] (b) (4)

Thanks,

Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
02/03/2014

From:DeBellas, Carmen
Sent:Friday, January 24, 2014 8:10 AM
To:Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject:Tedizolid information request

Hi Mary Celine,

Please find information request for tedizolid NDAs.

We would like to confirm whether the ISS has laboratory results in US Conventional Units.

We would like to request the inclusion of the laboratory results also in US Conventional units and Conventional Normal Range variables Upper Limit and Lower Limit in the ISS datasets. This would be consistent with the individual studies submitted. The individual studies, however use different dataset variables for the laboratory results in conventional units, and we would like this resolved in the ISS ADLB dataset.

In addition, we would like to know when we can expect the submission of ISS analysis datasets with the AUSUBJID variable as requested previously for ADEX, ADEG, ADPE.

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
01/24/2014

From:DeBellas, Carmen
Sent:Friday, January 24, 2014 12:27 PM
To:Mary Celine Scott (MaryCeline.Scott@cubist.com)
Subject:Response to IR request for comment

We have discussed this query with our team and have a few comments and requests for clarification:

We will resubmit the following ISS analysis datasets with the AUSUBJID variable as requested: ADEX, ADEG, ADPE.
This would be acceptable.

The AUSUBJID variable can also be added to all ISS tabulation datasets as requested, however, the addition of AUSUBJID to the SDTM tabulation datasets will cause validation errors. Would you like us to proceed with adding AUSUBJID despite the fact that this will create validation errors?
To preserve valid SDTM datasets we would like the value of the AUSUBJID variable to replace the USUBJID value so the USUBJID variable is truly a unique subject Identifier variable in BOTH tabulations and analysis datasets.

Also, would you like us to update the Define.pdf files associated with the updated analysis datasets and the Define.XML associated with the SDTM datasets?
An update of the Define.pdf's would be appreciated

Last, but not least, we would like to point out that the differences between USUBJID and AUSUBJID can be identified in ISS Listing 1.1.2 where AUSUBJID is identified in the column titled "Subject/Patient ID" and USUBJID can be identified in the column titled "Unique Subject/Patient ID".
This has been reviewed and is helpful.

We would be glad to arrange a brief teleconference with the stat teams, if that would be helpful. Thanks for your support!

Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
01/24/2014

To: Mary Celine Scott (MaryCeline.Scott@cubist.com)
Cc: Jennifer Grodberg (Jennifer.Grodberg@cubist.com)
Subject: Information Request

Hi Mary Celine & Jennifer,

I have a new information request:

Please resubmit the following ISS datasets with the AUSUBJID variable truly reflecting one record per subject.

1.) ISS Analysis datasets: ADEX, ADEG, ADPE
2.) All ISS Tabulation datasets

Per the submitted ISS Analysis define file pertaining to Datasets for TR-701 FA Integrated Safety:

AUSUBJID
Analysis Unique Subject ID
Character type

AUSUBJID
Derived by combining STUDYID and SITEID and SUBJID from DM

AUSUBJID=strip(STUDYID)||'-'||strip(SUBJID) if
SUBJID included both SUBJID and SITEID
Or AUSUBJID =strip(STUDYID)||'-
'||strip(SITEID)||'-'||strip(SUBJID);

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
01/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205435
NDA 205436

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Trius Therapeutics, Inc
Attention: Karen Potts, PhD
Senior Vice President, Regulatory Affairs
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121

Dear Dr. Potts:

Please refer to your New Drug Application (NDA) dated October 18, 2013, received October 21, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for NDA 205435 Tedizolid Phosphate Tablets and NDA 205436 Tedizolid Phosphate Injection.

We also refer to your amendments dated November 18 and 20, 2013.

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 June 20, 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 March 30, 2014.

In addition, the planned date for our internal mid-cycle review meeting is February 18, 2014. We are 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 request that you submit the following information:

1. Provide the protocol and the final report for qualification of the sterility test method (i.e. bacteriostasis/fungistasis) for release of the drug product.
2. Provide the protocol and the final report for the drug product specific qualification of the release assay for bacterial endotoxins. The report/data should identify the final dilution [redacted] (b) (4) that you have established for routine analysis. In addition, the report should also identify the three drug product lots used for the [redacted] (b) (4) studies as well as the results of those studies.
3. Provide a detailed summary of the qualification of the test method used for determining the [redacted] (b) (4) bioburden [redacted] (b) (4).

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.

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.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

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
12/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205436

METHODS VALIDATION MATERIALS RECEIVED

Trius Therapeutics, Inc.
Attention: Mary Celine Scott, Ph.D.; MBA
6310 Nancy Ridge Drive
Suite 105
San Diego, CA 92121

Dear Dr. Scott:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sivextro (tedizolid phosphate) for injection, 200 mg and to our November 20, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 16, 2013, 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
12/20/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 205435
NDA 205436

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Trius Therapeutics, Inc.
6310 Nancy Ridge Drive, Suite 105
San Diego, CA 92121

ATTENTION: Muriel Spooner
Director, Regulatory Affairs

Dear Ms. Spooner:

Please refer to your New Drug Applications (NDAs) dated October 18, 2013, and received October 21, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tedizolid Phosphate for Injection, 200 mg per vial and Tedizolid Phosphate Tablets, 200 mg.

We also refer to your correspondences dated December 4, 2013, received December 5, 2013, requesting review of your proposed proprietary name, Sivextro. We have completed our review of the proposed proprietary name Sivextro, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your December 4, 2013, submissions are altered, the names must 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 the Office of New Drugs (OND) Regulatory Project Manager, Carmen Debellas at (301) 796-1203.

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/

AZEEM D CHAUDHRY
12/19/2013

TODD D BRIDGES on behalf of KELLIE A TAYLOR
12/19/2013

From: DeBellas, Carmen
Sent: Sunday, December 08, 2013 5:04 PM
To: Jennifer Grodberg (jgrodberg@triusrx.com)
Subject: Information Request #5

Hi Jennifer,

Please find information request #5.

Please remove the single double quote from the SAS Label of every dataset that was recently re-submitted and then resubmit these revised datasets to the Agency. The double quote is causing a parsing error for our statistical review. If you wish, the SAS Label can have the single double quote replaced with an appropriate description of the dataset. Please note that the re-submitted datasets should not have any special characters in the SAS labels or variable names.

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
12/08/2013

From: DeBellas, Carmen
Sent: Monday, December 02, 2013 3:28 PM
To: Jennifer Grodberg (jgrodberg@triusrx.com)
Subject: Information Request #4

Hi Jennifer,

Please find the random CRF request discussed at the Pre-NDA meeting. Also, please provide the identifiers for CRF of patients who had a surgical procedure and indeterminates at EOT. The list attached is a complete list the bottom of the chart did not copy.

Table 4: Requested Random CRF

TR-112		TR-113	
103-277	101-263	103-019	289-493
105-391	103-657	103-035	289-640
240-666	129-336	105-165	291-447
101-429	130-371	143-116	292-503
130-249	135-395	143-159	292-570
103-193	101-481	146-419	292-629
129-128	126-090	160-243	296-366
175-293	103-012	160-516	297-291
105-196	128-224	162-344	298-172
103-231	120-591	165-478	298-299
105-421	102-082	286-565	358-500
255-572	104-117	289-235	441-358
130-538	242-617	289-265	449-602
105-324	130-089	289-269	450-266
105-265	105-510	289-304	450-448
105-291		289-371	450-461
		289-474	

Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
12/02/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205436

REQUEST FOR METHODS VALIDATION MATERIALS

Trius Therapeutics, Inc.
Attention: Mary Celine Scott, Ph.D.; MBA
6310 Nancy Ridge Drive
Suite 101
San Diego, CA 92121

Dear Dr. Mary Celine Scott:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sivextro (tedizolid phosphate) tablets, 200 mg.

We will be performing methods validation studies on tedizolid phosphate for injection, 200 mg, as described in NDA 205436.

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

Method, current version

AP-020 HPLC Method for identity, assay, related substances of Tedizolid Phosphate in Tedizolid Phosphate for injection
AP-022 HPLC Method for Chiral Purity of Tedizolid Phosphate in Tedizolid Phosphate for injection
AP-025 Analysis of reconstitution time

Samples and Reference Standards

60 vials of Tedizolid phosphate for injection, 200 mg

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: Sample Custodian
1114 Market Street, Room 1002
St. Louis, MO 63101

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
11/20/2013

From:DeBellas, Carmen
Sent:Thursday, November 14, 2013 3:04 PM
To:Jennifer Grodberg (jgrodberg@triusrx.com)
Subject:Tedizolid information request #3

Hi Jenny, Another Request. This one from Quality Microbiology people.

1. Provide the protocol and the final report for the qualification of the sterility test method (i.e., bacteriostasis/fungistasis) for the release of drug product.

2. Provide the protocol and the final report for the drug product specific qualification of the release assay for bacterial endotoxins. The report/data should identify [redacted] (b) (4) that you have established for routine analysis. In addition [redacted] ify the three drug product lots used for the [redacted] (b) (4) studies as well as the results of those studies.

3. Provide a d [redacted] y of the qua [redacted] used for determining the [redacted] (b) (4) bioburden [redacted] (b) (4).

Thanks,
Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
11/14/2013

From: DeBellas, Carmen
Sent: Tuesday, November 12, 2013 3:05 PM
To: Jennifer Grodberg (jgrodberg@triusrx.com)
Cc: kpotts@triusrx.com
Subject: Tediazolid NDAs - Information Request #2

Hi Jenny,

Please find information request number 2 for today.

We note that for Study 112 the Tabulation and Analysis datasets do not use similar nomenclature for unique subject identifiers. Specifically, the tabulation datasets have unique subject identifiers that concatenate the study identifier to the subject identifier while the analysis datasets only have the subject identifier (without any concatenation to the study identifier). For study 113, concatenation of both study and subject identifiers to create a unique subject identifies is present for both the tabulation and analysis datasets. As it currently stands, proper analyses of study 112 cannot be undertaken, and pooling of data from studies 112 and 113 cannot be performed. Please readjust the study 112 nomenclature for unique subject identifier so that they are the same for both the analysis and tabulation datasets and can be pooled with study 113. If there are any questions, please do not hesitate to email us.

Thanks,
Carmen

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/s/

CARMEN L DEBELLAS
11/12/2013

From:DeBellas, Carmen
Sent:Tuesday, November 12, 2013 9:19 AM
To:Jennifer Grodberg (jgrodberg@triusrx.com)
Subject:Tedizolid Question

Hi,

In the NDA submission there should be a rationale for assuming the applicability of foreign data to US population/practice of medicine. The reviewer states that he can usually find this statement/discussion in the Clinical Overview or Individual Study Reports. He has so far been unable to find it. Can you provide some direction to the location of such information?

Thanks,
Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
11/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205435
NDA 205436

NDA ACKNOWLEDGMENT

Trius Therapeutics, Inc.
Attention: Karen Potts, PhD
Senior Vice President, Regulatory Affairs
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121

Dear Dr. Potts:

We have received your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: NDA 205435 Tedizolid Phosphate Tablet
NDA 205436 Tedizolid Phosphate Intravenous

Date of Application: October 18, 2013

Date of Receipt: October 21, 2013

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on December 20, 2013, 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 numbers provided above should be cited at the top of the first page of all submissions to these applications. 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, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CARMEN L DEBELLAS
10/31/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77872
IND 106307

MEETING MINUTES

Trius Therapeutics, Inc.
Attention: Jennifer Grodberg, PhD, RAC
Senior Regulatory Affairs
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121

Dear Dr. Grodberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tedizolid Phosphate Oral Tablets and Intravenous formulations.

We also refer to the meeting between representatives of your firm and the FDA on May 13, 2013. The purpose of the meeting was to discuss your NDA submission.

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 Carmen DeBellas, Regulatory Project Manager at (301) 796-1203.

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: Type B
Meeting Category: Pre-NDA

Meeting Date May 13, 2013

Application Number: IND 77872 & IND 106307
Product Name: Tedizolid Phosphate Oral Tablets and Intravenous Formulation
Indication: Acute Bacterial Skin and Skin Structure Infections
Sponsor/Applicant Name: Trius Therapeutics, Inc.

FDA ATTENDEES

Office of Antimicrobial Products

Dr. Edward Cox	Office Director
Mr. David Roeder	Associate Director Regulatory Affairs

Division of Anti-Infective Products

Dr. John Farley	Acting Director
Dr. Dorota Matecka	Product Assessment Leader
Dr. George Lunn	Chemistry, Manufacturing and Controls Reviewer
Dr. Sheral Patel	Clinical Reviewer
Dr. Yan (Grace) Zhixia	Clinical Pharmacology Reviewer
Dr. Seong Jang	Acting Team Leader Clinical Pharmacology
Dr. James Wild	Pharmacology/Toxicology Reviewer
Dr. Avery Goodwin	Clinical Microbiology Reviewer
Dr. Aleksander Winiarski	Safety Evaluator, Division of Medical Errors Prevention and Analysis
Dr. Sumathi Nambiar	Deputy Director for Safety
Dr. Katherine Laessig	Deputy Director
Dr. Eileen Navarro	Clinical Team Leader
Dr. Meg Gamalo	Statistical Reviewer
Dr. Alma Davidson	Clinical Reviewer
Dr. Thamban Valappil	Statistical Team Leader
Dr. Shrimant Mishra	Clinical Reviewer
Ms. Naseya Minor	Regulatory Project Manager
Dr. Carmen DeBellas	Regulatory Project Manager
Ms. Kimberly Taylor	Operations Research Analyst

By Phone

Dr. Wendelyn Schmidt	Pharmacology/Toxicology Team Leader
Dr. Kassa Ayalew	Office of Scientific Investigations
Dr. Ronald Wassel	Office of Surveillance and Epidemiology
Dr. Jamie Wilkins Parker	Office of Surveillance and Epidemiology

Reference ID: 3317728

EASTERN RESEARCH GROUP ATTENDEES

Mr. Christopher Sese	Contractor

SPONSOR ATTENDEES
Trius Therapeutics, Inc.

Dr. Karen Potts	Senior Vice President, Regulatory Affairs
Ms. Muriel Spooner	RAC, Director, Regulatory Affairs
Dr. Philippe Prokocimer	Chief Medical Officer
Dr. Ken Bartizal	Chief Development Officer
Dr. Jeff Barker	Vice President, Pharmaceutical Sciences
Dr. Shawn Flanagan	Executive Director, Clinical Pharmacology
(b) (4)	Regulatory Affairs (Consultant)
(b) (4)	
Dr. Janet Herrington	Global Regulatory Affairs, Bayer

By Phone

Dr. Mary Celine Scott	Senior Director, Regulatory Affairs
Mr. Paul Bien	Executive Director, Project Management
Ms. Robin Weaver	Director, Clinical Communication
(b) (4)	Pharmacovigilance Consultant
	Clinical Data Consultant, (b) (4)
	CMC Consultant

1.0 BACKGROUND

The Sponsor requested this Type B, Pre-NDA meeting to address the following

1. To review top-line data for study TR-701-113 entitled "A Phase 3 Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of Intravenous to Oral 6-Day TR-701 Free Acid and Intravenous to Oral 10-Day Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections."
2. Gain Agency agreement that the safety and efficacy data from Studies TR701-112 and TR701-113 support filing NDAs for oral and IV formulations for the proposed indication of treatment of ABSSSI. Obtain Agency feedback on several technical issues/questions on the planned NDA submissions, as outlined below.
3. Initiate preliminary discussions on the product profile, as reflected in the proposed package insert (USPI), and on potential post marketing commitments for the NDA.
4. Discuss milestones for the NDA review based on the PDUFA V ("The Program Review") Model including mid-cycle communication, late-cycle meeting and advisory committee meeting.

Reference ID: 3317728

2. DISCUSSION

The Sponsor received Agency responses to the meeting background package questions prior to the meeting. The meeting discussion consisted of clarifications concerning questions 1, 4, 5, 20 and an additional ISS clarification. The Sponsor also reviewed key highlights from the Phase 3 study, nonclinical and clinical studies that addressed the potential targeted safety issues.

Question 1: Does FDA agree that the overall clinical development, as presented herein, including the results from registration Studies TR-701-112 and TR701-113 support filing NDAs for both oral and IV formulations of TR701-FA for the treatment of ABSSSI?

Agency Response: The overall clinical development, as presented in the briefing package, appears sufficient to support an NDA filing for both oral and IV formulations of TR-701 FA for the treatment of ABSSSI.

We have the following additional comments/requests that can be addressed in the NDA dossier:

- We note that the minimum surface area of lesions included in the wound category is 22.5 cm in the tedizolid arm. Describe the distribution of the surface area of the lesion size by infection type and by outcome in both study arms through frequency tables. You may explore cutoffs for the class intervals that will yield meaningful interpretation.

Meeting Discussion:

The Sponsor acknowledged that the patient mentioned in the response was a protocol violation and that 24 patients in the Phase 3 studies had a minimum surface area lesion <75cm^2. The Agency asked how these patients were distributed between treatment arms. The Sponsor replied that 1 patient was in Study 113 and that the rest were in Study 112 and were evenly distributed among the treatment arms.

The Sponsor added that the ISE will include analyses of early clinical response at 48-72 hours and the investigator assessment at PTE by lesion area with cut-offs as follows: ≤150, >150-300, >300-600,>600-1000 and >1000 cm^2. The Agency requested that analysis be performed using additional cut-offs at <75, and 75 to 150 cm^2.

The Sponsor stated that an analysis of efficacy outcomes by both lesion area and infection type will be included where sufficient numbers exist in the subgroups.

- Reasons for Exclusion from Analysis Sets for both Study 112 and 113: CE-PTE EOT and CE-PTE under Reasons for Exclusion- Confounding surgical procedure, please identify these patients with ABSSSI and type and timing of surgery performed for both tedizolid and linezolid treatment groups.

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Meeting Discussion:
The Sponsor responded that these data will be provided as line listing and summary tables in the CSRs for study 112 and 113. They added that a line listing for the type of surgery will be provided in the ISE. In addition, the Agency requested the eCRFs of these patients.

Question 4: Does FDA agree with the Sponsor's proposed format of the CRFs in the NDA and that CRFs and narratives for only deaths, SAEs and withdrawals due to AE will be included?

Agency Response: Please submit eCRFs for the following patients:

- patients in the ITT analysis found to have an indeterminate response due to missing data
- all patients excluded from the CE-EOT and CE PTE analysis sets for the following reasons (described in Table 3 page 22 of your backgrounder): Missing data did have response assessment, did not receive minimum dose amount and met unspecified disqualifying exclusion criteria in Study 113.

Additional CRFs may be requested from Study 112 and 113 upon initial review of your NDA submission.

Meeting Discussion:
The Sponsor agreed to provide CRFs for patients with indeterminate response for the primary endpoint (early clinical response at 48-72 hours). The Sponsor asked if the Agency wanted CRFs for patients with an indeterminate response for the Investigator assessment of response at EOT and PTE? The Sponsor stated that CE-EOT is defined based in the programmatic determination of clinical response at EOT and they agreed to provide CRFs for patients who had missing data for this response assessment, did not receive the minimum dose amount and who met disqualifying exclusion criteria. The Sponsor added that CE-PTE is defined based on the Investigators assessment of clinical response at PTE and agreed to provide CRFs for patients who had missing data for this response assessment, did not receive the minimum dose amount and who met disqualifying exclusion criteria.

The Agency replied to submit assessment of clinical response at EOT and PTE for evaluating consistency of the results and also stated that the ITT analysis should include all randomized patients without any post-randomization exclusion.

Question 5: Does FDA agree with the Sponsor's proposed plans for the Clinical Study Datasets as outlined in Appendix 7?

Agency Response: Please provide the study tabulations datasets in CDISC SDTM format. Please also provide the analysis sets in CDISC ADaM with accompanying SAS codes for the creation of ADaM datasets for the primary efficacy and key secondary analyses for the individual studies and for any integrated analyses across studies. For purposes of trial site inspections and assessment of drug-induced liver injury, we also request specific data

Reference ID: 3317728

be submitted in additional formats (see attached OSI-pre-NDA request information and eDish data requirements).

Meeting Discussion:
The Sponsor responded that all clinical datasets in the NDA will be in CDISC SDTM format. The analysis set formats will be as follows:

- **Phase 2 Study 126, Phase 3 Study 113 and the ISS will be in CDISC ADaM**
- **Phase 1 studies that have analysis datasets, Phase 2 Study 104, Phase 3 Study 112, the ISE, and ISM will be in SDS version 1.6**

The Sponsor explained that even if Study 112 datasets were written in SDS version 1.6, they generally follow the ADaM structure and format. They added that a Define.pdf file will clearly indicate how the variables were programmed from source data. This will ensure full traceability from the CRFs> source data set>analysis datasets>TFLs>CSRs.

The Sponsor also stated that they will provide programs for the creation of SDS or AdaM datasets from their source files. Another set of programs used for the primary efficacy and key secondary analyses results will be provided as well. These will all be written in ASCII format. The Sponsor will also submit information in accordance with the FDA guidance (Dec2012) for OSI and the eDish data requirements.

Question 20: Does the FDA agree that it is acceptable for Module 2. 7 Clinical Summary to exceed the recommended size?

Agency Response: The FDA prefers that Module 2.7 Clinical Summary should not exceed the recommended size. Other clinical information that cannot be included into this module should be included in the ISE and ISS module.

Meeting Discussion:
The Sponsor stated that in accordance with ICH guidance M4E for the common components of Section 2.7 shared across all therapeutic areas, the recommended size of 400 pages is maintained. The guidance allows for a greater number of pages when circumstances require it, such as where multiple indications are included. The ICH M4E questions and answers (R4) specifies that in the case of microbiology data, summary information for microbiology data should be provided in the appropriate section 2.7 Clinical summary and individual reports in 5.3.5.4. Per FDA draft guidance "Microbiological Data for Systemic Antibacterial Drug Products-Development, Analysis and Presentation" (2009). Sponsors are directed to place summary microbiology data in Section 2.7.2.4. The Sponsor proposes to include microbiological data within Section 2.7.2.4 in accordance with FDA and ICH guidance resulting in Module 2.7 with an estimated size of 600-700 pages. Is this acceptable to the Agency?
The Agency found this to be acceptable.

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Additional Clarification of ISS: The Sponsor stated that all adverse events in the Safety Analysis Set of the ISS were recorded to the same MedDRA Version (13.1)

- Phase 1 studies
- Phase 2 studies
- Phase 3 studies : these were originally coded in V13.1

The Sponsor also stated that there may be slight differences in the preferred terms between the Phase 3 CSRs and the ISS and a list indicating any differences in preferred terms for all studies will be provided in the reviewers guide.

Meeting Discussion: Establish -1 and Establish-2 Efficacy and Safety Data
The Sponsor provided slides showing top-line data from the aforementioned trials. The Sponsor presented key demographic data for both trials. Also presented were slides containing information for US and European efficacy endpoints, as well as microbiologic response data (MITT). Slides were presented containing overall safety information, as well as, slides specifically discussing hematologic effects, mitochondrial toxicity, optic and peripheral neuropathy. In conclusion, slides were shown containing data concerning the less likelihood of inhibition of monoamine oxidase inhibition. (for more information see attached slides).

3. DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. As the Sponsor stated that they intend to submit a complete application there are no agreements for late submission of application components.

4. 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then: if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application

Reference ID: 3317728

as was required under the Food and Drug Administration Amendments Act (FDAAA). if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

5. 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 following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

6. MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Reference ID: 3317728

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's meeting slides.

28 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 3317728

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/s/

JOHN J FARLEY
06/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 77,872 **MEETING MINUTES**

Trius Therapeutics
Attention: Jennifer Grodberg, PhD, RAC
Director, Regulatory Affairs
6310 Nancy Ridge Drive, Suite 101
San Diego, California 92121

Dear Dr. Grodberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TR-701 (torezolid phosphate).

We also refer to the End of Phase 2 meeting between representatives of your firm and the Division of Anti-Infective and Ophthalmology Products on October 19, 2009. The purpose of the meeting was to discuss aspects of your product development project.

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

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely yours,

{See appended electronic signature page}

Wiley Chambers, M.D.
Acting Division Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes
Trius's October 16, 2009 responses to Division's comments

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2 meeting
Meeting Date and Time:	October 19, 2009, 3:00 PM – 4:00 PM (EST)
Meeting Location:	Food and Drug Administration 10903 New Hampshire Ave, Building #22, Room 1313 Silver Spring, MD 20993
Application Number:	IND 77,872
Product Name:	TR-701 (torezolid phosphate)
Indication:	Treatment of acute bacterial skin structure infections
Sponsor/Applicant Name:	Trius Therapeutics, Inc.
Meeting Chair:	Wiley Chambers, MD
Meeting Recorder:	Kyong Hyon

FDA ATTENDEES: (FDA)

Division of Anti-Infective and Ophthalmology Products (DAIOP)

Wiley Chambers, MD, Acting Division Director
Sumathi Nambiar, MD, MPH, Deputy Director for Safety
Janice Pohlman, MD, MPH, Clinical Team Leader
Alma Davidson, MD, Clinical Reviewer
Wendelyn Schmidt, PhD, Pharmacology/Toxicology Team Leader
Maria Rivera, PhD, Pharmacology/Toxicology Reviewer
Thamban Valappil, PhD, Statistical Team Leader
Mark Gamalo, PhD, Statistical Reviewer
Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
Aryun Kim, PharmD, Clinical Pharmacology Reviewer
Frederic Marsik, PhD, Clinical Microbiology Team Leader
George Lunn, PhD, Chemistry Reviewer, Branch IV, ONDQA
Kyong Hyon, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES: (Sponsor)

Trius Therapeutics, Inc.

Alison Portnoy, MD, Director, Anti-Infectives Discovery Medicine
Scott White, MD, Director, Anti-Infectives Clinical Development
Cindy Fishman, VMD, PhD, DACVP, Director, Pathology, Safety Assessment
Beth Romach, PhD, DABT, Director, Projects, Safety Assessment
Kitaw Negash, PhD, Investigator, Preclinical DMPK
Mike Gwynn, MS, Director, Microbiology
Richard Phillips, Group Director, CEDD Regulatory Affairs

BACKGROUND: On August 5, 2009, Trius Therapeutics, Inc. (Trius) requested an End of Phase 2 meeting with DAIOP to discuss: 1) key nonclinical and clinical Phase 2 results; 2) the Target Product Profile; 3) product development plans. The face-to-face meeting was granted on August 20, 2009 and scheduled to occur on October 19, 2009. The meeting package (MP) was submitted on September 16, 2009. In addition to the meeting package, Trius submitted clarification information to its MP on October 9, 2009 via e-mail and followed by a formal submission. The Division sent preliminary written response to Trius's questions from the meeting package on October 16, 2009 via e-mail; Trius sent additional clarification to Question #1 of the Division's comment on October 16, 2009 via e-mail (appended). The questions from MP are in bold followed by the Division's October 16, 2009 comments and points discussed during the face-to-face meeting.

SUMMARY OF DISCUSSION:

The meeting started with the introduction of the attendees and a brief description of the purpose of the meeting followed by discussion in the order of the questions listed in MP.

Clinical

Question 1. Phase 3 Dose Selection: Does the FDA agree that the Phase 1 and Phase 2 clinical data, along with the clinical and nonclinical PK/PD investigations provided in this briefing package, support the selection of torezolid phosphate at 200 mg QD dose, over 7 days of therapy, for the conduct of ABSSI Phase 3 studies?

Division Response (per October 16, 2009 e-mail): The summary Phase 2 clinical study data along with the non-clinical PK/PD data support the use of the 200 mg dose of torezolid phosphate for the ABSSI Phase 3 study. However, based on results of the non-clinical pharmacology/toxicology studies, the Division has safety concerns regarding the potential visual effects of torezolid phosphate. The Division strongly recommends the following ophthalmologic examinations be performed on a subpopulation of Phase 3 study patients (at least 60 patients) at baseline, end of therapy (2-3 days after the last dose of study medication), and late follow-up examination for patients at 3 months:

- Optical Coherence Tomography (OCT)
- Best corrected distance visual acuity
- Dilated fundoscopy
- Color Vision: Farnsworth-Munsell 28, 40, or 100 hue tests for color vision testing are recommended since these tests discriminate well between congenital and acquired defects.
- Slit lamp examination
- Humphrey Visual Field (24-2)
- Optic Nerve Photograph

Discussion at the October 19, 2009 face-to-face meeting

- The Division commented that ocular AEs were listed in the clinical study report (CSR) for the Phase 1 study, TR701-101, but the actual line listings including those for the ophthalmologic data or case report forms (CRFs) were not included. Therefore, the Division requested Trius submit CRFs for 24 subjects from the Phase 1 study. Trius agreed to submit the requested information.

- Trius requested a clarification on the Division's written comments regarding the nonclinical study results causing concern for potential visual effects of torezolid phosphate. The Division stated that there might be the potential for retinal effect because the non-clinical pharmacokinetic data (not nonclinical pharmacology/toxicology investigations as stated in written comments) showed the accumulation of the drug product in the uveal tract and long retention in the eyes of pigmented rats. It is a concern that needs to be evaluated. Trius stated that the accumulation of torezolid was seen only in pigmented tissues (melanin containing), but not in nerve tissues.

- The Division restated that these ophthalmologic assessments should be performed on a subpopulation of at least 60 patients. Phase 3 study patients at baseline, end of therapy (2-3 days after the last dose of study medication), and late follow-up examination for patients at 3 months could be considered, although testing could be done in conjunction with another Phase 1 multiple dose study (such as thorough ECG study). Whether the 24 patients mentioned in the first bullet could contribute to the 60 required patients depends upon the actual data collected (based on a sample CRF, this is unlikely).

Question 2. Projected Safety Population for NDA: The entire safety database is anticipated to include approximately 1221 subjects/patients. Does the Agency agree that the approximate size of the safety database is adequate to approve the drug in ABSSI, with the understanding that we would be providing additional safety information from other patient studies (e.g., additional indication) to supplement the database by approximately 200-400 patients at marketed dose in the NDA filing?

Division Response (per October 16, 2009 e-mail): Absent an unexpected safety signal, a safety database of this size is acceptable.

Discussion at the October 19, 2009 face-to-face meeting: No further discussion was needed.

Question 3. Additional Phase 1 Studies, including Special Population Studies:

- **TR701-106: ADME Study**

Because of the low renal clearance observed in these initial studies, Trius proposes to initiate the oral and IV ADME study at the same time as the first Phase 3 trial. Does the Agency agree with this approach?

Division Response (per October 16, 2009 e-mail): The approach is acceptable. A mass balance study for both PO and IV formulations is not necessary. We also note that renal and hepatic impairment studies are planned to occur concurrently with Phase 3 studies. We strongly recommend performing pharmacokinetic studies in special populations prior to Phase 3 trials to allow enrollment of such subjects (with any dosage adjustments that may be necessary) and obtain pertinent safety and efficacy data.

Discussion at the October 19, 2009 face-to-face meeting: The Division recommended conducting renal and hepatic impairment studies early, to allow adequate time for pharmacokinetic analysis and subsequent enrollment of such special populations into Phase 3 trials in order to support safety and efficacy considerations in these patient groups. Trius agreed to conduct special population studies as early as possible, and indicated their clinical development timeline was updated so that renal and hepatic impairment studies will now start and be conducted in parallel with Phase 3. Trius also stated Phase 3 trials will be staggered to facilitate enrollment of patients with renal or hepatic impairment midway into Phase 3, following completion of the special population studies. Trius indicated Phase 3 protocols currently exclude patients with creatinine clearance <30 mL/min or Child-Pugh Class B and C scores. Lastly, the Division recommended Trius to conduct a full renal impairment study for proper characterization of torezolid phosphate in mild, moderate, and severe renal impairment. Although torezolid phosphate may not be predominantly renally eliminated, the Division stated hepatic function may also be compromised in the presence of renal impairment and made reference to past experiences where renal-adjusted dosing was found to be necessary for compounds with minimal renal excretion.

Provided that the human ADME study confirms the low level of renal excretion, does the Agency agree that an elderly PK study will not be necessary?

Division Response (per October 16, 2009 e-mail): Regardless of the level of renal excretion, the pharmacokinetics in elderly subjects should be evaluated. In lieu of a dedicated Phase 1 study, you may consider sparse sampling of patients, including elderly subjects, in Phase 3 trials for population pharmacokinetic analysis with evaluation of covariates such as age.

Discussion at the October 19, 2009 face-to-face meeting: Trius agreed with the Division's recommendation and therefore, no further discussion was needed.

- **TR701-115: Thorough QTc (TQT) Study**

In the absence of a thorough QT study performed by the time of initiation of the Phase 3 pivotal trials, the Agency has requested (Reviewers' comments (dated September 02, 2009) additional ECG monitoring to be performed in patients. Trius proposes to perform the TQT study early during the Phase 3 trials. Provided the TQT study shows no arrhythmogenic potential, does the Agency agree that the additional ECG monitoring can be discontinued after Agency review of a draft TQT study report together with ECG data from approximately 100 patients from the Phase 3 oral study TR701-112?

Division Response (per October 16, 2009 e-mail): We strongly recommend that the TQT study be performed prior to initiation of the Phase 3 studies for early detection of any arrhythmogenic potential of torezolid phosphate. However, your proposal to perform the TQT study early during Phase 3 trials with subsequent decrease in the intensity (frequency) of ECG monitoring is acceptable, if the study protocol has been designed in accordance with ICH E14 and reviewed and found acceptable by the FDA interdisciplinary QT team, no arrhythmogenic potential is noted, and a draft TQT study report is reviewed by the Division.

Discussion at the October 19, 2009 face-to-face meeting: Trius agreed with the Division's recommendation and therefore, no further discussion was needed.

Question 4. Proposed Pediatric Plan: Recognizing all the details of a complete plan have yet to be finalized, are the number and types of studies and the defined pediatric populations identified in the briefing package (including adolescents as part of the initial NDA filing) acceptable?

Division Response (per October 16, 2009 e-mail): No. We recommend that you submit a synopsis of the pediatric plan for both IV and PO formulations in pediatric populations (including those <12 years of age to infants and toddlers, ages 28 days to 2 years) and neonates (term and pre-term). Based on the safety and efficacy results of the initial Phase 3 study in adults and adolescents, pediatric studies in other age groups could be initiated. Submit a timeline for the pediatric plan.

Additionally, we recommend increasing the sample size for the proposed single-dose pharmacokinetic studies to ensure there are a sufficient number of subjects receiving the PO or IV formulation for each of the pediatric populations.

Discussion at the October 19, 2009 face-to-face meeting: Trius agreed to submit a full pediatric plan including a timeline as recommend by the Division and asked if 10 subjects in the oral group and 10 subjects in the intravenous group would be acceptable for each study. The Division recommended enrolling a sufficient number of patients to ensure 10 evaluable subjects in the oral and intravenous groups (i.e., a total of 20 evaluable patients in each age group).

Nonclinical

Question 5. Proposed Photo Irritation Toxicology Study: Both torezolid and TR-701 have been found to absorb ultraviolet/visible radiation and torezolid has been shown to partition in eye solids in rats and dogs. In accordance with FDA's guidance on photo-safety testing, Trius plans to conduct a short-term photochemical irritation study in an appropriate and sensitive animal model after acute drug exposure (followed by simulated sunlight exposure), concurrent to initiation of Phase 3 ABSSI studies.

Does the Agency agree with this proposal?

Division Response (per October 16, 2009 e-mail): Agree. Precautions should be taken to protect the subjects from exposure to sunlight.

Discussion at the October 19, 2009 face-to-face meeting: Trius agreed with the Division's recommendation and therefore, no further discussion was needed.

<u>Question 6. Proposed Neuropathy Toxicology Study</u>: Trius intends to investigate the potential for torezolid phosphate to produce neuropathies in chronic (3 month) animal toxicity studies in 2 species in parallel with Phase 3 ABSSI studies. Peripheral/sciatic and optic nerve damage will be monitored (including histopathology), as recommended by the Agency in correspondence from the 30-day, safety review of our initial IND 77,872 application. Comments and recommendations as follows:

PHARMACOLOGY/TOXICOLOGY: " Based on findings for Zyvox® (linezolid), we suggest to carefully monitor for peripheral/sciatic and optic nerve damage in future chronic toxicology studies."

Based on the results of the proposed neuropathy toxicology studies, does the Agency agree that these 2 studies would adequately address concerns of drug-induced neuropathy?

<u>Division Response (per October 16, 2009 e-mail)</u>: Based on the experience with linezolid, study duration of 3 months may not be long enough for the development of neuropathies. The duration of the studies should be increased to at least 6 months in the rodent and 9 months in the non-rodent species.

<u>Discussion at the October 19, 2009 face-to-face meeting</u>: Trius agreed to conduct a 6 month study in rats and a 9 month study in dogs to monitor peripheral/sciatic and optic nerve damage separately from the 3 month chronic toxicity studies to support registration. Furthermore, Trius stated that they plan to submit neuropathy toxicology study protocols to obtain the Division's comments and asked if they can perform the assessments only at the 6 month time point in rats and 9 month time points in dogs. Trius inquired about the possibility of using only the rat. The Division recommended the use of both species in the event no findings are observed in the rat. The Division agreed with Trius' assessment time points, using two species and requested the protocol be submitted at least one month prior to initiation of the study. The Division recommended the use of pigmented rats rather than non-pigmented.

Overall Development

<u>Question 7. Target Product Profile Update</u>: The Target Product Profile for torezolid phosphate has been updated based upon information obtained to date from the development of torezolid phosphate, with the key revisions identified below:

- **Indication and clinical studies updated to reflect proposed Phase 3 protocol**
- **Dose selection of torezolid phosphate 200 mg orally administered once daily for ABSSI based on completed Phase 2 study and PK/PD simulations**
- **Hematological effects subsection revised based on the proposed treatment dose (200 mg) to note projected risk versus comparator**
- **Pharmacodynamics section revised include new in vivo bactericidal activity reported in nonclinical pharmacodynamic studies**

Recognizing that sections will be updated based upon the results from Phase 3 and special population studies yet to be conducted, does the Agency have any other comments on the studies to support the proposed Target Product Profile and related anticipated label claims being sought?

<u>Division Response (per October 16, 2009 e-mail)</u>: Many sections contained within the Target Product Profile contain information subject to change during labeling discussions. For example, data from Phase 2 clinical trials is generally not included in the clinical studies section.

<u>Discussion at the October 19, 2009 face-to-face meeting</u>: Trius asked the Division about specific aspects of the Phase 3 study designs; 1) the appropriate timing of the test-of-cure assessment and 2) the definition of clinical success in order to prepare their Special Protocol Assessment submission. The Division stated that they could not provide an answer to these specifics at this time because there is no internal consensus yet and encouraged Trius to submit a SPA for review.

October 19, 2009 End of Phase 2 Meeting

Trius Clarification to FDA's Question 1 Response

Question 1. Phase 3 Dose Selection

Does the FDA agree that the Phase 1 and Phase 2 clinical data, along with the clinical and nonclinical PK/PD investigations provided in this briefing package, support the selection of torezolid phosphate at 200 mg QD dose, over 7 days of therapy, for the conduct of ABSSI Phase 3 studies?

Division Response:

The summary Phase 2 clinical study data along with the non-clinical PK/PD data support the use of the 200 mg dose of torezolid phosphate for the ABSSI Phase 3 study. However, based on the results of the non-clinical pharmacology/toxicology studies, the Division has safety concerns regarding the potential visual effects of torezolid phosphate. The division strongly recommends the following ophthalmologic examinations be performed on a subpopulation of Phase 3 study patients (at least 60 patients) at baseline, end of therapy (2-3 days after last dose of study medication), and late follow-up examination for patients at 3 months.

Trius Response:

In response to the Division's recommendation in correspondence dated Feburary 5, 2008,), Trius amended the clinical protocol for the Phase 1 single-ascending dose/multiple-ascending dose study (TR701-101 Amendment 2, Serial 0003) , TR701-101, to include the following ophthalmologic examinations in the multiple-ascending dose portion of the study:

- Dilated slit lamp biomicroscopy
- Dilated ophthalmoscopy
- Visual acuity (Snellen eye chart)
- Non-dilated ophthalmoscope examination of optic fundi
- Slit lamp examination
- Humphrey visual field (24-2)
- Optic and retinal nerve photography
- Color vision (Roth 28-color disc vision test)

In the multiple-ascending dose (200, 300, 400 mg QD for 21 days) portion of the study, these ophthalmologic examinations were performed prior to study enrollment (Check-in on Day-1) and within 3 days of Clinical Discharge (Days 21-24). The number of subjects randomized to each

dosing arm was as follows: 8 subjects each dose TR-701 for a total of 24 subjects, 8 subjects linezolid, and 8 subjects placebo. The results detailed in the TR701-101 clinical study report (Serial 0036) revealed no changes in test measurements from baseline to Clinic discharge for any subject with the exception of the visual field test measurement for Subject No. 55 (200 mg TR-701). The Clinic Discharge visual field for Subject No. 055 revealed bitemporal visual field defects. The subject did not report any related symptoms and these visual field changes were felt to be incidental findings most likely due to daily variation in visual testing rather than a change from baseline. The visual field findings were not considered related to the study drug. Routine follow-up with an appropriate specialist was recommended.

In light of the absence of any clinical findings insubjects exposed for 21 days with up to 400 mg TR-701, together with the planned short duration of dosing (6 days 200 mg torezolid phosphate) in the oral Phase 3 study, Trius believes that additional ophthalmologic examination of patients in the oral Phase 3 study is not warranted. Furthermore, the conduct of such examinations even on a subset of patients would be logistically difficult for this patient population since the patients in the oral Phase 3 trial will be primarily outpatients coming from emergency room and primary care centers that are not equipped to perform such evaluations. Similarly, the outpatient nature of this patient population inherently makes a 3 month follow up logistically challenging.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77872	GI-1	TRIUS THERAPEUTICS INC	TR 701

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/s/

WILEY A CHAMBERS
11/13/2009

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205435
NDA 205436

LATE-CYCLE MEETING MINUTES

Cubist Pharmaceuticals, Inc.
Attention: Mary Celine Scott, PhD, MBA
Senior Director, Regulatory Affairs
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121

Dear Dr. Scott:

Please refer to your New Drug Applications (NDAs) dated October 18, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

NDA 205435 Sivextro (tedizolid phosphate) Tablets
NDA 205436 Sivextro (tedizolid phosphate) Injection

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on March 14, 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 Carmen DeBellas, Regulatory Project Manager at (301) 796-1203.

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 Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date: March 14, 2014

Application Number: NDA 205435
NDA 205436

Product Name: Sivextro (tedizolid phosphate) Tablets
Sivextro (tedizolid phosphate) Injection

Applicant Name: Cubist Pharmaceuticals, Inc.

Proposed Indication: Acute Bacterial Skin and Skin Structure Infections

PDUFA goal date: June 21, 2014

FDA ATTENDEES

Office of Antimicrobial Products

Dr. Edward Cox	Director
Dr. John Farley	Deputy Director
Mr. David Roeder	Associate Director

Division of Anti-Infective Products

Dr. Sumathi Nambiar	Director
Dr. Katherine Laessig	Deputy Director
Dr. Shrimant Mishra	Cross-Discipline Team Leader
Dr. Sheral Patel	Clinical Reviewer
Dr. Benjamin Lorenz	Acting Clinical Team Leader
Dr. Dorota Matecka	Product Analysis Leader
Dr. Grace (Zhixia) Yan	Clinical Pharmacology Reviewer
Dr. Margaret Gamalo	Statistical Reviewer
Dr. Thamban Valappil	Statistical Team Leader
Dr. James Wild	Pharmacology/Toxicology Reviewer
Dr. Wendelyn Schmidt	Pharmacology'/Toxicology Team Leader
Dr. Avery Goodwin	Clinical Microbiology Reviewer
Dr. Minerva Hughes	Biopharmaceutics Reviewer
Dr. Rajiv Agarwal	Chemistry Reviewer
Ms. Kimberly Taylor	Operations Research Analyst

EASTERN RESEARCH GROUP ATTENDEES

Mr. Christopher SeSe	Contractor

APPLICANT ATTENDEES

Dr. Philippe Prokocimer	Chief Medical Officer
[redacted] (b) (4)	
Dr. Carissa De Anda	Vice President, Clinical Research
Dr. Shawn Flanagan	Executive Director, Clinical Pharmacology
[redacted] (b) (4)	Consultant- Pharmacovigilance/Safety
[redacted] (b) (4)	
Dr. Jeff Locke	Senior Scientist II (previously Trius)
Dr. Ken Bartizal	[redacted] (b) (4)
[redacted] (b) (4)	
Dr. Mary Celine Scott	Senior Director, Regulatory Affairs
Dr. Jennifer Grodberg	Senior Director, Regulatory Affairs
Mr. Michael Monahan	Director, Regulatory Affairs Strategy, Cubist Pharmaceuticals
Ms. Carol Waldo	Senior Director, Regulatory Affairs Strategy, Cubist
Dr. Janet Herrington	Global Head, Global Regulatory Affairs Primary Care, Bayer Healthcare

1.0 BACKGROUND

FDA sent the applicant a background package in preparation for this meeting on March 11, 2014.

2.0 DISCUSSION

1. Introductory Comments

The purpose of a LCM is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, 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

Reference ID: 3484462

this background package prior to this LCM or the AC meeting, we may not be prepared to discuss that new information at this meeting.

2. Discussion of Substantive Review Issues

   No substantive review issues have been identified to date.

3. Discussion of Minor Review Issues

   a. Discuss pediatric age cutoff for use of study drug.

   b. Discuss whether enough information for some of the proposed indicated organisms has been submitted to support inclusion in labeling (particularly *Staphylococcus haemolyticus* and *Staphylococcus lugdunensis*).

   Discussion: The applicant informed the Agency that pediatric patients were added late in the trial because of the timing of the pharmacokinetic trial. The applicant noted that *Staphylococcus haemolyticus* and *Staphylococcus lugdunensis* can cause significant disease. The applicant also clarified that they had no additional data regarding these two organisms at this time.

4. Information Requests:

   Discussion: The Agency stated that to this date, all information requests have been answered and that a new Chemistry, Manufacturing and Controls (CMC) information request was issued on March 11, 2014. The applicant stated that the response would be submitted on March 20, 2014.

5. Discussion of Upcoming Advisory Committee Meeting

   Discussion: The Agency reminded the applicant that some information in the Agency briefing document may be preliminary in nature as responses to multiple information requests were received around the time the background document was being prepared and have not yet been reviewed.

   Furthermore, due to dataset formatting issues and the necessity to resubmit datasets, there were significant delays in reviewing the safety aspects of the application. Hence, any conclusions regarding safety presented by the FDA at the AC meeting will be preliminary.

   The applicant stated that they would provide an erratum to their briefing document and some minor corrections to the Agency's briefing document.

6. REMS or Other Risk Management Actions

   Discussion:

   The Agency stated that at this time no risk management actions have been recommended.

Reference ID: 3484462

7. Postmarketing Requirements/Postmarketing Commitments

Discussion: The Agency stated that they would be asking for a post marketing microbiology surveillance study to monitor for the development of resistance to tedizolid.

The Agency noted that the applicant had completed the safety and pharmacokinetic study in adolescents (12-17 years old). In addition, the following studies are planned:

- Two planned studies for safety and PK in subjects 2 to < 12 years old and under 2 years old, respectively.
- Three planned studies for safety and effectiveness studies in ABSSSI in pediatric subjects aged 12 to < 18 years old, > 3 months to < 12 years old, and 0 days old to ≤ 3 months of age (preterm and full term neonates), respectively.

The applicant provided a document discussing the differences between the proposed clinical studies submitted to the NDA and clinical study designs approved by the European Medicines Agency/Pediatric Committee. (Attached)

The Agency also stated that a meeting has been planned with the Pediatric Review Committee (PeRC) to discuss the proposed pediatric plan for tedizolid and that recommendations will be discussed with the after the discussion at PeRC.

8. Major Labeling Issues

Discussion:
The Agency referenced each section of the label that would need further discussion

Clinical:

a. Section 14: Inclusion of the results of each individual trial including the prespecified primary endpoint for each trial.

Nonclinical:

a. Section 13: Inclusion of language discussing myelosuppression, immunotoxicity, MAO inhibition, and inhibition of mitochondrial protein synthesis noted in nonclinical studies.

b. Section 8.1 to be revised to clarify risk as well as nonclinical study findings.

Microbiology:

A. Section 12.4: Clarification regarding resistance language as well as revision of list of indicated organisms. Currently it is not clear whether adequate information has not been provided to support inclusion of some of the proposed microorganisms (specifically *S. haemolyticus* and *S. lugdunensis*).

Reference ID: 3484462

9. Wrap-up and Action Items

This application has not yet been fully reviewed by the Signatory Authority, Division Director, and CDTL and therefore, this meeting did not address the final regulatory decision for the application.

Action Items: (applicant)

1. Errata would be submitted on March 20, 2014.
2. The CMC information response would be submitted on March 20, 2014.
3. They would be available to provide any information that would help the Agency prepare for PeRC.

Reference ID: 3484462

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/s/

SUMATHI NAMBIAR
04/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205435
NDA 205436

LATE CYCLE MEETING
BACKGROUND PACKAGE

Trius Therapeutics, Inc.
Attention: Mary Celine Scott, PhD, MBA
Senior Director, Regulatory Affairs
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121

Dear Dr. Scott:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA 205435 Sivextro (tedizolid phosphate) Tablets
NDA 205436 Sivextro (tedizolid phosphate) Injection

We also refer to the Late-Cycle Meeting scheduled for March 14, 2014. Attached is our background package, including our agenda, for this teleconference.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

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: March 14, 2014

Application Numbers NDA 205435
NDA 205436

Product Name: Sivextro (tedizolid phosphate) Tablets
Sivextro (tedizolid phosphate) Injection

Indication: Acute Bacterial Skin and Skin Structure Infection

Applicant Name: Cubist Therapeutics, 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, Advisory Committee (AC) meeting plans, 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 or the AC meeting, 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. Information Requests have been sent.

2. Substantive Review Issues

Reference ID: 3469203

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

Date of AC meeting: March 31, 2014

Date AC briefing package will be sent under separate cover by the Division of Advisory Committee and Consultant Management: March 11, 2014

Topics for AC discussion:
Has the applicant provided substantial evidence of the safety and effectiveness of tedizolid phosphate for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms?

- If yes, please provide any recommendations concerning labeling.
- If no, what additional studies/analyses are needed?

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:
http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues that would require a REMS have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Shrimant Mishra –CDTL)

2. Discussion of Substantive Review Issues – None

3. Discussion of Minor Review Issues –
    a. Discuss pediatric age cutoff for use of study drug.
    b. Discuss whether enough information for some of the proposed indicated organisms has been submitted to warrant inclusion in labeling (particularly *Staph. haemolyticus* and *Staph. lugdunensis*).
4. Additional Applicant Data – 10 minutes (Applicant)
5. Information Requests

Reference ID: 3469203

To this date all information requests have been answered. A new information request from CMC was sent on 3/11/14.

6. Discussion of Upcoming Advisory Committee Meeting – 15 minutes

   Dataset formatting issues, differences in endpoint criteria, and the necessity to resubmit datasets led to significant delays in reviewing the safety aspects of the application. Any conclusions regarding safety presented by the FDA at the AC meeting will be preliminary.

7. Postmarketing Requirements – 10 minutes

   Pediatrics

   We note your currently completed safety and PK study in adolescents (12-17 years old). We also note your proposed plans for pediatric studies as follows:

   - Two planned studies for safety and PK in subjects 2 to < 12 years old and under 2 years old, respectively.
   - Three planned studies for safety and effectiveness studies in ABSSSI in pediatric subjects aged 12 to < 18 years old, > 3 months to < 12 years old, and 0 days old to ≤ 3 months of age (preterm and full term neonates), respectively.

   A meeting has been planned with the Pediatric Review Committee (PeRC) to discuss the proposed pediatric plan for tedizolid in patients 0 to < 18 years of age. We will share the recommendations with you after the discussion at PeRC.

   Microbiology
   A surveillance study to monitor for the development of resistance to tedizolid.

8. Major labeling issues – 15 minutes

   Clinical:

   a. Section 14: Inclusion of the results of each individual trial including the prespecified primary endpoint for each trial.

   Nonclinical:

   a. Section 13: Inclusion of language discussing myelosuppression, immunotoxicity, MAO inhibition, and inhibition of mitochondrial protein synthesis noted in nonclinical studies.
   b. Section 8.1 to be revised to clarify risk as well as nonclinical study findings.

Reference ID: 3469203

Microbiology:

a. Section 12.4: Clarification regarding resistance language as well as revise list of indicated organisms. Currently it is not clear whether adequate information has been provided to warrant an indication for some of the proposed microorganisms (specifically *Staph. haemolyticus* and *Staph. lugdunensis*)

b. List of indicated organisms will need discussion. Currently enough evidence has not been provided to demonstrate activity of tedizolid against some of the proposed microorganisms (specifically *Staph. haemolyticus* and *Staph. lugdunensis*)

9. Review Plans, Wrap-up and Action Items –5 minutes

Currently discipline reviews are expected to be completed within prespecified timelines.

Reference ID: 3469203

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/s/

SUMATHI NAMBIAR
03/11/2014