CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205435Orig1s000

<u>OTHER REVIEW(S)</u>

M E M O R A N D U M

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

PRELIMINARY CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: June 20, 2014

TO: Carmen DeBellas, Regulatory Project Manager
Sheral Patel, M.D., Medical Officer
Shrimant Mishra, M.D., Cross Discipline Team Leader
Division of Anti-Infective Products

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 205435

APPLICANT: Cubist Pharmaceuticals

DRUG: tedizolid phosphate

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATIONS: Treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of gram positive microorganisms

INSPECTION SUMMARY GOAL DATE: June 19, 2014
DIVISION ACTION GOAL DATE: June 20, 2014
PDUFA DATE: June 20, 2014

I. BACKGROUND:

NDA 205435 (oral formulation) and NDA 205436 (intravenous formulation) for tedizolid phosphate were submitted to the Agency by Trius Therapeutics, Inc. on October 21, 2013. Trius Therapeutics became a wholly owned subsidiary of Cubist Pharmaceuticals, Inc. on September 11, 2013. Cubist Pharmaceuticals officially assumed sponsorship for NDAs 205435 and 205436 on May 8, 2014.

Tedizolid is an oxazolidinone pro-drug antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety. It is a protein synthesis inhibitor that interacts with the bacterial 23S ribosome initiation complex, thereby preventing translation and synthesis of proteins. The proposed indication for tedizolid is for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the select gram-positive microorgansims.

Each NDA was supported by a single clinical study, TR701-112 for NDA 205435 and Study TR701-113 for NDA 205436.

Routine bioresearch monitoring (BIMO) inspections were conducted for both studies at three domestic sites: Sinikka Green (Le Mesa, CA, Site #105), Jeffrey Kingsley (Columbus, GA, Site #101), and Purvi Mehra (San Diego, CA, Site #103). All three inspections were classified as Voluntary Action Indicated (VAI). The original sponsor, Trius Therapeutics (San Diego, CA) was inspected as well and that inspection was classified as No Action Indicated (NAI). A Russian site had been selected to be inspected for Study TR701-113 (NDA 205436), but the inspection was not conducted due to travel restrictions. The Clinical Inspection Summary (CIS) written by Anthony Orencia, M.D. containing a detailed review of inspectional findings was entered into DARRTS on March 11, 2014.

On January 14, 2014 Trius submitted an amendment to the NDA indicating that based on their review of monitoring reports and essential documents in the trial master file, they identified three sites participating in Study TR701-112 that raised concerns. An audit of the three sites was conducted on July 16 to 18, 2014. This was followed by a focused audit of source data on October 7 to 10, 2013. It was determined that source data did not fully meet GCP ALCOA (attributable, legible, contemporaneous, original, accurate) standards to support eCRF data. After reviewing the audit observations, it was decided that TR701-112 data should be reanalyzed excluding data from Sites #120 (Alan Nolasco, M.D.), #121 (William Clark, M.D., deceased, Dr. Nolasco assumed responsibility), and #122 (Jennifer Johnson-Caldwell, M.D.). The sponsor stated that this reanalysis did not change efficacy or safety conclusions.

A second inspection assignment for NDA 205435 was issued by OSI on March 27, 2014. The rationale for this inspection assignment was to verify whether data submitted by the three sites (Site #s 120, 121, and 122) identified by the sponsor as having GCP issues should be included in the study analyses.

Study TR701-112
TR701-112 was a randomized, double-blind, double-dummy, multicenter, Phase 3 study of

oral tedizolid 200 mg once daily for 6 days versus oral Zyvox®. The primary objective was to determine the non-inferiority in the early clinical response rate of 6-day oral tedizolid compared with that of 10-day oral linezolid treatment at 48-72 hours in the Intent-to-Treat Analysis set in patients with acute bacterial skin and skin structure infections. The primary efficacy outcome was the early clinical response rate at the 48-72 hour visit. An early clinical response required the subject be afebrile with cessation of spread of the primary ABSSSI lesion from baseline. This endpoint was determined programmatically from lesion measurements and temperature data recorded on the electronic case report form.

II. RESULTS (by Site):

Name and location of CI	Site #/Protocol #/Subject #	Inspection Date	Final Classification
Alan E. Nolasco, M.D. Westbury Medical Clinic 3400 Bissonet, Suite 165 Houston, TX 77005	Site #120 TR701-112 Screened 5 subjects Enrolled 5 subjects Site #121 TR701-112 Screened 6 subjects Enrolled 5 subjects	June 2-10, 2014	Pending Preliminary: VAI
Jennifer Johnson-Caldwell, M.D. 1315 St. Joseph Parkway, Suite 140 Houston, TX 77002	Site #122 TR701-112 Screened 9 subjects Enrolled 8 subjects	Ongoing (started June 3, 2014)	Pending

Key to Classifications

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

1.. Alan Nolasco, M.D.
Houston, TX

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from June 2 to June 10, 2014.

Records reviewed included informed consent forms, source documents, case report

forms, drug accountability records, sponsor and IRB correspondence, and monitoring reports.

b. General observations/commentary:
At Site #120, there were 51 subjects screened (seven of whom had case report forms), five subjects were enrolled and 5 subjects completed the study.

At Site #121, there were 61 subjects screened (10 of who had case report forms), five subjects were enrolled, and five subjects completed the study.

Source data and case report forms were compared with data listings provided in the NDA. The primary efficacy endpoint was verifiable at the study sites. There was no under-reporting of serious adverse events.

At the close of inspection, a one-item Form FDA 483, Inspectional Observations was issued for failure to obtain informed consent in accordance with 21 CFR Part 50, from each human subject prior to conducting study-related tests. Specifically, there were no Informed Consent forms for 44/51 (86%) study subjects at Site 120 and 51/61 (84%) study subjects at Site 121. The screened subjects missing informed consent completed some or all of the screening-related tests before being excluded from this trial.

OSI reviewer comment: It is not clear from the information obtained or provided whether the Informed Consent forms were missing because subjects weren't consented or the documents weren't retained. All of the missing informed consent documents were for subjects who were screen failures. Although failure to obtain informed consent is a regulatory violation, the screening procedures outlined for this study are procedures that would normally be done in the course of medical practice in caring for patients with acute bacterial skin infections. Procedures that may not be routinely done such as photographs of the skin lesions or ECGs represent no risk to human subject safety. The violation would not be expected to impact efficacy assessment.

At the close-out meeting with Dr. Nolasco, the ORA investigator discussed the following issues:

- Monitoring reports noted several occasions of alleged falsification of records during the trial. Instances cited included two patients' diary notes which had two sets of handwriting, training memos documenting that all of the staff completed training on Amendments 1-4 even though some had left by the time the IRB approved the amendment, and source data (paper CRFs) appear to have been completed after the monitor left and were not noted to be late entries (eCRFs had been complete at the time of the monitor's visit).
  OSI Reviewer Comment: Assessment of the impact of this observation on data reliability will be made once the EIR and accompanying exhibits are reviewed.

- Two adverse events were not documented per the monitor's request: Subject 120-053 (anemia after dosing) and 120-537 (allergic reaction – pruritus).
- Temperatures for study subjects were not taken four times daily in the first 48-72 hours of the study.

c. Assessment of data integrity:
Based on the information available to date, the data from this site may be used in support of the indication.

Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Jennifer Johnson-Caldwell
Houston, TX

a. What was inspected:
The inspection is being conducted in accordance with Compliance Program 7348.811. The inspection began on June 3, 2014 and is ongoing.

Records reviewed included informed consent forms, source documents, case report forms, drug accountability records, sponsor and IRB correspondence, and monitoring reports.

b. General observations/commentary (preliminary):
The screening log indicated that 75 subjects were screened. Eight subjects were enrolled (only six of whom were listed on the screening log) and eight subjects completed the study. All eight subject files were reviewed.

Source records and case report forms were compared to data listings from the NDA. The primary efficacy data was verifiable based on the measurements of the lesions and subjects record of their temperature in a diary. There was no under-reporting of adverse events.

A Form FDA 483 will be issued at the end of the inspection. Observations include, but may not be limited to, failure to conduct an investigation according to the investigational plan.

c. Assessment of data integrity:
This inspection is ongoing. An assessment of data integrity will be made once the inspection has been completed.

Observations noted above are based on preliminary communications with the field investigator. An inspection summary addendum will be generated when the inspection is completed.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Initially BIMO inspections were performed at three clinical investigator sites and the sponsor, Trius Therapeutics. The clinical investigator inspections of Drs. Green, Kingsley, and Mehra were classified as VAI. The inspection of the sponsor was classified as NAI.

Three additional clinical investigator inspections were performed by OSI of Study TR701-112 supporting NDA 205435 because the sponsor had identified these sites in a January 14, 2014 submission to the NDA as being GCP noncompliant. These sites were Sites #120 (Alan Nolasco, M.D.), #121 (William Clark, M.D., deceased, Dr. Nolasco assumed responsibility), and #122 (Jennifer Johnson-Caldwell, M.D.).

The inspection of Dr. Nolasco covering Site #s 120 and 121 has been completed and been preliminarily classified as VAI. A Form FDA 483 was issued for failure to obtain informed consent from all subjects screened for the study. Based on information provided, it is unclear whether consent was ever obtained or the documents were just not maintained. Although failure to obtain consent is a regulatory violation, the majority of screening procedures would be performed in actual clinical practice when treating patients with acute bacterial skin and skin structure infections. Other procedures performed would have presented no risk to human subject safety. Therefore, data from this site can be used in support of the indication.

The inspection of Dr. Johnson-Caldwell (Site #122) has not been officially closed. The FDA investigator plans to close out the inspection when the clinical investigator returns to the office next week and a preliminary classification of inspectional observations will then be made. To date, based on our communication with the FDA field investigator, the primary efficacy data submitted to the NDA was verified with source records of skin lesion measurements and subjects' record of temperature in a diary. There was no under-reporting of adverse events at the site.

Observations noted above for Dr. Nolasco (Site #s 120 and 121) are based on the Form FDA 483 and communications with the field investigator. The inspection of Dr. Johnson-Caldwell (Site #122) is not closed and information reported above is based on preliminary communications with the field investigator. An inspection summary addendum will be generated after the inspection has been completed and the results have been evaluated by OSI.

{See appended electronic signature page}

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

CONCURRENCE: ***{See appended electronic signature page}***

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

CONCURRENCE: ***{See appended electronic signature page}***

Ni Khin, M.D.
Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

JANICE K POHLMAN
06/20/2014

SUSAN D THOMPSON
06/20/2014

NI A KHIN
06/20/2014

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

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

Memorandum

Date: May 12, 2014

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

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

Subject: NDA #205435, 205436
SIVEXTRO® (tedizolid phosphate) Injection and Tablet

As requested in your consults dated February 21 and May 2, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the draft labeling for SIVEXTRO (tedizolid phosphate) injection for intravenous use and tablet for oral use (Sivextro).

OPDP's comments on the PI are based on the substantially complete clean WORD version of the labeling titled, "Sivextro working label.doc " which was received via email from DAIP on May 5, 2014. OPDP's comments are provided in the attached, clean version of the labeling.

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

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

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/s/

CHRISTINE G CORSER
05/12/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review:	May 2, 2014
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 205435 and 205436
Product Name and Strength:	Sivextro (tedizolid phosphate) for Injection, 200 mg per vial Sivextro (tedizolid phosphate) Tablets, 200 mg
Product Type:	Single Ingredient Products
Rx or OTC:	Rx
Applicant/Sponsor Name:	Trius Therapeutics
Submission Date:	October 18, 2013
OSE RCM #:	2013-2714 and 2013-2715
DMEPA Primary Reviewer:	Aleksander Winiarski, PharmD
DMEPA Acting Team Leader:	Tingting Gao, PharmD, BCPS
DMEPA Acting Team Leader:	Julie Neshiewat, PharmD, BCPS

1 REASON FOR REVIEW

Trius Therapeutics submitted labels and labeling for Sivextro (Tedizolid) tablets, 200 mg, under NDA 205435 and Sivextro (Tedizolid) for Injection, 200 mg per vial, under NDA 205436. This is a New Molecular Entity (NME) application under the PDUFA V program.

The Division of Anti-Infective Products (DAIP) requested that we review the submitted Sivextro label and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Proposed Labels and Labeling	G

N/A = Not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the submitted labels and labeling, and we identified some areas where the use and prescribing information may require revision to improve clarity and readability. Additionally, we identified the use of abbreviations such as IV, which should be replaced with the corresponding words for clarity. We provide specific recommendations in sections 4.1 and 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

The submitted label and labeling for Sivextro may be improved to communicate important use information and to improve readability.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for the Division's consideration:

A. Dosage and Administration Section

1. We note the use of abbreviations in the section, for example "IV" 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". Other symbols, such as: "≥" sign should also be replaced with the corresponding words for clarity. Throughout the section, replace the "IV" abbreviation with the word "Intravenous" and the statement "≥ 12 years of age" with "12 years of age and older" for clarity.

2. The following statement describing the intravenous product, "TRADENAME is supplied as a sterile, lyophilized powder for injection in single-use vials, (b) (4) [redacted] " already appears in section 3, section 11, and section 16.2. Recommend to delete this statement in section 2.2 and delete reference to (b) (4) [redacted] in sections 3 and 16.2 to help prevent confusion with the deliverable amount of 200 mg.

3. The following information is not currently provided in the prescribing information but appears on the carton back panel: "Do not break, crush, or chew tablet". Please determine if these directions are appropriate for the product. If the directions are appropriate, please ensure that the instructions are provided in the insert labeling for consistency. If the directions are <u>not</u> appropriate, please ensure that the instructions are removed from the carton labeling.

B. Dosage Forms and Strengths Section

1. See A2 above.

C. How Supplied Section

1. See A2 above.

2. The Applicant submitted carton labeling for a package of 10 single-dose vials. Please request that the Applicant revises this section to include that packaging configuration and

provides a corresponding NDC number that is different from the individual vial if both are considered a unit of sale.

4.2 RECOMMENDATIONS FOR THE APPLICANT

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

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.

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

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.

[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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sivextro from the submitted insert labeling on October 21, 2013.

Table 2. Relevant Product Information for	
Active Ingredient	Tedizolid phosphate
Indication	Treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the specific gram-positive microorganisms
Route of Administration	Intravenous infusion or Oral
Dosage Form	Powder for injection Tablet
Strength	200 mg per vial and 200 per tablet
Dose and Frequency	200 mg orally or via intravenous infusion daily (no dose adjustments) for 6 days
How Supplied	Intravenous • Each vial individually packaged in a carton • Package of 10 vials per carton Oral • Unit dose blister pack containing 6 tablets • Bottles containing 30 tablets
Storage	Intravenous and Oral • Room Temperature
Container Closure	Intravenous: Glass vial Oral: Blister pack and plastic bottle

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Sivextro labels and labeling submitted by Trius on March 25, 2014.

G.2 Label and Labeling Images

Oral Tablet Blister Labels

(b) (4)

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

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/s/

ALEKSANDER P WINIARSKI
05/02/2014

TINGTING N GAO
05/02/2014

JULIE V NESHIEWAT
05/02/2014

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

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

Application: NDA 205435
NDA 205436

Application Type: New Molecular Entity NDA

Name of Drug/Dosage Form: Sivextro (tedizolid) 200 mg Tablets
Sivextro (tedizolid) 200 mg Injection

Applicant: Cubist Pharmaceuticals

Receipt Date: October 21, 2014

Goal Date: June 20, 2014

1. Regulatory History and Applicant's Main Proposals

These NDAs are new molecular entities submitted for the indication of Acute Bacterial Skin and Skin Structure Infections.

2. Review of the Prescribing Information

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

The review of the prescribing information was reviewed and found to be acceptable.

3. Conclusions/Recommendations

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

Highlights

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

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

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

Comment:

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

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

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES**" in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

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

Comment:

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

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

Reference ID: 3476324

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

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

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The initial approval date will read June 20, 2014*

Reference ID: 3476324

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment: *A boxed warning is not required*

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

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

Comment: *oxazolidinone*

Dosage Forms and Strengths in Highlights

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

Reference ID: 3476324

Comment:

Contraindications in Highlights

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

Comment:

Adverse Reactions in Highlights

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

Comment:

Patient Counseling Information Statement in Highlights

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

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

- **"See 17 for PATIENT COUNSELING INFORMATION"**

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

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

Comment:

Revision Date in Highlights

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

Comment:

Reference ID: 3476324

Contents: Table of Contents (TOC)

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

NO 25. The TOC should be in a two-column format.

Comment: *The Sponsor managed to place all information in one column*

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 3476324

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment:

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"[see Warnings and Precautions (5.2)]"*.

Comment: *There are no cross references in the label*

Reference ID: 3476324

NO 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *This a new NDA*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment: *The is an orginal NDA and has not been marketed yet.*

PATIENT COUNSELING INFORMATION Section in the FPI

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

Reference ID: 3476324

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

Comment:

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

Comment:

Reference ID: 3476324

Appendix A: Format of the Highlights and Table of Contents

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

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

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

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

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

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

Reference ID: 3476324

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
03/24/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: March 11, 2014

TO: Carmen DeBellas, Regulatory Project Manager
Sheral Patel, M.D., Medical Officer
Shrimant Mishra, M.D., Cross Discipline Team Leader
Katherine Laessig, M.D., Associate Director
Division of Anti-infective Drug Products (DAIP)

FROM: Anthony Orencia, M.D., Ph.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 205435, 205436

APPLICANT: Trius Therapeutics, Inc.

DRUG: tedizolid

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority review

INDICATION: treatment of acute bacterial skin and skin structure infections (ABSSSI)

CONSULTATION REQUEST DATE:	November 22, 2013
INSPECTION SUMMARY GOAL Original DATE:	February 27, 2014
INSPECTION SUMMARY (DAIP-extended) DATE:	March 11, 2014
DIVISION ACTION GOAL DATE:	June 20, 2014
PDUFA DATE:	June 21, 2014

I. BACKGROUND:
Acute Bacterial Skin and Skin Structure Infections (ABSSSI) involve patients with cellulitis/erysipelas, major cutaneous abscesses, or wound infections (surgical site infections or post-traumatic wound infections). The only oral agent approved for methicillin-resistant *Staphylococcus aureus* (MRSA) is linezolid (Zyvox®). While linezolid has good efficacy, adverse reversible hematologic effects (including anemia, leucopenia, thrombocytopenia, or pancytopenia) have been reported. Novel antimicrobial agents are sought as alternative drug treatments for ABSSSI.

Tedizolid is an oxazolidinone pro-drug antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety. Tedizolid is a protein synthesis inhibitor that interacts with the bacterial 23S ribosome initiation complex, thereby preventing translation and synthesis of proteins.

Three domestic clinical sites, participating in Study TR701-112 and TR701-113, were selected for inspection principally because the sites had enrollment of a large number of study subjects. A foreign clinical site participating in TR701-113 was also selected because the site enrolled a large number of study subjects.

Study TR701-112
TR701-112 was a randomized, double-blind, double-dummy, multicenter, Phase 3 study of oral tedizolid 200 mg once daily for 6 days versus oral Zyvox®. The primary objective was to determine the non-inferiority in the early clinical response rate of 6-day oral tedizolid compared with that of 10-day oral linezolid treatment at 48-72 hours in the Intent-to-Treat Analysis set in patients with acute bacterial skin and skin structure infections. The primary efficacy outcome was the early clinical response rate at the 48-72 hour visit. An early clinical response required the subject be afebrile with cessation of spread of the primary ABSSSI lesion from baseline. This endpoint was determined programmatically from lesion measurements and temperature data recorded on the electronic case report form.

Study TR701-113
TR701-113 was a randomized, double-blind, double-dummy, multicenter, global Phase 3 study of intravenous (IV) to oral tedizolid 200 mg once daily for 6 days versus IV to oral Zyvox® (linezolid) 600 mg every 12 hours for 10 days for the treatment of ABSSSI in adults. The primary objective was to determine the non-inferiority in the early clinical response rate of IV to oral 6-day tedizolid compared with that of IV to oral 10-day linezolid treatment at 48-72 hours after the first infusion of study drug in the intent-to-treat analysis set in patients with ABSSSIs. Early clinical response was defined by lesion area only. Response required a ≥20% reduction from baseline in the area of erythema,

edema, and/or induration from baseline of the primary ABSSSI lesion. This was determined programmatically from lesion area measurements recorded on the electronic case report form.

II. RESULTS:

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Final Classification*
Sinikka Green, M.D. La Mesa, CA	TR701-112/Site 105 N=99 TR701-113/Site 105 N=54	Jan. 6 to 24, 2014	Preliminary: VAI
Jeffery Kingsley,M.D. Columbus, GA	TR701-112/Site 101 N=49 TR701-113/Site 101 N=18	Jan. 13 to 24, 2014	Preliminary: VAI
Purvi Mehra, M.D. San Diego, CA	TR701-112/Site 103 N=85 TR701-113/Site 103 N=55	January 6 to 29, 2014	Preliminary: VAI
Alexander Konychev, M.D. St. Petersburg, Russia	TR701-113/Site 289 N=99		Pending
Trius Therapeutics, Inc. San Diego, CA	Sponsor	Jan.28 to Feb. 5, 2014	Preliminary: NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. **Sinikka Green, M.D./Protocol TR701-112/Site 105 Site and TR701-113/Site 105**
   La Mesa, CA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from January 6 to 24, 2014. For Study 112, a total of 103 subjects were screened, 99 subjects were enrolled, and 88 subjects completed the study. An audit of 49 subjects' records was conducted.

For Study 113, a total of 57 subjects were screened, 54 subjects were enrolled, and 44 subjects completed the study. An audit of 11 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. The efficacy endpoints were centrally adjudicated. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for failure to follow the study protocol according to the investigational plan and deficiencies with maintaining adequate and accurate records. Specifically,

(1) For TR701-112:
(A) The digital photographs of the following patients were not maintained in the source documents nor in the e-CRFs for the corresponding calendar dates:
(a) Patient 105-046 (9/29/2010)
(b) Patient 105-052 (10/8/2010)
(c) Patient 105-054 (10/8/2010)
(d) Patient 105-093 (10/21/2010 and 10/28/2010)
(e) Patient 105-152 (11/29/2010)
(f) Patient 105-278 (2/28/2011)
(g) Patient 105-400 (4/30/2011)
(h) Patient 105-421 (5/16/2011)
(i) Patient 105-438 (5/23/2011)
(j) Patient 105-463 (6/8/2011)
(k) Patient 105-540 (7/10/2011)

(B) Patient 105-184's upper respiratory infection (10/26/2010 onset) in the source document was not reported in the eCRF.

(C) Patients with the following ABSSSI wound signs and symptoms were incorrectly recorded in the eCRF:
(a) Patient 105-002's (8/29/2010) fluctuance in the source record was absent, but the eCRF was recorded as present
(b) Patient 105-018's (9/7/2010) fluctuance in the source record was absent, but the eCRF was recorded as present
(c) Patient 105-052's (9/27/2010) pain in the source record was absent, but the eCRF was recorded as present
(d) Patient 105-054's (10/1/2010) pain in the source record was absent, but the eCRF was recorded as present

(e) Patient 105-190's (12/23/2010) erythema in the source record was absent, but the eCRF was recorded as present

(2) For TR701-113, patient 105-014's chest rash (11/10/2011-11/13/2011) included in the source document was not reported in the eCRF.

The List of Inspectional Observations (Form FDA 483) was communicated to the DAIP Medical Team who did not consider the above findings as clinically important. Dr. Green responded adequately to these observations in a letter dated February 6, 2014.

c. Assessment of data integrity:
The regulatory deficiencies noted above are considered minor. Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Jeffery Kingsley, M.D./Protocol TR701-112/Site 101 and TR701-113/Site 101
Columbus, GA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from January 13 to 24, 2014. For Study 112, a total of 53 subjects were screened, 48 subjects were enrolled, and 43 completed the study. An audit of 16 subjects' records was conducted. For Study 113, a total of 38 subjects were screened, 18 subjects were enrolled and 14 completed the study. An audit of 7 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for failure to follow the study protocol according to the investigational plan. Specifically,

(1) For Study 112:
(A) Patient 101-081 was enrolled into the study after using Neosporin, a prohibited medication, on the primary lesion four days prior to enrollment.

(B) Patient 101-225 had a major cutaneous abscess and was prescribed metronidazole. Per study protocol, metronidazole was permitted in patients with wound infections only

(C) Twenty-three of 43 patients who completed the 48-72 hour visit had temperature measurements prior to the 48 hours after randomization.

(2) For Study 113, Patient 101-026 was administered toradol on the day of enrollment. Nonsteroidal anti-inflammatory drugs were prohibited medication between enrollment and the 48-72 hour visit, unless used chronically prior to enrollment.

The List of Inspectional Observations (Form FDA 483) was communicated to the DAIP Medical Team who did not consider the above findings as clinically important, except for the 23 patients in Study 112 which was a clinical trial design and conduct matter. Specifically, obtaining temperatures in Study 112 taken at certain time points proved to be difficult and burdensome in the conduct of this clinical trial. Thus, the efficacy endpoint criteria, in part, were modified in a second adequate and well controlled trial, Study 113.

c. Assessment of data integrity:
The regulatory deficiencies noted above are considered minor. Data submitted by this clinical site appear acceptable for this specific indication.

3. Purvi Mehra, M.D./Protocol TR701-112/Site 103 and TR701-113/Site 103
San Diego, CA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from January 6 to 29, 2014. For Study 112, a total of 88 subjects were screened, 85 subjects were enrolled, and 78 subjects completed the study. An audit of 50 enrolled subjects' records was conducted. For Study 113, a total of 62 subjects were screened, 55 subjects were enrolled, and 52 subjects completed the study. An audit of 25 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for failure to follow the study protocol according to the investigational plan and deficiencies with maintaining adequate and accurate records. Specifically,

(1) For Study 112:
(A) Intermittent tachycardia adverse events were not consistently reported using the following patients as examples:
(a) Patient 103-231: onset (1/24/2011), resolution (1/28/2011)
(b) Patient 103-551: onset (7/13/2011), resolution (ongoing)
(c) Patient 103-624: onset (8/9/2011), resolution (8/15/2011)

(B) Records for Patient 103-307 on 3/14/2011 indicate that the patient consented to a digital photograph, however, a copy was not found in the e-CRF. Also, this patient's visit on 4/4/2011 indicated clinical failure assessed on 4/29/2011, however, the e-CRF indicated clinical success.

(2)For Study 113:
(A) Patients 103-007, 103-011, 103-015, 103-017, 103-019, 103-048, 103-064, and 103-088 were randomized into the major cutaneous abscess group strata. The e-CRFs were re-categorized into the post-traumatic wound group.
(B) Patient 103-015's photograph lesions contained duplicate photos for the screening visit (11/3/2011) and 48-72 hour visit (11/6/2011).

The List of Inspectional Observations (Form FDA 483) was communicated to the DAIP Medical Team. Dr. Mehra responded adequately to these observations in a letter dated February 7, 2013.

Medical Officer's Comments:
Dr. Mehra, in his response letter, commented that the criteria for both clinical skin infection syndromes were met: major cutaneous abscess and post-traumatic wound infections. However, Dr. Mehra stated that the study protocol was not specific in cases where both strata qualified for assignation. The sponsor's preference was communicated to Dr. Mehra, documented in an e-mail exchange, a preference for the post-traumatic wound infection group based on "drainage" after an incision and drainage.

DAIP discussed with OSI whether or not this was a systemic occurrence. To examine the extent of reclassification of the category of skin infections and whether or not this was a systemic issue, OSI requested that the sponsor report the total number of re-classifications during the sponsor site audit. For TR701-112, there were 21 cases re-classified out of 667 patients randomized. For TR701-113, there were a 43 cases re-classified of 666 patients randomized. DAIP is aware of the reclassifications.

c. Assessment of data integrity:

Except for the reclassification of skin infection types, the regulatory deficiencies noted above are considered minor. Data submitted by this clinical site appear acceptable for this specific indication.

4. **Alexander Konychev, M.D./ Protocol TR701-113/Site #289**
   St. Petersburg, Russian Federation

INSPECTION PENDING: Tentatively scheduled for March 31 – April 11, 2014

SPONSOR

5. Trius Therapeutics, Inc.
San Diego, CA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.810, from January 28 to February 5, 2014. In September 2013, Trius Therapeutics, Inc. was acquired by Cubist Pharmaceuticals.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors, and extent of reclassification of type of skin infection syndrome.

Specific attention was paid to monitoring records for Dr. Konychev (Site 289) and Dr. Johnson-Caldwell (Site 122).

b. General observations/commentary:
The sponsor generally maintained adequate oversight of the clinical trial. There was no evidence of under-reporting of adverse events. Monitoring records from Dr. Konychev's study site were considered adequate.

On January 14, 2014, the sponsor submitted an amendment to NDAs 205435 and 205436 identifying three GCP noncompliant sites. These sites were Sites 120 and 121 (Alan E. Nolasco) and Site 122 (Jennifer Johnson-Caldwell, M.D.) The findings were based on a focused internal audit in October 2013 performed in response to a review of monitoring reports in the trial master file in July 2013. The amendment included an addendum to their clinical study report which included analyses with these study sites excluded. The CDTL for the application, Dr. Shirmant Mishra, reports that there is no difference in overall efficacy if the three sites are excluded from the analyses.

No Form FDA 483 was issued at the end of the sponsor inspection.

c. Assessment of data integrity:

Other than GCP non-compliance at three sites reported by the sponsor, the study appears to have been conducted adequately. Except for Study TR701-112 Sites, 1201, 121 and 122 where inspections are pending, data submitted by this sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three domestic sites were selected for inspection of Studies TR701-112 and TR701-113 supporting this NDA: Sinikka Green, M.D., Jeffery Kingsley, M.D., and Purvi Mehra, M.D. A single foreign investigator was selected for inspection: Alexander Konychev, M.D. (Russia) for Study TR701-113.

The preliminary classification for the three completed domestic clinical site inspections of Drs. Green, Kinglsey, and Mehra is VAI (Voluntary Action Indicated).The study data collected from these three domestic clinical sites (Drs. Sinikka Green, Jeffery Kingsley and Purvi Mehra) that have been inspected appear generally reliable in support of the requested indication. The observation noted at Dr. Mehra's site (i.e. reclassification of skin infection type by the sponsor/monitor) which may have some impact on efficacy analyses has been discussed with DAIP.

The foreign clinical site inspection of Dr. Konychev (St. Petersburg, Russia) is pending. Given current events in Ukraine and Russia, inspection of the Russian site may be postponed or cancelled. DAIP may wish to consider alternative methods in their analytic considerations for the NDA's efficacy and safety.

The sponsor, Trius Therapeutics, Inc. (purchased by Cubist Pharmaceuticals after the studies were completed) was audited. The preliminary classification is NAI (No Action Indicated). Based on the sponsor's January 14, 2014 amendment to the NDA identifying three GCP noncompliant sites (Sites 120 and 121, Dr. Alan Nolasco, and Site 122, Dr. Jennifer Johnson-Caldwell), OSI is planning on inspecting these sites for this application. Pending the results of these inspections, OSI agrees with the review division conducting sensitivity analyses excluding the sites.

Note: *The inspectional observations noted above are based on the preliminary communications with the field investigator. CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity (eg, principal investigator). A clinical inspection summary addendum will be generated to incorporate findings from the inspections of Dr. Nolasco and Dr. Johnson-Caldwell or if conclusions on the currently reported inspections change significantly upon receipt and final review of the Establishment Inspection Report (EIR).*

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
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CONCURRENCE:

{See appended electronic signature page}

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

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

/s/

ANTHONY J ORENCIA
03/11/2014

JANICE K POHLMAN
03/11/2014

KASSA AYALEW
03/11/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 205435 NDA # 205436		
Proprietary Name: Sivextro Established/Proper Name: tedizolid phosphate Dosage Forms: Tablets and Injection Strengths: 200 mg tablets & 200 mg Injection		
Applicant: Trius Therapeutics		
Date of Application: October 18, 2013 Date of Receipt: October 21, 2013		
PDUFA Goal Date: June 21, 2014	Action Goal Date (if different): June 20, 2104	
Filing Date: December 20, 2013	Date of Filing Meeting: November 26, 2013	
Chemical Classification: 1P		
• Proposed indications Acute Bacterial Skin and Skin Structure Infections		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	X 505(b)(1) X 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	Standard X Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

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X Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): Oral IND 77872 Injection IND 106307	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	☐		

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User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.	X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	X	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	X	☐	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	X	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	X	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

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

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

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

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

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X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) **If no**, explain.				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	☐	☐	
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X		☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and***	X	☐	☐	

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the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	x	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?	X	☐	☐	

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

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If no, request in 74-day letter				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	x	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	x	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	x	☐		
Is the PI submitted in PLR format?[4]	x	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	x	

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

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

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All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x	☐	☐	
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☒	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** October 19, 2009 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** May 13, 2013 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** Meetings February 26, 2010 & May 17, 2010 Agreement Letters: June 9, 2010 & August 2, 2011 Modification Letter: December 7, 2012 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

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ATTACHMENT

MEMO OF FILING MEETING

DATE: November 26, 2013

PROPRIETARY NAME: Sivextro

ESTABLISHED/PROPER NAME: tedizolid phosphate

DOSAGE FORM/STRENGTH: 200 mg Tablets & 200 mg Injection

APPLICANT: Trius Therapeutics

Proposed indications
Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

BACKGROUND:
NDAs 205435 (tablet) & 205436 (injection) have been submitted under section 505(b)(1) of the Food, Drug and Cosmetic Act. The proposed indication for tedizolid phosphate is for the treatment of ABSSSI caused by susceptible isolates of the following gram-positive microorgansims: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin susceptible [MSSA] isolates, and cases with concurrent bacteremia), *Staphylococcushaemolyticus, Staphylococcus lugdunensis, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus,* Group (including, *Streptococcus anginosus, Streptococcus intermedius* and *Streptococcus constellatus),* and *Enterococcusfaecalis.*

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Carmen DeBellas	Yes
	CPMS/TL:	Frances LeSane	No
Cross-Discipline Team Leader (CDTL)	Shrimant Mishra		Yes
Clinical	Reviewer:	Shrimant Mishra & Sheral Patel	Yes
	TL:	Benjamin Lorenz	Yes
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Avery Goodwin	Yes
	TL:	Kerry Snow	Yes

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Clinical Pharmacology	Reviewer:	Grace Yan	Yes
	TL:	Kimberly Bergman	Yes
Biostatistics	Reviewer:	Margaret Gamalo	Yes
	TL:	Thamban Valappil	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer	James Wild	Yes
	TL:	Wendelyn Schmidt	
Biopharmaceutics	Reviewer:	Minerva Hughes	Yes
	TL:	Angelica Dorantes	No
Product Quality (CMC)	Reviewer:	Rajiv Agarwal	Yes
	TL:	Dorota Matecka	Yes
Quality Microbiology *(for sterile products) IV only*	Reviewer:	Robert Mello	Yes
	TL:	Bryan Riley	No
Facility Review/Inspection	Reviewer:	Steven Hertz	No
OSE/DMEPA (proprietary name)	Reviewer:	TBA	
	TL:		

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FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO BA/BE studies
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	X Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: 505(b)(2) no clinical trials performed	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the***	X YES Date if known: March, 31, 2014 ☐ NO ☐ To be determined

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drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease	
• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed? Inspection has been requested	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC)	☐ Not Applicable X FILE ☐ REFUSE TO FILE

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Comments:	☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 X YES ☐ NO ☐ YES ☐ NO X YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable X YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES ☐ NO
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	 X YES ☐ NO X YES ☐ NO

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• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	X YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X Yes
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): February 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> X No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☐ Standard Review X Priority Review

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	ACTIONS ITEMS
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
NA	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
X	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
NA	BLA/BLA supplements: If filed, send 60-day filing letter
X	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
X	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
NA	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]

Reference ID: 3444015

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

/s/

CARMEN L DEBELLAS
01/29/2014