

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205436Orig1s000**

**CHEMISTRY REVIEW(S)**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Rajiv Agarwal, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: rajiv.agarwal@fda.hhs.gov  
Phone: (301)-796-1322  
Fax: (301)-796-9877

**FROM:** FDA

Division of Pharmaceutical Analysis  
Michael Trehy, MVP Coordinator  
645 S Newstead Avenue  
St. Louis, MO 63110  
Phone: (314) 539-3815

**Through:** John Kauffman, Deputy Director  
Phone: (314) 539-2168

**SUBJECT:** Methods Validation Report Summary

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Application Number: 205436

Name of Product: tedizolid phosphate for injection, 200 mg

Applicant: Trius Therapeutics, Inc.

Applicant's Contact Person: Mary Celine Scott, Ph.D., MBA

Address: 6310 Nancy Ridge Drive, Suite 105, San Diego, CA

Telephone: (858) 452-0370 x 312      Fax: (858) 408-3002

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Date Methods Validation Consult Request Form Received by DPA: 11/15/2013

Date Methods Validation Package Received by DPA: 11/15/2013

Date Samples Received by DPA: 12/16/2013

Date Analytical Completed by DPA: 5/21/2014

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Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes.   
**2.** Methods are acceptable with modifications (as stated in accompanying report).   
**3.** Methods are unacceptable for regulatory purposes.

Comments: Analyst's comments and link to work sheets are provided in attached summary sheet.



DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration

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Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
St. Louis, MO 63101  
Tel. (314) 539-2158

Date: May 21, 2014  
To: Rajiv Agarwal, Method Validation Requestor  
Through: John Kauffman, Deputy Director, Division of Pharmaceutical Analysis  
From: Daniel J. Mans, Staff Fellow, Division of Pharmaceutical Analysis  
Subject: Methods Validation for NDA 205436  
Tedizolid Phosphate for Injection  
Trius Therapeutics, Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

[HPLC Method for the Identity, Assay, Related Impurities of Tedizolid Phosphate in Tedizolid Phosphate for Injection \(Trius Therapeutics AP-020.0\)](#)

[HPLC Method for Chiral Purity of Tedizolid Phosphate in Tedizolid Phosphate for Injection \(Trius Therapeutics AP-022.0\)](#)

Link to analyst's work sheets and chromatograms is available at:  
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8806ef8b0>

## Summary of Results

NDA 205436

HPLC Method for the Identity, Assay, Related Impurities of Tedizolid Phosphate in Tedizolid Phosphate for Injection (Trius Therapeutics AP-020.0)

AVG % Total Vial Content = (b) (4)

**Specification** = (b) (4)

Impurity	AVG RRT	AVG Area %	Specification
(b) (4)			

Total Impurities = (b) (4)

**Specification** = NMT (b) (4)

HPLC Method for Chiral Purity of Tedizolid Phosphate in Tedizolid Phosphate for Injection (Trius Therapeutics AP-022.0)

Not Detected (Detection Limit = (b) (4))

**Specification** = NMT (b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHAEL L TREHY  
05/23/2014

JOHN F KAUFFMAN  
05/23/2014

# **NDA 205436**

**Sivextro  
(Tedizolid phosphate) for injection**

**Trius Therapeutics, Inc.**

**Rajiv Agarwal**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch V**

**CMC REVIEW OF NDA 205436  
For the Division of Anti-Infective Products**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 205436
2. REVIEW #: 2
3. REVIEW DATE: 13-MAY-2014
4. REVIEWER: Rajiv Agarwal, Ph.D.; Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	21-OCT-2013
Amendment	22-NOV-2013
Amendment	05-DEC-2013
Amendment	18-DEC-2013
Amendment	12-FEB-2014
<b><u>Other Documents</u></b>	
Information Request (CMC)	11-MAR-2014
CMC review # 1	17-MAR-2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	20-MAR-2014
Amendment	25-MAR-2014
Amendment	09-APR-2014
Amendment	21-APR-2014
Amendment	13-MAY-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Trius Therapeutics, Inc.  
Address: Suite 101, 6310 Nancy Ridge Drive  
San Diego, CA 92121  
Representative: Ms. Mary Celine Scott  
Telephone: 858-452-0370 x 312

## CMC Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Sivextro  
 b) Non-Proprietary Name: (tedizolid phosphate)  
 c) Code Name/# (ONDQA only): N/A  
 d) Chem. Type/Submission Priority (ONDQA only):  
     • Chem. Type: 1  
     • Submission Priority: Priority

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Acute bacterial skin and skin structure infections

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

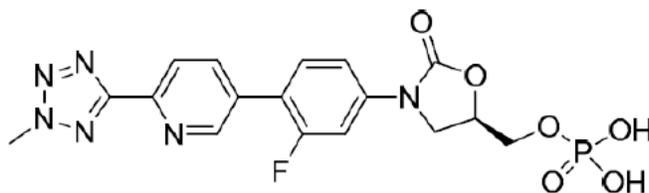
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[(5*R*)-(3-{3-Fluoro-4-[6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl]phenyl}-2-oxooxazolidin-5-yl)methyl hydrogen phosphate



Molecular formula: C<sub>17</sub>H<sub>16</sub>FN<sub>6</sub>O<sub>6</sub>.P  
 Molecular weight: 450.32

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3,4	Active	Reviewed by Dr. Yung De Lu on 28-JAN-2011 for NDA 21253 (SCS-11)	Type 1 USP (b) (4) vial
(b) (4)	III	(b) (4)	(b) (4)	1, 4	Active	Reviewed by OPS Quality Microbiologist on 8-JAN-2014	The information submitted in (b) (4) (CBER Master File) was also submitted in the CDER DMF (b) (4). Refer to Microbiology review of DMF# (b) (4) dated 11 DEC-2013.
(b) (4)	III	(b) (4)	(b) (4)	4	Active	Information is provided in the NDA and reviewed	DMF (b) (4) is housed in CBER and contains the CMC information of the stopper. NDA contains the testing per USP <381> and <88>, Adequate

<sup>1</sup> Action codes for DMF Table:  
 1 – DMF Reviewed.  
 Other codes indicate why the DMF was not reviewed, as follows:  
 2 –Type 1 DMF  
 3 – Reviewed previously and no revision since last review  
 4 – Sufficient information in application  
 5 – Authority to reference not granted  
 6 – DMF not available  
 7 – Other (explain under "Comments")

CMC Review Data Sheet

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77872	Active
NDA	205435	In house for tablet

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	16-JAN-2014	Office of Compliance
Methods Validation	Submitted to the St. Louis Laboratory on 15-NOV-2013	Pending	Dr. Michael Trehy, OTR
EA	Categorical exclusion is requested, and granted (see review)	17-MAR-2014 (CMC review # 1)	Dr. Rajiv Agarwal
Microbiology	Adequate	8-JAN-2013	Dr. Robert Mello
Pharmacology and Toxicology	Adequate (via Email)	12-DEC-2013	Dr. James J. Wild

## Executive Summary Section

# The CMC Review for NDA 205436

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the requested information identified in the CMC review #1 dated 17-MAR-2014 via amendment dated 20-MAR-2014. This NDA has provided adequate information to assure the identity, strength, purity and quality of the drug product.

The Office of Compliance has made an "Acceptable" recommendation for the facilities involved in this application.

Revisions to the proposed labeling (Highlights and Description sections) will be finalized during team review of the labeling.

Therefore, from the ONDQA perspective, this NDA may be approved with a 36 month expiration dating period.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

*The drug substance, Tedizolid phosphate, a pro-drug, is manufactured*

(b) (4)

(b) (4)

## Executive Summary Section

(b) (4)

*Process development studies concluded that the tedizolid phosphate drug substance manufacturing process is well controlled and robust. Assessment of key operations and parameters for each step of synthesis is performed and based on the process understanding, both critical and non-critical parameters are identified and reported in the submission. As a result, proven acceptable ranges have been defined which enable a robust manufacturing process and a high level of impurity control in the drug substance.*

(b) (4)

*As per an email dated 12-DEC-2013 from Dr. James Wild, Pharmacology and Toxicology reviewer, the applicant's analysis of potentially carcinogenic impurities and the limits they have set are consistent with the recommendations from the FDA draft guidance (Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches)*

## Executive Summary Section

The applicant amended the application with 12 more months of stability data via amendment dated 9-APR-2014. There was no observed change in (b) (4) form, bacterial endotoxins, or microbial limits for any of the test conditions (25°C/60% RH or 40°C/75% RH) at any of the time points for up to 48 months at 25°C/60% RH and 6 months 40°C/75% RH for batch 02090118 and up to 24 months at 25°C/60% RH and 6 months 40°C/75% RH for the other primary batches. No trends were noted in (b) (4) impurity levels for the primary batches or the supportive batch for up to 48 months when held at 25°C/60% RH and 6 months 40°C/75% RH. Two potential degradation products (b) (4) identified during the forced degradation studies and are included in the specification, even though they were not seen during long term and accelerated stability testing. The process-related impurities were also tracked on stability. The acceptance criterion for (b) (4) at the time of manufacture was NMT (b) (4), which was (b) (4) in the current specification.

Dr. Robert Mellow, OPS Microbiologist accepts the endotoxin limits and the microbial limits specification for the **drug substance** (refer to Dr. Robert Mello, OPS Quality Microbiologist review on 8-JAN-2014).

The stability data supports a retest period (b) (4) when the drug substance is stored (b) (4) as defined by USP (b) (4)

The applicant has provided the adequate responses to the requested information identified in the CMC review #1 dated 17-MAR-2014 via amendment dated 20-MAR-2014.

The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug substance manufacturing and testing operations is Acceptable.

## (2) Drug Product

Tedizolid phosphate for injection, 200 mg, is a sterile lyophilized powder for injection. (b) (4)

Each vial of tedizolid phosphate for injection contains (b) (4) of tedizolid phosphate. Following reconstitution of the vial contents with 4 mL of Sterile Water for Injection, a final volume (b) (4) is obtained (b) (4). This (b) (4) facilitates withdrawal of 4 mL of the (b) (4) tedizolid phosphate solution for full recovery of the label contents (i.e., 200 mg). This was confirmed according to Extractable Volume USP <1> Injections.

## Executive Summary Section

The reconstituted dose volume (4 mL) is to be added to an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. The drug product is presented in an (b) (4) USP Type I (b) (4) vial with (b) (4) (u) (v) stopper, and a (u) (v) seal with a (u) (v) flip-off top.

A 24 hour study was performed to assess the compatibility of tedizolid phosphate for injection with a 250 mL bag of 0.9% Sodium Chloride Injection USP, (saline) in combination with different IV administration sets (b) (4) that represent those typically found in the clinical setting. The data presented in the submission show no significant change in appearance, particulate matter, assay, impurities, pH, or microbial bioburden in tedizolid phosphate for injection reconstituted solutions.

The manufacturing process steps (unit operations) and processing parameters were evaluated for their criticality. The relationship between the quality attributes of the drug product and the control strategy for each critical process parameter are detailed and deemed adequate. In-process control testing is performed to ensure that the manufacture of tedizolid phosphate for injection routinely meets product specifications. (b) (4) lyophilization processes are the parameters or steps that are considered critical and monitored during the manufacturing of tedizolid phosphate for injection. The acceptance criterion for each critical process is in place to ensure the purity, quality and strength of the lyophilized drug product can be maintained during the manufacturing process.

In accordance with ICH Q6A, impurities from the drug substance that are synthesis related, and not degradation products, are controlled in the drug substance and do not need to be controlled in the drug product specification. Two degradation products, (b) (4) are however, controlled. There were no significant changes in the reconstitution time of the product. The pH of tedizolid phosphate for injection, reconstituted with 4 mL of Sterile Water for Injection, is tested in accordance with USP <791>. The pH ranged from (b) (4) (b) (4) for the lots tested on stability. All values at all-time points are within the proposed acceptance criterion (b) (4). All primary stability lots tested on stability have met the USP requirements for particulate matter. The dye ingress test method consists of the determination of leakage of a methylene blue solution into sealed vials by a spectrophotometric determination and assurance of sterility over time. The acceptance criterion of the Dye Ingress Test Method is “no detectable ingress of dye” and this is met.

The analytical procedures including the stability-indicating HPLC method and their validation were reviewed and found to be adequate. Method validation packages was sent to FDA laboratory (in DARRTS dated 15-NOV-2013) per

## Executive Summary Section

*ONDQA policy for its evaluation. Recommendation is pending, although the results of method validation are not necessary for the regulatory action.*

*In-use reconstitution stability studies were performed at the 18 and 24 month (via amendment dated 21-APR-2014) time point for batches 12TR1, 12TR2, 12TR3 and at the 12 and 18 month time point for batch 12TR4. The vials were stored in the horizontal position. The samples were tested for appearance, assay, degradation products, reconstitution time, clarity of solution, and visible particulate matter. The results indicate that there are no significant changes for any of the tests for reconstituted solutions after 24 hours storage at room temperature. All samples tested for lots 12TR1, 12TR2, 12TR3 and 12TR4 passed dye ingress testing at 12 and 24 months after storage at 25°C/60% RH and 30°C/75% RH.*

*Via amendment dated 21-APR-2014, the applicant provides stability data for up to **24 months** under the long-term conditions of 25°C/60% RH and the intermediate conditions of 30°C/75% RH. Stability data are also available for tedizolid phosphate for injection stored under the accelerated conditions of 40°C/75% RH for **6 months**.*

*The applicant now requests 36 months of expiration dating period, for the drug product manufactured at the (b) (4) site, when stored at 20°C to 25°C with excursions permitted to 15°C to 30°C (USP Controlled Room Temperature). After evaluating stability data for each attribute at all storage conditions it was apparent that little or no change occurred over time and thus it was determined that, as per ICH Q1E, statistical analysis was not necessary to support extrapolating the long-term stability data and that an expiration dating period of 2X of the long term data, but not to exceed X + 12 months, was appropriate*

*Therefore, the provided stability data now support 36 month expiration dating period when stored at the labeled conditions of 20°C to 25°C with excursions permitted to 15°C to 30°C (USP Controlled Room Temperature).*

*The applicant has provided the adequate responses to the requested information identified in the CMC review #1 dated 17-MAR-2014 via amendment dated 20-MAR-2014.*

*The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug product manufacturing and testing operations is "Acceptable"..*

## **B. Description of How the Drug Product is Intended to be Used**

The recommended dosage of SIVEXTRO is 200 mg administered once daily for six (6) days as an intravenous (IV) infusion (1 hour infusion time) in patients  $\geq 12$  years of age.

## Executive Summary Section

**C. Basis for Approvability Recommendation**

The Office of Compliance has made an overall site recommendation of “Acceptable.”

The OPS Quality Microbiology review recommends approval of the NDA.

Labeling revisions are marked up in the CMC review #1 and communicated to the clinical division and will be finalized during team review of the labeling. Container/labels are updated on 13-MAY-2014 and are now adequate.

The applicant has provided the adequate responses to the requested information identified in the CMC review #1 dated 17-MAR-2014 via amendment dated 20-MAR-2014.

This NDA has provided adequate information to assure the identity, strength, purity and quality of the drug product. Therefore, from the ONDQA perspective, this NDA may be approved.

**III. Administrative****A. Reviewer’s Signature:**

*(See appended electronic signature page)*

**B. Endorsement Block:**

Rajiv Agarwal, Ph.D.; Ph.D.

*(See appended electronic signature page)*

Rapti Madurawe, Ph.D., Branch Chief, Branch V, DNDQA II, ONDQA

**C. CC Block:** entered electronically in DARRTS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAJIV AGARWAL  
05/22/2014

RAPTI D MADURawe  
05/22/2014

# **NDA 205436**

**Sivextro  
(Tedizolid phosphate) for injection**

**Trius Therapeutics, Inc.**

**Rajiv Agarwal**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch V**

**CMC REVIEW OF NDA 205436  
For the Division of Anti-Infective Products**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 205436
2. REVIEW #: 1
3. REVIEW DATE: 14-MAR-2014
4. REVIEWER: Rajiv Agarwal, Ph.D.; Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	21-OCT-2013
Amendment	22-NOV-2013
Amendment	05-DEC-2013
Amendment	18-DEC-2013
Amendment	12-FEB-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Trius Therapeutics, Inc.  
Address: Suite 101, 6310 Nancy Ridge Drive  
San Diego, CA 92121  
Representative: Ms. Mary Celine Scott  
Telephone: 858-452-0370 x 312

8. DRUG PRODUCT NAME/CODE/TYPE:

- |   |                       |
|---|-----------------------|
| a) Proprietary Name:                            | Sivextro              |
| b) Non-Proprietary Name:                        | (tedizolid phosphate) |
| c) Code Name/# (ONDQA only):                    | N/A                   |
| d) Chem. Type/Submission Priority (ONDQA only): |                       |
| • Chem. Type:                                   | 1                     |
| • Submission Priority:                          | Priority              |

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

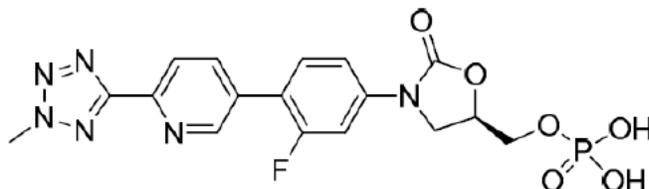
10. PHARMACOL. CATEGORY: Acute bacterial skin and skin structure infections

## CMC Review Data Sheet

11. DOSAGE FORM: Lyophilized powder for injection
12. STRENGTH/POTENCY: 200 mg
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED:  Rx  OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):  
 SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[(5*R*)-(3-{3-Fluoro-4-[6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl]phenyl}-2-oxooxazolidin-5-yl)methyl hydrogen phosphate



Molecular formula: C<sub>17</sub>H<sub>16</sub>FN<sub>6</sub>O<sub>6</sub>.P

Molecular weight: 450.32

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3,4	Active	Reviewed by Dr. Yung De Lu on 28-JAN-2011 for NDA 21253 (SCS-11)	Type 1 USP (b) (4) vial

CMC Review Data Sheet

(b) (4)	III	(b) (4)	1, 4	Active	Reviewed by OPS Quality Microbiologist on 8-JAN-2014	The information submitted in (b) (4) (CBER Master File) was also submitted in the CDER DMF (b) (4). Refer to Microbiology review of DMF (b) (4) dated 11 DEC-2013.
	III		4	Active	Information is provided in the NDA and reviewed	DMF (b) (4) is housed in CBER and contains the CMC information of the stopper. NDA contains the testing per USP <381> and <88>, Adequate

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77872	Active
NDA	205435	In house for tablet

## CMC Review Data Sheet

## 18. STATUS:

## ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	16-JAN-2014	Office of Compliance
Methods Validation	Submitted to the St. Louis Laboratory on 15-NOV-2013	Pending	Dr. Michael Trehy, OTR
EA	Categorical exclusion is requested, and granted (see review)	13-DEC-2013	Dr. Rajiv Agarwal
Microbiology	Adequate	8-JAN-2013	Dr. Robert Mello
Pharmacology and Toxicology	Pending	Pending	Dr. James J. Wild

## Executive Summary Section

# The CMC Review for NDA 205436

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Although the NDA in general has satisfactory CMC information, a CMC information request sent on 11-MAR-2014 is currently pending a response from the applicant.

The Office of Compliance has made an “Acceptable” recommendation for the facilities involved in this application.

Revisions to the proposed labeling (High Light and Description sections) will be finalized during team review of the labeling.

Therefore, from the ONDQA perspective, approval of this NDA is contingent upon satisfactory resolution of the CMC information request and final labeling. A recommendation for approval is not made at this time.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

*The drug substance, Tedizolid phosphate, a pro-drug, is manufactured*

(b) (4)

(b) (4)

## Executive Summary Section

(b) (4) *Process development studies concluded that the tedizolid phosphate drug substance manufacturing process is well controlled and robust. Assessment of key operations and parameters for each step of synthesis is performed and based on the process understanding, both critical and non-critical parameters are identified and reported in the submission. As a result, proven acceptable ranges have been defined which enable a robust manufacturing process and a high level of impurity control in the drug substance.*



(b) (4) *. As per an email dated 12-DEC-2013 from Dr. James Wild, Pharmacology and Toxicology reviewer, the applicant's analysis of potentially carcinogenic impurities and the limits they have set are consistent with the recommendations from the FDA draft guidance (Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches)*

*There was no observed change in (b) (4) form, bacterial endotoxins, or microbial limits for any of the test conditions (25°C/60% RH or 40°C/75% RH) at*

## Executive Summary Section

any of the time points for up to 36 months at 25°C/60% RH and 6 months 40°C/75% RH for batch 02090118 and up to 12 months at 25°C/60% RH and 6 months 40°C/75% RH for the other primary batches. No trends were noted in (b) (4) impurity levels for the primary batches or the supportive batch for up to 36 months when held at 25°C/60% RH and 6 months 40°C/75% RH. Two potential degradation products (b) (4) identified during the (b) (4) studies and are included in the specification, even though they were not seen during long term and accelerated stability testing. The process-related impurities were also tracked on stability. The acceptance criterion for (b) (4) at the time of manufacture was NMT (b) (4), which was (b) (4) in the current specification.

Dr. Robert Mellow, OPS Microbiologist accepts the endotoxin limits and the microbial limits specification for the **drug substance** (refer to Dr. Robert Mello, OPS Quality Microbiologist review on 8-JAN-2014).

The stability data supports a retest period of (b) (4) when the drug substance is stored (b) (4) as defined by USP (b) (4).

The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug substance manufacturing and testing operations is Acceptable (See Attachment).

**(2) Drug Product**

Tedizolid phosphate for injection, 200 mg, is a sterile lyophilized powder for injection. (b) (4)

Each vial of tedizolid phosphate for injection contains (b) (4) tedizolid phosphate. Following reconstitution of the vial contents with 4 mL of Sterile Water for Injection, a final volume (b) (4) is obtained (b) (4). This (b) (4) facilitates withdrawal of 4 mL of the (b) (4) tedizolid phosphate solution for full recovery of the label contents (i.e., 200 mg). This was confirmed according to Extractable Volume USP <1> Injections.

The reconstituted dose volume (4 mL) is to be added to an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. The drug product is presented in an (b) (4) USP Type I (b) (4) vial with a (b) (4) stopper, and a (b) (4) seal with a (b) (4) flip-off top.

## Executive Summary Section

*A 24 hour study was performed to assess the compatibility of tedizolid phosphate for injection with a 250 mL bag of 0.9% Sodium Chloride Injection USP, (saline) in combination with different IV administration sets (b) (4)*

*that represent those typically found in the clinical setting. The data presented in the submission show no significant change in appearance, particulate matter, assay, impurities, pH, or microbial bioburden in tedizolid phosphate for injection reconstituted solutions.*

*The manufacturing process steps (unit operations) and processing parameters were evaluated for their criticality. The relationship between the quality attributes of the drug product and the control strategy for each critical process parameter are detailed and deemed adequate. In-process control testing is performed to ensure that the manufacture of tedizolid phosphate for injection routinely meets product specifications. (b) (4)*

*lyophilization processes are the parameters or steps that are considered critical and monitored during the manufacturing of tedizolid phosphate for injection. The acceptance criterion for each critical process is in place to ensure the purity, quality and strength of the lyophilized drug product can be maintained during the manufacturing process.*

*In accordance with ICH Q6A, impurities from the drug substance that are synthesis related, and not degradation products, are controlled in the drug substance and do not need to be controlled in the drug product specification. Two degradation products, (b) (4) are however, controlled. There were no significant changes in the reconstitution time of the product. The pH of tedizolid phosphate for injection, reconstituted with 4 mL of Sterile Water for Injection, is tested in accordance with USP <791>. The pH ranged from (b) (4) for the lots tested on stability. All values at all-time points are within the proposed acceptance criterion of (b) (4). All primary stability lots tested on stability have met the USP requirements for particulate matter. The dye ingress test method consists of the determination of leakage of a methylene blue solution into sealed vials by a spectrophotometric determination and assurance of sterility over time. The acceptance criterion of the Dye Ingress Test Method is “no detectable ingress of dye” and this is met.*

*In-use reconstitution stability studies were performed at the 18 month time point for batches 12TR1, 12TR2, 12TR3 and at the 12 month time point for batch 12TR4. The vials were stored in the horizontal position. The samples were tested for appearance, assay, degradation products, reconstitution time, clarity of solution, and visible particulate matter. The results indicate that there are no significant changes for any of the tests for reconstituted solutions after 24 hours storage at room temperature.*

## Executive Summary Section

*Full stability evaluation of the five primary stability batches is provided. The analytical procedures including the stability indicating HPLC method and their validation were reviewed and found to be adequate. Method validation packages was sent to FDA laboratory (in DARRTS dated 15-NOV-2013) per ONDQA policy for its evaluation. Recommendation is pending.*

*A photostability study was performed on tedizolid phosphate for injection batch 12TR1.* (b) (4)

*No decrease in assay, increase in degradation products, or significant change in chiral purity, moisture or reconstitution time was observed for exposed vials as compared to the dark control. These results indicate that the tedizolid phosphate for injection drug product is not photosensitive and consequently does not require any special labeling or packaging to mitigate exposure to light. Leachable compounds confirmed to be present in the reconstituted samples include* (b) (4)

*The leachable compounds observed are not expected to pose a toxicological concern. Biological Reactivity tests, (USP <87> and <88>) were conducted on stopper and it passes the tests. Thus, the materials of construction of the containers and closures are appropriate for the intended application.*

*The applicant requests (b) (4) of expiration dating period, for the drug product manufactured at (b) (4) site, when stored at 20°C to 25°C with excursions permitted to 15°C to 30°C (USP Controlled Room Temperature), based on the primary stability batches manufactured at (b) (4) and the supportive stability batches manufactured at (b) (4) (36 months). The manufacturing process used at (b) (4) is very similar (not identical) to that used* (b) (4)

*(b) (4). In addition, the applicant did not do full testing (i.e., particulate matter and seal integrity) on the supportive stability samples. These tests are considered to be important for product quality during the shelf life. Therefore, the requested (b) (4) expiration dating for this lyophilized drug product for injection CANNOT be granted unless real time stability data is available on the product manufactured at (b) (4) site.*

*Therefore, the provided stability data support only (b) (4) expiration dating period when stored at the labeled conditions of 20°C to 25°C with excursions permitted to 15°C to 30°C (USP Controlled Room Temperature).*

## Executive Summary Section

*The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug product manufacturing and testing operations is "Acceptable" (See Attachment).*

**B. Description of How the Drug Product is Intended to be Used**

The recommended dosage of SIVEXTRO is 200 mg administered once daily for six (6) days as an intravenous (IV) infusion (1 hour infusion time) in patients  $\geq 12$  years of age.

**C. Basis for non-Approvability Recommendation**

The Office of Compliance has made an overall site recommendation of "Acceptable."

Labeling revisions are marked up in this review and will be finalized during team review of the labeling.

The NDA in general has satisfactory CMC information. However, the specification (per 21CFR 314.125(b)(1)) for the drug substance is not deemed adequate pending finalized acceptance criterion of impurity (b) (4) and optical rotation.

Therefore, from the ONDQA perspective, approval of this NDA in its present form is contingent upon satisfactory resolution of the deficiencies.

**III. Administrative****A. Reviewer's Signature:**

*(See appended electronic signature page)*

**B. Endorsement Block:**

Rajiv Agarwal, Ph.D.; Ph.D.

*(See appended electronic signature page)*

Rapti Madurawe, Ph.D., Branch Chief, Branch V, DNDQA II, ONDQA

**C. CC Block:** entered electronically in DARRTS

102 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAJIV AGARWAL  
03/16/2014

RAPTI D MADURAWA  
03/17/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications

## IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205436**

2. DATES AND GOALS:

Letter Date: October 21, 2013	Submission Received Date: October 21, 2013
PDUFA Goal Date: June 21, 2014	

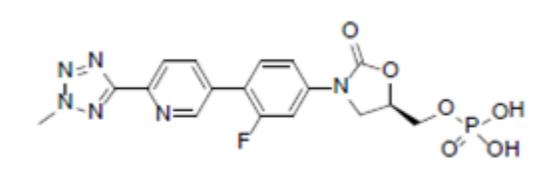
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Sivextro ( <i>proposed name</i> )
Established or Non-Proprietary Name (USAN):	Tedizolid Phosphate
Dosage Form:	Powder for Injection
Route of Administration	IV
Strength/Potency	200 mg
Rx/OTC Dispensed:	Rx

4. INDICATION:

Treatment of acute bacterial skin and skin structure infections (ABSSSI)

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h):

Trius Therapeutics, Inc. (Trius)

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**7. SUBMISSION PROPERTIES:**

Review Priority:	Priority
Submission Classification (Chemical Classification Code):	1
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAIP

**8. CONSULTS:**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology			<i>TBD</i>
Establishment Evaluation Request (EER)			<i>Submitted by Navi Bhandari on November 8, 2013</i>
Pharmacology/Toxicology			<i>TBD</i>
Methods Validation			<i>Submitted by Dr. Rajiv Agarwal on November 15, 2013</i>
Environmental Assessment		X	<i>Categorical exclusion claim</i>
CDRH			N/A
Other			N/A

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## Overall Filing Conclusions and Recommendations

### CMC:

<b>Is the Product Quality Section of the application fileable from a CMC perspective?</b> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
CMC Filing Issues: <i>None</i>

<b>Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?</b> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
CMC Comments for 74-Day Letter: <i>None</i>

### Biopharmaceutics:

<b>Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?</b> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
Biopharmaceutics Filing Issues: <i>N/A</i> <i>It has been determined by the Biopharmaceutics Reviewer assigned to this NDA (Dr. Minerva Hughes) that a Biopharmaceutics review is not needed for this NDA, and no further action is warranted from the ONDQA-Biopharmaceutics.</i>

<b>Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?</b> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Biopharmaceutics Comments for 74-Day Letter: <i>N/A</i>

### Microbiology:

<b>Is the Product Quality Section of the application fileable from a Microbiology perspective?</b> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
Microbiology Filing Issues: See Microbiology Filing Review for details and for any potential Microbiology review issues.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Summary of Initial Quality Assessment**

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
	X		

<b>Is a team review recommended?</b>	Yes	No	X
Suggested expertise for team:			

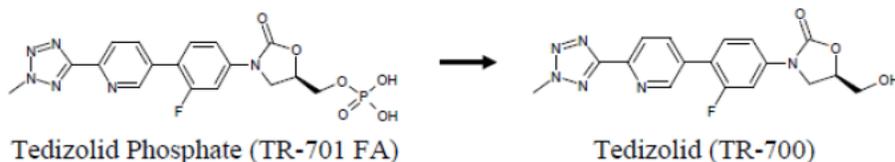
**Summary of Critical Issues and Complexities**

*This NDA provides for an IV formulation (sterile powder for injection) of a new synthetic antibiotic, tedizolid phosphate. It should be noted that this Applicant has submitted a concurrent NDA for an oral dosage form; tedizolid phosphate tablets (NDA 205435). The drug substance sections of the two NDAs are the same. For summary of the proposed drug substance, tedizolid phosphate, and the drug product for an oral administration (tedizolid phosphate tablets) refer to the IQA for NDA 205435. A brief summary of the proposed drug product for IV administration is provided in the IQA below.*

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

## Initial Quality Assessment

Tedizolid phosphate (TR-701 FA) is a novel oxazolidinone prodrug antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety tedizolid (TR-700), which has been shown to be the microbiologically active moiety against a variety of primarily gram-positive pathogens:



Tedizolid phosphate (200 mg) has been developed for intravenous (IV) and oral administration (once daily) for the treatment of acute bacterial skin and skin structure infections (ABSSSI). This NDA provides for tedizolid phosphate for injection, 200 mg; a separate NDA is pending for tedizolid phosphate tablets, 200 mg (NDA 205435).

The IV formulation of tedizolid has been developed via IND 106307. Important meetings with the Agency (which included a discussion of CMC issues) include:

1. EoP2 meeting on January 25, 2012 (preliminary responses dated January 20, 2012 and meeting minutes dated January 27, 2012 in DARRTS)
2. Pre-NDA meeting on May 13, 2013 (preliminary comments dated May 9, 2013 and meeting minutes dated June 3, 2013 in DARRTS)

### Drug Substance

Refer to IQA for NDA 205435.

### Drug Product

The drug product, tedizolid phosphate for injection, 200 mg, is a sterile lyophilized powder for injection. Each vial of tedizolid phosphate for injection contains (b) (4) tedizolid phosphate. The inactive components of the proposed drug product include mannitol, sodium hydroxide, hydrochloric acid and water for injection (Attachment 1, below). (b) (4)

Following reconstitution of the vial contents with 4 mL of Sterile Water for Injection, a final volume (b) (4) is obtained (b) (4). This (b) (4) facilitates withdrawal of 4 mL of the (b) (4) tedizolid phosphate solution for delivery of the drug label contents (i.e., 200 mg). The reconstituted solution of tedizolid phosphate (4 mL) is to be further diluted in 250 mL of 0.9% Sodium Chloride Injection, USP.

## ONDQA Initial Quality Assessment (IQA) and Filing Review For Pre-Marking Applications

The manufacturing process of the drug product, tedizolid phosphate for injection, involves conventional (b) (4) processes. Per applicant, lyophilization was selected during prototype formulation development (b) (4)

The applicant states that the proposed formulation and general process for commercial manufacture of this drug product are the same as those used to manufacture the drug product throughout the clinical program. The drug product formulation used in the Phase 3 studies is the same as the proposed commercial formulation. The batch size proposed to be validated for the commercial manufacture of tedizolid phosphate for injection, 200 mg, manufactured (b) (4) is (b) (4) (a table listing all the clinical and stability batches has been provided in the application and is reproduced below, Attachment 2).

The Pharmaceutical Development (PD) section is quite extensive and contains information on the selection of excipients, formulation, and process development, including discussions on the quality target product profile (QTPP), critical quality attributes (CQAs), critical process parameters (CPPs), Risk Assessment and Control Strategy approaches for the proposed drug product. The PD section contains also information on the suitability of the proposed container closure system (including potential extractables and leachables). In addition, the evaluation of the stability and compatibility of the proposed formulation with the proposed reconstitution (water) and dilution (saline) agents has been included in the PD section. *Comments: These data should be evaluated along with the information proposed in the labeling for the reconstituted and further diluted drug product (the adequacy of the proposed hold times and storage conditions included in the product labeling should also be consulted with the product quality microbiology reviewer). In addition, information provided on the leachables will need to be evaluated in detail and consulted with the pharm/tox reviewer, as necessary.*

The proposed drug product specification includes the following tests: appearance, identification, reconstitution time, constituted solution, pH of reconstituted solution, particulate matter, assay, degradation products, uniformity of dosage units, loss on drying, bacterial endotoxins, and sterility (reproduced below, Attachment 3).

Container closure system constitutes of the (b) (4) USP Type I (b) (4) vial with a (b) (4) (b) (4) stopper, and a (b) (4) seal with a (b) (4) (b) (4) flip-off top.

The stability data for 5 primary batches of tedizolid phosphate for injection manufactured by (b) (4) (as outlined in the table below) and stored under the long-term (25°C/60% RH) and intermediate (30°C/75% RH) conditions have been provided. Stability data are also available for tedizolid phosphate for injection stored under the accelerated conditions of 40°C/75% RH for 6 months.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Table 1 Summary of Tedizolid Phosphate for Injection Lots – Primary Stability Program**

Lot Number	Manufacture Site	Drug Substance Batch Number	Lot Size	Freeze Dryer Scale	Manufacture Date	Stability Start Date	Container Closure System	Data Available
P42601	(b) (4)	02090141R	(b) (4)	(b) (4)	Oct 2011	Nov 2012	(b) (4)	18 months
12TR1	(b) (4)	02110106R	(b) (4)	(b) (4)	Feb 2012	Feb 2012	(b) (4)	12 months
12TR2	(b) (4)	02110106R	(b) (4)	(b) (4)	Feb 2012	Feb 2012	(b) (4)	12 months
12TR3	(b) (4)	02110106R	(b) (4)	(b) (4)	Feb 2012	Feb 2012	(b) (4)	12 months
12TR4	(b) (4)	02120030	(b) (4)	(b) (4)	Aug 2012	Aug 2012	(b) (4)	9 months

As outlined in the table above, the initial NDA submission contains 12 months of stability data for three batches of the proposed drug product (12TR1, 12TR2, and 12TR3). In addition, Trius has submitted a stability update, in the amendment dated December 4, 2013, which includes 18 months of long-term stability data for these primary stability batches and additional stability data for other batches. *Comment: It should be noted that the applicant was informed during the pre-NDA meeting (on May 13, 2013) that this additional information (submitted during the NDA review) may or may not be reviewed during this review cycle depending on the available Agency's resources and internal timelines.*

A shelf-life of (b) (4) for the drug product, tedizolid phosphate for injection, to be stored at 20°C to 25°C with excursions permitted to 15°C to 30°C (USP Controlled Room Temperature) has been proposed. *Comment: The proposed expiration dating will be assessed based on the overall data available.*

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**FILING REVIEW CHECKLIST**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

<b>B. FACILITIES*</b>				
<b>* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			<i>Not applicable</i>

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

**C. ENVIRONMENTAL ASSESMENT**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		<i>Same as NDA 205435</i>
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		<i>Same as NDA 205435</i>
14.	Does the section contain information regarding the characterization of the DS?	X		<i>Same as NDA 205435</i>
15.	Does the section contain controls for the DS?	X		<i>Same as NDA 205435</i>
16.	Has stability data and analysis been provided for the drug substance?	X		<i>Same as NDA 205435</i>
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	X		<i>QbD elements (same as NDA 205435)</i>
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			<i>Not immediately obvious but not required either (same as NDA 205435)</i>

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<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		<i>QbD elements (risk assessment, control strategy, CQAs, etc.)</i>
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			<i>Not immediately obvious (but not required either)</i>

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
28.	Is there a methods validation package?	X		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		
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<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	July 26, 2012	
	III			July 23, 2012	(b) (4) (CBERMF)
	III			July 23, 2012	(b) (4) (CBER MF)

<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Attachment 1**

**Table 1 Unit Composition of Tedizolid Phosphate Solution for Lyophilization**

Component	Quality Standard	Function	Theoretical Quantity
Tedizolid Phosphate	In-house	Active Ingredient	(b) (4)
Mannitol	USP		(b) (4)
Sodium Hydroxide	USP		(b) (4)
Hydrochloric Acid	NF		pH adjustment
			(b) (4)
Water for Injection <sup>a</sup>	USP		(b) (4)

Abbreviations: NF=National Formulary; qs=quantity sufficient; USP=United States Pharmacopeia

<sup>a</sup>Water for Injection is essentially removed during lyophilization.

**Table 2 Unit Composition of Tedizolid Phosphate for Injection, 200 mg**

Component	Quality Standard	Function	Unit Formula
Tedizolid Phosphate	In house	Active Ingredient	(b) (4)
Mannitol	USP	(b) (4)	105 mg
Sodium Hydroxide	USP		(b) (4)
Hydrochloric Acid	NF	pH adjustment	qs for pH adjustment
			(b) (4)
Water for Injection <sup>b</sup>	USP		(b) (4)

Abbreviations: NF=National Formulary; qs=quantity sufficient; USP=United States Pharmacopeia

(b) (4)

<sup>b</sup>Water for Injection is essentially removed during lyophilization.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Attachment 2**

**Table 19 History, Disposition and Batch Size Comparison of Clinical  
Tedizolid Phosphate for Injection Batches**

Drug Product Lot	Strength <sup>a</sup> (mg vial)	Drug Product Manufacturing Site	Drug Substance Lot	Mfg. Date	Batch Size	Lot Use
B090135	200	(b) (4)	5133-D-R1-01-16-01	March 2009	(b) (4)	Stability
B100238	200		02090118	March 2010		Stability
B110185	200		02090141R	March 2011		Stability
P42601A <sup>b</sup>	200		02090141R	October 2011		Phase 1 study 16102
12TR1	200		02110106R	February 2012		Phase 3 study TR701-113
12TR2	200		02110106R	February 2012		Phase 1 study TR701-123 and 16101
12TR3	200		02110106R	February 2012		Stability
12TR4	200		02120030	August 2012		Phase 1 study TR701-113
			02110106R			Phase 3 study TR701-113
						Registration stability
						Registration stability
						Registration stability

<sup>a</sup>The (b) (4) clinical batches of tedizolid phosphate for injection manufactured to date is the same as the proposed commercial formulation.

<sup>b</sup>The container closure (vial, stopper, and seal) was changed to the proposed commercial configuration starting with batch P42601A, in October 2011 see Section 4.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**Attachment 3**

**Table 1 Proposed Commercial Specification for Tedizolid Phosphate for Injection, 200 mg**

Test	Acceptance Criteria	Analytical Procedure
Appearance	White to off-white lyophilized cake in a (b) (4) vial with stopper, (b) (4) with (b) (4) flip off top	Visual
Identification A	The spectrum of the sample corresponds to the reference spectrum	FTIR (USP <197> and AP-024)
Identification B	The retention time of the sample corresponds to the retention time of the reference standard	HPLC (AP-020)
Reconstitution Time	NMT (b) (4)	USP <1> and AP-025
Constituted Solutions Completeness Clarity Particulate Matter	Meets USP <1> requirements for constituted solutions	USP <1>
pH of reconstituted solution	(b) (4)	USP <791>
Particulate Matter Particle count (b) (4) Particle count (b) (4)	NMT (b) (4) NMT (b) (4)	USP <788> Method 2
Assay	90.0%-110.0% of total vial content <sup>a</sup>	HPLC (AP-020)
Degradation Products Specified (b) (4) Unspecified Any other individual, each Total	NMT (b) (4) NMT NMT NMT	HPLC (AP-020)
Uniformity of Dosage Units by Weight Variation	Meets USP <905> requirements	USP <905>
Loss on Drying	NMT (b) (4)	USP <731> TGA
Sterility	No evidence of microbial growth	USP <71>
Bacterial Endotoxins	NMT (b) (4)	USP <85> Gel Clot

Abbreviations: EU=endotoxin unit; FTIR= Fourier Transform Infrared Spectrometry; HPLC=high performance liquid chromatography; NMT=not more than; TGA=thermogravimetric analysis; USP=United States Pharmacopeia

(b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

*See appended electronic signature page*

*Dorota Matecka, Ph.D.*

CMC-Lead

Division II

Office of New Drug Quality Assessment

*{See appended electronic signature page}*

*Rapti Madurawe, Ph. D.*

Branch Chief

Division II

Office of New Drug Quality Assessment

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/s/  
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DOROTA M MATECKA  
12/18/2013

RAPTI D MADURawe  
12/18/2013

**METHODS VALIDATION CONSULT REQUEST FORM**

**TO: FDA**  
**Division of Pharmaceutical Analysis**  
**Attn: Michael Trehy**  
**Suite 1002**  
**1114 Market Street**  
**St. Louis, MO 63101**

**FROM:** Rajiv Agarwal, Method Validation Requestor, CMC Reviewer  
Dorota M Matecka, Method Validation Requestor, CMC Lead  
Office of New Drug Quality Assessment (ONDQA)  
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**Through:** Rapti Madurawe, Branch Chief  
Phone: (301)-796-1408  
**And** Youbang Liu  
ONDQA Methods Validation Project Manager  
Phone: 301-796-1926

**SUBJECT:** Methods Validation Request

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Application Number: NDA 205436

Name of Product: Tradename(tedizolid phosphate) [for injection](#), 200 mg

Applicant: Trius Therapeutics, Inc.

Applicant's Contact Person: Mary Celine Scott, Ph.D; MBA

Address: 6310 Nancy Ridge Drive, Suite 105, San Diego, CA

Telephone: 858-452-0370 x 312

Fax: 858-408-3002

Email: [mccott@triusrx.com](mailto:mccott@triusrx.com)

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Date NDA Received by CDER: **18-OCT-2013**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **19-Jun-2013**

Special Handling Required: No

DATE of Request: **15-NOV-2013**

DEA Class: N/A

Requested Completion Date: 21-FEB-2014

**Format of Methods Validation Package (MVP)**

PDUFA User Fee Goal Date: **21-APR-2014**

Paper      x Electronic       Mixed

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We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

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MVP Reference #	<b>METHODS VALIDATION REQUEST</b>			NDA # 205436
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
To be requested by FDA Lab				
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1 and S.4.2
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1 and P.5.2
Supporting Data for Accuracy, Specificity, etc.				3.2.S.4.3 and 3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.S.4.4 and 3.2.P.5.4
Other:				
⇒ ITEM 3: <b>REQUESTED DETERMINATIONS</b> Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
AP-020	HPLC Method for Identity, Assay and Related Substances of Tedizolid Phosphate in Tedizolid Phosphate for Injection	*See below	0	
AP-022	HPLC Method for Chiral Purity of Tedizolid Phosphate in Tedizolid Phosphate for Injection	*See below	0	
Additional Comments:				
All information in EDR. All tests and validation listed in <u>Section 3.2.R: Methods Validation Package</u> with links to 3.2.S and 3.2.P.				
<b>A companion NDA 205435 contains identical method for drug substance and a method validation is requested separately.</b>				

## Methods Validation Request Criteria

MV Request Category	Description
<b>0</b>	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
<b>1</b>	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
<b>2</b>	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
<b>3</b>	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
<b>4</b>	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
<b>5</b>	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
<b>6</b>	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
<b>7</b>	Methods that are subject to a “for cause” reason

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/s/  
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RAJIV AGARWAL  
11/15/2013

RAPTI D MADURawe  
11/15/2013

YOUBANG LIU  
11/15/2013