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RESEARCH**

APPLICATION NUMBER:

205435Orig1s000

CHEMISTRY REVIEW(S)

NDA 205435

Sivextro (Tedizolid phosphate) Tablets

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 205435
For the Division of Anti-Infective Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 205435
2. REVIEW #: 2
3. REVIEW DATE: 23-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	12-FEB-2014
<u>Other documents</u>	
Information request (CMC)	11-MAR-2014
CMC review # 1	17-MAR-2014

6. SUBMISSION(S) BEING REVIEWED:

Amendment	20-MAR-2014
Amendment	25-MAR-2014
Amendment	09-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

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Sivextro
- b) Non-Proprietary Name: (tedizolid phosphate)

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	7-MAR-2008	Reviewed by Dr. Bogdon Kurtyka of ONDQA
(b) (4)	III	(b) (4)	(b) (4)	3,4	Adequate	13-MAY-2010	Reviewed by Dr. Wendy Wilson of ONDQA
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	20-NOV02013	Sufficient information in the NDA. Refer to section S.6.
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	20-NOV-2013	Sufficient information (compliance to 21 CFR and USP 661 in the NDA.
(b) (4)	III	(b) (4)	(b) (4)	3,4	Adequate	12-JAN-2005	Reviewed by Dr. James Vidra of ONDQA
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate*	5-DEC-2013	Reviewed by this reviewer*

¹ 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")

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

* Due to the system Error in DARRTS for the DMF (b) (4), electronic submission of the review in DARRTS and its concurrence was not performed by this reviewer and Branch Chief, Rapti Madurawe. Individual components of the color coating are described in CMC review (see Description section on page 104 of CMC review #1). The components meet the current USP requirement and have been used in other FDA approved products.

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77872	Active
NDA	205436	In house for injection

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 CMC review #1)	17-MAR-2014	Dr. Rajiv Agarwal
Microbiology	Adequate	07-NOV-2013	Dr. Bryan Riley
Pharmacology and Toxicology (Drug substance and tablet drug product)	Adequate (via Email)	12-DEC-2013	Dr. James J. Wild
Biopharmaceutics	Tablet dissolution	11-MAR-2014	Dr. Minerva Hughes

Executive Summary Section

The CMC Review for NDA 205435

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 (Highlight 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)



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)

(b) (4)

(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)

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)

Executive Summary Section

(b) (4) 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 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 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 (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 (See CMC review # 1).

(2) Drug Product

The drug product, an oral tablet of 200 mg strength, is available as immediate-release, film coated yellow oval-shaped tablets debossed with "TZD" on the obverse and "200" on the reverse side. Tedizolid phosphate tablets will be packaged in high density polyethylene (HDPE) 40 cc bottles with white (b) (4) Child Resistant Closure (b) (4) (30 tablets for commercial and (b) (4) tablets for physician's sample) or as blister packs (child resistant, push/peel) with (b) (4) aluminum foil backing (6 tablets). (b) (4) manufacturers the tablet drug product.

All excipients used in the manufacture of the drug product are listed in the FDA's Inactive Ingredient Guide (IIG) at or below the levels outlined for oral formulations

Executive Summary Section

Tedizolid phosphate tablets, 200 mg is an immediate release film coated tablet

(b) (4)

Manufacturing process development did not identify any critical process parameters or any drug substance attributes important to the manufacturability and performance of the drug product

The process for the proposed (b) (4) batch size of immediate-release tablets is the same process used for the development batch size. The tedizolid phosphate tablets manufacturing process (Batches FXGB, GNFH, GNFF, GNFG, and KCVX) has not changed since the first clinical lot of tablets (01138-085, 01138-089, RD0950, B090282 and B090406).

(b) (4)

Adequate in-process tests and critical parameters and their acceptance criterion are in place to ensure the purity, quality and strength of the tablet drug product can be maintained during the manufacturing process. The dissolution method and the proposed acceptance criteria (at release and during stability testing) is deemed acceptable to the Biopharmaceutics reviewer, Dr. Minerva Hughes (refer to the review on 11-MAR-2014).

In accordance with ICH Q6A, impurities from the drug substance that are synthesis related, and not degradation products, are controlled

(b) (4)

Full stability evaluation of the three primary lots packaged in bottles are being conducted to support 30 tablet packaging configurations.

(b) (4)

(b) (4)

Dr. Bryan Riley, OPS Microbiologist accepts the microbial limits specification for the drug product (refer to Dr. Bryan Riley, OPS Quality Microbiologist review on 7-NOV-2013).

The analytical procedures including the stability indicating HPLC method and their validation were reviewed and found to be adequate. Method validation

Executive Summary Section

packages was sent to FDA laboratory (in DARRTS dated 15-NOV-2013) per ONDQA policy for its evaluation. Recommendation is pending.

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 and 13-MAY-2014.

The stability data provide support for packaging tablets in an HDPE bottle container/closure and (b)(4) foil blisters. Based on the updated stability data package on 9-APR-2014, a 36 month expiration dating period, as requested, is granted, 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 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 CMC review # 1).

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

The recommended dosage of Sivextro is 200 mg administered orally once daily for six (6) days (with or without food).

C. Basis for Approvability Recommendation

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

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.

Both the Biopharmaceutics and OPS Quality Microbiology reviews recommend approval of the NDA.

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.

Executive Summary Section

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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/s/

RAJIV AGARWAL
05/22/2014

RAPTI D MADURawe
05/22/2014

NDA 205435

Sivextro (Tedizolid phosphate) Tablets

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 205435
For the Division of Anti-Infective Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 205435
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	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)

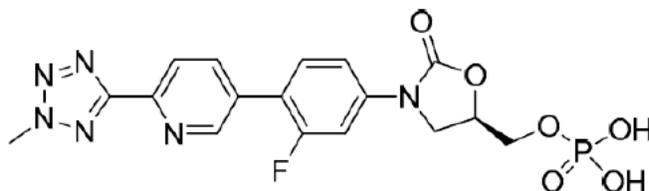
10. PHARMACOL. CATEGORY: Acute bacterial skin and skin structure infections

CMC Review Data Sheet

11. DOSAGE FORM: Tablets (immediate release)
12. STRENGTH/POTENCY: 200 mg
13. ROUTE OF ADMINISTRATION: Oral
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:

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



Molecular formula: C₁₇H₁₆FN₆O₆.P
Molecular weight: 450.32

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	7-MAR-2008	Reviewed by Dr. Bogdon Kurtyka of ONDQA
(b) (4)	III	(b) (4)	(b) (4)	3,4	Adequate	13-MAY-2010	Reviewed by Dr. Wendy Wilson of ONDQA

CMC Review Data Sheet

(b) (4)	III	(b) (4)	4	Adequate	20-NOV02013	Sufficient information in the NDA. Refer to section S.6.
	III		4	Adequate	20-NOV-2013	Sufficient information (compliance to 21 CFR and USP 661 in the NDA.
	III		3,4	Adequate	12-JAN-2005	Reviewed by Dr. James Vidra of ONDQA
	III		1	Adequate*	5-DEC-2013	Reviewed by this reviewer*

¹ 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")

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

* Due to the system Error in DARRTS for the DMF (b) (4) electronic submission of the review in DARRTS and its concurrence was not performed by this reviewer and Branch Chief, Rapti Madurawe. Individual components of the color coating are described in this review (see Description section on page 104). The components meet the current USP requirement and have been used in other FDA approved products.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77872	Active
NDA	205436	In house for injection

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		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)	14-MAR-2014	Dr. Rajiv Agarwal
Microbiology	Adequate	07-NOV-2013	Dr. Bryan Riley
Pharmacology and Toxicology (Drug substance and tablet drug product)	Adequate for Drug substance (via Email) Pending for tablet drug product	12-DEC-2013 Pending	Dr. James J. Wild
Biopharmaceutics	Pending (BCS Classification of the drug substance and tablet dissolution)	11-MAR-2014	Dr. Minerva Hughes

Executive Summary Section

The CMC Review for NDA 205435

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 pending 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)

Process development studies concluded that the tedizolid

Executive Summary Section

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)



(b) (4)



(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) 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 36 months at 25°C/60% RH and 6 months

Executive Summary Section

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) 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 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

The drug product, an oral tablet of 200 mg strength, is available as immediate-release, film coated yellow oval-shaped tablets debossed with "TZD" on the obverse and "200" on the reverse side. Tedizolid phosphate tablets will be packaged in high density polyethylene (HDPE) 40 cc bottles with white (b) (4) Child Resistant Closure (b) (4) (b) (4) tablets for commercial and (b) (4) tablets for physician's sample) or as blister packs with (b) (4) aluminum foil backing (6 tablets). (b) (4) manufacturers the tablet drug product.

All excipients used in the manufacture of the drug product are listed in the FDA's Inactive Ingredient Guide (IIG) at or below the levels outlined for oral formulations

Tedizolid phosphate tablets, 200 mg is an immediate release film coated tablet (b) (4)

Manufacturing process development did not identify any critical process parameters or any drug substance attributes important to the manufacturability and performance of the drug product

Executive Summary Section

The process for the proposed (b) (4) batch size of immediate-release tablets is the same process used for the development batch size. The tedizolid phosphate tablets manufacturing process (Batches FXGB, GNFH, GNFF, GNFG, and KCVX) has not changed since the first clinical lot of tablets (01138-085, 01138-089, RD0950, B090282 and B090406). (b) (4)

(b) (4) Adequate in-process tests and critical parameters and their acceptance criterion are in place to ensure the purity, quality and strength of the tablet drug product can be maintained during the manufacturing process. The dissolution method and the proposed acceptance criteria (at release and during stability testings) is deemed acceptable to the Biopharmaceutics reviewer, Dr. Minerva Hughes (refer to the review on 11-MAR-2014).

In accordance with ICH Q6A, impurities from the drug substance that are synthesis related, and not degradation products, are controlled (b) (4)

Full stability evaluation of the three primary lots packaged in bottles (b) (4) are being conducted to support 30 tablet packaging configurations. (b) (4)

Dr. Bryan Riley, OPS Microbiologist accepts the microbial limits specification for the drug product (refer to Dr. Bryan Riley, OPS Quality Microbiologist review on 7-NOV-2013).

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.

The stability data provide support for packaging tablets in an HDPE bottle container/closure and (b) (4) foil blisters. Based on the stability data package, a (b) (4) expiration dating period is granted 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 orally once daily for six (6) days (with or without food).

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 following CMC issues are currently pending resolution.

- 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.
- A complete description of the commercial scale drug product manufacturing process including all critical process parameter and process parameter targets and ranges that are in the batch manufacturing instruction for the production of drug product should be provided.

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

Executive Summary Section

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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/s/

RAJIV AGARWAL
03/15/2014

RAPTI D MADURawe
03/17/2014