CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date May 23, 2014

From Steven B. Hertz, Consumer Safety Officer

Subject Non-concurrence with (b) (4)-DO Withhold Recommendation for NDA 21883, DALBAVANCIN (b) (4) 500MG INJECTION

Thru Mahesh Ramanadham, Branch Chief (Acting), NDMAB, OMPQ/DGMPA

To Navdeep Bhandari, CDER/OAP/DAIP, ONDQA

Applicant: Durata Therapeutics
200 South Wacker Dr, Suite 2550
Chicago, IL 60606

Establishment: (b) (4)

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of a pre-approval inspection (PAI) and GMP inspection conducted by (b) (4) DO investigators from (b) (4) at the (b) (4). DGMPA has also reviewed the firm's written responses dated May 14, 2014, May 20, 2014, and May 21, 2014 to the FDA Form-483 observations. This inspection was initiated by (b) (4) to provide pre-approval coverage of NDA 21883. (b) (4) is named in NDA 21883 as the site for drug product (b) (4) manufacturing, labeling, and packaging, release testing, and stability testing.

DGMPA does not concur with (b) (4) DO's withhold recommendation for NDA 21883. (b) (4)-DO recommended withholding approval of this application due to product specific deficiencies. The following deficiencies specific to NDA 21883, DALBAVANCIN (b) (4)/500MG INJECTION were observed:

1. Observation 1: Control procedures are not established which validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in-process material and the drug product.

   Firm response to observation 1: Firm provided justification for its "unit operation" approach to process performance qualification and determination that it had completed Stage 2 process validation.

   (b) (4)-DO evaluation of firm's response: (b) (4)-DO determined that the firm's response was not adequate. The response did not address firm's ambiguous acceptance criteria for process validation and insufficient procedures for how process validation evaluation would be conducted. Additionally, (b) (4)-DO determined the firm did not adequately address and evaluate multiple deviations observed during process validation manufacturing operations.

CDER/OMPQ/DGMPA evaluation of firm's response: DGMPA concurred with (b) (4)-DO's assessment of the firm's response. Additional communication via teleconference was held between DGMPA, (b) (4)-DO, and the firm (b) (4). The firm submitted an additional addendum to its response, as well as written commitments, to revising its procedures regarding process validation, manufacturing two additional process performance qualification batches, and performing additional process performance analysis with respect to batch release and deviation review. Both DGMPA and (b) (4)-DO deemed the additional addendum and commitments as acceptable.

Conclusion: Response and additional addendums/commitments are acceptable.

CDER/OC/OMPQ/DGMPA Recommendation:

Based on the above assessment of the inspection findings, the firm's response to Form 483 observations, and additional addendum and commitments from the firm, DGMPA does not concur with the (b) (4)DO's recommendation to withhold approval of NDA 21883, DALBAVANCIN (b) (4)/500MG INJECTION. DGMPA recommends that corrective actions to the Form 483 should be verified on a follow up inspection.

If you have any questions, please contact me at (301) 796-3203 or by email at steven.hertz@fda.hhs.gov.

Steven B. Hertz
Consumer Safety Officer

cc:

(b) (4) Pre-Approval Manager (PAM),
NDMAB Acting Team Leader
CMS case #: (b) (4)

Reference ID: 3512162

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/s/

STEVEN B HERTZ
05/23/2014

MAHESH R RAMANADHAM
05/23/2014

NDA 21-883

DALVANCE™
(dalbavancin) for injection
500 mg / vial

Durata Therapeutics, Inc.

Balajee Shanmugam
Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Anti-Infective Products

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1. NDA 21883

2. REVIEW #: 4.1 Addendum

3. REVIEW DATE: 22-MAY-2014

4. REVIEWERS: Balajee Shanmugam
   Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date	Status
Original, as amended	21-DEC-2004	AE 21-SEP-2005
Resubmission, as amended (Class 2)	20-DEC-2005	AE 20-DEC-2007
Resubmission (Class 2)	30-MAY-2008	Withdrawn 15-SEP-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
Resubmission after Withdrawal (0000) [sdn-083]	26-SEP-2013
Amendment (1004) (b) (4) cross-contamination	21-OCT-2013
Amendment (1005) Stability update	25-OCT-2013
Amendment (1013) Stability update	27-NOV-2013
Amendment (1014) Stability update	05-DEC-2013
Amendment (1020) Response to information request; labeling	09-JAN-2014
Amendment (1024) Stability update	13-FEB-2013
Amendment (1030) Infusion solution compatibility	18-MAR-2014
Amendment (1032) Labeling, container / carton	01-APR-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Durata Therapeutics, Inc.
HQ Address:	200 South Wacker Drive, Suite 2550 Chicago, IL 60606
Representative:	Briton Shell, Ph.D., Director, Regulatory Affairs
Address:	322 East Main Street, 3rd Floor Branford, CT 06405
Telephone:	203-871-4609
email:	bshell@duratatherapeutics.com

Reference ID: 3511395

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Dalvance™
   b) Non-Proprietary Name (USAN): dalbavancin
   c) Code Name/#: DUR001; VER001; BI397; MDL 64,397; A-A-1
   d) CAS Registry Number: CAS-171500-79-1
   e) Chem. Type/Submission Priority:
      i. Chem. Type: 1 NME (in *'the Program'*)
      ii. Submission Priority: Priority

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

10. PHARMACOL. CATEGORY: Antibacterial Antibiotic - Systemic (4010900)

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 500 mg free base / vial

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
    _____SPOTS product – Form Completed

    ___X__Not a SPOTS product

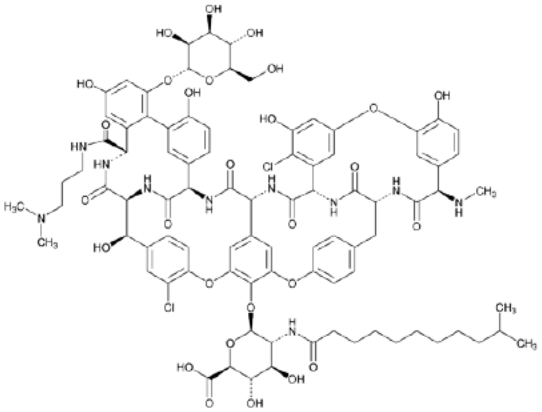
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

USAN/INN: Dalbavancin

CAS Chemical Name (B_0): Ristomycin A aglycone, 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-[2-deoxy-2-[(10-methyl-1-oxoundecyl)amino]-β-D-gluco-pyranuronosyl]-38-[[[3-(dimethylamino)propyl]amino]carbonyl]-42-*O*-α-D-mannopyranosyl-N^{15}-methyl-;

Reference ID: 3511395

Structural Formula: Dalbavancin (B_0)



Molecular Formula (Dalbavancin B_0): $C_{88}H_{100}Cl_2N_{10}O_{28}$ (free base)

Molecular Weight (Dalbavancin B_0): 1816.7

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	-	-	LoA 05/07/2013
	III			3,4	Adequate	19-SEP-2012	LoA 04/19/2013

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)

B. Other Documents:

APPLICATION	DESCRIPTION	DOCUMENT
IND 60613	IND for Dalbavancin	see darrts
NDA 21883	Original Dalbavancin NDA	Filing Checklist, R. Madurawe, 01/26/2005
NDA 21883	Original Dalbavancin NDA	Chemistry Review #1, R. Madurawe, 09/20/2005
NDA 21883	First resubmission	Chemistry Review #2, B. Shanmugam, 05/24/2006
NDA 21883	Second resubmission	Chemistry Review #3, B. Shanmugam, 11/02/2007
NDA 21883	Current (third) resubmission	Initial Quality Assessment, D. Matecka, 11/26/2013
NDA 21883	"	Chemistry Review #4, M. Seggel/B. Shanmugam, 2/26/2014
NDA 21883	"	Chemistry Review #4.1, M. Seggel/B. Shanmugam, 5/16/2014

Reference ID: 3511395

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION*	DATE	REVIEWER
Biometrics	n/a		
EES	Approval	5/22/14	S. Hertz, Office of Compliance
Pharm/Tox	Approval	3/10/14	T. Miller
ONDQA Biopharmaceutics	Approval	3/4/14	H. Mahayni
LNC	n/a		
Methods Validation	Acceptable	5/15/14	CDER/DPA
DMEPA	Proprietary name acceptable Labeling revisions recommended	11/25/13 02/28/14	A. Winiarski
EA	Categorical exclusion (based on $EIC_{aquatic} < 1$ ppb) is acceptable	this review	M. Seggel
Quality Microbiology	Approval	12/24/13	S. Donald, OPS/NDMS

*See darrts for associated reviews of NDA 21883.

19. REVIEW TIMELINE AND GOAL DATES

GRMP Goal	26-FEB-2014
PDUFA Goal	26-MAY-2014

Reference ID: 3511395

The Chemistry Review for NDA 21-883

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient information to assure identity, strength, quality, purity, potency and bioavailability of dalbavancin, a new molecular entity, and the finished drug product, dalbavancin for injection. The proposed regulatory analytical procedures were found "acceptable for control and regulatory purposes," by CDER's St. Louis Laboratory (DPA). As revised, the labeling (package insert, container and carton) is acceptable from the CMC perspective.

The drug substance facility and the drug product facility, as well as one testing laboratory, have been inspected. On May 22, 2014, the Office of Compliance issued an overall recommendation of Acceptable.

Therefore, from the CMC perspective this NDA is recommended for Approval.

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

PMC: Replace [redacted] (b) (4) used for preparing the Master Cell Bank with a [redacted] (b) (4). To be completed by June 30, 2016.

Pre-Marketing Commitment: Submit batch release test results from upcoming process performance qualification lot(s) when process performance qualification activities have been completed. To be completed by November 30, 2014. (See Office of Compliance memo.)

II. Summary of Chemistry Assessments

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

The drug substance dalbavancin hydrochloride is a semi-synthetic purified lipoglycopeptide antibacterial agent derived from the modification of dalbavancin. Dalbavancin acts by inhibiting bacterial cell wall biosynthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking of disaccharide subunits. Dalbavancin hydrochloride is present in two major class of structural homologs, dalbavancin A and dalbavancin B. Dalbavancin A comprises of two subtypes dalbavancin A_0 and A_1 and constitutes about [redacted] (b) (4) of the active drug substance. Dalbavancin B which constitutes about [redacted] (b) (4) of the drug substance is comprised of 3 subtypes, dalbavancin B_0, B_1 and B_2. All components

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of dalbavancin share the core component and primarily differ in the length and branching of the fatty acid side-chain and presence of a methyl group. The drug substance occurs as a white to tan solid and is freely soluble in water. Dalbavancin is manufactured by fermentation and subsequent chemical modification to obtain the API.

Dalbavancin for Injection is a sterile, lyophilized powder for injection. Each single use vial contains 500 mg dalbavancin free base, (b) (4) mg mannitol and (b) (4) mg lactose monohydrate. Mannitol and lactose serve as (b) (4) . The pH is adjusted to (b) (4) with sodium hydroxide (and/or hydrochloric acid). The container/closure system consists of a 50 mL Type I glass vial and a (b) (4) . The stoppered vials are sealed with a (b) (4) .

The drug product is manufactured in (b) (4)

The quality, purity, potency and strength of the drug product is assured through appropriate in-process controls and regulatory testing that includes (b) (4) Tests for solution pH and particulate matter in reconstituted product are also part of the regulatory specification.

Compatibility with 5% Dextrose for Injection infusion solution was demonstrated by acceptable results from tests for appearance (visual inspection), assay, degradation products, pH and sub-visible particulate contamination (USP<788>).

Long term (25°C/60% RH) and accelerated (40°C/75% RH) stability studies on primary and supporting batches support an expiration dating period of 36 months at 25°C.

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

Dalvance™ (dalbavancin) for injection is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of Gram-positive microorganisms. A 1000 mg dose (contents of 2 vials) is administered on Day of the treatment followed by 500 mg on Day 8. Vial contents are reconstituted with 25 mL Sterile Water for Injection, USP, and subsequently diluted only with 5% Dextrose Injection, USP to a final concentration of 1 to 5 mg/mL. The dose is then administered by intravenous infusion over 30 minutes.

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The unreconstituted drug product should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature]. The currently established expiration dating period is 36 months under the labeled storage conditions. It should be noted that storage of the lyophilized powder at refrigerated conditions is acceptable, but this is not mentioned in the labeling. See S. Donald's Product Quality Microbiology review regarding holding reconstituted solution and infusion solution (the product does not contain a preservative, although dalbavancin is an antibacterial agent).

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product throughout the shelf life.

Inspections of the drug substance and drug product manufacturing and testing facilities have been completed. An overall recommendation of Acceptable was issued by the Office of Compliance on May 22, 2014. See attached EES Detail Report. See also Office of Compliance memo.

The regulatory methods (and in particular the HPLC assay for both drug substance and drug product) have been verified by FDA's St Louis laboratory (CDER/DPA).

The applicant originally labeled the product as [redacted] (b) (4) [redacted] the non-proprietary name has been revised to 'dalbavancin for injection' in accordance with the USP salt policy. The strength of the product was already given as 500 mg as the free base, so no changes to the strength statement were required as a result of implementation of the salt policy. All labels have the required 'CMC' information. The proposed trademark, Dalvance, has been found acceptable by DMEPA.

Reference ID: 3511395

III. Administrative

A. Reviewer's Signature

{see electronic signature page}
Balajee Shanmugam, Ph.D.

{see electronic signature page}
Mark R. Seggel, Chemistry Reviewer

B. Endorsement Block

{see electronic signature page}
Dorota Matecka, Ph.D., CMC Lead and Secondary Reviewer

{see electronic signature page}
Rapti Madurawe, Ph.D., Branch Chief

C. CC Block

{see DARRTS}

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Reference ID: 3511395

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/s/

MARK R SEGGEL
05/22/2014

BALAJEE SHANMUGAM
05/22/2014

DOROTA M MATECKA
05/22/2014

RAPTI D MADURAWE
05/22/2014

NDA 21-883

DALVANCE™
(dalbavancin) for injection
500 mg / vial

Durata Therapeutics, Inc.

Balajee Shanmugam
Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Anti-Infective Products

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Chemistry Review Data Sheet

1. NDA 21883

2. REVIEW #: 4.1

3. REVIEW DATE: 15-MAY-2014

4. REVIEWERS: Balajee Shanmugam
   Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date	Status
Original, as amended	21-DEC-2004	AE 21-SEP-2005
Resubmission, as amended (Class 2)	20-DEC-2005	AE 20-DEC-2007
Resubmission (Class 2)	30-MAY-2008	Withdrawn 15-SEP-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
Resubmission after Withdrawal (0000) [sdn-083]	26-SEP-2013
Amendment (1004) (b) (4) cross-contamination	21-OCT-2013
Amendment (1005) Stability update	25-OCT-2013
Amendment (1013) Stability update	27-NOV-2013
Amendment (1014) Stability update	05-DEC-2013
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Amendment (1024) Stability update	13-FEB-2013
Amendment (1030) Infusion solution compatibility	18-MAR-2014
Amendment (1032) Labeling, container / carton	01-APR-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Durata Therapeutics, Inc.
HQ Address:	200 South Wacker Drive, Suite 2550 Chicago, IL 60606
Representative:	Briton Shell, Ph.D., Director, Regulatory Affairs
Address:	322 East Main Street, 3rd Floor Branford, CT 06405
Telephone:	203-871-4609
email:	bshell@duratatherapeutics.com

Reference ID: 3507877

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Dalvance™
   b) Non-Proprietary Name (USAN): dalbavancin
   c) Code Name/#: DUR001; VER001; BI397; MDL 64,397; A-A-1
   d) CAS Registry Number: CAS-171500-79-1
   e) Chem. Type/Submission Priority:
      i. Chem. Type: 1 NME (in *'the Program'*)
      ii. Submission Priority: Priority

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

10. PHARMACOL. CATEGORY: Antibacterial Antibiotic - Systemic (4010900)

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 500 mg free base / vial

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
    _____SPOTS product – Form Completed

    ___X__Not a SPOTS product

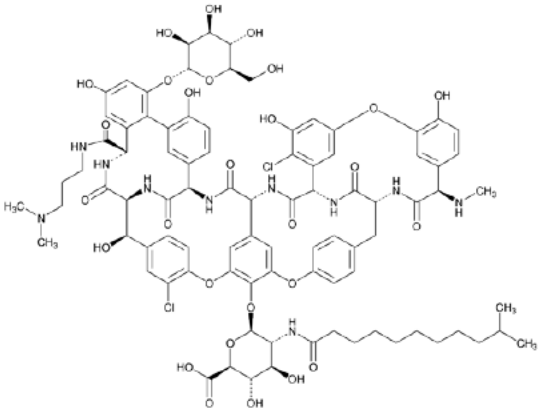
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

USAN/INN: Dalbavancin

CAS Chemical Name (B_0): Ristomycin A aglycone, 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-[2-deoxy-2-[(10-methyl-1-oxoundecyl)amino]-β-D-gluco-pyranuronosyl]-38-[[[3-(dimethylamino)propyl]amino]carbonyl]-42-*O*-α-D-mannopyranosyl-N^{15}-methyl-;

Reference ID: 3507877

Structural Formula: Dalbavancin (B_0)



Molecular Formula (Dalbavancin B_0): $C_{88}H_{100}Cl_2N_{10}O_{28}$ (free base)

Molecular Weight (Dalbavancin B_0): 1816.7

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	-	-	LoA 05/07/2013
	III			3,4	Adequate	19-SEP-2012	LoA 04/19/2013

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Other codes indicate why the DMF was not reviewed, as follows:
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4 – Sufficient information in application
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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)

B. Other Documents:

APPLICATION	DESCRIPTION	DOCUMENT
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NDA 21883	Original Dalbavancin NDA	Chemistry Review #1, R. Madurawe, 09/20/2005
NDA 21883	First resubmission	Chemistry Review #2, B. Shanmugam, 05/24/2006
NDA 21883	Second resubmission	Chemistry Review #3, B. Shanmugam, 11/02/2007
NDA 21883	Current (third) resubmission	Initial Quality Assessment, D. Matecka, 11/26/2013
NDA 21883	"	Chemistry Review #4, M. Seggel/B. Shanmugam, 2/26/2014

Reference ID: 3507877

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION*	DATE	REVIEWER
Biometrics	n/a		
EES	*pending*		
Pharm/Tox	Approval	3/10/14	T. Miller
ONDQA Biopharmaceutics	Approval	3/4/14	H. Mahayni
LNC	n/a		
Methods Validation	Acceptable	5/15/14	CDER/DPA
DMEPA	Proprietary name acceptable Labeling revisions recommended	11/25/13 02/28/14	A. Winiarski
EA	Categorical exclusion (based on $EIC_{aquatic} < 1$ ppb) is acceptable	this review	M. Seggel
Quality Microbiology	Approval	12/24/13	S. Donald, OPS/NDMS

*See darrts for associated reviews of NDA 21883.

19. REVIEW TIMELINE AND GOAL DATES

GRMP Goal	26-FEB-2014
PDUFA Goal	26-MAY-2014

Reference ID: 3507877

The Chemistry Review for NDA 21-883

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient information to assure identity, strength, quality, purity, potency and bioavailability of dalbavancin, a new molecular entity, and the finished drug product, dalbavancin for injection. The proposed regulatory analytical procedures were found "acceptable for control and regulatory purposes," by CDER's St. Louis Laboratory (DPA). As revised, the labeling (package insert, container and carton) is acceptable from the CMC perspective.

The drug substance facility and the drug product facility, as well as one testing laboratory, have been inspected, but the Office of Compliance has not issued an overall recommendation.

The application cannot be recommended for approval from the CMC perspective until an overall Acceptable recommendation is issued by the Office of Compliance.

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

PMC #1: Replace [redacted] (b) (4) used for preparing the Master Cell Bank with a [redacted] (b) (4). To be completed by June 30, 2016.

II. Summary of Chemistry Assessments

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

The drug substance dalbavancin hydrochloride is a semi-synthetic purified lipoglycopeptide antibacterial agent derived from the modification of dalbavancin. Dalbavancin acts by inhibiting bacterial cell wall biosynthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking of disaccharide subunits. Dalbavancin hydrochloride is present in two major class of structural homologs, dalbavancin A and dalbavancin B. Dalbavancin A comprises of two subtypes dalbavancin A_0 and A_1 and constitutes about [redacted] (b) (4) of the active drug substance. Dalbavancin B which constitutes about [redacted] (b) (4) of the drug substance is comprised of 3 subtypes, dalbavancin B_0, B_1 and B_2. All components of dalbavancin share the core component and primarily differ in the length and branching of the fatty acid side-chain and presence of a methyl group. The drug substance occurs as a white to tan solid and is freely soluble in water. Dalbavancin is manufactured by fermentation and subsequent chemical modification to obtain the API.

Reference ID: 3507877

Dalbavancin for Injection is a sterile, lyophilized powder for injection. Each single use vial contains 500 mg dalbavancin free base, (b) (4) mg mannitol and (b) (4) mg lactose monohydrate. Mannitol and lactose serve as (b) (4) . The pH is adjusted to (b) (4) with sodium hydroxide (and/or hydrochloric acid). The container/closure system consists of a 50 mL Type I glass vial and a (b) (4) stopper. The stoppered vials are sealed with a (b) (4)

The drug product is manufactured in (b) (4)

The quality, purity, potency and strength of the drug product is assured through appropriate in-process controls and regulatory testing that includes (b) (4) Tests for solution pH and particulate matter in reconstituted product are also part of the regulatory specification.

Compatibility with 5% Dextrose for Injection infusion solution was demonstrated by acceptable results from tests for appearance (visual inspection), assay, degradation products, pH and sub-visible particulate contamination (USP<788>).

Long term (25°C/60% RH) and accelerated (40°C/75% RH) stability studies on primary and supporting batches support an expiration dating period of 36 months at 25°C.

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

Dalvance™ (dalbavancin) for injection is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of Gram-positive microorganisms. A 1000 mg dose (contents of 2 vials) is administered on Day of the treatment followed by 500 mg on Day 8. Vial contents are reconstituted with 25 mL Sterile Water for Injection, USP, and subsequently diluted only with 5% Dextrose Injection, USP to a final concentration of 1 to 5 mg/mL. The dose is then administered by intravenous infusion over 30 minutes.

The unreconstituted drug product should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature]. The currently established expiration dating period is 36 months under the labeled storage conditions. It should be noted that storage of the lyophilized powder at refrigerated conditions is

Reference ID: 3507877

acceptable, but this is not mentioned in the labeling. See S. Donald's Product Quality Microbiology review regarding holding reconstituted solution and infusion solution (the product does not contain a preservative, although dalbavancin is an antibacterial agent).

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product throughout the shelf life.

Inspections of the drug substance and drug product manufacturing and testing facilities have been completed but the evaluation of the results by the Office of Compliance is ongoing. The application cannot be recommended for approval from the CMC perspective until an overall Acceptable recommendation is issued by the Office of Compliance. A review addendum will be entered into the record at that time.

The regulatory methods (and in particular the HPLC assay for both drug substance and drug product) have been verified by FDA's St Louis laboratory (CDER/DPA).

The applicant originally labeled the product as '[redacted] (b) (4) [redacted]; the non-proprietary name has been revised to 'dalbavancin for injection' in accordance with the USP salt policy. The strength of the product was already given as 500 mg as the free base, so no changes to the strength statement were required as a result of implementation of the salt policy. All labels have the required 'CMC' information. The proposed trademark, Dalvance, has been found acceptable by DMEPA.

Reference ID: 3507877

III. Administrative

A. Reviewer's Signature

{see electronic signature page}
Balajee Shanmugam, Ph.D.

{see electronic signature page}
Mark R. Seggel, Chemistry Reviewer

B. Endorsement Block

{see electronic signature page}
Dorota Matecka, Ph.D., CMC Lead and Secondary Reviewer

{see electronic signature page}
Rapti Madurawe, Ph.D., Branch Chief

C. CC Block

{see DARRTS}

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Reference ID: 3507877

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

/s/

MARK R SEGGEL
05/16/2014

BALAJEE SHANMUGAM
05/16/2014

DOROTA M MATECKA
05/16/2014

RAPTI D MADURAWE
05/16/2014

NDA 21-883

DALVANCE™
(dalbavancin) for injection
500 mg / vial

Durata Therapeutics, Inc.

Balajee Shanmugam
Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Anti-Infective Products

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Chemistry Review Data Sheet

1. NDA 21883

2. REVIEW #: 4

3. REVIEW DATE: 26-FEB-2014

4. REVIEWERS: Balajee Shanmugam
   Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date	Status
Original, as amended	21-DEC-2004	AE 21-SEP-2005
Resubmission, as amended (Class 2)	20-DEC-2005	AE 20-DEC-2007
Resubmission (Class 2)	30-MAY-2008	Withdrawn 15-SEP-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
Resubmission after Withdrawal (0000) [sdn-083]	26-SEP-2013
Amendment (1004) (b) (4) cross-contamination	21-OCT-2013
Amendment (1005) Stability update	25-OCT-2013
Amendment (1013) Stability update	27-NOV-2013
Amendment (1014) Stability update	05-DEC-2013
Amendment (1020) Response to information request; labeling	09-JAN-2014
Amendment (1024) Stability update	13-FEB-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Durata Therapeutics, Inc.
HQ Address:	200 South Wacker Drive, Suite 2550 Chicago, IL 60606
Representative:	Briton Shell, Ph.D., Director, Regulatory Affairs
Address:	322 East Main Street, 3rd Floor Branford, CT 06405
Telephone:	203-871-4609
email:	bshell@duratatherapeutics.com

Reference ID: 3461511

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Dalvance™
   b) Non-Proprietary Name (USAN): dalbavancin
   c) Code Name/#: DUR001; VER001; BI397; MDL 64,397; A-A-1
   d) CAS Registry Number: CAS-171500-79-1
   e) Chem. Type/Submission Priority:
      i. Chem. Type: 1 NME (in *'the Program'*)
      ii. Submission Priority: Priority

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

10. PHARMACOL. CATEGORY: Antibacterial Antibiotic - Systemic (4010900)

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 500 mg free base / vial

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
    _____SPOTS product – Form Completed

    ___X__Not a SPOTS product

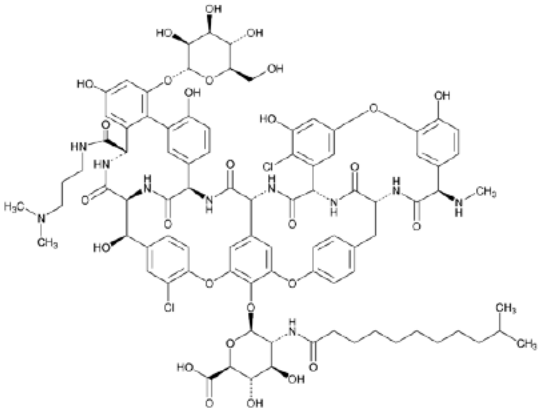
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

USAN/INN: Dalbavancin

CAS Chemical Name (B_0): Ristomycin A aglycone, 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-[2-deoxy-2-[(10-methyl-1-oxoundecyl)amino]-β-D-gluco-pyranuronosyl]-38-[[[3-(dimethylamino)propyl]amino]carbonyl]-42-*O*-α-D-mannopyranosyl-N^{15}-methyl-;

Reference ID: 3461511

Structural Formula: Dalbavancin (B_0)



Molecular Formula (Dalbavancin B_0): $C_{88}H_{100}Cl_2N_{10}O_{28}$ (free base)

Molecular Weight (Dalbavancin B_0): 1816.7

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	-	-	LoA 05/07/2013
	III			3,4	Adequate	19-SEP-2012	LoA 04/19/2013

[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)

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	DOCUMENT
IND 60613	IND for Dalbavancin	see darrts
NDA 21883	Original Dalbavancin NDA	Filing Checklist, R. Madurawe, 01/26/2005
NDA 21883	Original Dalbavancin NDA	Chemistry Review #1, R. Madurawe, 09/20/2005
NDA 21883	First resubmission	Chemistry Review #2, B. Shanmugam, 05/24/2006
NDA 21883	Second resubmission	Chemistry Review #3, B. Shanmugam, 11/02/2007
NDA 21883	Current (third) resubmission	Initial Quality Assessment, D. Matecka, 11/26/2013

Reference ID: 3461511

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	*pending*		
Pharm/Tox			
ONDQA Biopharmaceutics	NAI		H. Mahayni
LNC	n/a		
Methods Validation	*pending*		
DMEPA	Proprietary name acceptable *labeling review pending*	11/25/13	A. Winiarski
EA	Categorical exclusion (based on $EIC_{aquatic} < 1$ ppb) is acceptable	this review	M. Seggel
Quality Microbiology	Approval	12/24/13	S. Donald, OPS/NDMS

19. REVIEW TIMELINE AND GOAL DATES

GRMP Goal	26-FEB-2014
PDUFA Goal	26-MAY-2014

Reference ID: 3461511

The Chemistry Review for NDA 21-883

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient information to assure identity, strength, quality, purity, potency and bioavailability of dalbavancin, a new molecular entity, and the finished drug product, dalbavancin for injection. The proposed regulatory analytical procedures are currently being verified at CDER's St. Louis Laboratory (DPA). This is not an approvability issue although, if any issues are identified, the applicant is expected to address them in a timely manner. The drug substance facility and the drug product facility, as well as one testing laboratory, are scheduled for inspections. Therefore, from the CMC perspective, this NDA is recommended for approval pending satisfactory cGMP inspections and issuance of an overall acceptable recommendation from the Office of Compliance, and finalization of labeling.

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

Not applicable.

II. Summary of Chemistry Assessments

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

The drug substance dalbavancin hydrochloride is a semi-synthetic purified lipoglycopeptide antibacterial agent derived from the modification of dalbavancin. Dalbavancin acts by inhibiting bacterial cell wall biosynthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking of disaccharide subunits. Dalbavancin hydrochloride is present in two major class of structural homologs, dalbavancin A and dalbavancin B. Dalbavancin A comprises of two subtypes dalbavancin A_0 and A_1 and constitutes about (b) (4) of the active drug substance. Dalbavancin B which constitutes about (b) (4) of the drug substance is comprised of 3 subtypes, dalbavancin B_0, B_1 and B_2. All components of dalbavancin share the core component and primarily differ in the length and branching of the fatty acid side-chain and presence of a methyl group. The drug substance occurs as a white to tan solid and is freely soluble in water. Dalbavancin is manufactured by fermentation and subsequent chemical modification to obtain the API.

Dalbavancin for Injection is a sterile, lyophilized powder for injection. Each single use vial contains 500 mg dalbavancin free base, (b) (4) mg mannitol and (b) (4) mg lactose monohydrate. Mannitol and lactose serve as (b) (4)

Reference ID: 3461511

(b) (4). The pH is adjusted to (b) (4) with sodium hydroxide (and/or hydrochloric acid). The container/closure system consists of a 50 mL Type I glass vial and a (b) (4) stopper. The stoppered vials are sealed with a (b) (4)

The drug product is manufactured in (b) (4)

The quality, purity, potency and strength of the drug product is assured through appropriate in-process controls and regulatory testing that includes (b) (4) Tests for solution pH and particulate matter in reconstituted product are also part of the regulatory specification.

Long term (25°C/60% RH) and accelerated (40°C/75% RH) stability studies on primary and supporting batches support an expiration dating period of 36 months at 25°C.

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

Dalvance™ (dalbavancin) for injection is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of Gram-positive microorganisms. A 1000 mg dose (contents of 2 vials) is administered on Day of the treatment followed by 500 mg on Day 8. Vial contents are reconstituted with 25 mL Sterile Water for Injection, USP, and subsequently diluted only with 5% Dextrose Injection, USP to a final concentration of 1 to 5 mg/mL. The dose is then administered by intravenous infusion over 30 minutes.

The unreconstituted drug product should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature]. The currently established expiration dating period is 36 months under the labeled storage conditions. It should be noted that storage of the lyophilized powder at refrigerated conditions is acceptable, but this is not mentioned in the labeling. See S. Donald's Product Quality Microbiology review regarding holding reconstituted solution and infusion solution (the product does not contain a preservative, although dalbavancin is an antibacterial agent).

Reference ID: 3461511

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product throughout the shelf life.

Inspections of the drug substance and drug product manufacturing and testing facilities have not been completed as of this date. The application cannot be recommended for approval from the CMC perspective until an overall Acceptable recommendation issued by the Office of Compliance. A review addendum will be entered into the record at that time.

The regulatory methods (and in particular the HPLC assay for both drug substance and drug product) have been submitted to the FDA's St Louis laboratory (CDER/DPA) for verification. While completion of the validation process by DPA is not a requisite for approval of the application, the applicant is expected to promptly address any issues that may be identified.

The applicant originally labeled the product as [redacted] (b) (4) '; the non-proprietary name has been revised to 'dalbavancin for injection' in accordance with the USP salt policy. The strength of the product was already given as 500 mg as the free base, so no changes to the strength statement were required as a result of implementation of the salt policy. All labels have the required 'CMC' information, [redacted] (b) (4) The proposed trademark, Dalvance, has been found acceptable by DMEPA. Additional evaluation of the labels (PI, vial, carton) by DMEPA is pending. Labeling negotiations with the applicant are ongoing.

Reference ID: 3461511

III. Administrative

A. Reviewer's Signature

{see electronic signature page}
Balajee Shanmugam, Ph.D.

{see electronic signature page}
Mark R. Seggel, Chemistry Reviewer

B. Endorsement Block

{see electronic signature page}
Dorota Matecka, Ph.D., CMC Lead and Secondary Reviewer

C. CC Block

{see DARRTS}

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Reference ID: 3461511

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/s/

MARK R SEGGEL
02/26/2014

BALAJEE SHANMUGAM
02/26/2014

DOROTA M MATECKA
02/26/2014

IQA and Filing Review for Pre-Marketing Applications
Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **21883**

2. DATES AND GOALS:

Letter Date: September 27, 2013	Submission Received Date : September 27, 2013
PDUFA Goal Date: May 26, 2014	

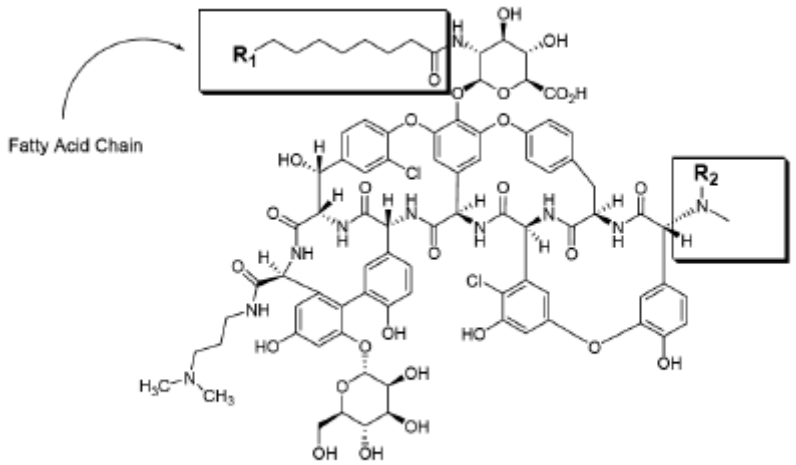
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	DALVANCE™ (*proposed*)
Established or Non-Proprietary Name (USAN):	Dalbavancin
Dosage Form:	Powder for injection
Route of Administration	Intravenous
Strength/Potency	500 mg
Rx/OTC Dispensed:	Rx

4. INDICATION:

Treatment of adult patients with Acute Bacterial Skin and Skin Structure Infections (abSSSI) caused by susceptible strains of Gram-positive bacteria.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



Reference ID: 3412259

Table 3.2.S.1.2-1 Substitution Patterns for Dalbavancin Homologues

Homologue	R_1	Number of Carbons R_1	R_2
A_0	$CH(CH_3)_2$	3	H
A_1	$CH_2CH_2CH_3$	3	H
B_0	$CH_2CH(CH_3)_2$	4	H
B_1	$CH_2CH_2CH_2CH_3$	4	H
B_2	$CH_2CH(CH_3)_2$	4	CH_3

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

   Durata Therapeutics, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Priority (PDUFA V NDA)
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		X	
Establishment Evaluation Request (EER)	X		*Submitted by Navdeep Bhandari*
Pharmacology/Toxicology			*TBD*
Methods Validation	X		*Submitted by Dr. Mark Seggel*
Environmental Assessment		X	Categorical exclusion
CDRH		X	
Other			

Reference ID: 3412259

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? **Yes**
CMC Filing Issues:
None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? **Yes**
CMC Comments for 74-Day Letter:
1. Please revise the established name of the drug substance from [redacted] (b) (4) " to "dalbavancin" in the package insert and container labels. *Additional comments have been identified by the drug substance and the drug product reviewers and should be included in the 74-day letter.*

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? **Yes**
Biopharmaceutics Filing Issues:
None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? **Yes**
Biopharmaceutics Comments for 74-Day Letter:
None

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? **Yes**
Microbiology Filing Issues:
See Microbiology Filing Review for details and for any potential Microbiology review issues.

Summary of Initial Quality Assessment

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

Is a team review recommended?	Yes	No
Suggested expertise for team:		

Summary of Critical Issues and Complexities
The assessment below describes the important issues for this NDA.

Reference ID: 3412259

INITIAL QUALITY ASSESSMENT

Dalbavancin is a new semi-synthetic cyclic lipoglycopeptide antibiotic, which has been developed under IND 60613. The original Sponsor of dalbavancin IND 60613 was Versicor, Inc. Versicor, Inc. merged with Biosearch Italia to form Vicuron Pharmaceuticals Inc. The original dalbavancin NDA 21883 was submitted by Vicuron Pharmaceuticals Inc. in 2004. Subsequently, Vicuron Pharmaceuticals, Inc. became a wholly owned subsidiary of Pfizer, Inc. The NDA was withdrawn by Pfizer in 2008 and it was acquired in 2009 by Durata Therapeutics, the current NDA 21883 applicant. Dalbavancin has been granted a QIPD designation on October 12, 2012.

The previous NDA submission (2004) provided for [redacted] (b) (4) 500 mg vial as the intended strength of the commercial drug product. The intended commercial manufacturer of the 500 mg vial drug product is [redacted] (b) (4)

The most recent discussions between the Applicant and the Agency include a Type A CMC meeting on July 15, 2013 and a Type B, End-of-Phase 2 CMC meeting on March 7, 2012. Per agreements with the Agency during the March 7, 2012 meeting, a complete CMC section has been resubmitted for review in the current NDA.

Drug Substance

Dalbavancin drug substance is a semi-synthetic cyclic lipoglycopeptide antibiotic consisting of two major families based on structural homology: dalbavancin A and dalbavancin B. The dalbavancin A family, which constitutes approximately [redacted] (b) (4) of the active drug substance, consists of two subtypes, designated as dalbavancin A0 and A1. Dalbavancin B, which constitutes approximately [redacted] (b) (4) of the active drug substance, is comprised of the subtypes designated as dalbavancin B0, B1, and B2.

Dalbavancin drug substance contains [redacted] (b) (4) per mole of dalbavancin. Dalbavancin drug substance is freely soluble in water. Dalbavancin drug substance is an amorphous solid. All lots that have been analyzed by [redacted] (b) (4)

Dalbavancin drug substance is a semi-synthetic antibiotic that is manufactured by chemical modification of a lipoglycopeptide antibiotic (A-40,926), which is produced through a fermentation process. A description of the manufacturing processes involved in the manufacture of dalbavancin has been provided in section 3.2.S.2.2 (reproduced below, Attachment 1). The applicant states that although several changes in ownership have occurred, the fermentation and synthetic processes to make dalbavancin drug substance have remained essentially the same throughout development. As agreed during the March 7, 2012 meeting, a comparison of the manufacturing processes, including fermentation, and comparability of drug substance over the

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course of development, has been provided (section 3.2.S.2.6). This section includes also a discussion of the contamination of some batches of dalbavancin drug substance [redacted] (b) (4) (which was discussed at the July 15, 2013 meeting with the Agency. *Comment: Additionally, a subsequent amendment dated October 21, 2013 provides a list of the various locations in Module 3 where information is presented regarding the microbiological purity and control of the dalbavancin master cell bank and fermentation process, along with a summary and conclusions (as requested during the July 15, 2013 meeting).*

The drug substance specification is reproduced below (Attachment 2). This includes all the previously listed attributes including overall assay and component distribution and related substances. *Comments: Justification of all limits has been provided in the justification section (3.2.S.4.5) using data from drug substance batches utilized in the pharm/tox and clinical studies. The specification is mostly comparable to the original NDA (some of the proposed limits are actually* [redacted] (b) (4) *); although, the distribution limits are slightly different from the original application. These issues will need to be assessed in detail during the NDA review.*

As agreed during the CMC Type A meeting dated July 15, 2013, stability information for the drug substance includes data on the primary and supportive batches outlined in the following table:

Table 3.2.S.7.1–1. Listing of Dalbavancin Drug Substance Primary Stability

Lot Number	Manufacturing Site	Date of Manufacture	Storage Conditions	Stability Data Available at Time of Submission
WP3003	[redacted] (b) (4)			
WP3002				
WP3001				
DAL_08_013/R				
DAL_07_008				
DAL_07_007				
DAL_07_005				

Comments: Per July 15, 2013 CMC Type A Meeting Minutes: "The Sponsor would have 3 months of primary stability data for the WP3001 and WP3002 drug substance batches at submission, then 5 months stability data for WP3001 and 4 months stability data for WP3002 for the update within 30 days. Within 60 days of submission, a stability update will be submitted for 6 months, 5 months and 4 months of data for lots WP3001, WP3002 and WP3003, respectively at -20 ºC and 5 ºC. FDA stated that this plan seems reasonable. FDA prefers that the update (provided within 30 days of submission) contain the most available data for lots WP 3001, WP3002, and WP3003." It should be noted that, as agreed, a subsequent amendment dated October 25, 2013 provides updated stability data for the three recently manufactured drug substance stability batches (WP3001, WP3002, and WP3003.

A retest date of (b) (4) months when stored at (b) (4) has been proposed for dalbavancin drug substance. *Comment: It should be noted that this issue was discussed during the March 7, 2012 EoP2 CMC meeting with the Sponsor and no agreement was reached. The meeting minutes state "The Agency clarified that assignment of a retest date or expiry date will be an NDA review issue."*

Drug Product

Dalbavancin for injection is a lyophilized solid. The proposed commercial product contains dalbavancin hydrochloride equivalent to 500 mg of dalbavancin free base per vial as the active ingredient (Attachment 3, below). The dalbavancin IV concentrate solution is prepared by reconstituting the lyophilized solid with sterile water for injection (sWFI). Prior to dosing, the reconstituted solution must be diluted in an appropriate IV solution. The dalbavancin infusion solution is administrated intravenously.

The proposed commercial formulation for the drug product differs from the earlier clinical formulations as follows:

(b) (4)

The applicant stated that the 500 mg/vial formulation was utilized for all Durata clinical trials, including two pivotal Phase 3 studies. The quantitative compositions of the clinical formulations and the 500 mg commercial formulation are presented in Table 2 of section 2.3 P.2 Pharmaceutical Development (reproduced in Attachment 4, below).

All excipients are compendial. BSE/TSE statements for lactose, mannitol, hydrochloric acid, and sodium hydroxide are provided in Section 3.2.A.2 (Adventitious Agents Safety Evaluation).

The flow chart for manufacturing process of the drug product is attached below as Attachment 5. The process include [redacted] (b) (4)

The container closure system consists of a round Type1 glass vial (48 mL) with a [redacted] (b) (4) Description of the container closure system is provided in section 3.2.P.7 including a reference to two Type III DMFs. Information on suitability of the proposed container closure system (including leachable assessment) is provided in the Pharmaceutical Development section.

The proposed specification (Attachment 6, below) for the drug product includes the following attributes: description of lyophilized and reconstituted drug product, ID (IR and HPLC), reconstitution time, constituted solution, assay, drug components, degradation products, [redacted] (b) (4) pH, uniformity of dosage forms, sterility, particulate matter, bacterial endotoxins, sterility, [redacted] (b) (4) *Comment: The proposed specification appears very similar to the originally submitted with some of the acceptance criteria* [redacted] (b) (4) *. The ranges of the components in the component distribution seem slightly changed.*

Batch analysis data have been provided for the following batches:

Table 3.2.P.5.4–1. Index for Drug Product Batch Data

Lot Number	Manufacture Site	Purpose
301453F	[redacted] (b) (4)	Proposed Commercial
CL2-283		Primary Stability
CL2-263		Primary Stability
161303F		Primary Stability
CL1-339		Primary Stability / Clinical (500 mg)
CL1-042		Primary Stability / Clinical (500 mg)
2170044		Clinical (500 mg)
8SQ06		Clinical (500 mg)
554399		Supportive Stability
640978		Supportive Stability
667802		Supportive Stability
149570		Clinical (200 mg)
285048		Clinical (200 mg)
442378		Clinical (250 mg)
518711		Clinical (250 mg)

Stability information provided in the NDA include stability results for samples stored 25ºC/60% RH and 40ºC/75% RH for 5 primary stability batches (manufactured at the proposed commercial facility, [redacted] (b) (4), and for three batches manufactured by [redacted] (b) (4), [redacted] (b) (4) In addition, initial data (time = 0 months) for one batch of the drug product (301453F, proposed commercial) manufactured with [redacted] (b) (4) drug substance (Lot WP3001) was also submitted (per agreement during the July 15, 2013 meeting, a stability update for this batch should be submitted during the NDA review per timelines agreed). *Comment: A subsequent amendment dated October 25, 2013 provides a 1-month stability data for this batch along with*

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updated stability data for the three recently manufactured drug substance stability batches (WP3001, WP3002, and WP3003).

The following table provides a summary of the primary stability data submitted in the current NDA:

Table 24 Summary of Primary Stability Batches of Dalbavancin for Injection 500 mg/vial

Lot No.	Batch Size (vials)	Ingoing Drug Substance Lot #	Drug Product Mfg Date	Conditions	Stability Data Available
CL1-042	(b) (4)	DAL_08_012	April 2011	40°C/75% RH	6 M
				25°C/60% RH	24 M
				In Use @ 5°C	24 M
				In Use @ 25°C/60% RH	24 M
CL1-339		DAL_08_012	Sept 2011	40°C/75% RH	6 M
				25°C/60% RH	18 M
161303F		DAL_08_012	April 2012	40°C/75% RH	6 M
				25°C/60% RH	12 M
				In Use @ 5°C	12 M
				In Use @ 25°C/60% RH	12 M
CL2-263		DAL_08_014	April 2012	40°C/75% RH	6 M
				25°C/60% RH	12 M
				In Use @ 5°C	12 M
				In Use @ 25°C/60% RH	12 M
CL2-283		DAL_08_012 DAL_08_014	Aug 2012	40°C/75% RH	6 M
				25°C/60% RH	9 M
				In Use @ 5°C	Time 0
				In Use @ 25°C/60% RH	Time 0

M = months

In addition, in-use stability studies of the reconstitution WFI solution and further diluted solutions of dalbavancin using several infusion agents were also conducted. The applicant concludes that dalbavancin drug product is physically and chemically stable at both ambient (20 to 25°C) and refrigerated temperatures (2 to 8°C) for at least 48 hours between the concentrations of 1 mg/mL and 5 mg/mL in 50 mg/mL (5% (b) (4) for infusion is recommended as the most common and customary infusion solution. *<u>Comments:</u> These statements and studies will need to be evaluated in connection with the labeling proposed for this product. Also, it will need to be confirmed that these use dates are appropriate from the product quality microbiology view point.*

The expiration dating of 36 months is proposed for the drug product to be stored at room temperature.

The vial and carton labels have been submitted. *<u>Comment</u>: The established name* (b) (4) *will need to be revised to read "dalbavancin in all parts of labels and labeling.*

Manufacturing facilities involved in the manufacture of the drug substance and drug product include (b) (4), respectively. *<u>Comment:</u> The proposed manufacturing facility for the drug product (* (b) (4) *) is currently coded as OAI in EES. Office of Compliance does not consider this a filing issue.*

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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:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
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. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
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? **This question is not applicable for synthesized API.**	X		

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

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	Parameter	Yes	No	Comment
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: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		Categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	*Not immediately obvious*
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	*Not immediately obvious*

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
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		Executed batch records for 3 recent (primary stability) batches: CL2-283, CL2-263, and CL1-042 in section 3.2.R.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?			*See biopharmaceutics review*
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	*Not immediately obvious*
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	*Not immediately obvious*

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	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)		April 19, 2013	
	III			May 7, 2013	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

BIOPHARMACEUTICS FILING REVIEW

NDA Number	21-883
Product name, generic name of the active, and dosage form and strength	Dalbavancin (DUR001), Injection, 500 mg
Submission date	September 26, 2013
Indication	Treatment of acute bacterial skin and skin structure infections (abSSSI) caused by susceptible strains of Gram-positive bacteria
Applicant	Durata Therapeutics Inc.
Medical Division	DAIP
Type of Submission	NME Original - Priority
Biopharmaceutics Reviewer	Houda Mahayni, Ph.D.
Acting Biopharmaceutics Team Leader	Sandra Suarez, Ph.D.

Background
This NDA was initially submitted by Vicuron Pharmaceuticals, Inc. (Vicuron), on December 21, 2004, and withdrawn by Pfizer, Inc. (Pfizer), on September 15, 2008. Durata Therapeutics Inc. (Durata) assumed responsibility of this NDA 21-883 on December 11, 2009.

Dalbavancin (DUR001) for injection is a semisynthetic lipoglycopeptide antibiotic. It was developed as an IV treatment for serious bacterial infections, in particular those caused by staphylococci and streptococci including methicillin-resistant staphylococci. The proposed indication for dalbavancin is for the treatment of adult patients with acute bacterial skin and skin structure infections (abSSSI). The recommended dosing regimen is 1000 mg of IV dalbavancin on the first day of therapy (Day 1), followed a week later (Day 8) by 500 mg of IV dalbavancin. Both doses of dalbavancin are infused over a 30-minute period.

Dalbavancin drug substance is an amorphous solid. It is freely soluble in water and more soluble in acidic aqueous solutions below pH (b) (4) The solubility of dalbavancin drug substance at ambient temperatures is provided in Table 1.

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Table 1: Dalbavancin Solubility in Aqueous Buffers

pH	Buffer	Solubility (µg/mL)
3.4	HCl/KCl	>200000
3.8	KH_2PO_4/H_3PO_4	>160000
3.5	KH_2PO_4/NaOH	>150000
5.0	KH_2PO_4/NaOH	>150000
5.9	KH_2PO_4/NaOH	62
7.2	K_2HPO_4/KH_2PO_4	20
8.4	KH_2PO_4/KOH	32
9.3	H_3BO_3/KCl/NaOH	8270

During the course of development three product strengths have been produced utilizing two different formulations, but the manufacturing process has remained essentially the same. The initial clinical formulation was a 200 mg/vial strength that was developed and manufactured at the original clinical manufacturing site, [redacted] (b) (4) During the course of development at [redacted] (b) (4), 250 mg/vial strength was also developed and both strengths were used in Vicuron-sponsored Phase 2/3 studies. Concurrent with the initial Phase 3 studies, a 500 mg product was developed and produced at [redacted] (b) (4). The 500 mg product was then transferred to the current manufacturing site, [redacted] (b) (4) The proposed 500 mg product was used in Phase 3 studies sponsored by Durata.

The Applicant highlighted the differences between the proposed commercial formulation and the earlier clinical formulations in the following ways:

[redacted] (b) (4)

The quantitative compositions of the earlier clinical formulations and the 500 mg commercial formulation are presented in Table 2.

Table 2: Comparison of Quantitative Compositions of Dalbavancin Drug Product Formulations

Ingredient	Quantity per vial		Function
	(b) (4)	500 mg Vials [b]	
Dalbavancin		(b) (4)	Active Ingredient
Mannitol			(b) (4)
Lactose monohydrate			
Hydrochloric acid [d]			
Sodium hydroxide [d]			
(b) (4)			

a (b) (4)
b
c (b) (4)
d
e

The Applicant stated that the 200, 250, and 500 mg per vial formulations were administered as an aqueous intravenous solution and were administered with the same active substance concentration range. In addition, the concentration of total (b) (4) is consistent across the formulations. Therefore, a bioequivalence study is not required. According to the Applicant, the (b) (4) did not alter the bioavailability or disposition of the drug. The amounts of these inactive ingredients are similar to those used in other parenteral products, and are well below any pharmacologically active dosage.

The proposed commercial formulation is a sterile lyophilized solid, which is reconstituted at the time of use. The product contains dalbavancin hydrochloride equivalent to 500 mg of dalbavancin free base per vial as the active ingredient. Dalbavancin drug product requires two preparatory steps prior to administration: reconstitution with sterile water for injection to form the reconstituted product (the reconstituted product contains 20 mg/mL dalbavancin, (b) (4) mg/mL mannitol and (b) (4) mg/mL lactose monohydrate); and the reconstituted product is then diluted with a suitable infusion solution to a concentration between 1 and 5 mg/mL prior to infusion.

The quantitative composition of the proposed commercial product is provided in Table 3.

Table 3: Composition of Dalbavancin for Injection, 500 mg Vials

Ingredient	Composition of Fill Solution	Quantity per Vial[a]	Function	Reference to Standards
Dalbavancin	(b) (4)		Active Ingredient	N/A
Mannitol				(b) (4)
Lactose Monohydrate				
(b) (4)				
Sodium hydroxide[c]				
Hydrochloric acid[e]				
(b) (4)				
Total Weight				

(b) (4)

Reviewer's Note:
Durata clinical trials, including two Phase 3 studies (DUR001-301 and 302), utilized the proposed 500 mg/vial product. The biopharmaceutics review will be focused on the evaluation of the data supporting the bridging across the phases of development for the proposed product.

From Biopharmaceutics perspective, this NDA is fileable and no review issues are identified.

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

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?		x	NA
2.	Is the dissolution test part of the DP specifications?		x	NA
3.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		x	NA
4.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
5.	Does the application include a biowaiver request?		x	
6.	Is there any information to support the approval of the lower strength(s)?		x	Only one strength is proposed for commercialization (500 mg). However, the reviewer will confirm proper bridging of formulations used in differences phases of drug product development.
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	NA
8.	Does the application include an IVIVC model?		x	NA
9.	Is there enough information to assess the extended release designation claim?		x	NA
10.	Does the application include information/data on in vitro alcohol dose-dumping potential?		x	NA
11.	Is there any in *vivo* BA or BE information in the submission?		x	

12.	Is there any design space proposed using in vitro release as a response variable?		x	
13.	Are there any data supporting a manufacturing change?		x	
14.	Is the control strategy related to in vitro drug release?		x	
B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
15.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
16.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
17.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
18.	Are there any **potential review** issues identified?		x	
19.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	
20.	Are there any internal comments to other disciplines?		x	

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
Branch V, Division II
Office of New Drug Quality Assessment

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Rapti Madurawe, Ph.D.
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Branch V, Division II
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Attachment 1

(b) (4)

[redacted]

Attachment 2

Table 3.2.S.4.1-1 Specification for Dalbavancin

TEST	TEST METHOD	ACCEPTANCE CRITERIA
PHYSICAL CHARACTERISTICS		
Appearance[a]	Visual	White to tan solid
IDENTIFICATION		
Infrared Spectroscopy (IR)	Ph Eur	Infrared absorption spectrum compares to that of the standard of dalbavancin
High Performance Liquid Chromatography (HPLC)	GNTM-017	Sample chromatogram exhibits a major peak with the same retention time as that of the standard of dalbavancin B_0 (b) (4)
ASSAY		
Assay[a] (HPLC, anhydrous, free base)	GNTM-017	(b) (4)
Component Distribution[a]	GNTM-017	
$A_0 + A_1$		
B_0		
$B_1 + B_2$		
Microbial Limit	USP	NMT (b) (4) NMT (b) (4)

Table 3.2.S.4.1-1 Specification for Dalbavancin (cont'd)

(b) (4)

[redacted]

Attachment 3

Table 3.2.P.1-1 Quantative Composition of Dalbavancin for Injection, 500 mg Vials

Ingredient	Composition of Fill Solution	Quantity per Vial[a]	Function	Reference to Standards
Dalbavancin	(b) (4)	(b) (4)	Active Ingredient	N/A
Mannitol			(b) (4)	USP
Lactose Monohydrate				USP/NF
(b) (4)				USP
Sodium hydroxide[e]				USP/NF
Hydrochloric acid[e]				USP/NF
(b) (4)				USP/NF
				(b) (4)

Attachment 4

Table 2 Comparison of Quantitative Compositions of Dalbavancin Drug Product Formulations

Ingredient	Quantity per vial		Function
	(b) (4)	500 mg Vials [b]	
		(b) (4)	
Dalbavancin			Active Ingredient
Mannitol			(b) (4)
Lactose monohydrate			
Hydrochloric acid [d]			
Sodium hydroxide [d]			
(b) (4)			
			(b) (4)

Attachment 5

(b) (4)

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Attachment 6

Table 3.2.P.5.1-1 Specification, Dalbavancin for Injection, 500 mg

Test	Procedure	Acceptance Criteria
Description (Lyophilized) [a]	Visual	White to off-white to pale yellow solid
Description (Reconstituted) [a, b]	Visual	Clear, colorless to yellow solution
Identification (IR)	USP <197K> <197A>	Conforms to reference spectrum
Identification (HPLC)	PR-1623	B_0 has the same retention time as reference standard
Reconstitution Time [a]	PR-1479	NMT (b) (4)
Constituted Solution [a, b, c]	USP <1> <631>	Meets USP Specification
Dalbavancin Assay [a, b]	PR-1623	90.0–110.0%
Drug Components [a] (%AUC) $(A_0 + A_1)$ B_0 $(B_1 + B_2)$	PR-1623	(b) (4)
Degradation Products [a, b] (%AUC)	PR-1623	(b) (4)
pH [a, b]	USP <791>	4.0–5.0
Uniformity of Dosage Units	USP <905>	Meets USP Specification
Sterility [a]	USP <71>	Meets USP Specification
Particulate Matter (per vial) [a, b]	USP <788>	(b) (4)

NMT=not more than

Note: If reconstitution is necessary, use 25.0 mL of water for each vial unless otherwise stated.

[a] Tests performed on Stability (lyophilized product)

[b] Tests performed on Stability (reconstituted product)

[c] USP testing for Constituted Solution consists of Completeness and Clarity of Solution and Particulate Matter (visual)

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

/s/

DOROTA M MATECKA
11/24/2013

HOUDA MAHAYNI
11/25/2013

SANDRA SUAREZ
11/25/2013

RAPTI D MADURAWE
11/26/2013

NDA 21-883

(b) (4)

(dalbavancin HCl) For Injection

Pfizer Pharmaceuticals, Inc.

Balajee Shanmugam, Ph.D
Office of New Drug Quality Assessment
Division Pre-Marketing Assessment II
Branch IV

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III. Administrative 6

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data **7**

S DRUG SUBSTANCE **7**

P DRUG PRODUCT **7**

Chemistry Review Data Sheet

1. NDA 21-883 - Resubmission

2. REVIEW #: 3 (See Chemistry Reviews 1 and 2 by Drs. Rapti Madurawe and Balajee Shanmugam, respectively).

3. REVIEW DATE: 30-Oct-07

4. REVIEWER: Balajee Shanmugam, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 21-883 (original NDA)	21-Dec-04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
General correspondence	12-May-06
General correspondence	17-Nov-06
General correspondence	07-May-07
Resubmission	19-June-07
General correspondence	17-Aug-07

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 235 East 42nd Street, New York, NY 10017.

Representative: Elina-Srulevitch-Chin

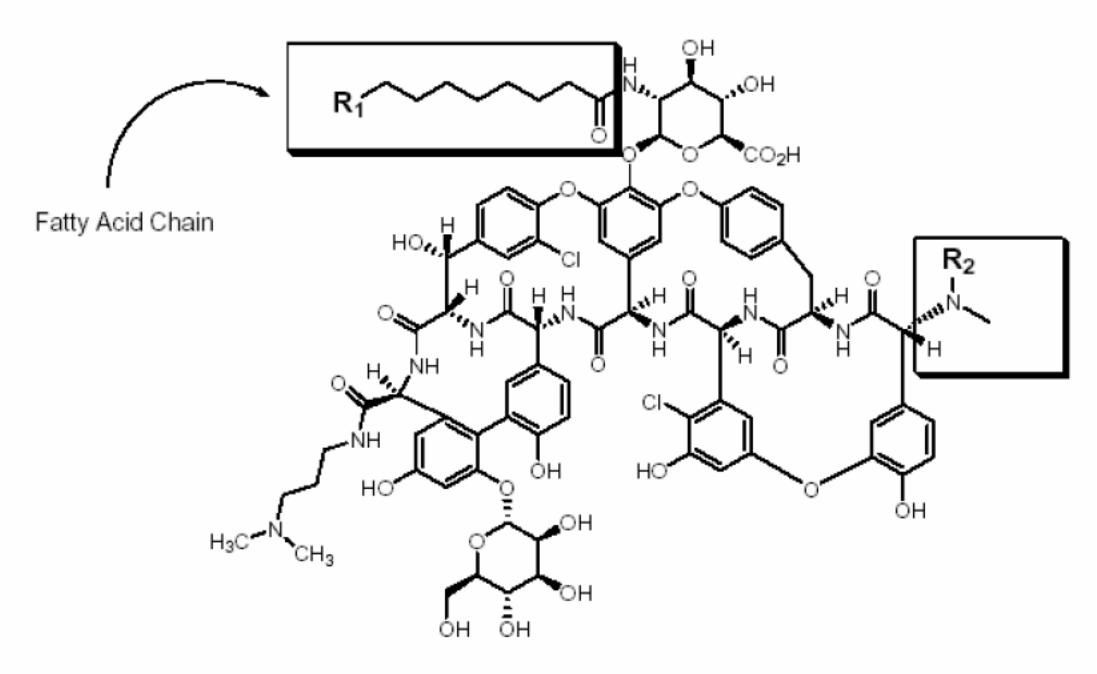
Telephone: 212-733-4471

8. DOSAGE FORM & STRENGTH: Lyophilized powder for injection; 500 mg per vial

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

(b) (4)

Molecular formula: (b) (4)
Molecular weight: (b) (4)
Molecular weight (base): (b) (4)
CAS: 86393-32-0


Fatty Acid Chain
R1
R2

The Chemistry Review for NDA 21-883

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

In response to the second cycle submission dated December 20, 2005, an approvable letter was issued by the Agency on 21 June, 2006 which asked the company to, "Determine the specific cause for high bacterial endotoxin levels discovered in active pharmaceutical ingredient (API) and drug product (DP) lots, as reported to the Agency on May 12, 2006".

On April 11, 2006 Pfizer informally informed the Agency of the high levels of endotoxin that were discovered during the formal process validation batches of the API and the drug product and subsequently submitted additional information on May 12, 2006 which provided data on the endotoxin levels. The company came up with a remediation plan which was the subject of the submissions dated May 12, 2006, November 17, 2007 and May 07, 2007. The third resubmission dated June 19, 2007 which addresses the endotoxin issue is the subject of this review. The endotoxin related remediation plan and supporting data reviewed by Dr. John Metcalfe, OPS/NDMS, HFD-805 was found to be adequate (review dated October 11, 2007) and he recommended Approval. The (b) (4) facility which manufactures the drug product has been cited for non-compliance with cGMP which prompted a "Withhold" recommendation by OC. This reviewer concurs with the "withhold" decision and recommends an Approvable action pending satisfactory resolution of all outstanding cGMP issues with OC.

II. Summary of Chemistry Assessments

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

See Chemistry Review # 1 by Dr. Madurawe.

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

See Chemistry Review # 1 by Dr. Madurawe.

C. Basis for Approvability or Not-Approval Recommendation

The original submission reviewed by Dr. Madurawe had found all CMC information other than those cited in Chemistry Review # 1 to be adequate. The deficiencies noted in the original submission were satisfactorily resolved during the second review cycle (see Chemistry Review # 2 by Balajee Shanmugam). However, during this review, the (b) (4) facility which manufactures the drug product was initially issued a 483 and subsequently sent a warning letter for non-compliance with cGMP which has prompted a "Withhold" recommendation by the Office of Compliance. Because of the above noted cGMP deficiency, this NDA is recommended Approvable pending resolution of the cGMP issues.

Chemistry Issues from the Third Cycle Review of NDA 21-883

During review of the second submission, the company informed the Agency of high endotoxin levels in several of the API and DP lots. The third resubmission provides data which demonstrates that the endotoxin levels are considerably lowered and consistently controlled. The Microbiology review, noted above, recommends Approval of the NDA. However, inspection of the drug product manufacturer (b) (4) facility showed it to be non-compliance with cGMP and the Office of Compliance has issued a warning letter. Furthermore, OC has recommended "withhold" and in agreement with this decision, this application is recommended Approvable pending satisfactory resolution of the cGMP issues.

III. Administrative

A. Reviewer's Signature

{see Electronic Signature Page}

B. Endorsement Block

Chemist: Balajee Shanmugam
Chemistry Team Leader: Norman Schmuff
Project Manager: Christopher Davi

C. CC Block

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/s/

Balajee Shanmugam
11/2/2007 12:31:32 PM
CHEMIST
CMCReview3

Norman Schmuff
11/2/2007 12:33:34 PM
CHEMIST

NDA 21-883

(b) (4) (dalbavancin HCl) For Injection

Pfizer Pharmaceuticals, Inc.

Balajee Shanmugam
Office of New Drug Quality Assessment
Division Pre-Marketing II
Branch IV

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Chemistry Assessment **10**

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Chemistry Review Data Sheet

1. NDA 21-883 - Resubmission

2. REVIEW #: 2

See Chemistry Review of NDA 21-883 by Dr. Rapti Madurawe.

3. REVIEW DATE: 10-May-06

4. REVIEWER: Balajee Shanmugam, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 21-883 (original NDA)	21-Dec-04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Supplement (AZ)	20-Dec-05
Supplement (BL)	13-Apr-06
Supplement (BC)	09-May-06
Supplement (BC)	12-May-06

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 235 East 42nd Street, New York, NY 10017.

Representative: Elina-Srulevitch-Chin

Telephone: 212-733-4471

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Dalbavancin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Glycopeptide - Antibacterial

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: (b) (4) 500 mg per vial

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_Rx ___OTC

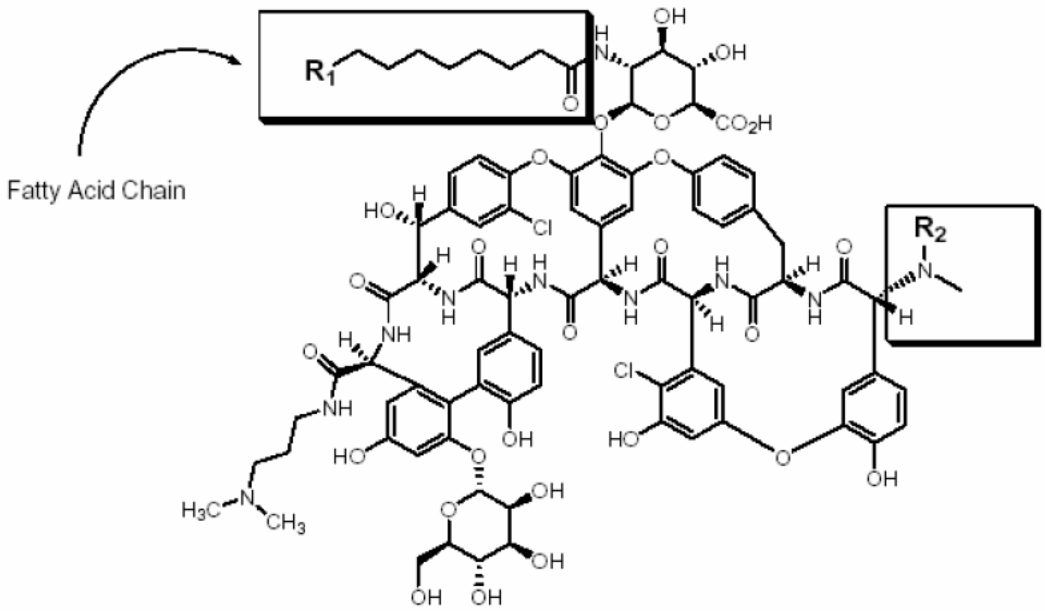
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

(b) (4)

Molecular formula: (b) (4)
Molecular weight (b) (4)
Molecular weight (base): (b) (4)
CAS: 86393-32-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See Chemistry Review #1 by Dr. Madurawae

B. Other Documents:

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
DMETS			
EA			
Microbiology			

The Chemistry Review for NDA 21-883

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Sponsor has adequately addressed all the CMC deficiencies cited in the first Chemistry Review and other deficiencies in the subsequent review of the drug substance and drug product batches. While most issues on labeling have been resolved the table detailing the preparation and dilution of (b) (4) in Preparation and Administration section remains to be addressed. The Sponsor has been provided with comments on the required revision to the table via email on May 12, 2006.

On April 11, 2006 Pfizer informally informed the Agency of the high levels of endotoxin that were discovered during the formal process validation batches of the API and the drug product. The Agency had a teleconference with the sponsor on April 14, 2006 to discuss the endotoxin issue when the Agency was briefed on the details of the issue. As was discussed during the teleconference, the sponsor submitted additional information on May 12, 2006 which provided data on the endotoxin levels from the various API and DP lots. The submission also details the plans for investigation to determine the specific cause of the issue and approaches the company plans to take to resolve this issue. According to the sponsor, preliminary investigation has attributed the high levels of bacterial endotoxin (b) (4) Pfizer proposes to enforce additional (b) (4) API batches to demonstrate that these batches meet the proposed limits. Pfizer anticipates resolving the issue by the end of 2006 and commits to submitting a major amendment to this NDA which will provide the proposed process modifications to control the levels of endotoxin. Since elevated levels of endotoxin are a safety concern, and the sponsor has just undertaken an investigation to address the issue but anticipates correcting the problem, it is recommended that NDA 21-883 be issued Approvable from CMC perspective.

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

(b) (4)

On the endotoxin issue, the sponsor has committed to provide an appropriate solution and justification for the remediation plan. It is recommended that the sponsor submit this plan to the Agency and implement the same upon approval by the Agency. The sponsor should provide data to demonstrate that the endotoxin levels are controlled consistently to the corrected and revised limits. The company has indicated its plan to submit a major amendment which will address the revisions to mitigate the endotoxin levels.

II. Summary of Chemistry Assessments

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

See Chemistry Review # 1 by Dr. Madurawe.

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

See Chemistry Review # 1 by Dr. Madurawe.

C. Basis for Approvability or Not-Approval Recommendation

The original submission reviewed by Dr. Madurawe had found all CMC information other than those cited in Chemistry Review # 1 to be adequate.

The following CMC deficiencies cited in Chemistry Review # 1, Action Letter dated September 21, 2005 and in the General Advice Letter dated October 4, 2005 formed the basis from Chemistry perspective for issuing an Approvable. The resubmission has addressed all the issues adequately.

1. Isolated Intermediate Storage: Provide data, based on stability-indicating HPLC assay, to support the storage temperatures and expiry dates for the intermediates (b) (4) The proposed storage temperatures and expiry periods for these intermediates are not adequately supported in your application, and inappropriate storage could adversely affect the strength and the purity of the drug product.

2. Labeling: Submit proposed annotated labeling based on the Agency's attached draft labeling. Note that comments have been provided for your consideration. Final labeling discussions with the Agency will be required prior to approval.

3. We remind you of your commitments in the amendments dated September 9, 2005 (b) (4)

(b) (4)

4. Concerns remain regarding the safety of the regulatory HPLC assays, as peak purity was demonstrated only by (b) (4). A method with greater specificity such as LC-MS should be provided. Please provide foe additional drug substance and drug product samples to be sent to the following individual at our St. Louis lab (address provided).

While these issues from the first cycle review have been resolved satisfactorily, a new issue related to elevated levels of endotoxin came up during the present review (see below).

Chemistry Issues from the Second Cycle Review of NDA 21-883

While in the process of the second cycle review the Sponsor informed the Agency of high endotoxin levels in several of the API and DP lots. The sponsor attributes high levels of bacterial endotoxins (b) (4) (b) (4) The company plans to investigate further to determine the specific cause of the elevated levels and provide an appropriate solution and justification for the remediation plan. The Sponsor anticipates having the necessary data to demonstrate that the endotoxin levels meet the proposed limits by the end of 2006.

III. Administrative

A. Reviewer's Signature

{see Electronic Signature Page}

B. Endorsement Block

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

Balajee Shanmugam
5/24/2006 11:31:28 AM
CHEMIST
N21-883

Elaine Morefield
5/24/2006 12:58:54 PM
CHEMIST

ONDC Deputy Division Director's Memo to File

NDA 21-883

[redacted] (b) (4) (dalbavancin) for Injection

Vicuron Pharmaceutical Inc.

Norman R. Schmuff, Ph.D.
Deputy Division Director (Acting)
Division of New Drug Chemistry III
HFD-830

In the 20 September 2005 CMC review of Rapti D. Madurawe, Ph.D. four approvability issues are cited, and listed below. An "approvable" action is recommended. Although I agree that these are issues of concern, aside from issue #3, I disagree that these rise to the level of approvability. However, I still recommend an "approvable" action based on item #3.

Approvability Issues (i.e. deficiencies)

1. The Master and Working Cell Banks (MCB, WCB): The MCB/WCB cell bank should be sufficient to supply cell substrate for the continued manufacture of the product (i.e. for a reasonable estimate of product life). The MCB/WCB should be characterized for purity/lack of contamination and identity using tests for phenotypic and genotypic characterization, and Specifications established to match future cell banks to the original MCB. A WCB consisting of (b) (4) is not acceptable. Lyophilized vials (like the MCB) with a suitably long expiration date are recommended for the WCB.

COMMENT:

Although the expiry of the MCB, and WCB seem atypical, they seem adequately characterized based on minimal phenotypic characterization, sequencing of an initial strain. The firm has also committed to do (b) (4) genotyping in the future. The stability of the cell line seems acceptable given the relative stability of the metabolite profile from two MCBs generated in 1998 and 2004 (b) (4)

Furthermore, in an amendment dated 9/6/05 the firm committed to "…establish a permanent MCB lot sufficient for product life-time", and a WCB sufficient to support production needs for a period of (b) (4) I believe this issue has been adequately addressed, and is not an approvability issue

2. Regulatory HPLC assay for DS and DP: The specificity, peak purity and adequate peak resolution (for components, impurities and degradants) of the DS and DP regulatory HPLC assay should be demonstrated.

COMMENT:

The specificity/peak purity concern arises because peak purity was assessed based on (b) (4) *UV detection. While it is possible that unidentified impurities under existing peaks have overlapping undetectable UV spectra, this seems unlikely since small structural changes give peaks that are at least partially separated, and major structural variants would be expected to probably have different UV spectra.*

Based on the following HPLC chromatograms, resolution of the components seems adequate in the drug substance and drug product assays. Consequently, I do not view these items as approvability issues.

(b) (4)

Drug Substance HPLC

(b) (4)

Drug Product HPLC

3. Isolated intermediate storage: Storage temperature and expiry date of isolated Intermediates (b) (4) should be supported by stability data based on a stability indicating HPLC assay. More comprehensive specifications should be provided for (b) (4). The (b) (4) specification should also contain an (b) (4) measure (alternately, this could be added to the DS specification). Component and degradant separation and peak purity of the assays should be demonstrated.

COMMENT:

(b) (4)

4. DP Storage: [redacted] (b) (4)

COMMENT:
In item #5 of an amendment dated 9/6/05 the firm committed to either market only the 500 mg vial or to market both labeled for storage under refrigerated conditions. Consequently, this item has been adequately addressed and is not an approvability issue.

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/s/

Christopher Davi
9/21/2005 01:41:03 PM
CSO

Norman Schmuff
9/21/2005 08:47:42 PM
CHEMIST

NDA 21-883

(b) (4) (dalbavancin) for Injection

Vicuron Pharmaceutical Inc.

Rapti D. Madurawe, Ph.D.
HFD-520

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Chemistry Review Data Sheet

1. NDA 21-883

2. REVIEW #: 1

3. REVIEW DATE: 01-Feb-2005

4. REVIEWER: Rapti D. Madurawe, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 60-613/N-177	02-Sep-04
IND 60-613/N-183	27-Sep-04
IND 60-613: Pre-NDA CMC Meeting Review	27-Oct-04
IND 60-613: Pre-NDA CMC Meeting Minutes	16-Nov-04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Letter Date	CDER Stamp Date
N-000/FG	21-Dec-04	21-Dec-04
Amendment/BZ	17-Feb-05	18-Feb-05
Amendment/BC	18-Feb-05	22-Feb-05
Amendment/BC	22-Feb-05	23-Feb-05
Amendment/C	25-Mar-05	28-Mar-05
Amendment/BC	08-Apr-05	13-Apr-05
Amendment/C	04-May-05	04-May-05
Amendment/AC	04-May-05	05-May-05
Amendment/BC	10-Jun-05	13-Jun-05
Amendment/AC	10-Jun-05	13-Jun-05
Amendment/BC	08-Jul-05	11-Jul-05
Amendment/BC	15-Jul-05	18-Jul-05
Amendment/AC	19-Jul-05	20-Jul-05
Amendment/BC	07-Sep-05	09-Sep-05
Amendment/BC	08-Sep-05	12-Sep-05

7. NAME & ADDRESS OF APPLICANT:

Name: Vicuron Pharmaceuticals Inc.

Address:	455 South Gulph Road Suite 310 King of Prussia, PA 19406
Contact:	Judith Hoglind, Director of Regulatory Affairs
Telephone:	610-491-2298

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Dalbavancin
c) Code Name/# (ONDC only): VER0001; BI 397; MDL 63,397; V-glycopeptide
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: 4010700 (glycopeptide antibiotic)

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: (b) (4) 500 mg per vial

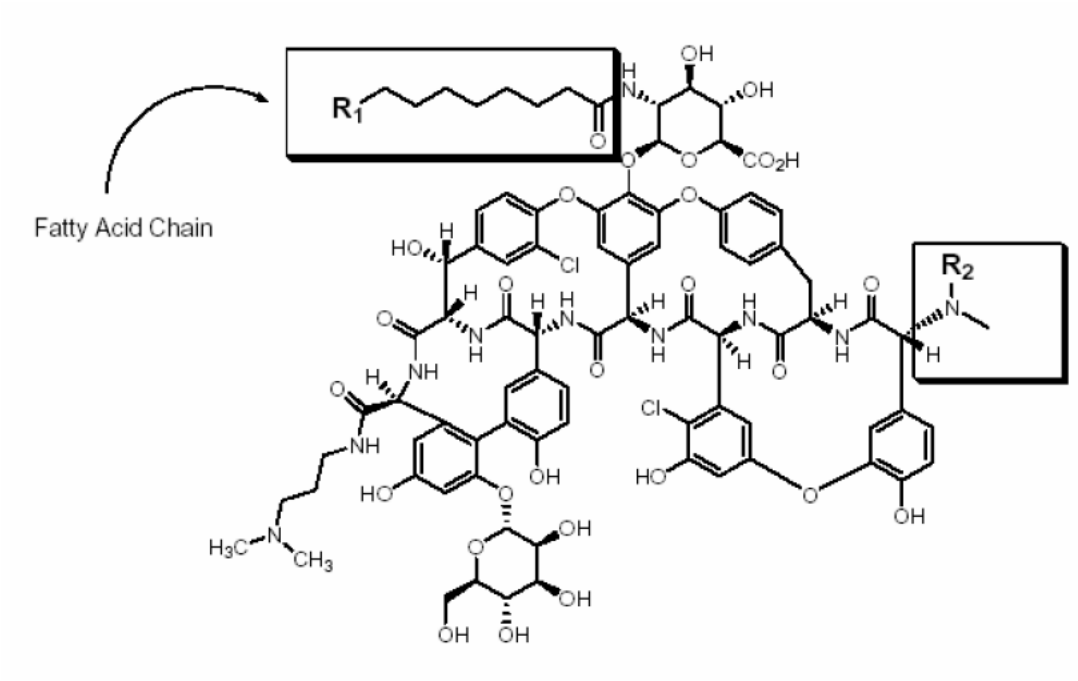
13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__X__Not a SPOTS product

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

The dalbavancin base form is shown below. Dalbavancin drug substance is an HCl salt.



Drug substance has 5 active forms: Dalbavancin A0, A1, B0, B1 and B2

Dalbavancin Homologue	R1	# Carbons R1	R2	Molecular Formula	Molecular Weight (base)
A0	CH(CH3)2	3	H	$C_{87}H_{98}N_{10}O_{28}Cl_2$	1802.7
A1	CH2CH2CH3	3	H	$C_{87}H_{98}N_{10}O_{28}Cl_2$	1802.7
B0	CH2CH(CH3)2	4	H	$C_{88}H_{100}N_{10}O_{28}Cl_2$	1816.7
B1	CH2CH2CH2CH3	4	H	$C_{88}H_{100}N_{10}O_{28}Cl_2$	1816.7
B2	CH2CH(CH3)2	4	CH_3	$C_{89}H_{102}N_{10}O_{28}Cl_2$	1830.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	05/24/04	No amendments to this formulation since date of last review
	III			7	NA	NA	DMF for glass not reviewed under new review guidelines
	III			7	NA	NA	DMF for glass not reviewed under new review guidelines
	V			7	NA	NA	Acceptable per Product Quality Micro consult.

[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)

B. Other Documents:

DOCUMENT DESCRIPTION	Document Date
Fileability Checklist Review	27-Jan-05
Methods Validation Request	04-Feb-05
Drug Substance Manufacturing Facility Inspection	01-Aug-05

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	08-Sep-05	N/A
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Acceptable	07-Apr-05	Duckhee Toler, HFD-590
OPDRA	N/A	N/A	N/A
EA	N/A	N/A	N/A
Microbiology	Acceptable	17-May-05	John W. Metcalfe, Ph.D.

19. ORDER OF REVIEW (OGD Only) N/A

20. COMMENTS

The NDA was granted priority review status. The review clock was extended by 3-months to accommodate Sponsor response to outstanding CMC issues. During the review period, the Sponsor merged with Pfizer and subsequently notified the Agency that the product labeling will not be finalized before the NDA due date. Therefore, the NDA was given an Approvable (AE) recommendation and all CMC issues that were to be resolved as post-approval Phase IV commitments are reviewed as deficiencies.

The Chemistry Review for NDA 21-883

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21,883 is approvable (AE) from a chemistry review perspective.

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

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product (DP) and Drug Substance (DS)

Drug Product (DP): [redacted] (b) (4) (dalbavancin) for Injection is a sterile, lyophilized, powder packaged in [redacted] (b) (4) 500 mg (anhydrous, free base) strengths in clear glass vials. The DP is reconstituted in sterile Water for Injection and administered intravenously with 5% Dextrose for Injection [redacted] (b) (4) infusion solution. The DP is manufactured at [redacted] (b) (4) Due to the uncomplicated formulation and dosage form, DP manufacturing is relatively simple. [redacted] (b) (4) There are no major deficiencies relating to DP manufacture. [redacted] (b) (4) Although DP packaged in labeled clear glass vials (where light protection is provided by label coverage) is stable, use of dark (amber) glass vials for light protection is recommended.

The [redacted] (b) (4) 500 mg/vial presented in the NDA have different formulations. All clinical and toxicology data were developed using the [redacted] (b) (4). Although the 500 mg formulation was not clinically tested, this formulation was accepted for CMC review under the same NDA number based on a Biopharmacology waiver. [redacted] (b) (4) [redacted] (b) (4) The 500 mg formulation is at pH [redacted] (b) (4) and contains both Mannitol and Lactose. The formulation pH and solubility criteria need to be carefully balanced for product stability [redacted] (b) (4) Due to the formulation difference, the two vials have different storage and expiry conditions [redacted] (b) (4) [redacted]). Although it was recommended that both vials should be stored at [redacted] (b) (4) prevent pharmacy storage errors, the Sponsor did not resolve this issue by the NDA due date.

Drug Substance (DS): Dalbavancin is a lipoglycopeptide antibiotic obtained by the chemical modification of a teicoplanin-like natural antibiotic, A-40926, that is fermented by a species of *Nonomuraea*. The DS, the hydrochloride salt of dalbavancin, is a New Molecular Entity (NME). It comprises of 5 homologous active components (Dalbavancin A_0, A_1, B_0, B_1 and B_2) present in defined amounts. Greater than 80% of the DS is Dalbavancin B_0. Each

active component contains approximately 1.6 equivalents of HCl salt. The DS components share the same core structure, and differ in the length and branching of the fatty acid side chain and in the presence or absence of a methyl group. As dalbavancin is administered as a solution, DS solubility is a key physicochemical attribute while particle size and (b) (4) are not significant. The DS is freely soluble in water and low pH solutions (hence DP is formulated at pH (b) (4), but has low solubility at neutral pH, and precipitates when the sodium chloride level (in water) is above 0.8%. Therefore, saline and physiological pH solutions should not be used with dalbavancin. (b) (4)

The DS is manufactured at (b) (4) as a white to tan powder. The manufacturing process is complex and consists of numerous unit operations. The key process stages (b) (4) Most of the related substance impurities/degradants exhibit antimicrobial activity to varying degrees. It is stated that the *in vitro* bioactivity would be retained even if the DS is degraded completely. As the clinical significance of this is not known, the review division has concurred that product should be manufactured with a similar active component and impurity profile as that tested in clinical and toxicology studies to maintain equivalent efficacy and safety. Although the Sponsor has not specifically addressed this issue, use of the same biological starting material (i.e. Master and Working Cell Banks) for consistent fermentation with similar active component/impurity profiles, addition of both upper and lower limits to the DS/DP active component specifications, impurity specification limits, and manufacturing controls are reviewed as important factors for batch reproducibility. Although DS manufacturing batches show reasonable batch consistency, the greater than (b) (4) failure rate for the fermentation process is of concern. Many significant review issues are associated with the DS CMC.

CMC Quality: The CMC submission of this NDA is of poor quality. Numerous review issues on DS/DP manufacture, control, analysis, characterization, etc., were conveyed to the Sponsor early during the review process and discussed further with the Sponsor and ONDC management. The tardy and often incomplete or inconsistent responses provided to these questions indicate insufficient process knowledge and process development. Although discussions took place to resolve outstanding CMC review issues as post-approval Phase IV commitments with defined time-lines, the Sponsor was unable to resolve some of these issues and the product labeling before the NDA due date.

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

(b) (4) is packaged in (b) (4) 500 mg/vial strengths (as anhydrous, free base) in a pack of 1 or pack of 10 vials. The recommended expiry dates (b) (4)

(b) (4) 18 months for the 500 mg vial. The recommended storage temperature for (b) (4) even though the 500 mg vial is stable at room temperature.
The recommended dosage is as follows:

- Skin and skin structure infections: 1000 mg on Day 1 followed by 500 mg on Day 8.
- Renal impairment: 750 mg on Day 1 followed by 375 mg on Day 8.

In preparation for administration, (b) (4) is first reconstituted in sterile Water for Injection ((b) (4) 25 mL for 500 mg vial) to obtain a 20 mg/mL solution, with slow water addition and swirling to avoid foaming. It is then diluted with 5% Dextrose for Infusion to a final concentration of 1-5 mg/mL for intravenous administration. Saline based diluents and infusion solutions should not be used as it may cause precipitation. Other solutions should not be used as compatibility is not known. The reconstituted DP and DP in infusion solutions may be stored at (b) (4) 25 °C and used within (b) (4) to minimize the risk of microbial contamination.

C. Basis for Approvability or Not-Approval Recommendation

The NDA approvability issues are listed at the end of this section. These deficiencies affect the quality, safety and consistent production of the DS and DP. Lack of an adequate cell bank is a serious deficiency (b) (4) product and there by the DS. A consistent active component and impurity profile is particularly important for this product as most of the impurities exhibit bioactivity. The current MCB and WCB do not assure a continuous supply (b) (4) (b) (4) and is not adequately characterized. The regulatory HPLC assay for DS/DP assures product quality, safety (i.e. impurity levels), and establishes product expiry. The NDA does not demonstrate the specificity and peak purity of the regulatory HPLC assays. The storage plans for the isolated Intermediates are not based on HPLC assays that are demonstrated to have the necessary specificity for evaluating the quality of the isolated intermediates. (b) (4), and is not according to agency standard practice. The (b) (4) failure rate for the fermentation process does not assure that the Sponsor is able to manufacture this product in a reliable manner.

Approvability Issues (i.e. deficiencies)

1. The Master and Working Cell Banks (MCB, WCB): The MCB/WCB cell bank should be sufficient to supply cell substrate for the continued manufacture of the product (i.e. for a reasonable estimate of product life). The MCB/WCB should be characterized for purity/lack of contamination and identity using tests for phenotypic and genotypic characterization, and Specifications established to match future cell banks to the original MCB. A WCB consisting of (b) (4) is not acceptable. (b) (4) are recommended for the WCB.

2. Regulatory HPLC assay for DS and DP: The specificity, peak purity and adequate peak resolution (for components, impurities and degradants) of the DS and DP regulatory HPLC assay should be demonstrated.

3. Isolated intermediate storage: Storage temperature and expiry date of isolated Intermediates [redacted] (b) (4) should be supported by stability data based on a stability indicating HPLC assay. More comprehensive specifications should be provided for [redacted] (b) (4). The [redacted] (b) (4) specification should also contain an [redacted] (b) (4) measure (alternately, this could be added to the DS specification). Component and degradant separation and peak purity of the assays should be demonstrated.

4. DP Storage: [redacted] (b) (4)

Additional recommendations for the NDA resubmission

1 [redacted] (b) (4)

2. The DS manufacturing process should be further improved [redacted] (b) (4)

3. The structural characterization of a new molecular entity (NME) needs to be rigorous and definitive in the primary NDA. The structural characterization information presented in the current NDA does not meet this standard. It is strongly recommended that the NDA resubmission contains a complete characterization of each of the five dalbavancin active components with data generated from high purity samples.

4. The high failure rate currently observed for the fermentation process [redacted] (b) (4) is of concern as it does not demonstrate the ability to manufacture product in a reliable manner. Reasons for these failures should be investigated and corrective actions implemented prior to NDA resubmission. The fermentation process should be successfully validated before marketing of product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Rapti D. Madurawe/14-Sep-05
ChemistryTeamLeaderName/Date: James D. Vidra/14-Sep-05
ProjectManagerName/Date: Christopher Davi/14-Sep-05

C. CC Block

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

/s/

Rapti Madurawe
9/20/2005 01:57:53 PM
CHEMIST

Jim Vidra
9/20/2005 02:29:18 PM
CHEMIST