

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202343Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 202343/000
Org. Code: 510
Priority: 4
Stamp Date: 07-DEC-2010
PDUFA Date: 07-OCT-2011
Action Goal:
District Goal: 08-AUG-2011

Sponsor: MERCK SHARP DOHME
UG2CD 48
NORTH WALES, PA 194541099
Brand Name: (b) (4) (sitagliptin/simvastatin) Tablet
Estab. Name:
Generic Name:
Product Number; Dosage Form; Ingredient; Strengths

001; TABLET; SITAGLIPTIN PHOSPHATE; 100MG
001; TABLET; SIMVASTATIN; 10MG
002; TABLET; SITAGLIPTIN PHOSPHATE; 100MG
002; TABLET; SIMVASTATIN; 20MG
003; TABLET; SITAGLIPTIN PHOSPHATE; 100MG
003; TABLET; SIMVASTATIN; 40MG

FDA Contacts: K. SHARMA Project Manager
S. TRAN Team Leader 301-796-1764

Overall Recommendation: ACCEPTABLE on 04-OCT-2011 by D. SMITH ()

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-DEC-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 1036761 FEI: 1036761
MERCK AND CO INC
4633 MERCK RD W
WILSON, NC 278939613

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-DEC-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-JAN-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9610180 FEI: 3002807560
MERCK SHARP & DOHME LTD.
CLONMEL, CO. TIPPERARY, , IRELAND

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-DEC-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

NIKOO N MANOCHEHRI-KALANTARI
10/13/2011

NDA #202-343

(b) (4)

**(sitagliptin phosphate (+) simvastatin) tablet: immediate
release, 100/10, 100/20, 100/40 mg/mg**

Merck Sharp & Dohme Corp.

Chemistry Review #2

John C. Hill, Ph.D.

ONDQA/DNDQA-III/Branch VII and OND/ODE II/DMEP

* On 22-JUN-2011, DMEPA denied the proprietary name (b) (4). As of the date of this review a new proprietary name has not been approved.

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Chemistry Review Data Sheet

1. NDA: 202-343
2. REVIEW # 2
3. REVIEW DATE: 02-AUG-2011
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original NDA Application	07-DEC-2010
Response to IR Request: (Manufacturing contact information)	16-DEC-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Response to IR Request: (Manufacturing contact information)	22-JUN-2011
Response to IR Request: (Manufacturing contact information)	01-AUG-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp & Dohme Corp.
Address:	P.O. Box 1000, UG2CD-48 North Wales, PA 19454-1099
Representative:	Richard J. Swanson, Ph.D., Senior Director, WW Regulatory Affairs
Telephone:	267-305-6871

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
- b) Non-Proprietary Name (USAN):

Chemistry Review Data Sheet

c) Code Name/# (ONDC only): MK-0431D Tablet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

Reference is made to the approved NDA 21995 Januvia (sitagliptin) Tablets (same applicant) for all CMC information on the sitagliptin phosphate monohydrate drug substance.

Reference is made to the approved NDA 19766 Zocor (simvastatin) Tablets (same applicant) for all CMC information on the simvastatin drug substance.

10. PHARMACOL. CATEGORY: TX of type II diabetes mellitus /
Hypercholesterolemia-cardiovascular disease

11. DOSAGE FORM: Fixed dose combination (FDC), bilayer, Immediate release tablet

12. STRENGTH/POTENCY: 100/10, 100/20, 100/40, mg/mg sitagliptin anhydrous free base/ simvastatin)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

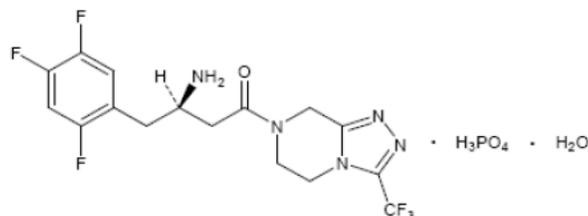
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Sitagliptin phosphate:

Molecular Weight: 523.32

Chemical Formula: $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$

Chemical Name: 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate†



Chemistry Review Data Sheet

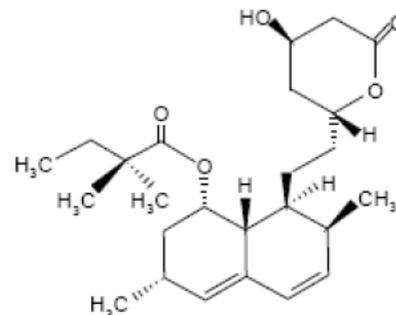
Laboratory Code: MK-0431D

Simvastatin

Molecular Weight: 418.57

Chemical Formula: C₂₅H₃₈O₅Chemical Name: a. [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 α β]]-1,2,3,7,8,8a-Hexahydro-3,7-

dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl-2,2-dimethylbutanoate

b. Butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a,hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester,[1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*), 8 α β]]c. 2,2-dimethylbutyric acid, 8-ester with (4R,6R)-6-[2-[(1S,2S,6R,8S,8 α R)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-oned. (1S,3R,7S,8S,8 α R)-8-[2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2,-dimethylbutanoate

Laboratory Code: MK-0733

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)	(b) (4)	4	Adequate		LOA: 20-APR-2010
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate*		LOA: 13-

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	Adequate*		MAY-2010
	III		4	Adequate		LOA: 20-APR-2010
	III		4	Adequate*		LOA: 01-APR-2010
	III		4	Adequate*		LOA: 11-MAY-2010
	III		4	Adequate*		LOA: 01-APR-2010
	III		4	Adequate*		LOA: 21-APR-2010
	III		4	Adequate*		LOA: 19-APR-2010
	III		4	Adequate*		LOA: 15-JUL-2010
III	4	Adequate*		LOA: 19-APR-2010		

* Review not required in accordance with review policy for container-closure systems for solid oral dosage forms

+ Pertinent information on continuous thread and child resistant closures may be found on 1 01-1 04, 6 01- 6 04, 9 01-9 38, 10 01-10 15, 11 01-11 25, 11 51, 12 01-12 02, 12 11, 13 01-13 129, 13 02-13 307, and 15 01 (one volume, submitted to FDA on May 9, 2003) and Annual Update in full (one volume, submitted to the FDA on August 24, 2009)

@ Pertinent information or (b) (4) material may be found on Pages 2 002-2 997, 3 01-3 02, 5 01-5 05, 6 01-6 02, 7 01, 8 01-8 09, 10 01, and 11 01 (one volume, submitted to FDA on June 30, 2004) and Annual Update submitted to the FDA on August 24, 2009

& Product information located on page 10, submitted on July 28, 2009

\$ (b) (4) Pertinent information for this (b) (4) may be found on pages G-VII-b-1 and G-II-nn-1, 2, 3, & 4 (which were submitted to the FDA on 15 April 1993 and November 1993, respectively)

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)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending	20-JUL-2011	
EES	Pending	21-JUL-2011	
OSE	Proprietary name denied	22-JUN-2011	Margarita V. Tossa



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Pharm/Tox	Acceptable	20-JUL-2011	Patricia M Brundage
Methods Validation	Not required at this time	21-JUL-2011	John C. Hill
EA	Adequate	21-JUL-2011	John C. Hill
Microbiology	Not required	21-JUL-2011	John C. Hill

The Chemistry Review for NDA 202-343

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final CMC recommendation is Approve; however we note that the facility inspection is still outstanding and that the CMC recommendation does not incorporate any potential facility inspection issues.

Based on the provided real-time stability data, a two and a half (2 1/2) year expiry period is granted for the 100/10, 100/20 and 100/40 mg /mg (b) (4) tablets supplied in 30 and 90 count bottles. This expiry period can be extended via the annual report according to the stability protocol.

Based on the provided real-time stability data, a one (1) year expiry period is granted for the 100/10, 100/20 and 100/40 mg /mg (b) (4) tablets supplied in the 1000 count bottle. This expiry period can be extended via the annual report according to the stability protocol.

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

None at this time.

II. Summary of Chemistry Assessments

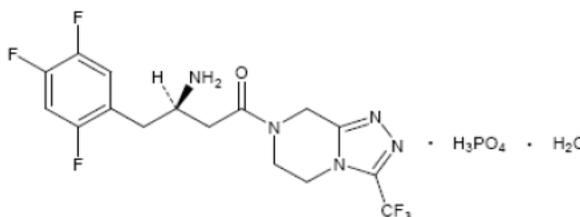
A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Two approved drug substances are used in the manufacturing process:

1. Sitagliptin phosphate has been reviewed in support of NDA 21-995 for Januvia. This NDA is active and up-to-date.

Sitagliptin phosphate monohydrate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate. Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and *N,N*-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate. The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:

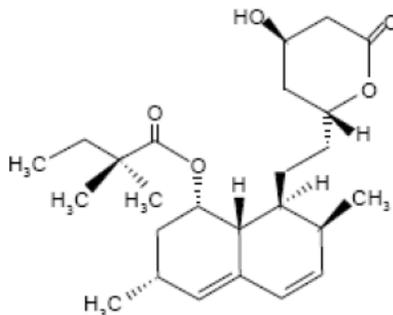


Executive Summary Section

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β -hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

2. Simvastatin has been reviewed in support of NDA 19-766 for Zocor. This NDA is active and up-to-date.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),-8a β]]. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:



Drug Product:

(b) (4) tablets (sitagliptin phosphate (+) simvastatin) are supplied as a bi-layer, film coated tablet.

Each bilayer tablet of (b) (4) contains 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 100 mg of free base, either 10 mg, 20 mg, or 40 mg of simvastatin and the following inactive ingredients: anhydrous dibasic calcium phosphate, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, magnesium stearate, ascorbic acid, citric acid monohydrate, lactose monohydrate, and pre-gelatinized corn starch. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, yellow iron oxide, and black iron oxide. Butylated hydroxyanisole is added as a preservative.

The inactive excipients used in the manufacture of (b) (4) tablets, with the exception of (b) (4), are the subjects of monographs in the USP-NF, Ph. Eur. and meet the requirements found therein, as applicable. (b) (4) (b) (4) is the subject of the (b) (4) monograph and is approved in the manufacture of Zocor. The (b) (4) film coatings have been reviewed and found to be acceptable.

Note: The 100 mg/ 80 mg strength was used during product development; however the Applicant does not intend to market this strength.

The product will be packaged in high-density polyethylene (HDPE) bottles containing silica gel desiccant with closures (either child resistant or non-child resistant). The inclusion of a

Executive Summary Section

desiccant is important in that the (b) (4)
The proposed packaging is:

(b) (4) 100 mg/10 mg tablets are pink-beige, bi-convex round, film-coated tablets, coded (b) (4) 753 on one side and plain on the other. They are supplied as follows:

NDC 0006-0753-31 unit of use bottles of 30
NDC 0006-0753-54 unit of use bottles of 90
NDC 0006-0753-82 bottles of 1000.

(b) (4) 100 mg/20 mg tablets are pink-beige, bi-convex modified capsule-shaped, film-coated tablets, coded (b) (4) 757 on one side and plain on the other. They are supplied as follows:

NDC 0006-0757-31 unit of use bottles of 30
NDC 0006-0757-54 unit of use bottles of 90
NDC 0006-0757-82 bottles of 1000.

(b) (4) 100 mg/40 mg tablets are orange-beige, bi-convex modified capsule-shaped, film-coated tablets, coded (b) (4) 773 on one side and plain on the other. They are supplied as follows:

NDC 0006-0773-31 unit of use bottles of 30
NDC 0006-0773-54 unit of use bottles of 90
NDC 0006-0773-82 bottles of 1000.

30 and 90 count bottles are to be stored at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F), in a dry place with cap tightly closed.

The contents of the 1000 count bottles are to be dispensed into a USP tightly closed, moisture-resistant container(s).

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

(b) (4) (sitagliptin phosphate (+) simvastatin) is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. (b) (4) is intended to be taken orally, in the evening, with or without food.

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Simvastatin is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events.
- Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbeta-lipoproteinemia.
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The final CMC recommendation is Approve; however we note that the facility inspection is still outstanding and that the CMC recommendation does not incorporate any potential facility inspection issues.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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

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/s/

JOHN C HILL
08/03/2011

ALI H AL HAKIM
08/03/2011

ERIC P DUFFY
08/04/2011

NDA #202-343

(b) (4)

**(sitagliptin phosphate (+) simvastatin) tablet: immediate
release, 100/10, 100/20, 100/40 mg/mg**

Merck Sharp & Dohme Corp.

**John C. Hill, Ph.D.
Theodore Carver, Ph.D.**

ONDQA/DNDQA-III/Branch VII and OND/ODE II/DMEP

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Chemistry Review Data Sheet

1. NDA: 202-343
2. REVIEW # 1
3. REVIEW DATE: 25-APR-2011 (Mid-Cycle 03-MAY-2011)
4. REVIEWERS: Theodore Carver, Ph.D. and John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA Application

Response to IR Request: (Manufacturing contact information)

Document Date

07-DEC-2010

16-DEC-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp & Dohme Corp.
Address:	P.O. Box 1000, UG2CD-48 North Wales, PA 19454-1099
Representative:	Richard J. Swanson, Ph.D., Senior Director, WW Regulatory Affairs
Telephone:	267-305-6871

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
- b) Non-Proprietary Name (USAN):
- c) Code Name/# (ONDC only): MK-0431D Tablet

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

Reference is made to the approved NDA 21995 Januvia (sitagliptin) Tablets (same applicant) for all CMC information on the sitagliptin phosphate monohydrate drug substance.

Reference is made to the approved NDA 19766 Zocor (simvastatin) Tablets (same applicant) for all CMC information on the simvastatin drug substance.

10. PHARMACOL. CATEGORY: TX of type II diabetes mellitus /

Hypercholesterolemia-cardiovascular disease

11. DOSAGE FORM: Fixed dose combination (FDC), bilayer, Immediate release tablet

12. STRENGTH/POTENCY: 100/10, 100/20, 100/40, mg/mg sitagliptin anhydrous free base/ simvastatin)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

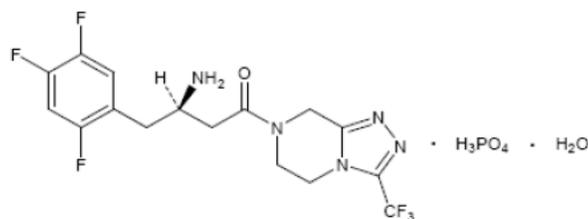
Sitagliptin phosphate:

Molecular Weight: 523.32

Chemical Formula: $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$

Chemical Name: 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate†

Laboratory Code: MK-0431D



Chemistry Review Data Sheet

Simvastatin

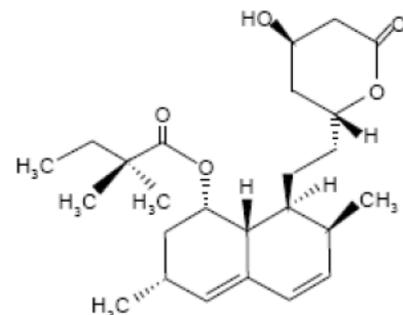
Molecular Weight: 418.57

Chemical Formula: C₂₅H₃₈O₅Chemical Name: a. [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 $\alpha\beta$]]-1,2,3,7,8,8a-Hexahydro-3,7-

dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl-2,2-dimethylbutanoate

b. Butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a,hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester,[1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*), -8 $\alpha\beta$]]c. 2,2-dimethylbutyric acid, 8-ester with (4R,6R)-6-[2-[(1S,2S,6R,8S,8 α R)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-oned. (1S,3R,7S,8S,8 α R)-8-[2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2,-dimethylbutanoate

Laboratory Code: MK-0733



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)	(b) (4)	4	Adequate		LOA: 20-APR-2010
(b) (4)	III	(b) (4)		4	Adequate*		LOA: 13-MAY-2010

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	Adequate*		LOA: 20-APR-2010
	III		4	Adequate		LOA: 01-APR-2010
	III		4	Adequate*		LOA: 11-MAY-2010
	III		4	Adequate*		LOA: 01-APR-2010
	III		4	Adequate*		LOA: 21-APR-2010
	III		4	Adequate*		LOA: 19-APR-2010
	III		4	Adequate*		LOA: 15-JUL-2010
	III		4	Adequate*		LOA: 19-APR-2010

* Review not required in accordance with review policy for container-closure systems for solid oral dosage forms

+ Pertinent information on continuous thread and child resistant closures may be found on 1 01-1 04, 6 01- 6 04, 9 01- 9 38, 10 01-10 15, 11 01-11 25, 11 51, 12 01-12 02, 12 11, 13 01-13 129, 13 02-13 307, and 15 01 (one volume, submitted to FDA on May 9, 2003) and Annual Update in full (one volume, submitted to the FDA on August 24, 2009)

@ Pertinent information on (b) (4) material may be found on Pages 2 002-2 997, 3 01-3 02, 5 01-5 05, 6 01- 6 02, 7 01, 8 01-8 09, 10 01, and 11 01 (one volume, submitted to FDA on June 30, 2004) and Annual Update submitted to the FDA on August 24, 2009

& Product information located on page 10, submitted on July 28, 2009

\$ (b) (4) Pertinent information for this (b) (4) may be found on pages G-VII-b-1 and G-II-nn-1, 2, 3, & 4 (which were submitted to the FDA on 15 April 1993 and November 1993, respectively)

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)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	The ONDQA Biopharmaceutics Review Staff will review all dissolution-related		

Chemistry Review Data Sheet

	information and biowaiver requests.		
EES	EER was sent to Compliance on 22-DEC-2010 by ONDQA PM.		
OSE	Labeling consult request will be sent as part of DMEP's request.		
Pharm/Tox	Evaluation of the genotoxicity potential of identified degradants.		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.		
EA	The categorical exclusion claim will be assessed by Primary Reviewer.		
Microbiology	May Not Be Applicable: solid oral dosage form.		

The Chemistry Review for NDA 202-343

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective a complete review of this Application cannot be approved at this time. The following information is required:

1. Satisfactory responses to the identified CMC deficiencies. These deficiencies include clarification of a manufacturing failure that has a potential negative impact on any approved expiry period.
2. Completion of the outstanding CGMP inspection(s)
3. Completion of the Biopharmaceutics review.
4. Completion of the final labeling.

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

None at this time.

II. Summary of Chemistry Assessments

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

Drug Substance:

Two approved drug substances are used in the manufacturing process:

1. Sitagliptin phosphate has been reviewed in support of NDA 21-995 for Januvia. This NDA is active and up-to-date.
2. Simvastatin has been reviewed in support of NDA 19-766 for Zocor. This NDA is active and up-to-date.

Drug Product:

(b) (4) tablets (sitagliptin phosphate (+) simvastatin) are supplied as a bi-layer, film coated tablet. Each bi-layer tablet contains 100 mg of sitagliptin and 10, 20, 40, or 80 mg of simvastatin drug substance. The 100 mg/ 80 mg strength was used during product development; however the Applicant does not intend to market this strength. The inactive excipients used in the manufacture of (b) (4) tablets, with the exception of (b) (4) are the subjects of monographs in the USP-NF, Ph. Eur. and meet the requirements found therein, as applicable (b) (4) is the subject of the (b) (4) monograph and is approved in the manufacture of Zocor. The (b) (4) film coatings have been

Executive Summary Section

reviewed and found to be acceptable. The drug product manufacturing process includes a number of proposed QbD elements including (b) (4)

(b) (4) supported by DOEs and mathematical modeling.

The product will be packaged in high-density polyethylene (HDPE) bottles containing silica gel desiccant with closures (either child resistant or non-child resistant). The inclusion of a desiccant is important in that (b) (4). The proposed packaging is:

(b) (4) 100 mg/10 mg tablets are pink-beige, bi-convex round, film-coated tablets, coded (b) (4) 753 on one side and plain on the other. They are supplied as follows:

NDC 0006-0753-31 unit of use bottles of 30

NDC 0006-0753-54 unit of use bottles of 90

NDC 0006-0753-82 bottles of 1000.

(b) (4) 100 mg/20 mg tablets are pink-beige, bi-convex modified capsule-shaped, film-coated tablets, coded (b) (4) 757 on one side and plain on the other. They are supplied as follows:

NDC 0006-0757-31 unit of use bottles of 30

NDC 0006-0757-54 unit of use bottles of 90

NDC 0006-0757-82 bottles of 1000.

(b) (4) 100 mg/40 mg tablets are orange-beige, bi-convex modified capsule-shaped, film-coated tablets, coded (b) (4) 773 on one side and plain on the other. They are supplied as follows:

NDC 0006-0773-31 unit of use bottles of 30

NDC 0006-0773-54 unit of use bottles of 90

NDC 0006-0773-82 bottles of 1000.

30 and 90 count bottles are to be stored at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F), in a dry place with cap tightly closed.

The contents of the 1000 count bottles are to be dispensed into a USP tightly closed, moisture-resistant container(s).

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

(b) (4) tablets (sitagliptin phosphate (+) simvastatin) is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. (b) (4) is intended to be taken orally, in the evening, with or without food.

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Simvastatin is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events.

Executive Summary Section

- Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbeta-lipoproteinemia.
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia.

C. Basis for Approvability or Not-Approval Recommendation

As reviewed, this application can not be recommended for approval due to several CMC specific deficiencies and several outstanding consultative reviews. Once these issues have been resolved, this review will be amended to reflect the final CMC recommendation

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

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/

THEODORE E CARVER

05/06/2011

May not be approved at this time.

ERIC P DUFFY

05/23/2011

ALI H AL HAKIM

05/23/2011

JOHN C HILL

05/31/2011

ONDQA
IQA (Initial Quality/CMC Assessment)

Division of Metabolism and Endocrinology Products

NDA: 202343

Applicant: Merck

Stamp Date: 07-DEC-2010

PDUFA Date: 07-OCT-2011

Proposed Proprietary Name: (b) (4)

Established Name: Sitagliptin/simvastatin

Dosage form and strength: Tablet: immediate release
100/10, 100/20, 100/40
(mg/mg sitagliptin anhydrous free base/
simvastatin)

Route of Administration: oral

Indications: All indications approved for each active ingredient

CMC Lead: Su (Suong) Tran, ONDQA

ONDQA Fileability: Yes

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CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	The ONDQA Biopharmaceutics Review Staff will review all dissolution-related information and biowaiver requests.
CDRH or CBER	<i>Not Applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
EES	EER was sent to Compliance on 22-DEC-2010 by ONDQA PM.
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>May Not Be Applicable: solid oral dosage form.</i>
Pharm/Tox	Evaluation of the genotoxicity potential of identified degradants.
Quality by Design	The application includes QbD elements (the ONDQA IO was notified on 08-DEC-2010).

This is an electronic NDA, filed as a 505(b)(1) application.

Reference is made to the approved NDA 21995 Januvia (sitagliptin) Tablets (same applicant) for all CMC information on the sitagliptin phosphate monohydrate drug substance.

Reference is made to the approved NDA 19766 Zocor (simvastatin) Tablets (same applicant) for all CMC information on the simvastatin drug substance.

Each bilayer tablet of (b) (4) contains 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 100 mg of free base, either 10 mg, 20 mg, or 40 mg of simvastatin and the following inactive ingredients: anhydrous dibasic calcium phosphate, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, magnesium stearate, ascorbic acid, citric acid monohydrate, lactose monohydrate, and pre-gelatinized corn starch. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, yellow iron oxide, and black iron oxide. Butylated hydroxyanisole is added as a preservative.

Maximum daily dose is 100 mg sitagliptin and 40 mg simvastatin.

Has all information requested during the IND phases, and at the pre-NDA meetings been included?
 Yes.

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Target Product Profile (TPP) for Sitagliptin Phosphate (+) Simvastatin Tablet

Clinical Attributes	
Indication	Type II diabetes mellitus / Hypercholesterolemia-cardiovascular disease
Mechanism	DPP-4 inhibitor / HMG-CoA reductase inhibitor (statin)
Route of Administration	Oral
Dose Frequency	QD
Treatment	Chronic
Safety and Efficacy	
Impurities and Degradates	Controlled below ICH or qualified levels
Doses	Sitagliptin/Simvastatin 100/10, 100/20, 100/40, (b) (4) mg/mg
Pharmacokinetic target	All strengths bioequivalent to respective sitagliptin and simvastatin monotherapies (coadministered), to be established via bioequivalency study or dissolution profile similarity as required
Patient Compliance Requirements	
Subjective Properties	Taste Masking
Dosage Form/Size	FDC film-coated tablet; not greater than (b) (4) target tablet weight
Packaging	HDPE bottles with desiccant

Resulting Product Critical Quality Attributes (CQA's) from TPP Categories for
 Sitagliptin Phosphate + Simvastatin Drug Product

TPP Category	Product CQA
Impurities and Degradates	Impurities and Degradates
	Moisture
Doses	Assay
	Dose Uniformity
	Identity
Pharmacokinetic target	Meet BE criteria
	Dissolution profile f2 between dosage strengths
Dosage Form Properties	Elegance
	Appearance

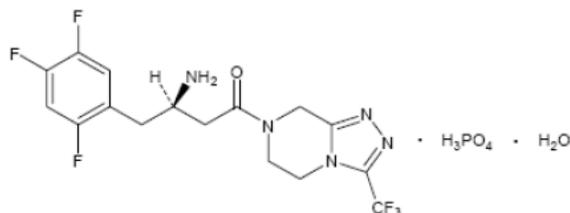
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Drug substance:

(b) (4) Tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme, and simvastatin, a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*.

Sitagliptin phosphate monohydrate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate.

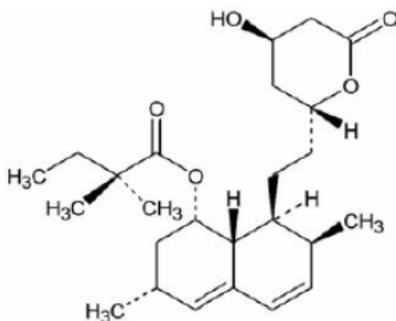
The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and *N,N*-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β -hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [*1S*-[1 α ,3 α ,7 β ,8 β (2*S**,4*S**),-8a β]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Review comments:

Reference is made to the approved NDA 21995 Januvia (sitagliptin) Tablets (same applicant) for all CMC information on the sitagliptin phosphate monohydrate drug substance. The drug substance specification is copied on page 16 of this review.

Reference is made to the approved NDA 19766 Zocor (simvastatin) Tablets (same applicant) for all CMC information on the simvastatin drug substance. The drug substance specification is copied on page 15 of this review.

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ONDQA
 IQA (Initial Quality/CMC Assessment)

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 202343

Established/Proper Name:
 Sitagliptin/simvastatin

Applicant: Merck

Letter Date: 07-DEC-2010

Stamp Date: 08-DEC-2010

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*				
	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.			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • 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		

ONDQA
IQA (Initial Quality/CMC Assessment)

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	x		

* 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.

C. ENVIRONMENTAL ASSESMENT

ONDQA
 IQA (Initial Quality/CMC Assessment)

	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to NDAs 21995 and 19766
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to NDAs 21995 and 19766
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to NDAs 21995 and 19766
15.	Does the section contain controls for the DS?			Reference is made to NDAs 21995 and 19766
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to NDAs 21995 and 19766
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Reference is made to NDAs 21995 and 19766
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Reference is made to NDAs 21995 and 19766
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		
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?	x		
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		It will be a review issue to determine whether the data and analysis are adequate to support the expiry.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

ONDQA
 IQA (Initial Quality/CMC Assessment)

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?			Solid oral dosage form.
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		
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		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

Su (Suong) Tran
 CMC Lead
 Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim
 Branch Chief
 Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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

/s/

SUONG T TRAN
12/28/2010

ALI H AL HAKIM
12/28/2010