

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202270Orig1s000

CHEMISTRY REVIEW(S)

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

Application: NDA 202270/000
Submission Date: 23-SEP-2010
Approval Date: 03-FEB-2012

Action Goal:
District Goal: 24-MAY-2011

Applicant: MERCK SHARP DOHME
 UG2CD 48
 NORTH WALES, PA 19454

Brand Name: Sitagliptin + Metformin Extended Release
Estab. Name:
Generic Name:

Priority: 3
Org. Code: 510

Product Number; Dosage Form; Ingredient; Strengths
 001; TABLET; SITAGLIPTIN; 50MG
 001; TABLET; METFORMIN HYDROCHLORIDE; 500MG
 002; TABLET; SITAGLIPTIN; 50MG
 002; TABLET; METFORMIN HYDROCHLORIDE; 1000MG

Application Comment: SEE ESTABLISHMENT COMMENTS FOR THIS NEW NDA (on 01-OCT-2010 by K. SHARMA ())

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

Overall Recommendation:	ACCEPTABLE	on 25-JAN-2012	by S. HERTZ	(HFD-320)	301-796-3203
	PENDING	on 05-JAN-2012	by EES_PROD		
	WITHHOLD	on 05-JAN-2012	by EES_PROD		
	WITHHOLD	on 04-DEC-2011	by EES_PROD		
	WITHHOLD	on 10-AUG-2011	by EES_PROD		
	PENDING	on 04-AUG-2011	by EES_PROD		
	PENDING	on 04-AUG-2011	by EES_PROD		
	PENDING	on 04-AUG-2011	by EES_PROD		
	PENDING	on 04-AUG-2011	by EES_PROD		
	PENDING	on 03-AUG-2011	by EES_PROD		
	WITHHOLD	on 03-AUG-2011	by EES_PROD		
	WITHHOLD	on 21-JUL-2011	by EES_PROD		
	WITHHOLD	on 25-MAY-2011	by EES_PROD		

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

Establishment: CFN: (b) (4) (b) (4)
 (b) (4)
 (b) (4)

DMF No: **AADA:**

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

Establishment Comment: DRUG SUBSTANCE (SITAGLIPTIN PHOSPHATE) MANUFACTURING, PACKAGING, AND RELEASE/STABILITY TESTING (on 01-OCT-2010 by K. SHARMA ())
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-OCT-2010				SHARMAKH
OC RECOMMENDATION	05-OCT-2010			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	04-AUG-2011				SHARMAKH
OC RECOMMENDATION	04-AUG-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

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

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

(b) (4)
(b) (4)

DMF No: **AADA:**

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

Establishment Comment: DRUG SUBSTANCE (METFORMIN HYDROCHLORIDE) MANUFACTURING, TESTING AND RELEASE (on 01-OCT-2010 by K. SHARMA ())
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-OCT-2010				SHARMAKH
OC RECOMMENDATION	05-OCT-2010			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	04-AUG-2011				SHARMAKH
OC RECOMMENDATION	04-AUG-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

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

Establishment: CFN: 2650235 FEI: 1000131917
 MERCK & CO., INC.
 RD 2, KM 60.3
 ARECIBO, PR 00688

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING AND RELEASE TESTING (on 01-OCT-2010 by K. SHARMA ())

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

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-OCT-2010				SHARMAKH
SUBMITTED TO DO	05-OCT-2010	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	14-OCT-2010	Product Specific			RHERNAND
INSPECTION SCHEDULED	15-OCT-2010		05-NOV-2010		RHERNAND
INSPECTION PERFORMED	14-APR-2011		14-APR-2011		JOSE.MELENDZ

The FDA-483 Observation reads as follows:



DO RECOMMENDATION 06-MAY-2011 WITHHOLD RHERNAND
 (b) (4) FIRM NOT READY



**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL 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

Establishment Comment: DRUG SUBSTANCE (SITAGLIPTIN PHOSPHATE) STABILITY TESTING. (on 01-OCT-2010 by K. SHARMA ())
DRUG PRODUCT PACKAGING AND STABILITY TESTING (on 01-OCT-2010 by K. SHARMA ())

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE
TABLETS, EXTENDED RELEASE NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-OCT-2010				SHARMAKH
OC RECOMMENDATION	06-OCT-2010			ACCEPTABLE BASED ON FILE REVIEW	STOCKM
SUBMITTED TO OC	04-AUG-2011				SHARMAKH
OC RECOMMENDATION	04-AUG-2011			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	05-OCT-2010				SHARMAKH
OC RECOMMENDATION	05-OCT-2010			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	04-AUG-2011				SHARMAKH
OC RECOMMENDATION	04-AUG-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

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

Establishment: CFN: 2510592 FEI: 2510592
MERCK AND CO INC
SUMNEYTOWN PIKE BLA20
WEST POINT, PA 19486

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
INTERMEDIATE MANUFACTURER

Establishment Comment: DRUG PRODUCT MANUFACTURING (METFORMIN HYDROCHLORIDE (b) (4) PROCESS AND ANALYTICAL DEVELOPMENT, MANUFACTURING, RELEASE TESTING AND STABILITY MONITORING AND TESTING. (on 01-OCT-2010 by K. SHARMA ())

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

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-OCT-2010				SHARMAKH
SUBMITTED TO DO	05-OCT-2010	Product Specific			STOCKM
DO RECOMMENDATION	18-OCT-2010			ACCEPTABLE	VMATUSOV
PREVIOUS GMP EI OF NON-STERILE AND STERILE DRUG OPERATIONS (INCLUDING MANUFACTURING OF TABLETS AND CAPSULES) IS DATED 8/3-18/10. PLEASE NOTE THAT THIS EI IS NOT YET ENDORSED BUT IT APPEARS THAT IT WILL BE CLASSIFIED NAI OR VAI. PROFILE CLASSES SIMILAR TO (b) (4) WERE COVERED AND ARE DOCUMENTED AS ACCEPTABLE. PROFILE CLASS (b) (4) WILL BE COVERED DURING THE NEXT SCHEDULED INSPECTION. THERE ARE NO PENDING REGULATORY ACTIONS WITH RESPECT TO PRODUCTION OF NON-STERILE OR STERILE DRUG PRODUCTS, ALTHOUGH CONCURRENT EI CONDUCTED BY TEAM BIO DID REVEAL SIGNIFICANT GMP VIOLATIONS ON THE VACCINE MANUFACTURING SIDE. PER THE LEAD PHI-DO CSO, THE UNCOVERED DEFICIENCIES WNT IMPACT MANUFACTURING OF STERILE AND NON-STERILE DRUGS.				BASED ON FILE REVIEW	
OC RECOMMENDATION	18-OCT-2010			ACCEPTABLE	INYARDA
SEE DO MILESTONE COMMENTS				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-AUG-2011				SHARMAKH
SUBMITTED TO DO	04-AUG-2011	10-Day Letter			STOCKM
PAI WAS WAIVED DURING FIRST REVIEW CYCLE. IT APPEARS AS THOUGH AN INSPECTION WAS JUST COMPLETED AT THIS FACILITY; NOT SURE IF THIS PRODUCT WAS COVERED.					
DO RECOMMENDATION	08-AUG-2011			WITHHOLD	VMATUSOV
ONGOING GMP INSPECTION OF THIS SITE THAT COMMENCED ON 7/18/11 UNCOVERED SIGNIFICANT GMP DEFICIENCIES INCLUDING MULTIPLE EXAMPLES OF INADEQUATE INVESTIGATIONS AND INSUFFICIENT CORRECTIVE ACTIONS IN RESPONSE TO VARIOUS PRODUCT CONTAMINATION INCIDENCES. SIMILAR VIOLATIONS WERE UNCOVERED DURING THE MOST RECENT 2010 TEAM BIO INSPECTION OF THE VACCINE MANUFACTURING SIDE. IT APPEARS THAT THE EI WILL BE CLASSIFIED OAI WITH THE RECOMMENDATION OF FURTHER REGULATORY ACTION.				INADEQUATE QA FUNCTIONS	
OC RECOMMENDATION	07-OCT-2011			WITHHOLD	CRUZC
CDER OC IS REVIEWING A WRNG LTR RECOMMENDATION.				DISTRICT RECOMMENDATION	
SUBMITTED TO DO	04-JAN-2012	10-Day Letter			SMITHDE
PLEASE REEVALUATE THE COMPLIANCE STATUS PER EMAIL FROM STEVE HERTZ					
DO RECOMMENDATION	05-JAN-2012			ACCEPTABLE	VMATUSOV
THE PREVIOUS GMP EI DATED 7/18-8/11/11 IS CLASSIFIED VAI (INITIAL CLASSIFICATION OF OAI WAS CHANGED TO VAI ON 1/5/12 BY PHI CB BASED ON THE PROPOSED ISSUANCE OF E UL WHICH IS CURRENTLY IN CDER). PROFILE CLASSES SIMILAR TO (b) (4)				BASED ON FILE REVIEW	

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

WERE COVERED AND ARE DOCUMENTED AS ACCEPTABLE. PROFILE CLASS (b) (4) WILL BE COVERED DURING THE NEXT SCHEDULED EI. THERE ARE NO PENDING REGULATORY ACTIONS WITH RESPECT TO NON-STERILE OR STERILE DRUG PRODUCTS.

OC RECOMMENDATION

06-JAN-2012

ACCEPTABLE

INYARDA

DISTRICT RECOMMENDATION

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

Establishment: CFN: 2623436 FEI: 2623436

MERCK SHARP AND DOHME QUIMICA
RD 2, KM 56.7
BARCELONETA, PR 00617

DMF No: **AADA:**

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

Establishment Comment: DRUG SUBSTANCE (SITAGLIPTIN PHOSPHATE) MANUFACTURING, PACKAGING AND RELEASE TESTING (on 01-OCT-2010 by K. SHARMA (1))

Profile: [REDACTED] (b) (4)

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	05-OCT-2010				SHARMAKH
OC RECOMMENDATION	05-OCT-2010			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	04-AUG-2011				SHARMAKH
SUBMITTED TO DO	04-AUG-2011	10-Day Letter			STOCKM
DO RECOMMENDATION	05-AUG-2011			ACCEPTABLE BASED ON FILE REVIEW	RHERNAND
ACCEPTABLE RECOMMENDATION BASED ON PREVIOUS INSPECTION RESULTS. LAST EI DATED 3/31/2011 AND CLASSIFIED AS VAI. CSN PROFILE ACCEPTABLE.					
OC RECOMMENDATION	17-AUG-2011			ACCEPTABLE DISTRICT RECOMMENDATION	TOULOUSEM

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/s/

NIKOO N MANOCHEHRI KALANTARI
02/07/2012

**CMC Memo to File**

To:	NDA
Date	26 Jan 2012
Sponsor:	Merck Sharp & Dohme Corp.
Drug:	Janumet XR (Sitagliptin, Metformin HCl Fixed Dose Combinations; 50/500, 50/1000, and 100/1000 mg sitagliptin/metformin XR)
Subject	Complete Response recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “acceptable” recommendation given on 25-Jan-2012 for the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 202-270 be approved. All labeling changes have been communicated to the applicant through the clinical project manager. There are no pending CMC review deficiencies.

HFD-/Division File
HFD-510
HFD-510/R. Chiang

Olen Stephens, Ph.D.
Chemistry Reviewer

Ali Al-Hakim, Ph.D.
Branch VII Chief, ONDQA

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/s/

OLEN M STEPHENS

01/26/2012

Overall quality recommendation is for approval. OC issued acceptable recommendation 25-Jan-2012. No CMC deficiencies remain.

ALI H AL HAKIM

01/26/2012



CMC Memo to File

To:	NDA
Date	4 Jan 2012
Sponsor:	Merck Sharp & Dohme Corp.
Drug:	Janumet XR (Sitagliptin, Metformin HCl Fixed Dose Combinations; 50/500, 50/1000, and 100/1000 mg sitagliptin/metformin XR)
Subject	Complete Response recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “withhold” recommendation given on 4-Dec-2011 for the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 202-270 receive a complete response. All labeling changes have been communicated to the applicant through the clinical project manager. There are no pending CMC review deficiencies.

HFD-/Division File
HFD-510
HFD-510/R. Chiang

Olen Stephens, Ph.D.
Chemistry Reviewer

Ali Al-Hakim, Ph.D.
Branch VII Chief, ONDQA

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/s/

OLEN M STEPHENS

01/04/2012

CMC recommendation: complete response pursuant to "withhold" recommendation by OC

ALI H AL HAKIM

01/04/2012

NDA 202270

Janumet XR
(Sitagliptin and Metformin HCl Fixed Dose Combinations;
50/500, 50/1000, and 100/1000 mg
sitagliptin/metformin HCl Extended Release)

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Merck Sharp & Dohme Corp.
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099

Indication: Management of type 2 diabetes mellitus.

Presentation: The drug product will be packaged in opaque high-density polyethylene (HDPE) bottles containing (b) (4). Each bottle will have a (b) (4) to match the corresponding bottle sizes. The 1000-count pharmacy bottles will have (b) (4) and the 30-, 60-, 90-, and 180-count configurations will have (b) (4).

Biopharm Recommendation: Acceptable

Establishments Evaluation Report (EER) Recommendation: **Withhold (5/25/11)**

Consults:	EA -	Not requested (categorical exclusion per 21CFR25.31 granted)
	Statistics -	N/A
	Methods Validation -	Not requested
	Clinical Pharm -	N/A
	Microbiology -	N/A
	Pharm Toxicology -	Acceptable

Original Submission: August 11, 2010

Re-submissions: N/A

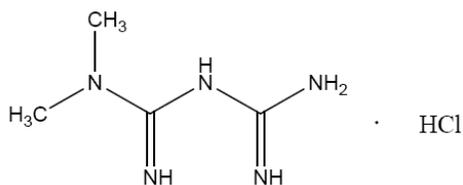
Post-Approval CMC Agreements: None at this time.

Drug Substances

Both drug substances, Sitagliptin and Metformin HCl, are active ingredients of previously approved drug products. Sitagliptin is the active ingredient in Januvia® (sitagliptin) Tablets (NDA 21-995), and metformin is the active ingredient in Glumetza (extended release metformin HCl reference) Tablets. The applicant is including all sitagliptin phosphate drug substance information by reference to NDA 21-995 (held by the same applicant). The metformin HCl active ingredient is controlled by DMF (b) (4). DMF (b) (4) was reviewed and found adequate.

Chemical Structures, Molecular Formula, and Chemical Names

Metformin Hydrochloride

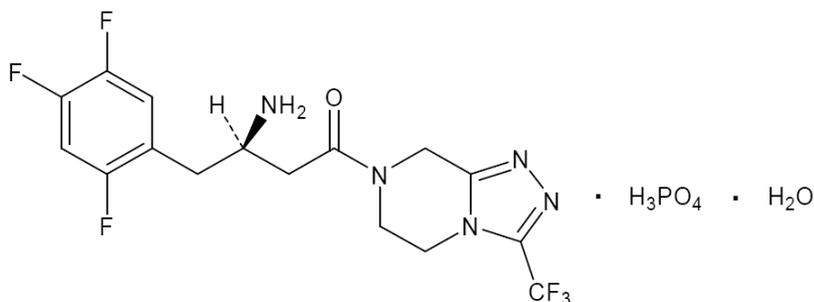


N,N-dimethylimidodicarbonimidic diamide hydrochloride

Molecular Formula: $C_4H_{11}N_5 \cdot HCl$

Molecular Mass: 165.63 g/mol

Sitagliptin Phosphate



7-[(3R)-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

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

Molecular Mass: 523.32 g/mol

Conclusion: Drug substances are satisfactory

Drug product

The drug products proposed in NDA 202-270 are designed to provide immediate release for sitagliptin and extended release for metformin HCl. The applicant is including all sitagliptin phosphate drug substance information by reference to NDA 21-995 (held by the same applicant). The metformin HCl active ingredient is controlled by DMF (b) (4). The (b) (4) film coats are supported by DMF (b) (4). All other components are compendial and controlled as per their respective monographs.

Three fixed dose combinations (FDC) have been developed for marketing: 50/500, 50/1000, and 100/1000 (mg sitagliptin as free base/mg metformin hydrochloride). The applicant is granted a biowaiver for the 50 mg/1000 mg potency. JANUMET® XR (sitagliptin/metformin XR) tablets will be packaged in 7- and 14- (all strengths), 30- (100/1000 mg tablets only), 60- (50/500 mg and 50 /1000 mg tablets), 90- (100/1000 mg tablets only), 180- (50/500 mg and 50 /1000 mg tablets), and 1000-(all strengths) count HDPE bottles.

The manufacturing process can be divided into (b) (4)

Specifications for the drug products include Assay, degradation products, dose uniformity, identity, dissolution, propyl gallate assay (b) (4)

The provided stability data provided in the NDA support an expiry dating period of 24 months.

Drug product is satisfactory

Overall Conclusion:

There are no pending CMC review deficiencies. However, CMC recommends complete response due to OC "withhold" recommendation.

Ali Al-Hakim, Ph.D.
Branch Chief, Division III
ONDQA/CDER/FDA

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/s/

ALI H AL HAKIM
06/17/2011



CMC Memo to File

To:	NDA
Date	25 May 2011
Sponsor:	Merck Sharp & Dohme Corp.
Drug:	Janumet XR (Sitagliptin, Metformin HCl Fixed Dose Combinations; 50/500, 50/1000, and 100/1000 mg sitagliptin/metformin XR)
Subject	Complete Response recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “withhold” recommendation given on 25-May-2011 for the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 202-270 receive a complete response. All labeling changes have been communicated to the applicant through the clinical project manager. The biopharmaceutics reviewer rendered an “acceptable” evaluation of the biowaiver request and has come to agreement for the dissolution specifications (refer to biopharmaceutics review filed in DARRTS 19-May-2011 by Dr. Sandra Suarez). There are no pending CMC review deficiencies.

HFD-/Division File
HFD-510
HFD-510/R. Chiang

Olen Stephens, Ph.D.
Chemistry Reviewer

Ali Al-Hakim, Ph.D.
Branch VII Chief, ONDQA

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/s/

OLEN M STEPHENS

05/25/2011

CMC recommendation: complete response due to OC "withhold" recommendation.

ALI H AL HAKIM

05/25/2011

NDA 202-270

**Janumet XR (Sitagliptin, Metformin HCl Fixed Dose
Combinations; 50/500, 50/1000, and 100/1000 mg
sitagliptin/metformin XR)**

Merck Sharp & Dohme Corp.

**Olen M. Stephens
Pre-Marketing Division III for the**

Division of Metabolic and Endocrinology Products

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Chemistry Review Data Sheet

1. NDA 202-270
2. REVIEW #: 1
3. REVIEW DATE: 28-Apr-2010
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Submission (0000)

24-Sep-2010

Amendment (0001)

30-Sep-2010

Amendment (0010)

11-Apr-2011

Amendment (0011)

11-Apr-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., Sr. Director, Regulatory Affairs

Chemistry Review Data Sheet

Telephone:

267-305-6871

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: JANUMET XR

b) Non-Proprietary Name (USAN): Sitagliptin/Metformin Hydrochloride Fixed Dose Combination

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) – Glumetza (extended release metformin -- Depomed)

10. PHARMACOL. CATEGORY: Sitagliptin is a dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor); metformin suppresses hepatic glucose production and sensitizes liver, muscle and fat tissue to insulin

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 50/500, 50/1000, 100/1000 mg sitagliptin/metformin XR

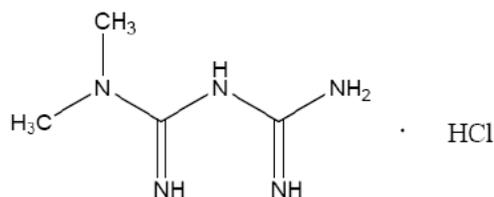
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

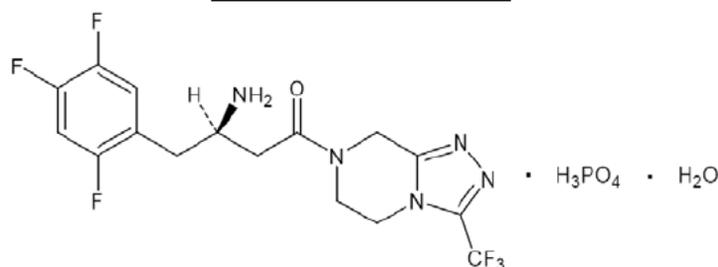
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Metformin Hydrochloride

Chemistry Review Data Sheet



1,1-Dimethylbiguanide hydrochloride
 $C_4H_{11}N_5 \cdot HCl$; MW 165.63

Sitagliptin Phosphate

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
 $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$; MW 523.32

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	2	(b) (4)	(b) (4)	1	Adequate	Feb-10-2011	(b) (4)
	2			1	Adequate	Feb-10-2011	
	2			1	Adequate	Feb-10-2011	

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)

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	All but DP site are acceptable		
Pharm/Tox	No outstanding issues		
Biopharm	Pending		

The Chemistry Review for NDA 202-270

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval, pending an Acceptable recommendation from ONDQA Biopharmaceutics.

This recommendation does not incorporate any potential facility inspection issues (an overall recommendation from the Office of Compliance is outstanding.)

The following recommendations are pending but will not have an impact on the specific findings discussed in this CMC review:

1. Office of Compliance – GMP status of the commercial manufacturing and testing facilities listed in the NDA.
2. ONDQA Biopharm Staff – biowaver for the 50 mg/1000 mg strength
3. OSE – Labeling.

The expiration dating period grantable for the JANUMET® XR (sitagliptin/metformin XR) tablets in 7-, 14-, 30-, 60, 90-, 180-, and 1000-count HDPE bottles is 24 months with storage conditions of 25°C (77°F); excursions permitted to 15- 30°C (59-86°F) [see USP Controlled Room Temperature]. ^{(b) (4)}

The applicant will submit data to support a site change for the metformin ^{(b) (4)} as a CBE-30 after NDA approval. The submission will include 3 months of accelerated stability data for the three batches at each strength (long term data will be sent to the annual report), dissolution data, and cGMP certification for the new site. This proposal is described in 3.2.P.3.3.3. Even though the drug product is a modified-release product, the site change will require supportive data as described in SUPAC-IR. Refer below for justification in R2.

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

II. Summary of Chemistry Assessments

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

NDA 202-270 is submitted by Merck for Janumet XR (sitagliptin/metformin HCl XR) tablets for oral administration, containing either 50 mg/500 mg, 50 mg/1000 mg or 100 mg/1000 mg fixed dose combination (FDC) of sitagliptin/metformin HCl. Both drug substances are active ingredients of previously approved drug products. Sitagliptin is the active ingredient in Januvia® (sitagliptin) Tablets (NDA 21-995), and metformin is the active ingredient in Glumetza (extended release metformin HCl reference) Tablets. The proposed indication is for treatment of patients with type 2 diabetes. The FDC drug products proposed in NDA 202-270 are designed to provide immediate release for sitagliptin and extended release for metformin HCl. The applicant is including all sitagliptin phosphate drug substance information by reference to NDA 21-995 (held by the same applicant). The metformin HCl active ingredient is controlled by DMF (b) (4). The (b) (4) film coats are supported by DMF (b) (4). All other components are compendial and controlled as per their respective monographs.

Three fixed dose combinations (FDC) have been developed for marketing: 50/500, 50/1000, and 100/1000 (mg sitagliptin as free base/mg metformin hydrochloride). The applicant is seeking a biowaiver for the 50 mg/1000 mg potency. JANUMET® XR (sitagliptin/metformin XR) tablets will be packaged in 7-, 14-, 30- (100/1000 mg tablet only), 60- (50/500 mg and 50 /1000 mg tablets), 90- (100/1000 mg tablet only), 180- (50/500 mg and 50 /1000 mg tablets), and 1000-count HDPE bottles. The 7- and 14-count physician samples and 1000-count pharmacy bottles (b) (4); the 30-, 60, 90-, and 180-count configurations (b) (4).

The manufacturing process can be divided into (b) (4)

Note that the applicant is not proposing a Design Space and has confirmed that a (b) (4) will be used for the manufacturing process.

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

Janumet XR tablets will be dispensed by prescription only for the management of type 2 diabetes mellitus. The recommended dose one tablet daily with food. The dose strength, 50 mg/500 mg, 50 mg/1000 mg or 100 mg/1000 mg (sitagliptin/metformin), will be prescribed on an individual basis by the clinician depending on the patient's individual glycemic control, renal function, and drug

Executive Summary Section

product tolerability. The drug product should be stored at 25°C (77°F) with excursions permitted to 15- 30°C (59-86°F) [see USP Controlled Room Temperature]. A 1000-count pharmacy bulk package and 7- and 14-count physician samples will also be available.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls deficiencies for the drug product were communicated to the applicant (14-MAR-2011) and have been sufficiently addressed.

The following recommendations are pending but will not have an impact on the specific findings discussed in this CMC review:

1. Office of Compliance – GMP status of the commercial manufacturing and testing facilities listed in the NDA.
2. ONDQA Biopharm Staff – Biowaiver for the 50 mg/1000 mg strength and IVVC for dissolution.
3. OSE – Labeling.

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

Olen M. Stephens

B. Endorsement Block

ChemistName/Date: Olen M. Stephens
ChemistryTeamLeaderName/Date: Dr. Ali Al-Hakim
ProjectManagerName/Date: Raymond Chiang

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/

OLEN M STEPHENS

04/28/2011

CMC recommendation is for approval pending acceptable recommendations from biopharmaceutics, office of compliance, and OSE.

ALI H AL HAKIM

04/28/2011

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Division of Metabolism and Endocrinology Products

NDA: 202270

Applicant: Merck

Stamp Date: 23-SEP-2010

PDUFA Date: 23-JUL-2011

Proposed Proprietary Name: Janumet XR

Established Name: Sitagliptin/metformin hydrochloride

Dosage form and strength: Tablet: immediate release sitagliptin and extended release metformin hydrochloride – 50/500, 50/1000, 100/1000 (mg/mg sitagliptin anhydrous free base/metformin hydrochloride)

Route of Administration: oral

Indications: Type 2 diabetes

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 (including data on dose dumping), and the biowaiver requests for the 50/1000 strength and for the debossed commercial tablet.
CDRH or CBER	<i>Not Applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
EES	EER was sent to Compliance by ONDQA PM on 05-OCT-2010.
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	Review of the qualification of a sitagliptin-related (b) (4) degradant (proposed limit: (b) (4)).
Quality by Design	The application includes QbD elements (the ONDQA IO was notified on 29-SEP-2010).

This is an electronic NDA, filed as a 505(b)(2) application, with the reference listed drug being Glumetza (metformin HCl extended release tablet). The associated IND is IND 101964.

Reference is made to the DMF (b) (4) (b) (4) all CMC information on the metformin HCl drug substance.

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

JANUMET XR consists of an extended-release metformin core tablet coated with an immediate-release layer of sitagliptin. The sitagliptin layer is coated with a soluble polymeric film (b) (4) (b) (4)

JANUMET XR is available for oral administration as tablets containing 64.25 mg sitagliptin phosphate monohydrate (equivalent to 50 mg sitagliptin as free base) and either 500 mg metformin hydrochloride extended-release (50 mg/500 mg) or 1000 mg metformin hydrochloride extended-release (50 mg/1000 mg). Additionally, JANUMET XR is available for oral administration as tablets containing 128.5 mg sitagliptin phosphate monohydrate (equivalent to 100 mg sitagliptin as free base) and 1000 mg metformin hydrochloride extended-release (100 mg/1000 mg).

All doses of JANUMET XR contain the following inactive ingredients: povidone, hypromellose, colloidal silicon dioxide, sodium stearyl fumarate, propyl gallate, polyethylene glycol, and kaolin. The JANUMET XR 50 mg/500 mg tablet contains the additional inactive ingredient microcrystalline cellulose. In addition, the film coating contains the following inactive ingredients: hypromellose, hydroxypropyl cellulose, titanium dioxide, FD&C Blue #2/Indigo Carmine Aluminum Lake and carnauba wax. The JANUMET XR 50 mg/1000 mg tablet contains the additional inactive ingredient yellow iron oxide.

Reference is also made to the approved NDA 22044 (sitagliptin/metformin HCl), from the same applicant, for supporting CMC information on the drug product manufacturing and testing.

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Maximum daily dose is 100 mg sitagliptin and 2000 mg metformin HCl.

Has all information requested during the IND phases, and at the pre-NDA meetings been included?
 No CMC information was requested during the late IND development.

Sitagliptin Phosphate (+) Metformin Hydrochloride Extended Release Tablets
 Target Product Profile

Clinical Attributes	
Indication Mechanism Route of Administration Dose Frequency Treatment	Diabetes DPP-4 inhibitor / Anti hyperglycemic Oral QD Chronic
Safety and Efficacy	
Impurities and Degradates Doses (Sitagliptin/Metformin Hydrochloride) Pharmacokinetic target	Controlled below ICH or qualified levels 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg Bioequivalent to co-administered doses of individual Sitagliptin Tablets (JANUVIA [®]) and Metformin Hydrochloride Extended Release Tablets (Glumetza [™])
Patient Compliance Requirements	
Subjective Properties Dosage Form/Size	Taste Masking Minimization of tablet size

Sitagliptin Phosphate (+) Metformin Hydrochloride Extended Release Tablets TPP
 Requirements with Corresponding Product Requirements or Associated Critical Quality
 Attributes

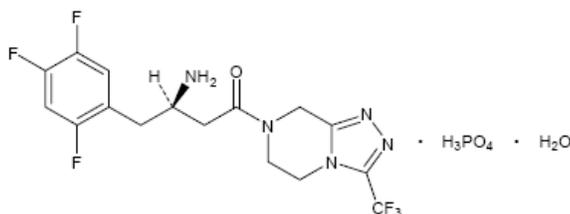
TPP Requirement(s)	Product Requirement or CQA
Taste Masking	<ul style="list-style-type: none"> • Dosage form selection: Film Coated Tablet • <u>Appearance</u> (CQA) • <u>Elegance</u> (CQA)
Tablet Size	<ul style="list-style-type: none"> • Dosage form selection: Active Coated Tablet
Impurities and Degradates controlled below ICH or Qualified Levels	<ul style="list-style-type: none"> • <u>Impurities and Degradates</u> (CQA)
50 mg/500 mg, 50 mg/1000 mg and 100 mg/1000 mg Doses	<ul style="list-style-type: none"> • <u>Content Uniformity and Assay</u> (CQA) • <u>Weight Uniformity</u> (CQA) • <u>Identity</u> (CQA)
Bioequivalence to Sitagliptin Tablets (JANUVIA [®]) and Metformin Hydrochloride Extended Release Tablets (Glumetza [®])	<ul style="list-style-type: none"> • <u>Dissolution</u> (CQA)

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Drug substance:

Sitagliptin

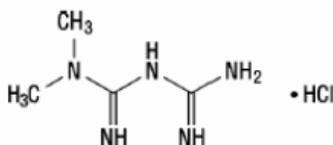
Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin phosphate monohydrate drug substance is used to manufacture JANUMET and JANUMET XR. Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate with an empirical formula of $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and a molecular weight of 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.

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



Review comments:

- Reference is made to the DMF [REDACTED] ^{(b) (4)} all CMC information on the metformin HCl drug substance. The applicant states that the drug substance is compendial-grade. The DMF has been reviewed seven times in support of other metformin applications. The primary reviewer will evaluate any new information in the DMF submitted since the most recent review.
- Reference is made to the approved NDA 21995 (same applicant) for all CMC information on the sitagliptin phosphate monohydrate drug substance. The applicant proposes to purchase the [REDACTED] ^{(b) (4)} from 2 suppliers with DMFs (DMF numbers are not provided; see the 74-day letter comment at the end of this review). The primary reviewer will evaluate the information in these DMFs as necessary.

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Drug product

Sitagliptin Phosphate (+) Metformin Hydrochloride is supplied as an extended release film-coated tablet. Each tablet contains 64.25 mg or 128.5 mg of sitagliptin phosphate (50 mg or 100 mg free base equivalent) and 500 mg or 1000 mg of metformin hydrochloride. Details of the composition are shown in [Table 2.3.P.1-0431a-xrtable: 1].

Table 2.3.P.1-0431a-xrtable: 1

Sitagliptin Phosphate (+) Metformin Hydrochloride
 Extended Release Tablet - Market Composition

Components	Compendial Testing	Function	Unit Strength (mg/tablet)		
			mg Sitagliptin Phosphate/mg Metformin Hydrochloride	50/500	50/1000
Core Tablet					
Metformin Hydrochloride	USP-NF, Ph. Eur.	Active	500.0	1000	1000
Povidone (b) (4)	USP-NF, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP-NF, Ph. Eur.				
Hypromellose (b) (4)	USP-NF, Ph. Eur.				
(b) (4)	USP-NF, Ph. Eur.				
Microcrystalline Cellulose (b) (4)	USP-NF, Ph. Eur.				
Silicon Dioxide, Colloidal Sodium Stearyl Fumarate	USP-NF, Ph. Eur.				
Core Tablet Weight					
API Film Coating					
Sitagliptin Phosphate [†]	-----	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Propyl Gallate (b) (4)	USP-NF, Ph. Eur.				
Hypromellose (b) (4)	USP-NF, Ph. Eur.				
Polyethylene Glycol (b) (4)	USP-NF, Ph. Eur.				
Kaolin (b) (4)	USP-NF				
(b) (4)	USP-NF, Ph. Eur.				
(b) (4) Film Coating (b) (4)	USP-NF, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP-NF, Ph. Eur.				
Carnauba Wax	USP-NF, Ph. Eur.				
Total Tablet Weight			1156	1589	1721
[†] 64.25 mg and 128.5 mg of the phosphate monohydrate salt is equivalent to 50 mg and 100 mg of the free base, respectively. [‡] (b) (4) [§] 50 mg/500 mg: (b) (4) consists of hypromellose, hydroxypropyl cellulose, titanium dioxide, and FD&C Blue #2/Indigo Carmine Aluminum Lake (21CFR82.51, 21CFR82.102, and E132) 50 mg/1000 mg: (b) (4) consists of hypromellose, hydroxypropyl cellulose, titanium dioxide, iron oxide yellow, and FD&C Blue #2/Indigo Carmine Aluminum Lake (21CFR82.51, 21CFR82.102, E132). 100 mg/1000 mg: (b) (4) consists of hypromellose, hydroxypropyl cellulose, titanium dioxide, and FD&C Blue #2/Indigo Carmine Aluminum Lake (21CFR82.51, 21CFR82.102, and E132). Compendial testing will be performed according to at least one of the compendia listed as applicable for the target market.					

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Review comments:

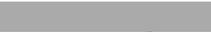
- **Established name and dosage strength.** The proposed established names of the product are “sitagliptin” and “metformin hydrochloride”, which are acceptable because they correlate with the dosage strengths as per current CDER policy on nomenclature. The dosage strength of sitagliptin is of the anhydrous free base.
- **Dosage form.** The product is a fixed dose combination tablet available in the strength of 50/500, 50/1000, 100/1000 (mg/mg sitagliptin anhydrous free base/metformin hydrochloride). Each tablet consists of the extended release metformin core coated with the immediate release sitagliptin layer [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
- **Excipients.** [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] The reviewer will consult with the PharmTox team on the safety of the higher excipient level.
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The Bioequivalence (BE) study 147 was conducted with the “final market composition” (“FMC”) tablets to demonstrate bioequivalence between the 50/500 and 100/1000 FDC tablets (batches WL00033696 and WL00034323) and the co-administered Januvia and Glumetza. This study included the bioequivalence of two 50/500 FDC tablets and one 100/1000 FDC tablet. The batches used in study P147 were manufactured at the commercial manufacturing site, using the commercial equipment, and at greater than [REDACTED] (b) (4) commercial scale. Their manufacture differs from the commercial manufacture (or “Final Market Image, FMI”): 1) the biobatch tablets [REDACTED] (b) (4), 2) the biobatch tablets contained more [REDACTED] (b) (4) [REDACTED] (b) (4) in the FMI), and 3) the commercial [REDACTED] (b) (4) process was optimized [REDACTED] (b) (4). The primary stability (or “Formal Stability Studies, FSS”) batches consist of 3 batches of each dosage strength and include the pivotal biobatches. Manufacturing sites and scales are copied

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below. The biowaiver requests for the 50/1000 strength and for the debossed commercial tablet will be evaluated by the ONDQA Biopharm team.

Comparison of Formal Stability Batch Sizes and Production Scale Batch Sizes



Manufacture of the  (b) (4) used for all batches was performed at the facility in West Point, PA. Manufacture of metformin core tablets, sitagliptin coated tablets and final coated tablets were performed at Arecibo, Puerto Rico. The manufacturing equipment in this facility consisted of fully qualified production equipment since both facilities are production facilities. A comparison of equipment used for each unit operation of the manufacture of the primary stability batches and for production batches can be found in [\[Table 3.2.P.8.1-0431a-xrtablet: 2\]](#).

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ONDQA
 IQA (Initial Quality/CMC Assessment)

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 202270

Established/Proper Name:
 Sitagliptin/Metformin hydrochloride

Applicant: Merck

Letter Date: 23-SEP-2010

Stamp Date: 23-SEP-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?			No CMC information was requested.
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 (b) (4) 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 (b) (4)			
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

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	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
D. drug substance/active pharmaceutical ingredient (DS/ ^{(b) (4)})				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to DMFs.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to DMFs.
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to DMFs.
15.	Does the section contain controls for the DS?			Reference is made to DMFs.
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to DMFs.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	
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		
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		

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 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		Provide the DMF numbers and letters of authorization for the 2 sources of the drug substance <div style="background-color: #cccccc; padding: 2px; text-align: right;">(b) (4)</div>

{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
11/03/2010

ALI H AL HAKIM
11/03/2010