

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202343Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202343

SUPPL # N/A

HFD # 510

Trade Name Juvisync

Generic Name sitagliptin and simvastatin fixed-dose combination tablets

Applicant Name Merck Sharp & Dohme Corp.

Approval Date, If Known October 7, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Merck conducted eight clinical pharmacology studies in support of the sitagliptin/simvastatin FDC NDA, as follows:

- Two bioequivalence studies - one using the lowest strength (Study P255: sitagliptin 100 mg / simvastatin 10 mg) and the other one using the highest strength (Study P153 Part I and Part II: sitagliptin 100 mg / simvastatin 80 mg)
- One study for the food effect on sitagliptin 100 mg / simvastatin 80 mg
- One study for the food effect on sitagliptin 100 mg/ simvastatin 80 mg
- Two relative bioavailability studies to explore preliminary formulations
- Two studies for assessment of drug-drug interaction

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Not a supplement. This is a new fixed- dose combination of sitagliptin and simvastatin.

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than

deesterification of an esterified form of the drug) to produce an already approved active moiety.

N/A YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# N/A

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

| | | |
|------|-------|--|
| NDA# | 21995 | Januvia (sitagliptin) tablets |
| NDA# | 22044 | Janumet (sitagliptin and metformin fixed-dose combination) tablets |
| NDA# | 19766 | Zocor (simvastatin) tablets |
| NDA# | 21687 | Vytorin (ezetimibe/simvastatin fixed-dose combination) tablets |
| NDA# | 21961 | Simvastatin orally disintegrating tablets |
| NDA# | 22078 | Simcor (niacin ER/simvastatin fixed-dose combination) tablets |

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Title: Cross- Discipline Team Leader

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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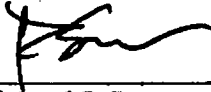
/s/

RAYMOND S CHIANG
10/06/2011

ILAN IRONY
10/06/2011

**MK-0431D Tablets
Debarment Certification**

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.



**Richard J. Swanson, Ph.D.
Senior Director
Worldwide Regulatory Affairs**

27 OCT 10

Date



Food and Drug Administration
CDER, Office of New Drug Quality Assessment
Mail Room 2562
10903 New Hampshire Ave.
Silver Spring, Maryland 20993
(301) 796-1679
(301) 796-9747 (FAX)

MEMORANDUM

DATE: 04-OCT-2011

FROM: John C. Hill, Ph.D., CMC Reviewer

THROUGH: Ali Al-Hakim, Ph.D., Chief, DNDQA III/Branch VII

TO: Khushboo Sharma, NDA 202-343 file

SUBJECT: Acceptable EES Inspection status for NDA 20-343

This memo serves to update the CMC review for NDA 202-343, noting that a final overall recommendation of "acceptable" was issued by Compliance (OMPQ) on 04-OCT-2011.

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/s/

JOHN C HILL
10/04/2011

ALI H AL HAKIM
10/04/2011

From: [Chiang, Raymond](#)
To: ["Swanson, Richard John";](#)
cc: ["carl_sparrow@merck.com"; Simoneau, Margaret A;](#)
Subject: RE: NDA 19766/S-083 (Zocor), NDA 21687/S-041 (Vytorin), and NDA 202343 (Juvисync) labeling comments
Date: Thursday, September 29, 2011 2:19:55 PM

Hello Dr. Swanson and Dr. Sparrow,

As per our phone conversation, see the Division's comments below (in black font) regarding proposed labeling for NDA 19766/S-083 (Zocor), NDA 21687/S-041 (Vytorin), and NDA 202343 (Juvисync).

We disagree with your modification under **5 Warnings and Precautions, 5.1 Myopathy/Rhabdomyolysis.** (b) (4)



We agree with your deletion of "including other lipid-lowering medications (other fibrates or ≥ 1 g/day of niacin)" from the HIGHLIGHTS OF PRESCRIBING INFORMATION, **WARNINGS AND PRECAUTIONS** section.

We disagree with your modification to the language under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS** section. We will consider modification of this section upon review of the final study report for HPS2-THRIVE.

If you have any questions, please do not hesitate to call or email.

thanks,

ray and margaret

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/s/

RAYMOND S CHIANG
09/29/2011

-----Original Message-----

From: Hill, John
Sent: Wednesday, September 28, 2011 8:17 AM
To: Chiang, Raymond
Subject: RE: Revised Carton and Container labeling-- nda202343 SDN17--
Juvisync (sita + simva FDC)

Ray:

Looks OK to me.

John

-----Original Message-----

From: Skariah, Sam
Sent: Monday, September 26, 2011 8:59 PM
To: Chiang, Raymond
Cc: Jones, Kendra
Subject: RE: Revised Carton and Container labeling-- nda202343 SDN17--
Juvisync (sita + simva FDC)

Hi Ray-

No comments from DDMAC.

Thanks!

Sam

-----Original Message-----

From: Tobenkin, Anne
Sent: Monday, September 26, 2011 4:03 PM
To: Chiang, Raymond; Hill, John; Skariah, Sam; Jones, Kendra
Cc: Tran, Suong T; Sharma, Khushboo; Merchant, Lubna; Tossa, Margarita;
Marchick, Julie
Subject: RE: Revised Carton and Container labeling-- nda202343 SDN17--
Juvisync (sita + simva FDC)

The revised Juvisync labels have incorporated all our recommendations, therefore DMEPA finds them acceptable.

Thanks for sending the revised labels for review prior to approval.

Anne

~~~~~

Anne Crandall Tobenkin, PharmD  
Safety Evaluator  
DMEPA

-----Original Message-----

From: Chiang, Raymond  
Sent: Monday, September 26, 2011 2:23 PM  
To: Tobenkin, Anne; Hill, John; Skariah, Sam; Jones, Kendra  
Cc: Tran, Suong T; Sharma, Khushboo; Merchant, Lubna; Tossa, Margarita;  
Marchick, Julie  
Subject: RE: Revised Carton and Container labeling-- nda202343 SDN17--  
Juvisync (sita + simva FDC)



Hi Anne, John, Sam, and Kendra,

See attached pdf file with the carton and container labels for the soon-to-be approved Juvisync NDA. This pdf file will be attached to the approval letter. As a FYI, these carton and container labels were officially submitted by Merck on September 2 and September 20, 2011.

Please review the carton and container labels in the pdf file and confirm that they are acceptable.

Please do not hesitate to contact me if you have any questions.

thanks!

ray

Raymond S. Chiang, MPT, MS, MS  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

Email: Raymond.Chiang@fda.hhs.gov  
phone: 301-796-1940

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-----Original Message-----

From: Chiang, Raymond

Sent: Monday, September 19, 2011 10:57 AM

To: Hill, John; Tossa, Margarita; Tobenkin, Anne; Merchant, Lubna

Cc: Skariah, Sam; Jones, Kendra; Sharma, Khushboo

Subject: RE: Revised Carton and Container labeling-- nda202343 SDN17-- Juvisync (sita + simva FDC)

Hi John,

Thanks for that observation!

I will relay that to the sponsor.

Do you have any other comments?

Hello Sam, Anne, and Kendra,

Before I send this information request, do you have any comments regarding these carton and container labels, or do the carton and

container labels look okay. Anne, as a FYI, most of the initial comments/information requests regarding these carton and container labels, came from your initial labeling review.

thanks,  
ray

-----Original Message-----

From: Hill, John  
Sent: Thursday, September 08, 2011 9:00 AM  
To: Chiang, Raymond; Tossa, Margarita; Tobenkin, Anne; Merchant, Lubna  
Cc: Skariah, Sam; Jones, Kendra; Sharma, Khushboo  
Subject: RE: Revised Carton and Container labeling-- nda202343 SDN17--  
Juvisync (sita + simva FDC)

I was looking at the proposed container labeling. It appears that the top line of the storage conditions on all of the 30 and 90 count labels has been clipped off at the top. I'm not sure if this is an artifact or a real issue.

I just wanted to call your attention to this.

John

John C. Hill, Ph.D., CAPT. USPHS

-----Original Message-----

From: Chiang, Raymond  
Sent: Thursday, September 08, 2011 8:40 AM  
To: Tossa, Margarita; Tobenkin, Anne; Merchant, Lubna  
Cc: Hill, John; Skariah, Sam; Jones, Kendra; Sharma, Khushboo  
Subject: Revised Carton and Container labeling-- nda202343 SDN17--  
Juvisync (sita + simva FDC)

Hi Rita and Anne,

See revised carton and container labeling incorporating responses to requests as per your labeling review dated June 21, 2011. They have also incorporated the pending trade name, JUVISYNC.

Please review and advise whether or not Merck has adequately revised the carton and container labels, assuming the proprietary tradename JUVISYNC is approved of course.

I have also requested Merck submit the revised carton and container labels with the established name, in case this NDA is approved... but the proprietary trade name is found to be not acceptable.

thanks,  
ray

-----Original Message-----

From: asr-dontreply@fda.hhs.gov [<mailto:asr-dontreply@fda.hhs.gov>]  
Sent: Friday, September 02, 2011 5:35 PM  
To: Chiang, Raymond; CDER-OND-DMEP-EDRNOTIFY; CDER-EDR\_ASR\_Document\_Coordinators; CDER-EDRSTAFF; CDER-EDRADMIN; CDER ESUB; Khalsa, Gurinders J; Livermore, Russell J; Thompson, Douglas L. \*; CDER-EDRSTAFF  
Subject: Successfully Processed eCTD: nda202343 in DARRTS

Successfully Processed eCTD: nda202343 in DARRTS. Details below:

EDR Location: <\\CDSESUB1\EVSPROD\NDA202343\202343.enx>

For Document Room Staff Use:

Application Type/Number: nda202343  
Incoming Document Category/Sub Category: Electronic\_Gateway  
Supporting Document Number: 17  
eCTD Sequence Number: 0017  
Letter Date: 09/02/2011  
Stamp Date: 9/2/2011

Receipt Date/Time from Notification: 09-02-2011, 15:37:19  
Origination Date/Time from Notification: 09-02-2011, 15:34:02  
DOCUMENT ID: 4924216

356H Form: <\\CDSESUB1\EVSPROD\NDA202343\0017\m1\us\form-356h.pdf>

Cover Letter: <\\CDSESUB1\EVSPROD\NDA202343\0017\m1\us\cover-letter.pdf>

3397 Form: NOT FOUND

3674 Form: NOT FOUND

For EDR Staff Use:

The submission has already been processed. The following information is provided if verification is required. No additional action is required on your part

EDR Location: <\\CDSESUB1\EVSPROD\NDA202343\0017>  
Submission Size: 1789522  
Gateway Location:  
<\\chdc9681\cderesub\inbound\ectd\cil314992041526.243547@llnap22.te>

Copy to EDR Status: Good-1

For CDER Project Manager Use:

The following submission received through the Electronic Submission Gateway has been processed using the following information. This information will be updated once Document Room personnel have been able to verify the content of the submission.

Application Type/Number: nda202343

Incoming Document Category/Sub Category: Electronic\_Gateway  
Supporting Document Number: 17  
eCTD Sequence Number: 0017  
Letter Date: 09/02/2011

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/s/  
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RAYMOND S CHIANG  
09/30/2011



NDA 202343

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corp.  
P.O. Box 1000, UG2C-50  
Upper Gwynedd, PA 19454-1099

Attention: Richard J. Swanson, Ph.D.  
Senior Director, Worldwide Regulatory Affairs

Dear Dr. Swanson:

Please refer to your New Drug Application (NDA) dated December 6, 2010, received December 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sitagliptin and Simvastatin Tablets, 100 mg/10 mg, 100 mg/20 mg and 100 mg/40 mg.

We also refer to your September 2, 2011, correspondence, received September 2, 2011, requesting review of your proposed proprietary name, Juvisync. We have completed our review of the proposed proprietary name, Juvisync, and have concluded that it is acceptable.

The proposed proprietary name, Juvisync, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 2, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Raymond Chiang at (301) 796-1940.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology

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/s/  
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CAROL A HOLQUIST  
09/26/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: NDA 202343 (sitagliptin/simvastatin XR FDC tablets)-- Label  
**Date:** Monday, September 19, 2011 1:57:26 PM

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Hello Dr. Swanson,  
As per our phone conversation, regarding your Medication Guide submitted on September 14, 2011, for ease of internal FDA review, please email me your revised Medication Guide only (minus the package insert). As a FYI, we will not be reviewing your September 14, 2011 MedGuide submission.

thanks,  
ray



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/s/  
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RAYMOND S CHIANG  
09/19/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: 202343 labeling response  
**Date:** Monday, September 19, 2011 8:36:44 AM

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Hello Dr. Swanson,  
Regarding your most recent NDA 202343 labeling revisions to the package insert/  
MedGuide. Below (in black font) is our response to your revisions and  
comments.

1. The HbA1c language is class labeling for the statins and is based on the results of 2 large meta-analyses - both of which implicate simvastatin.
2. We can consider the use of the term angioedema, rather than serious hypersensitivity, for the last paragraph under W and P 5.6, regarding occurrence of such events with another DPP-4 inhibitor.

Because of the fast approaching PDUFA date, please provide a response to these comments ASAP.

thanks,

ray

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/s/  
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RAYMOND S CHIANG  
09/19/2011



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

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Memorandum

**Date:** September 12, 2011  
**From:** Raymond Chiang, Regulatory Project Manager  
**Subject:** Tcon: NDA 202343 labeling request to incorporate Supplement Request letter of August 11, 2011 for Zocor

---

Dr. Swanson of Merck was told that DMEP discussed further this issue whether or not the Zocor label changes (as per our Supplement Request letter of August 11, 2011 for Zocor) should be incorporated into the sita + simva FDC PI/MedGuide. DMEP came to the conclusion that these label changes should be incorporated into the sita + simva FDC PI/MedGuide for the next round of labeling negotiations.

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/s/  
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RAYMOND S CHIANG  
09/13/2011



NDA 202343

**INFORMATION REQUEST**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Merck Sharp & Dohme Corp.  
Attention: Richard J. Swanson, Ph.D.  
Senior Director, Regulatory Affairs  
P. O. Box 1000, UG2C-50  
Upper Gwynedd, PA 19454-1099

Dear Dr. Swanson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (sitagliptin/simvastatin) Tablets, 100 mg/10 mg, 100 mg/20 mg, 100 mg/40 mg.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).<sup>1</sup> The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

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<sup>1</sup> These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

**Please respond to this query within 30 days from the date of this letter.**

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JULIE C MARCHICK

09/06/2011

J. Marchick signing for M. Parks



**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: NDA 202343 (sitagliptin/simvastatin XR FDC tablets)-- Label  
**Date:** Friday, September 02, 2011 2:35:14 PM  
**Attachments:** [label sent to Merck 9.2.11.doc](#)

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Hello Dr. Swanson,

As per our conversation, see attached sitagliptin/simvastatin XR FDC package insert. I will be emailing you the revised MedGuide hopefully early next week.

Please accept all FDA edits that you agree with. So, the document should only show in tracked changes (1) any new edits Merck has made to our prior edits and (2) any new edits from Merck unrelated to our prior edits.

To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state " Merck response to FDA change or Merck Comment." This will be useful for showing which edits come from FDA vs. which edits were from Merck.

You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you.

As per our conversation please email your revised package insert to us by COB, Friday, September 9, 2011. Please do not hesitate to call or email if you have any questions.

As always, please confirm receipt of email.

thanks,

ray

52 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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RAYMOND S CHIANG  
09/13/2011



NDA 202343

## REMS RETRACTION

Merck Sharp & Dohme Corp.  
Attention: Richard J. Swanson, Ph.D.  
Senior Director, Regulatory Affairs  
P. O. Box 1000, UG2C-50  
Upper Gwynedd, PA 19454-1099

Dear Dr. Swanson:

Please refer to your New Drug Application (NDA) dated December 6, 2010, received December 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (sitagliptin/simvastatin) Tablets, 100 mg/10 mg, 100 mg/20 mg, 100 mg/40 mg.

We acknowledge your amendment dated June 22, 2011 requesting to be released from the requirement for the risk evaluation and mitigation strategy (REMS) for (b) (4) (sitagliptin/simvastatin).

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

In our letter dated February 16, 2011, we notified you that a REMS was required for (b) (4) (sitagliptin/simvastatin) to ensure that the benefits of the drug outweighed the risks of acute pancreatitis, including necrotizing pancreatitis. We indicated that your REMS must include a Medication Guide and a timetable for submission of assessments of the REMS.

We acknowledge receipt of your submission dated March 25, 2011 that included a proposed REMS for (b) (4) (sitagliptin/simvastatin). The proposed REMS contains a Medication Guide and a timetable for submission of assessments of the REMS

We also refer to our April 14, 2011 Supplemental New Drug Application (sNDA) approval letters for JANUVIA (sitagliptin), sNDA 021995/S-017 and JANUMET (sitagliptin and metformin hydrochloride), sNDA 022044/S-016 that informed you that we were releasing the requirement for the approved REMS for those products. We further refer to our July 22, 2011 Complete Response letter for NDA 202270 JANUMET XR (sitagliptin and extended-release metformin hydrochloride fixed-dose combination) which retracted our December 3, 2010 REMS request.

If (b) (4) (sitagliptin/simvastatin) is approved, we have determined that having a Medication Guide as part of the approved labeling will be adequate to address the serious and significant public health concern and will meet the standard in 21 CFR 208.1. Therefore, it is not necessary

to include the Medication Guide as an element of the REMS to ensure that the benefits of the drug outweigh its risks, and a REMS for (b) (4) (sitagliptin/simvastatin) is not required.

We remind you that, should this NDA be approved, a Medication Guide will be part of the approved labeling in accordance with 21 CFR 208.

If you have any questions, contact Raymond Chiang, M.S., Consumer Safety Officer, at (301) 796-1940.

Sincerely,

*{See appended electronic signature page}*

Amy G. Egan, M.D., M.P.H.  
Deputy Director for Safety  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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AMY G EGAN  
08/29/2011

## Marchick, Julie

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**From:** Marchick, Julie  
**Sent:** Wednesday, August 17, 2011 8:14 AM  
**To:** 'richard\_swanson@merck.com'  
**Cc:** Chiang, Raymond  
**Subject:** NDA 20343 Sitagliptin/Simvastatin FDC - Response to Question

Good Morning Rick,

I'm sending this response to you on behalf of Ray Chiang, who is on leave. You had sent an email to Ray on August 12, 2011, with the following question. Our response follows in bold font.

Question: Does the Agency concur with the proposed analyses below to support the safety of MK-0431D doses with sitagliptin 50 mg in patients with type 2 diabetes and moderate renal impairment?

**Response: In addition, please conduct separate analyses of sitagliptin 50 mg versus placebo in the Phase 2/ Phase 3 dose-ranging trials in subjects with normal renal function. While we understand your rationale for not including data from Studies 10 and 14, (dose ranging studies), not conducted in the intended population of patients with moderate renal impairment, these studies may still provide important information on the concomitant use of sitagliptin 50 mg and simvastatin or other statins.**

Please let me know if you have questions.

Julie

**Julie Marchick**  
**Acting Chief, Regulatory Project Management Staff**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**U.S. Food and Drug Administration**  
**301-796-1280 (phone)**  
**301-796-9712 (fax)**  
**julie.marchick@fda.hhs.gov**

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/s/

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JULIE C MARCHICK  
08/17/2011



NDA 202343

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Merck Sharp & Dohme Corp.  
P.O. Box 1000, UG2C-50  
Upper Gwynedd, PA 19454-1099

Attention: Richard J. Swanson, Ph.D.  
Senior Director, Worldwide Regulatory Affairs

Dear Dr. Swanson:

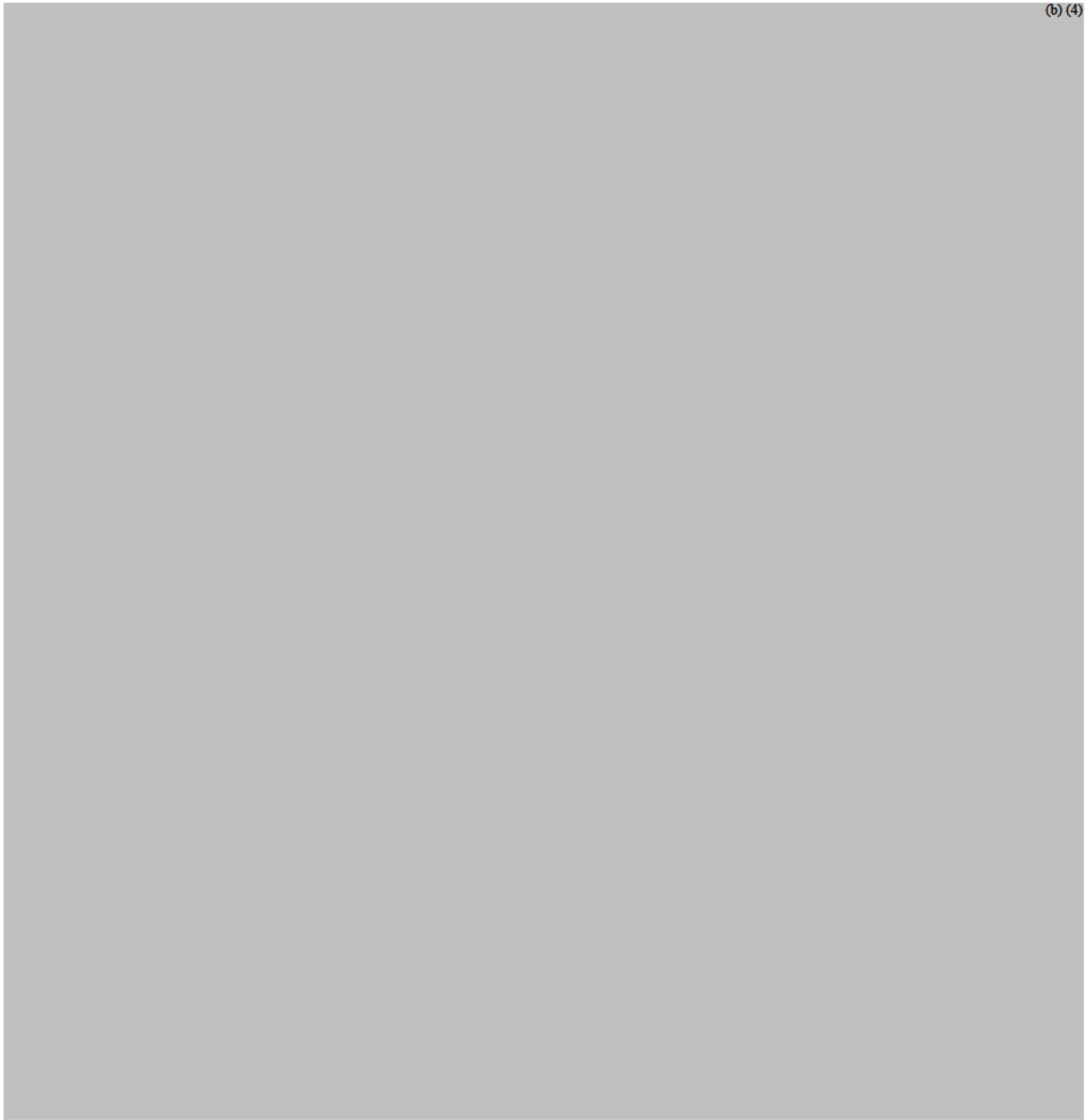
Please refer to your New Drug Application (NDA) dated December 07, 2010, received December 07, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sitagliptin Phosphate and Simvastatin Tablets, 100 mg/10 mg, 100 mg/20 mg and 100 mg/40 mg.

We also refer to your March 28, 2011, correspondence, received March 28, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is unacceptable for the following reasons.

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill. The redaction covers the majority of the lower half of the page.





We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

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<sup>1</sup> <http://www.diabetes.org/living-with-diabetes/complications/high-blood-pressure-hypertension.html>

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Raymond Chiang at (301) 796-1940.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology

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/s/  
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CAROL A HOLQUIST  
06/22/2011



NDA 202343

**INFORMATION REQUEST**

Merck Sharp & Dohme Corporation  
Attention: Richard J. Swanson, Ph.D.  
Senior Director, WW Regulatory Affairs  
P.O. Box 1000, UG2CD-48  
North Wales, PA 19454-1099

Dear Dr. Swanson:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sitagliptin Phosphate / Simvastatin Tablet.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The provided stability analysis indicates that samples of the 100/80 mg strength were falling out of the specified acceptable range for label claim at release (Lot WL00033418) and during the 52 week stability period (lots WL00033418 (weeks 13, 20, 52) and WL00033417 (weeks 30, 52)). Either revise your application to indicate that your product specification for assay is 90-110% (and submit the updated specifications for all dosage strengths to section 3.2.P.5.1) or submit successful, valid stability data for the 100/20 and 100/40 tablet strengths, or the 100/80 tablet strength.
2. Provide additional information regarding your evaluation of the simvastatin (b) (4) process and (b) (4). Discuss if, in your assessment of the (b) (4) (b) (4) process, you considered the effect of (b) (4) (b) (4)
3. Your approach to define a variable design space as outlined in section P.2.3 is not in concurrence with the definition of design space as outlined in ICH Q8(R2). Changes to an approved design space should follow appropriate post approval change mechanisms. Revise your submission accordingly.

4. Regarding the [REDACTED] (b) (4):



5. In section P3.3, provide clarification of the order of addition of the simvastatin [REDACTED] (b) (4) and the sitagliptin [REDACTED] (b) (4) during bilayer [REDACTED] (b) (4) for each tablet.
6. Provide a technical illustration of each strength of the bilayer tablet including dimensions and layers.
7. Clarify the reasons for large differences in minimum [REDACTED] (b) (4) for each tablet image (section 3.2.P.2.3.4.2.3)
8. For the development lots of 100 mg/80 mg tablets manufactured using different sources of simvastatin, there appear to be differences in friability as measured in the friabilator. Provide information regarding differences in the manufacturing of these lots that may affect the bilayer [REDACTED] (b) (4) operation and friability, including [REDACTED] (b) (4), and clarify the source of simvastatin drug substance used in each lot (section 3.2.P.2.3.4.3.3)
9. In section 3.2.P.2.3.4.4 you use the phrase “design space expansion”. Clarify that that you would use the appropriate regulatory notification if expanding the design space.
10. Describe whether variation in hold time and storage conditions, if any, for the tablet cores prior to film coating could have an adverse affect on product quality (e.g. levels of simvastatin-sitigliptin [REDACTED] (b) (4) dissolution, bi-layer [REDACTED] (b) (4)
11. Provide a stability update, including lots manufactured at the commercial facility.

12. The stress-stability studies (photostability study) reported in (section 3.2.P.8.1.4) did not assess (b) (4) tablets stored in an open dish or an open dish samples wrapped with aluminum foil (control) at 25 °C/ambient humidity for changes in either moisture or amount of simvastatin-sitagliptin (b) (4). Indicate where such data are located in the Application, provide these data to the Application or provide functional use data demonstrating that the desiccant maintains an acceptable moisture level once the container is opened.
13. With respect to the proposed (b) (4) release and stability specifications:
- Report specific/target retention times and UV maximum values for the identity test by HPLC (both Sitagliptin and Simvastatin).
  - Report the observed dissolution times as Sitagliptin and Simvastatin in addition to the Merck code.
  - Report the final in-process test results for tablet moisture content as part of the lot release specification for the (b) (4) tablet strengths. This can be denoted as being testing conducted in-process.
14. Provide a table summarizing any changes in the (b) (4) product quality specifications (release and stability) between the pilot scale and the commercial scale materials.
15. Provide stability data supporting the 1000 count pharmacy pack or indicate where these data are in the application.
16. In your amendment dated 4/27/2011, with regard to simvastatin dissolution acceptance criteria, you stated that "The corresponding raw data is included with this response as a SAS file due to the volume of data." However, the SAS file was not found. Resubmit this file.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ali Al-Hakim, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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ALI H AL HAKIM  
06/03/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: NDA 202343-- 4.15.11 IR  
**Date:** Friday, April 15, 2011 11:54:36 AM

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Hello Dr. Swanson,  
Please see information request below (in black font) from the FDA medical officer.  
As always, please confirm receipt of email.

thanks,  
ray

*Please clarify what is meant by "Merck prior environment" and "Merck current environment" in parts 1 and 2, respectively, of the financial disclosure information submitted to NDA 202-343.*



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/s/  
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RAYMOND S CHIANG  
04/15/2011



NDA 202343

**INFORMATION REQUEST**

Merck Sharp & Dohme Corporation  
Attention: Richard J. Swanson, Ph.D.  
Senior Director, WW Regulatory Affairs  
P.O. Box 1000, UG2CD-48  
North Wales, PA 19454-1099

Dear Dr. Swanson:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sitagliptin Phosphate / Simvastatin Tablet.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- The proposed dissolution acceptance criteria are not justified. Based on the proposed conditions and the limited data provided, the following are recommended.

Sitagliptin:  $Q = \text{(b) (4)}$  at 15 minutes  
Simvastatin:  $Q = \text{(b) (4)}$  at 30 minutes

If you have a different proposal, provide sufficient information to support it with all the raw data, including the dissolution values at different time points for each individual unit, the mean, the standard deviation and the plots, for the available lots.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ali Al-Hakim, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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ALI H AL HAKIM  
04/12/2011

**DATE:** April 6, 2011

**TO:** Sitagliptin phosphate (+)/Simvastatin Fixed Dose Combination (FDC) Tablets Review Team (NDA 202343)

**FROM:** Theodore Carver, Ph.D. ([Theodore.carver@fda.hhs.gov](mailto:Theodore.carver@fda.hhs.gov) 301-796-3878)/John Hill, Ph.D. ([John.Hill@fda.hhs.gov](mailto:John.Hill@fda.hhs.gov) 301-796-1679)

**THROUGH:** Christine Moore, Ph.D.

**SUBJECT:** Considerations for Inspection (CFI) memo

The purpose of this memo is to outline the manufacturing process and associated risks for NDA 202343. It is meant to provide an aid for investigators and compliance officers in preparing for inspection; it is not intended to provide inspectional instructions.

NDA 202-343 is submitted by Merck Sharp Dohme for Sitagliptin phosphate/Simvastatin fixed dose combination (FDC) tablets for treating Type II Diabetes Mellitus (T2DM) and hypercholesterolemia. The tablets consist of a bilayer configuration in which each layer is an immediate-release formulation of each drug. Each drug substance is an active ingredient of an approved drug product and is manufactured using the same chemistry, manufacturing, and controls as for its respective approved single-entity drug. Sitagliptin phosphate is the active ingredient in Januvia<sup>®</sup> (NDA 21-995) and Simvastatin is the active ingredient in Zocor<sup>®</sup> (NDA 19-766). The to-be-marketed strengths of the bilayer tablet are 100mg/10mg, 100mg/20mg, and 100 mg/40mg Sitagliptin phosphate/Simvastatin. In addition, the applicant has manufactured a 100mg/80mg formulation for use in development, bracketing stability studies, and bioequivalence studies in support of this NDA.

The bilayer tablets are manufactured by (b) (4) tablet, followed by film coating (b) (4) as shown in the schematic below:



In the NDA submission, the applicant has not clarified the (b) (4), so it is not yet known which drug comprises the first or second layer of the tablet. This

information is being requested from the applicant during review and should be confirmed for the commercial scale process.

(b) (4)  
steps in the approved process for manufacturing for Zocor tablets. For the Sitagliptin (b) (4) a development strategy that leveraged previous knowledge gained from Januvia was used (see Appendix 1 for more information).

On the basis of risk assessment the sponsor concluded that the following material attributes had a potential to impact product quality (b) (4)

A design space was defined for (b) (4) based on a multifactor DOE (see Appendix 1 for more information). For film coating of the tablets, a design space based on mathematical modeling of the film coating process and subsequent DOEs to define it were also described.

From the CMC point of view, there are no major quality issues identified in this application based on the drug product control and strategy provided by the applicant. However, there are a number of issues that may present significant risks to product quality if not clarified during review of this application. As part of our commitment to sharing CMC information across offices, we submit the following list of issues that may impact product quality, for consideration during inspection:

1. The design spaces were primarily defined by experiments conducted at pilot scale, simulations, and mathematical models. There is not enough information in the submission regarding verification of the design space at commercial scale. In general there is an elevated risk of operation when manufacturing at areas within the design space that are unverified at commercial scale. These risks could be mitigated, in part, by a more detailed evaluation of potential risks to product quality and by adopting an appropriate control strategy when moving to such regions of the design space. Typically, plans for handling movement within the design space are documented within the firm's Quality System. Such Quality Systems may include plans for handling movements within the design space (e.g. change control procedures, plans for updating batch records).
2. The applicant provided data indicating that a lot of the 100mg/80mg tablets fell out of specification for sitagliptin assay at the time of lot release, and the other two exhibit lots of the 100mg/80mg strength tablet failed to meet the proposed stability specification for assay at various time points upon stability. The Applicant has noted that these failures of the sitagliptin assay were due to an error in tablet manufacturing. It is important to get an understanding of the bilayer (b) (4) process that includes but is not limited to: order (b) (4)

(b) (4)

that are in place to minimize the risk of this error affecting manufacturing of the marketed tablet images at commercial scale. These data are critical in that this 100mg/80mg dosage strength represents the upper end of the proposed bracketing stability protocol to support the stability of the 100mg/20mg and 100mg/40mg dosage strengths.

3. From the current description of in process controls, it is unclear as to what circumstances dictate that use of (b) (4) his information could be included in the master batch record, but no master batch record was provided with the application.

4. (b) (4) are monitored as in process tests. The Applicant has identified (b) (4) as a critical quality attribute, and this test should be included in the product specification as an in process test. For stability of the finished product, an in-house, (b) (4) These data will be requested in the CMC IR letter if unavailable for assessment during the pre-approval inspection. Evaluation of testing procedures associated with measurement of (b) (4) (b) (4) would give an understanding of adequacy of the proposed approach. See Appendix I for additional information.

The CMC reviewers are willing to share their knowledge with the investigator prior to and during the inspection. If you have any questions, please email or call the CMC reviewers or email them: Theodore Carver, Ph.D. ([Theodore.carver@fda.hhs.gov](mailto:Theodore.carver@fda.hhs.gov) 301-796-3878)/John Hill, Ph.D. ([John.Hill@fda.hhs.gov](mailto:John.Hill@fda.hhs.gov) 301-796-1679/).

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/s/  
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THEODORE E CARVER  
04/07/2011  
CFI Memo

ALI H AL HAKIM  
04/07/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: NDA 202343-- March 25, 2011 submission  
**Date:** Tuesday, March 29, 2011 2:20:33 PM

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Hello Dr. Swanson,

I spoke with Dr. Silverman on the phone regarding this submission.

The cover letter for this submission states " *As advised by Dr. Raymond Chiang (FDA), the REMS for (b) (4) must be submitted and approved before a proposal to eliminate it can be submitted. The REMS for that medication is, therefore, submitted herein. Following the approval of the REMS, the Sponsor, will submit a PAS to eliminate it, as we have done for Januvia and Janumet.*"

This is not a true statement. This advice was in the context of Januvia, not (b) (4). Also included in this submission was a "Qualitative Evaluation of Januvia and Janumet REMS Survey Instruments." Please advise whether or not this was mistakenly submitted. Did you want us to review this with the Sita/Simva NDA?  
When you reply, please also include Dr. Robert E Silverman.

thanks,  
ray



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/s/  
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RAYMOND S CHIANG  
03/29/2011



NDA 202343

**FILING COMMUNICATION  
REMS NOTIFICATION**

Merck Sharp & Dohme Corp.  
Attention: Richard J. Swanson, Ph.D.  
Senior Director, Regulatory Affairs  
P. O. Box 1000, UG2C-50  
Upper Gwynedd, PA 19454-1099

Dear Dr. Swanson:

Please refer to your New Drug Application (NDA) dated December 6, 2010, received December 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (sitagliptin/simvastatin) Tablets, 100 mg/10 mg, 100 mg/20 mg, 100 mg/40 mg.

We also refer to your submission dated December 16, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 7, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 9, 2011.

During our filing review of your application, we identified the following potential review issues:

1. Submission of the sitagliptin/simvastatin tablet fixed dose combination (FDC) NDA only with 100 mg sitagliptin but not with 50 mg sitagliptin doses.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

#### Clinical

1. As discussed on September 30, 2010, the Four-Month Safety Update should include an update on the development of a fixed-dose combination tablet of sitagliptin/simvastatin with the sitagliptin 50 mg dose.
2. Please submit or direct us to the narratives for subjects who initiated a statin in the trials that constitute the pooled database, as discussed at the pre-NDA meeting on May 24, 2010.
3. You submitted a listing of subjects who discontinued due to adverse events. Please submit or direct us to the narratives and case report forms for these subjects.
4. Please direct us to the coding dictionary used for mapping investigator verbatim terms to preferred terms or submit it, if it was not previously submitted.

#### Nonclinical

1. Please submit or direct us to the Certificate of Analysis for drug lots of sitagliptin and simvastatin used in the 3-month oral combination toxicity study in rats (TT #09-1083).

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for (b) (4) (sitagliptin/simvastatin) to ensure the benefits of the drug outweigh the risks of acute pancreatitis, including necrotizing pancreatitis.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide, as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that (b) (4) (sitagliptin/simvastatin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of (b) (4) (sitagliptin/simvastatin). FDA has determined that (b) (4) (sitagliptin/simvastatin) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use (b) (4) (sitagliptin/simvastatin).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed (b) (4) (sitagliptin/simvastatin).

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to (b) (4) (sitagliptin/simvastatin) (see Appendix A). Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Before we can continue our evaluation of the NDA, you will need to submit the proposed REMS.

For administrative purposes, designate the proposed REMS submission as "**PROPOSED REMS for NDA 202343**" and all subsequent submissions related to the proposed REMS as "**PROPOSED REMS-AMENDMENT for NDA 202343.**" If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURES:  
REMS Appendices A and B

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/s/  
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MARY H PARKS  
02/16/2011

**From:** [Dharia, Pooja](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** NDA 202343 info request 2/14/11  
**Date:** Monday, February 14, 2011 11:48:18 AM

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Hi Dr. Swanson,

Please see the following information request for NDA 202343 (b) (4)

**Phase 3 protocol 801 is included in the Summary of Clinical Safety's pooled analysis. In the Summary of Clinical Efficacy, you describe which of the reports included in the pooled analysis were previously submitted and when. However, you do not mention P801 nor is it included in the Synopses of Individual Studies or recent Januvia and Janumet annual reports, although P801 is briefly described and included in various tables.**

**Please clarify the following:**

- 1. When was P801 conducted?**
- 2. Was the study report previously submitted for review? If so, when?**
- 3. If the P801 study report and synopsis were not previously submitted, please do so.**

You may e-mail this information to me, but please also submit officially to the NDA.

Thanks,  
Pooja

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
[pooja.dharia@fda.hhs.gov](mailto:pooja.dharia@fda.hhs.gov)  
(301) 796-5332

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/s/  
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POOJA DHARIA  
02/14/2011



**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** 12/15/2010

**TO:** Richard Swanson, Senior Director, Regulatory Affairs, Merck 267-305-6871

**THROUGH :** Khushboo Sharma, Regulatory Project Manager, ONDQA

**FROM:** Khushboo Sharma, Regulatory Project Manager, ONDQA

**SUBJECT: Memo of Telecon: Request for clarification on establishments information**

**APPLICATION/DRUG: NDA 202343**

\*\*Memo of Telecon:

The following clarifications were requested in a telephone conversation from Khushboo Sharma, RPM, ONDQA, to Richard Swanson, Senior Director, Regulatory Affairs, Merck regarding establishment information submitted to the original NDA on FDA Form 356h Attachment:

1. Provide contact name, phone number and fax numbers for all drug substance and drug product manufacturing facilities. Additionally, clarify which site will perform QbD elements.

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/s/  
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KHUSHBOO SHARMA  
12/15/2010



NDA 202343

**NDA ACKNOWLEDGMENT**

Merck Sharp & Dohme Corp.  
Attention: Richard J. Swanson, Ph.D.  
Senior Director, Regulatory Affairs  
P. O. Box 1000, UG2C-50  
Upper Gwynedd, PA 19454-1099

Dear Dr. Swanson:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

**Name of Drug Product:** (b) (4) (sitagliptin phosphate + simvastatin)  
**100/10 mg, 100/20 mg, 100/40 mg Tablet**

**Date of Application:** **December 6, 2010**

**Date of Receipt:** **December 7, 2010**

**Our Reference Number:** **NDA 202343**

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 5, 2011, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please call me at (301) 796-5332.

Sincerely,

*{See appended electronic signature page}*

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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POOJA DHARIA  
12/13/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 103183

(b) (4)

MEETING MINUTES

Merck Sharp and Dohme Corp.  
Attention: Richard J. Swanson, Ph.D.  
Director Regulatory Affairs  
P.O. Box 1000, UG2C-50  
North Wales, PA 19454-1099

Dear Dr. Swanson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0431 (sitagliptin/simvastatin fixed-dose combination) Tablets (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on September 30, 2010. The purpose of the meeting was to discuss the sitagliptin/simvastatin FDC and (b) (4)

This meeting was scheduled as a follow-up to the pre-NDA meeting held on May 24, 2010, and the teleconference held on July 12, 2010

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.  
Consumer Safety Officer  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

Reference ID: 2857492



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** A  
**Meeting Category:** Guidance

**Meeting Date and Time:** Thursday, September 30, 2010, 3:30 – 4:30 PM EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 4266  
Silver Spring, Maryland 20903

**Application Number:** 103183 and (b) (4)  
**Product Name:** Sitagliptin/Simvastatin FDC tablets and  
(b) (4)  
**Indication:** Type 2 Diabetes Mellitus  
**Sponsor/Applicant Name:** Merck Sharp and Dohme Corp.

**Meeting Chair:** Ilan Irony, M.D.  
**Meeting Recorder:** Raymond Chiang

**FDA ATTENDEES**

**Office of Drug Evaluation II**

Mary H. Parks, M.D. Director, Division of Metabolism and Endocrinology  
Products (DMEP)  
Raymond Chiang, M.S. Consumer Safety Officer, DMEP  
Ilan Irony, M.D. Clinical Team Leader, DMEP  
Valerie Pratt, M.D. Clinical Reviewer, DMEP

**Office of Clinical Pharmacology**

Sally Choe, Ph.D. Clinical Pharmacology Team Leader, Division of Clinical  
Pharmacology 2  
Jee Eun Lee, Ph.D. Clinical Pharmacology Reviewer

**Office of New Drug Quality Assessment**

Suong T. Tran, Ph.D. CMC Lead  
Houda Mahayni, Ph.D. Biopharmaceutics Reviewer

**SPONSOR ATTENDEES**

Helmut Steinberg, M.D. Associate Director, Clinical Research  
Barry Goldstein, M.D. Vice President, Clinical Research

**Reference ID: 2857492**

Elizabeth Migoya, Ph.D.  
Thomas Seck, M.D.  
Samuel Engel, M.D.  
Wen-Lin Luo, Ph.D.  
Matthew Anderson, Ph.D.  
Richard Swanson, Ph.D.  
Robert Silverman, M.D., Ph.D.  
Pramod Kotwal, Ph.D.  
Aubrey Stoch, M.D.  
Nicole Brown, Ph.D.  
Sandra Robertson

Director, Clinical Pharmacology  
Director, Clinical Research  
Associate Director, Clinical Research  
Senior Biometrician, Biostatistics  
Associate Director, Clinical Pharmacology  
Director, Regulatory Affairs  
Executive Director, Regulatory Affairs  
Associate Director, CMC  
Executive Director, Clinical Pharmacology  
Director, Manufacturing  
Director, Project Leadership



## 1.0 BACKGROUND

IND 103183 for MK-0431D (sitagliptin/simvastatin fixed-dose combination) tablet was submitted by Merck on December 8, 2008. (b) (4)

This meeting is a follow-up to a teleconference involving FDA and Merck on July 12, 2010.

The purpose of this meeting is to discuss the proposed timing for the development of the 50/10, 50/20, and 50/40 (mg sitagliptin/mg simvastatin) tablet strengths of MK-0431D, and to discuss whether (b) (4)

## 2. DISCUSSION

1. As requested by FDA during the teleconference with Merck on 12 July 2010, the Sponsor is submitting its proposed timing for the development and registration of the 50/10, 50/20, and 50/40 (mg sitagliptin/mg simvastatin) tablet strengths of MK-0431D, the fixed-dose combination (FDC) of sitagliptin and simvastatin. Submission of the MK-0431D NDA, for tablet strengths containing 100 mg sitagliptin, is proposed for December 2010. The Sponsor seeks FDA concurrence with the proposed timing for the supplemental NDA submission for the MK-0431D tablet strengths containing 50 mg sitagliptin in December 2011.

Discussion: FDA stated that the 100/80 ( mg sitagliptin/mg simvastatin) tablet strength is not approvable, because of the safety issues associated with the 80 mg simvastatin dose. Since the 100/80 (mg sitagliptin/mg simvastatin) tablet strength is not approvable, the biowaiver requests associated with this dose would no longer be valid. Merck stated that the bioequivalence (BE) study for 100/80 (mg sitagliptin/mg simvastatin) tablet strength has been completed and that the data is available. Merck asked whether data from the BE studies for 100/80 and 100/10 doses could be used to obtain biowaiver for the two middle strength sitagliptin/simvastatin FDC tablets (i.e. 100/20 and 100/40), and to bridge the 50 mg sitagliptin doses (i.e. 50/40, 50/20, and 50/10). FDA stated yes, in principle, but that this would be a review issue. Merck asked whether bridging studies with the 50 mg sitagliptin dose FDC could be performed *in vitro*. FDA stated that this would be acceptable.

FDA stated this product is a “convenience” product. Since diabetic patients with normal renal function may experience renal deterioration over time and may require an FDC with 50 mg sitagliptin, submission of an NDA without the 50 mg sitagliptin dose is a both a review issue and safety issue, not a drug utilization issue. If the sponsor chose to submit the NDA without the 50 mg sitagliptin dose, it should clearly convey the development status of the 50 mg dose in the application and 4-month safety update.

Post-meeting comment: If the NDA was submitted and approved without the 50 mg sitagliptin dose, the NDA may be subject to a post-marketing requirement with timeline for development of the 50 mg doses.

2.



### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion

### **4.0 ACTION ITEMS**

No action items were identified during the meeting.

### **5.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

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**RAYMOND S CHIANG**  
**10/29/2010**

Reference ID: 2857492

Reference ID: 3028282

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/s/  
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THEODORE E CARVER  
04/07/2011  
CFI Memo

ALI H AL HAKIM  
04/07/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 103183

Pre-NDA MEETING MINUTES

Merck Sharp and Dohme Corp.  
Attention: Richard J. Swanson, Ph.D.  
Director, Regulatory Affairs  
P.O. Box 1000, UG2C-50  
North Wales, PA 19454-1099

Dear Dr. Swanson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0431D (sitagliptin/simvastatin fixed-dose combination) tablets.

We also refer to the teleconference held between representatives of your firm and the FDA on May 24, 2010. The purpose of this pre-NDA meeting was to discuss the adequacy of the proposed components of the New Drug Application (NDA) for MK-0431D Tablets.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5073.

Sincerely,

*{See appended electronic signature page}*

Mehreen Hai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: FDA version of Pre-NDA Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** May 24, 2010, 9:30 AM – 10:30 AM (Eastern)  
**Meeting Location:** Teleconference

**Application Number:** 103183  
**Product Name:** MK-0431D Tablets  
(sitagliptin/simvastatin fixed-dose combination)

**Indication:** Treatment of Type 2 Diabetes Mellitus  
**Sponsor/Applicant Name:** Merck Sharp and Dohme Corp.

**Meeting Chair:** Valerie Pratt, M.D.  
**Meeting Recorder:** Mehreen Hai, Ph.D.

### FDA ATTENDEES

#### Office of Drug Evaluation II

Mary Parks, M.D. Director, Division of Metabolism and Endocrinology Products (DMEP)  
Ilan Irony, M.D. Diabetes Team Leader, DMEP  
Valerie Pratt, M.D. Clinical Reviewer, DMEP  
Patricia Brundage, Ph.D. Pharmacology/Toxicology Reviewer, DMEP  
Todd Bourcier, Ph.D. Pharmacology/Toxicology Team Leader, DMEP  
Patricia Brundage, Ph.D. Pharmacology/Toxicology Reviewer, DMEP  
Katrina Rhodes, M.D., M.S. Clinical Reviewer, DMEP  
Lina AlJuburi, Pharm.D. Chief, Project Management Staff, DMEP  
Mehreen Hai, Ph.D. Regulatory Project Manager, DMEP

#### Office of Biometrics

Japobrata Choudhury, Ph.D. Statistics Reviewer, DBII

#### Office of Clinical Pharmacology

Jaya Vaidyanathan, Ph.D. Clinical Pharmacology Reviewer, DCP2

#### Office of New Drug Quality Assessment

Suong T. Tran, Ph.D. CMC Lead, ONDQA  
Martin Haber, Ph.D. CMC Reviewer, ONDQA  
Angelica Dorantes, Ph.D. Biopharmaceutics Team Leader

## SPONSOR ATTENDEES

|                        |                                                                   |
|------------------------|-------------------------------------------------------------------|
| Thomas Seck, M.D.      | Associate Director, Clinical Research                             |
| Keith Kaufman, M.D.    | Vice President, Clinical Research                                 |
| Barry Goldstein, M.D.  | Vice President, Clinical Research                                 |
| Matt Anderson, Ph.D.   | Associate Director, Clinical Pharmacology                         |
| Richard Clay, Ph.D.    | Distinguished Senior Investigator, Preclinical Toxicology         |
| Sandra Mackenzie, BSc. | Director, Regulatory Affairs                                      |
| Scott Korn, M.D.       | Vice President, Regulatory Affairs                                |
| Greg Golm, Ph.D.       | Director, Statistics                                              |
| Kaifeng Lu, Ph.D.      | Senior Biometrician, Biostatistics                                |
| Deborah Shapiro, Ph.D. | Senior Director, Biostatistics                                    |
| Pramod Kotwal, Ph.D.   | Associate Director, Chemistry Manufacturing and Controls          |
| Sandra Morris          | Vice President, Franchise Project Management                      |
| Wen-Lin Luo, Sr.       | Biometrician Biostatistics, Early Clinical Development Statistics |
| Susie Li               | Research Fellow, Clinical PK/PD                                   |
| Aubrey Stoch           | Exec Director, Clinical Pharmacology                              |
| Clay B Frederick       | Distinguished Senior Investigator, Compound Management            |
| Andreas M Abend        | Associate Director, Pharm Analytical                              |
| Sandra Robertson       | Director, Project Leadership                                      |
| Kaifeng Lu             | Sr. Biometrician Biostatistics, Late Development Statistics       |
| Zhen Wang              | Project Manager, Project Management                               |

### 1.0 BACKGROUND

Merck submitted IND 103183 for MK-0431D (sitagliptin/simvastatin fixed-dose combination tablets) on December 8, 2008, for the treatment of patients with Type 2 diabetes mellitus.

On March 26, 2010, Merck submitted a Type B Pre-NDA meeting request for this product. The FDA has previously had a teleconference with Merck regarding this product. This teleconference was held on March 4, 2010, and was in regard to the need for a dedicated pharmacodynamics study for MK-0431D.

Sitagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4), and was approved by the FDA on October 16, 2006, under NDA 021995, for the treatment of type 2 diabetes mellitus (Tradename: Januvia). Simvastatin is an HMG-CoA reductase inhibitor, a member of the statin class of drugs. It was approved by the FDA on December 23, 1991, under NDA 019766, for the treatment of hypercholesterolemia (Tradename: Zocor).

The objective of this meeting was to discuss the adequacy of the proposed components of the New Drug Application (NDA) for MK-0431D Tablets.

## DISCUSSION

The Sponsor requested discussion and responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the Sponsor on May 21, 2010, follow in **bold** font. A summary of the meeting discussion is shown in *italicized bold* font.

### Question 1

Does the Agency concur that the data to be provided in the NDA (as listed below) are sufficient to support an NDA filing and registration of MK-0431D with the prototype labeling?

#### Question 1a: CMC data

**FDA Preliminary Response: No, we do not concur. On page 40 of the briefing document you mentioned that (b)(4) data were generated to bridge the MK-0431D 100/80 mg strength formulation used in the bioequivalence study and the three lower MK-0431 strengths 100/40 mg, 100/20 mg, and 100/10 mg.**

The proposed formulations presented in Table 10 ( page 41) of your meeting document for MK-0431D bilayer tablets (100/10 mg, 100/20 mg, 100/40 mg, and 100/80 mg sitagliptin/simvastatin FDC) (b)(4)

You may request a biowaiver for the middle MK-0431D strengths 100/40 mg, 100/20 mg. The waiver request should be supported by the following information: 1) acceptable bioequivalence data on the MK-0431 highest strength 100/80 mg and the lowest strength 100/10 mg, 2) dissolution profile comparison data for the middle MK-0431 strengths 100/40 mg and 100/20 mg in three media (i.e., pH 1.2, 4.5, and 6.8) using the same dissolution testing conditions, and 3) similarity f2 values using both, the highest and lowest strengths as the reference.

Please also see our response to Question 5 below.

**Meeting Discussion: No discussion**

#### Question 1b: Nonclinical data

**FDA Preliminary Response: Yes, the three-month toxicity study with the combination is adequate to support submission of the NDA. Comments on the preclinical sections of the label will be provided upon review of the NDA.**

**Meeting Discussion: No discussion**

#### Question 1c: Data from clinical pharmacology studies

**FDA Preliminary Response: Please refer to our response to Question 1a above regarding the need for a bioequivalence study with the low dose strength. These data along with the proposed clinical pharmacology data to be provided in the NDA are sufficient to support an NDA filing. However, the acceptability of these data will be a review issue.**



We noted that for study 153, a pre-specified confidence interval bound of 0.70 -1.43 was used for determining the bioequivalence of the FDC tablet to individual reference drugs. We recommend that you use the pre-specified bound of 0.80-1.25 as indicated in the **Guidance for Industry titled “Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations”** (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf>).

***Meeting Discussion:** The sponsor clarified that the bioequivalence analysis will be conducted as per the guidance.*

Question 1d: Integrated safety analyses of the existing sitagliptin clinical trial data to demonstrate the safety/tolerability of co-administration of sitagliptin and simvastatin from clinical studies that established the efficacy and safety/tolerability of sitagliptin in patients with type 2 diabetes and inadequate glycemic control

**FDA Preliminary Response:** The proposed clinical data to be provided in the NDA are sufficient to support an NDA filing. However, the acceptability of these data for approval will be a review issue. A clinical study investigating the effects of simvastatin on glycemic control may need to be conducted as a post-marketing requirement. This safety and efficacy study should include  $\geq 200$  diabetic subjects per group on metformin randomized to sitagliptin/simvastatin FDC or the component monotherapies for  $\geq 16$  weeks.

***Meeting Discussion:** The sponsor inquired when the clinical study protocol should be submitted. The agency responded that, if the NDA is approved, the study will be a post-marketing requirement (PMR). The approval letter will contain a timeline for protocol submission and study completion. Thus, the clinical study protocol for the PMR does not need to be submitted with the NDA.*

Question 2

Does the Agency concur with the doses of MK-0431 proposed to be developed by the Sponsor?

**FDA Preliminary Response:** No, your proposal to develop MK-0431D with only the 100 mg dose of sitagliptin and the 10, 20, 40, and 80 mg doses of simvastatin is not acceptable. According to the data you submitted, <sup>(b) (4)</sup> of the sitagliptin prescriptions in the USA are for sitagliptin 50 mg; this is not an inconsequential number of patients. In addition, as type 2 diabetes mellitus is a chronic disease and many patients will experience progressive renal failure, we believe the current drug utilization data underestimate the number of patients who will need sitagliptin 50 mg in the future. As previously stated, we believe the FDC should be available for relevant groups of patients within a spectrum of renal function from normal to moderate renal dysfunction in whom both sitagliptin and simvastatin are indicated. If use of the FDC is restricted to certain populations, this will be noted in the Indications and Usage (Important Limitations of Use) and/or Dosage and Administration sections of the label.

You should consider development of the following dose strengths: 50/10, 50/20, and 50/40 mg sitagliptin/simvastatin FDC tablets, for either one tablet or two tablets once daily

dosing. According to the drug utilization data you have provided, this approach will increase the potential use of the FDC in patients with co-prescriptions for sitagliptin and simvastatin from [REDACTED] <sup>(b) (4)</sup> This approach would require that you provide dosage form equivalence data to demonstrate that FDCs with these dose strengths taken as two tablets daily are equivalent to doses of 100 mg sitagliptin and 20, 40 and 80 mg of simvastatin respectively.

***Meeting Discussion:*** The agency will require that FDCs with sitagliptin 50 mg be developed, as this is a convenience product and a significant number of patients use sitagliptin 50 mg. However, the agency has not decided if the NDA must include FDCs with sitagliptin 50 mg or if development of these FDCs will be a PMR. The sponsor agreed to submit a timeline for development of FDCs with sitagliptin 50 mg. The agency will comment on the need for additional clinical pharmacology studies once the sponsor submits their development plan for the FDC containing sitagliptin 50 mg. The sponsor expressed concern about the feasibility of manufacturing FDCs with sitagliptin 50 mg, due to tablet size, and inquired about the possibility of addressing the requirement to offer this dose strength in the FDCs by co-packaging sitagliptin and simvastatin. The agency asked the sponsor to submit a proposal, which will be reviewed and discussed at a later time.

### Question 3

The background package provides an overview of the clinical data, key analyses to be provided with the NDA, a referenced Statistical Analysis Plan (SAP) for the Integrated Summary of Safety (ISS) as well as sample tables.

**Question 3a:** Does the Agency concur with the proposed analyses methods, populations, and subgroups for the ISS?

**FDA Preliminary Response:** No, we do not concur with the proposed analyses methods, populations, and subgroups for the ISS.

- Please assess the safety and tolerability of co-administration of sitagliptin 100 mg with simvastatin and of the co-administration of sitagliptin 100 mg with any statin *excluding simvastatin* in the ISS.
- If you develop sitagliptin/simvastatin FDC tablets with 50/10, 50/20, and 50/40 mg dose strengths, include relevant clinical pharmacology data in the NDA
- If you develop sitagliptin/simvastatin FDC tablets with 50/10, 50/20, and 50/40 mg dose strengths, please include the following in the ISS:
  - All data from patients randomized to take sitagliptin 50 mg per day, with or without concomitant use of simvastatin or other statin drugs.
  - All data from special population patients with moderate renal impairment and treated with sitagliptin 50 mg daily (i.e. protocols 047 and 028) treated with simvastatin or not.
- You propose that the simvastatin any dose population will be the primary analysis population and additional analyses will be performed in simvastatin dose-specific populations. However, if you develop sitagliptin/simvastatin FDC tablets with 50/10, 50/20, and 50/40 mg dose strengths, please also analyze data by 1) the sitagliptin any dose population and 2) sitagliptin dose-specific populations.

- **Table 1 of your Statistical Analysis Plan for Integrated Safety states that the per protocol (PP) population will be used for studies 024 and 049, whereas the full analysis set (FAS) will be used for all other protocols. Please perform one analysis with the FAS population for all studies and another analysis with the PP population for all studies, or justify an alternate proposal.**

***Meeting Discussion:*** Regarding the first bullet, the sponsor inquired why the agency wishes to compare sitagliptin 100 mg with simvastatin to sitagliptin 100 mg with any statin excluding simvastatin in the ISS. The sponsor feels that a comparison to “any statin” provides more power. The agency stated that a comparison to “any statin excluding simvastatin” would be cleaner and is required. However, if the sponsor wishes to do both analyses, they may do so. Regarding the last bullet, the sponsor clarified that they plan to analyze efficacy as described above (i.e. combination of PP and FAS) because studies 024 and 049 were non-inferiority studies and, in that case, PP analyses are recommended by ICH Guidance for Industry entitled “E9 Statistical Principles for Clinical Trials” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/s/ucm073137.pdf>). Furthermore, a secondary analysis of the FAS in these studies was consistent with the PP analyses. The sponsor plans to analyze safety using the FAS for all protocols. The agency responded that this is acceptable. However, for efficacy, the sponsor was asked to also submit an analysis using the FAS for all protocols. The agency confirmed that Phase 1 clinical pharmacology studies need not be included.

The agency also clarified that, if the NDA does not propose use of FDCs with sitagliptin 50 mg, some of the comments under 3a are not relevant.

**Question 3b:** Does the Agency concur with the format of the sample tables provided?

**FDA Preliminary Response:** Please also submit the following:

- An analysis of deaths and serious adverse events in the pooled database
- An analysis of glycemic control in subjects initiating a statin in the pooled database

***Meeting Discussion:*** The sponsor stated that an analysis of glycemic control was not proposed because only 5-10 subjects initiated a statin in the pooled database. The agency agreed that this population is not appropriate for analysis but narratives were requested instead.

**Question 4**

Does the Agency concur with the Sponsor’s plan for submission of the MK-0431D eCTD?

**FDA Preliminary Response:** Please direct any technical questions on eCTD submissions to Supervisory Program Analyst, Virginia Ventura.

***Meeting Discussion:*** The appropriate email address for questions is [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov).

Question 5

Does the Agency concur with the overall plan for providing the CMC data in the NDA including the utilization of the formal stability study data and technical justification to support the proposed commercial packages?

**FDA Preliminary Response:** No, the NDA must contain stability data from batches manufactured at the proposed commercial sites (drug substance and drug product commercial sites). This is an NDA filing issue. Your proposed commercial container closure systems will be evaluated during our NDA review and the associated shelf lives determined based on all available information in the NDA.

**Meeting Discussion:** *The sponsor inquired whether FDA has a response regarding the commercial product stability requirement. The ONDQA Senior Management finds the proposal acceptable, based on the clarification provided by the sponsor on May 21, 2010. Any stability data of the commercial product (manufactured at the commercial site) would be useful but not required.*

Question 6

A pediatric development program for Januvia is currently underway. The Sponsor does not consider additional pediatric studies of MK-0431D to be necessary. Does the Agency concur?

**FDA Preliminary Response:** Please address the Pediatric Research Equity Act (PREA) in your NDA. Be sure to include your rationale for your request in the NDA. A decision will be made during the review cycle.


**Meeting Discussion:** *No discussion*

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

- Whether development of FDCs with sitagliptin 50 mg will be required in the NDA or as a PMR

-  (b) (4)

**4.0 ACTION ITEMS**

- The sponsor will submit meeting minutes and a list of attendees.  
*[Post-Meeting Note: The sponsor submitted the list of attendees by email on May 24, 2010, and the draft meeting minutes on May 25, 2010.]*
- The sponsor will submit a timeline for the development of FDCs with sitagliptin 50 mg. The submission may include a proposal for  (b) (4)  
*[Post-Meeting Note: The sponsor submitted the information regarding the feasibility and timing for the development of doses for patients with Type 2 diabetes mellitus and*

*moderate renal impairment (sitagliptin/simvastatin 50/10, 50/20, 50/40 mg) on June 18, 2010.]*

**5.0 ATTACHMENTS AND HANDOUTS**

No attachments or handouts for the meeting minutes.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

IND-103183

GI-1

MERCK AND CO  
INC

MK-0431D (sitagliptin/simvastatin  
fixed dose combination) Tablets

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MEHREEN HAI  
06/24/2010

## MEMORANDUM OF TELECON

DATE: March 4, 2010 (2:00 – 3:00 pm EST)

APPLICATION NUMBER: IND 103183

DRUG NAME: Sitagliptin/Simvastatin Fixed-Dose Combination (Codename: MK-0431D)

**BETWEEN:**

Names            Robert Silverman, M.D. (Regulatory Affairs)  
                     Richard Swanson, Ph.D. (Regulatory Affairs)  
                     Scott Korn (Regulatory Affairs)

Phone:            [REDACTED] (b) (4)  
Representing: Merck & Co., Inc.  
                     P.O. Box 1000, UG2C-50  
                     North Wales, PA 19454-1099

**AND**

Mary Parks, M.D. (Division Director, DMEP)  
Eric Colman, M.D. (Deputy Division Director, DMEP)  
Lina AlJuburi, Pharm.D., M.S. (Chief, Project Management Staff, DMEP)  
Mehreen Hai, Ph.D. (Regulatory Project Manager, DMEP)

**SUBJECT:** Discussion regarding the requirement to conduct a clinical pharmacodynamic study assessing the effect of simvastatin on glycemic control among diabetic patients.

Background

Sitagliptin was approved by the FDA in October 2006, under the tradename Januvia, for the treatment of Type 2 Diabetes. Simvastatin was approved in 1991, under the tradename Zocor, for the treatment of hypercholesterolemia. Merck is developing a fixed-dose combination product (MK-0431D) combining these two products, under IND 103183, since a large number of patients with type 2 diabetes mellitus are also administered a statin. Merck intends to submit a New Drug Application for this product in the first half of CY 2011.

On February 9, 2009, FDA issued an advice letter, concurring with Merck's listing of the data that would be required for the submission of a New Drug Application (NDA) for MK-0431D. At that time, the Division did not think that a pharmacodynamic (PD) study was required.

However, in early 2010, the results of the JUPITER study demonstrated a greater incidence of diabetes mellitus in the group of patients treated with rosuvastatin. There were also data

suggesting that statin treatment may worsen glycemic control among diabetics. Therefore, at a teleconference held on March 1, 2010 for the sitagliptin-atorvastatin FDC (IND 105,247), Merck was requested to conduct a dedicated PD study. They were also informally informed that they would be required to do the same for the sitagliptin-simvastatin FDC.

**Mechanism of Action:** Sitagliptin: Selective inhibitor of dipeptidyl peptidase 4 (DPP-4)  
Simvastatin: HMG-CoA Reductase inhibitor (member of statin class of drugs)

### Teleconference

Summary: At the request of Dr. Robert Silverman at Merck, a teleconference was set up to discuss the requirement for a PD study for MK-0431D. Merck's position was that while the <sup>(b) (4)</sup>the sitagliptin-simvastatin FDC is nearing the end of development, and they hope to submit the NDA for this product within the year. The requirement to conduct a PD study would significantly delay this plan. The Division agreed to allow Merck to submit the NDA for MK-0431D without data from a dedicated PD clinical study, with the caveat that such a study may be a post-marketing requirement, if MK-0431D is approved. In addition, Merck was informed that they should submit data from other studies regarding patients co-administered sitagliptin and a statin, as an alternative to the PD study.

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Memo prepared by:

Mehreen Hai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research



Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

IND-103183

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MEHREEN HAI  
05/04/2010