

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202270Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202270

SUPPL # N/A

HFD # 510

Trade Name Janumet XR

Generic Name Sitagliptin/Metformin Hydrochloride Extended-Release Fixed Dose Combination

Applicant Name Merck Sharp and Dohme Corp.

Approval Date, If Known

### 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.

The pivotal study to support this NDA was a clinical pharmacology study, P147, to establish bioequivalence between the to-be-marketed formulation of Janumet XR to the co-administration of sitagliptin and an approved metformin XR product (Glumetza). This study also compared the administration of two 50/500 mg Janumet XR tablets to the administration of one 100/1000 mg Janumet XR tablet.

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 an NDA for a new fixed-dose combination of sitagliptin and

metformin extended-release (Glumetza).

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.

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# Glumetza (metformin 021748  
hydrochloride extended  
release) Tablets

NDA# Janumet (sitagliptin and 022044  
metformin) Tablets

NDA# Januvia (sitagliptin) 021995  
Tablets

NDA# Glucophage (metformin 020357  
hydrochloride) 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:

Investigation #1: Study P036, "A Multicenter, Double-Blind, Randomized, Placebo- and Active-Controlled Factorial Study of MK-0431 and Metformin Coadministration in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control"

Investigation #2: Study P020, "A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of MK-0431 to Patients With Type 2 Diabetes Mellitus Who have Inadequate Glycemic Control on Metformin Therapy"

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:

Investigation #1 was relied upon to support approval of NDA 022044 (Janumet). Investigation #2 was relied upon to support approval of NDA 021995 (Januvia) and NDA 022044 (Janumet).

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

|                  |                              |  |
|------------------|------------------------------|--|
| Investigation #1 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #2 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

|                  |                              |                               |
|------------------|------------------------------|-------------------------------|
| Investigation #1 |                              | !                             |
| IND #            | YES <input type="checkbox"/> | ! NO <input type="checkbox"/> |
|                  |                              | ! Explain:                    |



Title: Regulatory Project Manager  
Date: 1.30.12

Name of Office/Division Director signing form: Dr. Hylton Joffe signing off on behalf of Dr. Mary  
Parks  
Title: Cross-Discipline Team Leader

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

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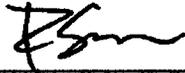
/s/  
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RAYMOND S CHIANG  
02/01/2012

HYLTON V JOFFE  
02/01/2012

**MK-0431A XR 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.  
Director  
Worldwide Regulatory Affairs

16 ~~SEP~~ 10

\_\_\_\_\_  
Date



NDA 202270

**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  
North Wales, 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 JANUMET XR (sitagliptin and extended-release metformin hydrochloride fixed-dose combination) Tablets, 100mg/1000mg, 50mg/500mg, and 50mg/1000mg.

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



NDA 202270

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

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

Dear Dr. Swanson:

We acknowledge receipt on August 3, 2011, of your August 3, 2011, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for JANUMET XR (sitagliptin and extended-release metformin hydrochloride fixed-dose combination) Tablets, 100mg/1000mg, 50mg/500mg, and 50mg/1000mg.

We consider this a complete, class 2 response to our July 22, 2011 action letter. Therefore, the user fee goal date is February 3, 2012.

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

Sincerely,

*{See appended electronic signature page}*

Raymond Chiang, M.S.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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RAYMOND S CHIANG  
08/15/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: XR quesiotns - follow up  
**Date:** Friday, July 29, 2011 9:51:24 AM

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Hello Dr. Swanson,  
Please see response to your questions below.  
thanks,  
ray

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**From:** Swanson, Richard John [mailto:richard\_swanson@merck.com]  
**Sent:** Thursday, July 28, 2011 9:05 AM  
**To:** Chiang, Raymond  
**Subject:** XR quesiotns - follow up

Hi Ray

we plan to submit the response to the CRL early next week but still need responses to a couple of the questions we had sent you

1. all of the data we have on XR was submitted with the NDA - there have been no additional preclinical or clinical studies completed or ongoing. Please confirm that, since there are no additional data with XR, an updated safety analysis is not required and in response to the request for the safety analyses, etc, we can simply state that there is no additional data

If there are no additional preclinical or clinical data to submit, an updated safety analysis is not required. However, you should explicitly state in your Complete Response submission that there are no additional data.

2. Do you want us to submit the responses to the the Arecibo 483 (and the response to the question about the Near IR QBD method, which had not been part of the 483) as part of this response to you or should they go only to FDA inspector in Puerto Rico ( or should we send to both) ?

Please officially submit your response to FDA and the FDA district office in Puerto Rico.

If possible, we 'd like answers to these this week so we can put the package together to submit early next  
thanks  
rick

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**From:** Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]  
**Sent:** Monday, July 25, 2011 1:44 PM  
**To:** Swanson, Richard John  
**Subject:** RE: Free to talk at 1 or 1:30 for a few minutes re XR?

Dr. Swanson,

Please submit the P147 CSR with your response to our our Complete Response (CR) letter.

Please submit everything at once in response to the Complete Response (CR) letter.

When you submit your labeling with the CR response, please clearly indicate what changes were made from the July 18, 2011 submission (i.e. revised URL and revision of Figure 1). As always, please submit a tracked-changes version of the label (with changes noted from your July 18, 2011 submission).

As per an earlier email, we were not be able to review your July 21, 2011 labeling submission because your July 18, 2011 submission (also containing a revised package insert/Medguide) was used to make our revisions. If you wish to incorporate these changes to the package insert, you may request to do so in the next review cycle. Regarding updating the PI/MedGuide and cartons with the new URL. This will need to be reviewed by OSE and DDMAC, and also addressed in the next review cycle.

thanks,  
ray

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**From:** Swanson, Richard John [mailto:richard\_swanson@merck.com]  
**Sent:** Monday, July 25, 2011 1:34 PM  
**To:** Chiang, Raymond  
**Subject:** RE: Free to talk at 1 or 1:30 for a few minutes re XR?

OK, thanks Ray.

We will have the P147 CSR amended completely by Friday and will send that to you by then (you already have the new tables and figures). I think the rate limiting step may be the 483 issues at the Arecibo manufacturing site - the site and the FDA officer have been discussing these things since April or May, we hope to resolve them this week but I don't know how realistic that is.

As you work on these questions - can you also let know if you want us to submit new labeling and carton artwork with the revised URL or does that not matter. All we propose to do is substitute the revised URL for the old one. nothing else will change

In addition, as before, if there's any way you can let us know when the labeling and cartons are approved, it would be appreciated so we can start printing in anticipation of the approval

thanks  
rick

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**From:** Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]  
**Sent:** Monday, July 25, 2011 1:27 PM  
**To:** Swanson, Richard John  
**Subject:** RE: Free to talk at 1 or 1:30 for a few minutes re XR?

Hello Dr. Swanson,  
No need to call.  
I will get back to you regarding your questions.  
When you plan to respond to the CR?

thanks,  
ray

---

**From:** Swanson, Richard John [mailto:richard\_swanson@merck.com]  
**Sent:** Monday, July 25, 2011 11:44 AM  
**To:** Chiang, Raymond  
**Subject:** Re: Free to talk at 1 or 1:30 for a few minutes re XR?

Thanks

Wanted to ask about the label we submitted last week with the better figure as well as the proposal to use the new URL in labeling and packaging

Also had couple of minor questions about how we should respond to the CRL

eg- can we submit responses as we finish them or do they have to go all at once, we'd like to confirm that no additional safety analysis is required since there have been no additional studies of XR since the NDA - all the data we have was included in that, and who should we respond to about the NIR Questions since that issue was not included in the 483 following the Arecibo inspection

Sent from my iPhone

On Jul 25, 2011, at 11:33 AM, "Chiang, Raymond" <[Raymond.Chiang@fda.hhs.gov](mailto:Raymond.Chiang@fda.hhs.gov)> wrote:

Dr. Swanson,  
Sure, give me a call.  
Can you tell me what you want to talk about.  
thanks,  
ray

---

**From:** Swanson, Richard John [mailto:richard\_swanson@merck.com]  
**Sent:** Monday, July 25, 2011 11:30 AM  
**To:** Chiang, Raymond  
**Subject:** Free to talk at 1 or 1:30 for a few minutes re XR?

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/s/  
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RAYMOND S CHIANG  
07/29/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: NDA 202270 SDN30-- July 21, 2011 submission  
**Date:** Friday, July 22, 2011 11:17:56 AM

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Hello Dr. Swanson,  
I reviewed your July 21, 2011 submission, which included a better rendition of Figure 1, as well as some minor editorial corrections to the Janumet XR package insert/MedGuide.

Unfortunately, we will not be able to review this submission because your July 18, 2011 submission (also containing a revised package insert/Medguide) was used to make our revisions. If you wish to incorporate these changes to the package insert, you may request to do so in the next review cycle. I also received your email regarding updating the PI/MedGuide and cartons with the new URL. This will need to be reviewed by OSE and DDMAC, and also addressed in the next review cycle.

thanks,  
ray

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/s/  
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RAYMOND S CHIANG  
07/22/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**cc:** [Silverman, Robert E. \(MRL\);](#)  
**Subject:** RE: Request regarding NDA 202270  
**Date:** Monday, July 18, 2011 9:25:30 AM

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Hello Dr. Swanson,  
See information request below.  
thanks,  
ray

We have reviewed (b) (4) July 11, 2011, response to our Form FDA 483 and the following request below in black italics font.

*Please repeat the bioequivalence determination using the new reintegrated data and re-evaluate the study outcomes.*

We request you submit your response (i.e. new datasets) no later than noon, Thursday, July 21, 2011.

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/s/  
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RAYMOND S CHIANG  
07/18/2011



NDA 202270

**DISCIPLINE REVIEW LETTER**

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

Dear Dr. Swanson:

Please refer to your September 23, 2010, New Drug Application (NDA) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Janumet XR (sitagliptin and metformin HCL extended-release) tablets, 100mg sitagliptin/1000mg metformin HCL extended-release, 50 mg sitagliptin/500mg metformin HCL extended-release, and 50 mg sitagliptin/1000mg metformin HCL extended-release.

During a recent inspection of the [REDACTED] <sup>(b) (4)</sup>, analytical site, our investigator conveyed deficiencies to the representative of the facility. Certain of those deficiencies must be resolved prior to approval of your application.

We are providing this comment to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, this comment does not reflect a final decision on the information reviewed and should not be construed to do so. This comment is preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If we receive a response to these issues during this review cycle, depending on the timing of the response, and in conformance with the user fee reauthorization agreements, we may not be able to consider the response before we take an action on your application during this review cycle.

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

Sincerely,

*{See appended electronic signature page}*

Julie Marchick, MPH  
Acting Chief, Project Management Staff  
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  
07/12/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**cc:** ["Silverman, Robert E. \(MRL\)";](#)  
**Subject:** RE: NDA 202270 (sitagliptin/metformin XR FDC tablets) PMRs  
**Date:** Tuesday, June 21, 2011 9:57:15 AM  
**Attachments:** [202270 proposed PMRs.pdf](#)

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Hello Dr. Swanson,  
Please see FDA's proposed PMRs for NDA 202270.  
If you agree to these PMRs, please provide dates and a commitment to the following PMRs within 5 business days of this email.  
If you have any questions, please do not hesitate to call or email.  
thanks,  
ray

PMR XX-2: A (b)(4) pharmacokinetic study of Janumet XR in pediatric patients 10 through 17 years (inclusive) of age with Type 2 Diabetes Mellitus. (b)(4)

Final Protocol Submission: by MM/DD/YR  
Trial Completion: by MM/DD/YR  
Final Report Submission: by MM/DD/YR

|        |
|--------|
| (b)(4) |
|        |
|        |

PMR XX-1: A (b)(4), randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of Janumet XR vs. metformin (b)(4) in pediatric patients who are inadequately controlled. As part of this study, you must evaluate whether pediatric patients can safely swallow Janumet XR. (b)(4)

Final Protocol Submission: by MM/DD/YR  
Trial Completion: by MM/DD/YR  
Final Report Submission: by MM/DD/YR

|        |
|--------|
| (b)(4) |
|        |
|        |

Merck, please proposed dates (include MM/DD/YR).

Based on timelines of recently approved antidiabetic drugs, FDA proposes the following timelines for the Janumet XR PMR pediatric plan:

1. PK: submission 1 y after approval; trial completion 15 mo later, submission 1 year after completion
2. S/E: submission 6 mo after approval; completion 4 years later; submission 8 mo after completion (Rather than 12/31/11; 1/31/19; 6/30/19. Therefore this will move submission up to the end of 2016)

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/s/  
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RAYMOND S CHIANG  
06/21/2011

**Henry, Don**

---

**From:** Henry, Don  
**Sent:** Wednesday, April 20, 2011 3:42 PM  
**To:** 'Swanson, Richard John'  
**Subject:** RE: NDA 202270

Hello Dr. Swanson

We have another CMC information request for your application (NDA 202270).

The dissolution data provided in your submission dated 04/11/11 for the sitagliptin component of your proposed 100/1000 mg strength of Janumet ER tablets do not support your proposed specification of  $Q = (b) (4)$  at 30 min. It is noted that the mean values for all the batches provided (number 0000056957, 0000056958, 0000056959 and 0000056960) have percent mean dissolution at 30 min higher than  $(b) (4)$ . Therefore, the following dissolution specification is recommended for the sitagliptin component of all the Janumet ER tablets strengths including the 100/1000 mg strength:  $Q = (b) (4)$  at 30 min.

If you have any questions, please feel free to contact me

Thank you  
Don

Don L. Henry  
Food and Drug Administration  
CDER/Office of New Drug Quality Assessment  
Phone: 301-796-4227  
Don.Henry@fda.hhs.gov

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/s/  
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DON L HENRY  
04/20/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: NDA 202270 (sitagliptin/metformin XR FDC tablets) IR- 4.13.11  
**Date:** Wednesday, April 13, 2011 5:01:38 PM

---

Hello Dr. Swanson,

Please see advice and information request (in black font) below.  
As always, please confirm receipt of email and respond ASAP.

thanks,  
ray

Please provide dates (i.e. month, day, year) for the protocol submission, trial completion, and final study report submission for the Swallowability and PK assessments that were proposed in your December 23, 2010 submission. Please note, at this time, we anticipate that we will recommend a PK assessment comparing Janumet to Janumet XR rather than use of historical reference PK data, as originally proposed.

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/s/  
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RAYMOND S CHIANG  
04/13/2011



NDA 202270

**INFORMATION REQUEST**

Merck Sharp & Dohme Corp.  
Attention: Richard J. Swanson, Ph.D.  
Senior Director, Worldwide 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/Metformin Hydrochloride Tablets.

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. It is unclear if you are claiming a design space based on your stated Proven Acceptable Ranges (PARs). We note the following statements provided in section

(b) (4)

2. The following comments and questions address your proposed dissolution method and specifications:

(b) (4)

(b) (4)



| <b>Drug Name</b>       | <b>Dosage Form</b> | <b>USP Apparatus</b> | <b>Speed (rpm)</b> | <b>Medium</b>                  | <b>Acceptance criteria</b>   |
|------------------------|--------------------|----------------------|--------------------|--------------------------------|--|
| Metformin /sitagliptin | ER Tablets         | USP Paddle           | 75                 | (50mM Phosphate Buffer, pH 6.8 | <b>Sitagliptin:</b><br>Min. (b) (4) in 30 minutes<br><br><b>Metformin:</b><br>(b) (4) in 1 hour<br>(b) (4) in 3 hours<br>(b) (4) in 10 hours<br><br>Meets USP <724> L1, L2 or L3 criteria as appropriate |

3. In order to support your approach for determining metformin content uniformity (b) (4)



4. [Redacted] (b) (4)

5. [Redacted] (b) (4)

6. Clarify the following for the method of determination of [Redacted] (b) (4) during development for the tablet coating process:

7. [Redacted] (b) (4)

8. [Redacted] (b) (4)

We have the following additional items for your consideration regarding your <sup>(b) (4)</sup>  
 <sup>(b) (4)</sup>

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  
03/14/2011

**From:** [Chiang, Raymond](#)  
**To:** ["Swanson, Richard John";](#)  
**Subject:** RE: NDA 202270 (sitagliptin/metformin XR FDC tablets)  
**Date:** Wednesday, March 09, 2011 10:42:22 AM

---

Hello Dr. Swanson,

Please information request below (in black font) from the FDA clinical pharmacology reviewer.  
Please confirm that you will respond to this information request.  
thanks,  
ray

In the pivotal BE study (P147), the BE reports were based on potency-normalized results. However, the potency-normalization for BE assessment is not acceptable.

Although you mentioned that the assessment with data without potency-normalization met the BE criteria, and justified the use of potency-normalized data for BE assessment for report completeness, we need a report based on the raw data without potency-normalization. Submit the updated BE report based on the data without the potency normalization.

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/s/  
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RAYMOND S CHIANG  
03/09/2011

**From:** Swanson, Richard John [mailto:richard\_swanson@merck.com]  
**Sent:** Monday, January 10, 2011 9:52 AM  
**To:** Chiang, Raymond  
**Subject:** RE: NDA 202270 (sitagliptin/metformin XR FDC tablets)

will do.  
thanks Ray

---

**From:** Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]  
**Sent:** Monday, January 10, 2011 9:50 AM  
**To:** Swanson, Richard John  
**Subject:** RE: NDA 202270 (sitagliptin/metformin XR FDC tablets)

Hello Dr. Swanson,  
See information request (in black italics) below from the FDA medical officer:

*In the P053 study report, table 14-7 shows the number (%) of patients with specific secondary diagnoses by system organ class including data after initiation of glycemic rescue therapy. Please clarify what is meant by "specific secondary diagnoses". Are these other diagnoses made during the trial or part of the past medical history?*

Please respond no later than Thursday, January 13, 2011.  
thanks!  
ray

Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (One Merck Drive, Whitehouse Station, New Jersey, USA 08889), and/or its affiliates Direct contact information for affiliates is available at <http://www.merck.com/contact/contacts.html>) that may be confidential, proprietary copyrighted and/or legally privileged. It is intended solely for the use of the individual or entity named on this message. If you are not the intended recipient, and have received this message in error, please notify us immediately by reply e-mail and then delete it from your system.

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/s/  
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RAYMOND S CHIANG  
01/10/2011

**From:** Chiang, Raymond  
**Sent:** Tuesday, January 04, 2011 11:02 AM  
**To:** 'Swanson, Richard John'  
**Subject:** RE: NDA 202270 (sitagliptin/metformin XR FDC tablets)

Dr. Swanson,

Please see information request below (in black font) from our medical officer regarding your December 23, 2010, submission which was submitted in response to our Filing Deficiencies letter. Please confirm receipt of this email. Please provide your response within 7 days of receipt of this email.

thanks!  
ray

*This is in regards to your response to our Filing Deficiencies letter. One comment in our letter was as follows: In tabular format, clarify the metformin formulations used in each of the 7 clinical trials submitted. Include whether or not the metformin was immediate or sustained release. You responded with the following clin pharm protocol information: Protocols 050, 110, 112, 163, 147, 164, and 165. This is helpful, but we had meant clinical studies 015, 020, 024, 035, 036, 052, and 053. Please provide similar information for those 7 clinical studies?*

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/s/  
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RAYMOND S CHIANG  
01/04/2011



NDA 202270

**FILING COMMUNICATION**

NDA 022044

**REMS NOTIFICATION  
REMS MODIFICATION NOTIFICATION**

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

Dear Dr. Swanson:

Please refer to your New Drug Application (NDA) dated September 23, 2010, received September 23, 2010, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Sitagliptin/Extended Release Metformin Fixed-Dose Combination Tablets (NDA 202270). We also refer to your approved NDA 022044 for Janumet (sitagliptin/metformin HCl) Tablets.

We have completed our filing review for NDA 202270 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 July 23, 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 June 25, 2011.

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

CLINICAL

1. Please state the location within the application where the coding dictionary used for mapping investigator verbatim terms to preferred terms is located. If it was not previously submitted, please submit it.
2. In tabular format, clarify the metformin formulations used in each of the 7 clinical trials submitted. Include whether or not the metformin was immediate or sustained release.

#### CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC) and BIOPHARMACEUTICS

3. Provide the Master File (MF) numbers and letters of authorization for the two sources of the drug substance [REDACTED] (b) (4).
4. Submit the complete dissolution profile data (raw data, mean values, and SD) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values) for both components of Janumet ER tablets.
5. Submit the dissolution method report including the complete dissolution profile (individual, mean, SD, profiles) data for both components of Janumet ER tablets collected during the development of the proposed dissolution method.
6. Clarify the dimensions of the sitagliptin/metformin XR FDC tablet compared to the sitagliptin tablet and compared to the metformin XR tablet. Clarify what is planned with regard to the formulation if the swallowability test results show that children cannot swallow the FDC tablet.

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.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

We acknowledge receipt of your request [REDACTED] (b) (4). [REDACTED] We will consider a waiver of the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impractical. We also will consider a deferral of the pediatric study for ages 10 to [REDACTED] (b) (4) years (inclusive). Please amend your application, within 30 days from the date of this letter, with your (revised) pediatric plan outlining the study(ies) you will conduct to meet the PREA requirements. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetic/pharmacodynamics including assessment of swallowability, safety and efficacy). The pediatric plan must contain a timeline for the completion of these studies, i.e., the dates of (1) protocol submission (2) study completion and (3) submission of study reports. In addition, you must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time

(Refer to Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>).

Pediatric studies conducted under the terms of Section 505B of the Federal Food, Drug and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of Section 505A of the Act. If you wish to qualify for pediatric exclusivity, consult the Division of Metabolism and Endocrinology Products. Please note that satisfaction of the requirements in Section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

### **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 Sitagliptin/Extended Release Metformin Fixed Dose Combination 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 Sitagliptin/Extended Release Metformin Fixed Dose Combination 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 Sitagliptin/Extended Release Metformin Fixed Dose Combination. FDA has determined that Sitagliptin/Extended Release Metformin Fixed Dose Combination 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 Sitagliptin/Extended Release Metformin Fixed Dose Combination.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Sitagliptin/Extended Release Metformin Fixed Dose Combination.

**Timetable for Submission of Assessments:** The timetable for submission of assessments of the REMS will be the same as that in the approved REMS for Janumet (sitagliptin/metformin HCl) Tablets, for the reasons described below.

We note that the proposed Medication Guide included in your original application to NDA 202270 contains reference to both Sitagliptin/Extended Release Metformin Fixed Dose Combination Tablets and Janumet (sitagliptin/metformin HCl) Tablets. Therefore, you should also have one REMS document for both products.

Before we can continue our evaluation of NDA 202270, you will need to submit the proposed REMS.

For administrative purposes, designate the proposed REMS submission as:

**PROPOSED REMS for NDA 202270**

All subsequent submissions related to the proposed REMS should be designated as:  
**PROPOSED REMS-AMENDMENT for NDA 202270**

In accordance with section 505-1(g)(1) of the FDCA, the addition of the extended release formulation to the approved Medication Guide for Janumet (sitagliptin/metformin HCl) is also considered a proposed modification to the Janumet (sitagliptin/metformin HCl) REMS that was approved on February 26, 2010. Therefore, you must also submit a proposed modified REMS for Janumet (sitagliptin/metformin HCl) as a prior approval supplement to NDA 022044 which would contain the same REMS document and Medication Guide as described above.

The REMS supporting document should also be updated to include a description of all proposed modifications to the REMS and the REMS assessment. Updates to the REMS supporting document should have all changes marked and highlighted.

In accordance with section 505-1, proposed modifications to an approved REMS must be accompanied by an assessment of that REMS. The assessment of the REMS for Janumet (sitagliptin/metformin HCl) may consist of a statement that the Medication Guide would be adequate with the proposed modifications to achieve its purpose.

Prominently identify the proposed REMS modification and REMS assessment submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR NDA 022044  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

Prominently identify subsequent submissions related to the proposed REMS modification for with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT <<insert assigned #  
PROPOSED REMS MODIFICATION-AMENDMENT**

Once FDA finds the content acceptable and determines that the applications can be approved, we will include these documents as attachments to the approval letters that includes the REMS. The REMS, once approved, will create enforceable obligations.

If you do not submit electronically, please send 5 copies of each submission.

**CONTENT OF LABELING**

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional 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.

If you have any questions, call Raymond Chiang, Consumer Safety Officer, 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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MARY H PARKS  
12/03/2010



NDA 202270

**NDA ACKNOWLEDGMENT**

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

Dear Dr. Swanson:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Sitagliptin/Extended Release Metformin Fixed Dose Combination tablets

Date of Application: September 23, 2010

Date of Receipt: September 23, 2010

Our Reference Number: NDA 202270

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 November 22, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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, 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

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RAYMOND S CHIANG  
11/09/2010

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/s/

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OLEN M STEPHENS

10/22/2010

Edited CFI memo

ALI H AL HAKIM

10/22/2010

**MEMORANDUM**

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

**DATE:** 9/29/2010

**TO:** Richard Swanson, Sr. Director, Regulatory Affairs, 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 202-270**

\*\*Memo of Telecon:

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

1. Provide Fax numbers for all the facilities listed in the Establishment information section.

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/s/

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KHUSHBOO SHARMA  
09/29/2010

**From:** Hai, Mehreen  
**To:** "Swanson, Richard John";  
**Subject:** RE: Pre-meeting response for IND 101964 pre-NDA tcon  
**Date:** Wednesday, May 12, 2010 1:07:24 PM

---

Hi Rick,  
In response to the two questions you had:

1) Yes, we concur that you do not need to conduct any further clinical studies at the moment. However, please keep in mind that in case the in vitro data show a potential of dose dumping with alcohol, you might need to conduct an additional in vivo study as outlined in the answer to question #3.

2) In response to why we are concerned about potential dose dumping with the 431A XR formulation, for any new modified release product we ask the sponsor to evaluate the potential of dose dumping. This is outlined in the guidance for industry " Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations". Usually we ask for a food-effect study (which you have already conducted) and the evaluation of potential dose dumping with alcohol.

Hope this helps. Let me know if you have any other questions.

**Mehreen Hai, Ph.D.**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
**mehreen.hai@fda.hhs.gov**  
**Ph: 301-796-5073**  
**Fax: 301-796-9712**

---

**From:** Swanson, Richard John [mailto:richard\_swanson@merck.com]  
**Sent:** Friday, May 07, 2010 3:03 PM  
**To:** Hai, Mehreen  
**Subject:** RE: Pre-meeting response for IND 101964 pre-NDA tcon

Hi Mehreen  
can you tell us why the Agency is concerned about potential dose dumping with the 431A XR formulation?  
thanks

---

**From:** Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]  
**Sent:** Friday, May 07, 2010 12:11 PM  
**To:** Swanson, Richard John  
**Subject:** RE: Pre-meeting response for IND 101964 pre-NDA tcon

ok, thanks!

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

**Food and Drug Administration**  
**mehreen.hai@fda.hhs.gov**  
**Ph: 301-796-5073**  
**Fax: 301-796-9712**

---

**From:** Swanson, Richard John [mailto:richard\_swanson@merck.com]  
**Sent:** Friday, May 07, 2010 11:59 AM  
**To:** Hai, Mehreen  
**Subject:** RE: Pre-meeting response for IND 101964 pre-NDA tcon

sounds great, I will cancel the mtg planned for monday and we will have a draft in vitro dose dumping proposal to you next week.

Thanks very much  
rick

---

**From:** Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]  
**Sent:** Friday, May 07, 2010 11:57 AM  
**To:** Swanson, Richard John  
**Subject:** RE: Pre-meeting response for IND 101964 pre-NDA tcon

Hi Rick,  
Got your voicemail and email.  
We're fine with you submitting a proposal for the dose-dumping study. We'll review it and if discussion is needed, we'll definitely set up a tcon.  
Does that work for you? We're fine with cancelling Monday's meeting, so please confirm that that's what you want to do.  
Thanks!

**Mehreen Hai, Ph.D.**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
**mehreen.hai@fda.hhs.gov**  
**Ph: 301-796-5073**  
**Fax: 301-796-9712**

---

**From:** Swanson, Richard John [mailto:richard\_swanson@merck.com]  
**Sent:** Friday, May 07, 2010 11:05 AM  
**To:** Hai, Mehreen  
**Subject:** RE: Pre-meeting response for IND 101964 pre-NDA tcon

Hi Mehreen

~~Just left you a voice mail but thought I'd follow up with an email as well.~~

Thanks very much for the response to the questions in the preNDA package. We are obviously very pleased with the response and the fact that the Agency has no real concerns with the proposed sNDA content with the exception of the new requirement for an in vitro dose dumping study. We would like to discuss that study with you to be sure that what we propose to do to address this requirement is acceptable to the Agency. However, rather than do it during the planned preNDA mtg on Monday, we think the most efficient way to handle this would be to send you a draft in vitro study protocol and then, after your technical people have had a chance to look at it, hold a brief teleconf between the technical people on both sides. We can have a proposal to you next week, if there's anything you disagree with.

If that's OK with you. I'll just cancel the planned mtg on Monday - so please let me know whether you agree with cancelling Monday's mtg.

Would it be also possible for you to schedule a short tcon with us in which the technical people on both sides can discuss the plans for this in vitro study, sometime within the following 2-3 weeks (eg, perhaps in the late May -Early June) so that we can understand exactly what the Agency wants us to do and get that completed? Please let me know what you think.

thanks  
rick

---

**From:** Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]  
**Sent:** Thursday, May 06, 2010 10:14 AM  
**To:** Swanson, Richard John  
**Subject:** Pre-meeting response for IND 101964 pre-NDA tcon

Hi Rick,  
Please find attached the pre-meeting response for the IND 101964 pre-NDA teleconference on Monday, May 10, 2010. After you've had a chance to review it, please let me know if you want to focus on any questions in particular during the meeting discussion, or if you think that a meeting is not necessary.

Thanks!

**Mehreen Hai, Ph.D.**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
**mehreen.hai@fda.hhs.gov**  
**Ph: 301-796-5073**  
**Fax: 301-796-9712**

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| Application Type/Number | Submission Type/Number | Submitter Name      | Product Name   |
|-------------------------|------------------------|---------------------|--|
| IND-101964              | GI-1                   | MERCK AND CO<br>INC | MK-0431A XR<br>(SITAGLIPTIN/METFORMIN<br>HCL) extended release TABLETs |

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/s/  
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MEHREEN HAI  
05/12/2010

**From:** Hai, Mehreen  
**To:** "Swanson, Richard John";  
**Subject:** Pre-meeting response for IND 101964 pre-NDA tcon  
**Date:** Thursday, May 06, 2010 10:14:11 AM  
**Attachments:** PRELIMINARY MTG RESPONSES IND 101964.doc

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Hi Rick,

Please find attached the pre-meeting response for the IND 101964 pre-NDA teleconference on Monday, May 10, 2010. After you've had a chance to review it, please let me know if you want to focus on any questions in particular during the meeting discussion, or if you think that a meeting is not necessary.

Thanks!

***Mehreen Hai, Ph.D.***  
***Regulatory Project Manager***  
***Division of Metabolism & Endocrinology Products***  
***Center for Drug Evaluation and Research***  
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***mehreen.hai@fda.hhs.gov***  
***Ph: 301-796-5073***  
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FDA PRELIMINARY RESPONSES SENT TO MERCK SHARP & DOHME CORP.  
ON THURSDAY, MAY 6, 2010

APPLICATION: IND 101964

DRUG PRODUCT: SITAGLIPTIN AND METFORMIN EXTENDED-RELEASE  
FIXED-DOSE COMBINATION

MEETING TYPE: TYPE B, PRE-NDA

INDUSTRY MEETING DATE: MAY 10, 2010

INDUSTRY MEETING PLACE: TELECONFERENCE

REGULATORY PROJECT MANAGER (RPM): MEHREEN HAI, PH.D.

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the TELECONFERENCE scheduled for MAY 10, 2010 at 3:00 PM – 4:00 PM between MERCK and the Division of Metabolism and Endocrinology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the RPM). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.*

## Sponsor's Questions and FDA's Preliminary Responses

### Question 1:

In previous feedback (5-March-2009), the Agency indicated that the Sponsor would need to provide pharmacokinetic comparability or clinical equivalency data between MK-0431A XR and Janumet considering that there are no such bridging data between Glumetza, a metformin reference for MK-0431A XR, and a generic metformin formulation, a metformin reference for Janumet. The Sponsor believes that sufficient data are available to support the appropriate bridging. Does the Agency concur?

**FDA Preliminary Response: Yes, we concur.**

### Question 2

The Sponsor considers biowaiver requirements for the 50-mg/1000-mg tablet strength of MK-0431A XR to be met. Does the agency concur?

**FDA Preliminary Response: Yes, we concur.**

### Question 3

The Sponsor believes analyses of the agreed-upon Phase I Clinical Pharmacology studies (listed in tabular form in the background package), in conjunction with the appropriate references to the product label for Glumetza and the NDA for Janumet are sufficient to support an NDA filing of MK-0431A XR as a 505(b)(2) application with the proposed prototype labeling. Does the Agency concur?

**FDA Preliminary Response: No, we do not concur. Please address the dose-dumping potential of your extended-release formulation with alcohol. You can evaluate the interaction *in vitro*, followed, if necessary, by an *in vivo* study.**

### Question 4

Does the Agency concur with the Sponsor's plan for submission of the MK-0431A XR eCTD?

**FDA Preliminary Response: Yes, we concur.**

Question 5

The Sponsor proposes [REDACTED] (b) (4). Does the Agency concur?

**FDA Preliminary Response:** A final decision will be made after we have discussed your proposal with the Pediatric Review Committee (PeRC). This will take place after you have submitted your NDA [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

| Application<br>Type/Number | Submission<br>Type/Number | Submitter Name      | Product Name   |
|----------------------------|---------------------------|---------------------|--|
| IND-101964                 | GI-1                      | MERCK AND CO<br>INC | MK-0431A XR<br>(SITAGLIPTIN/METFORMIN<br>HCL) extended release TABLETs |

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/s/  
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MEHREEN HAI  
05/06/2010



IND 101,964

Merck & Co., Inc.  
Attention: Richard 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-0431A XR (sitagliptin/metformin fixed-dose combination extended release) Tablets.

We also refer to your September 18, 2008, correspondence requesting an End of Phase 2 meeting to discuss your proposed development program. We denied your meeting request, however, we agreed to provide responses to your questions after review of a briefing document. You submitted a briefing document on October 31, 2008, and a revised briefing document on December 2, 2008.

We have the following comments and recommendations. Your questions are repeated below and our responses follow in bold print.

*Nonclinical Questions:*

1. The sponsor proposes that no additional nonclinical studies with the combination of sitagliptin and extended-release metformin are necessary to support registration of the extended-release formulation, MK-0431A XR, based on:
  - Previously conducted nonclinical toxicology studies and clinical studies in support of registration of each product;
  - Clinical experience with Janumet (an approved fixed dose combination product containing sitagliptin and immediate-release metformin) and co-administration of sitagliptin and immediate release metformin;
  - Results from a 3-month nonclinical toxicity study in dogs concomitantly administered sitagliptin and metformin indicating no toxicologic or pharmacokinetic interactions;
  - Similar pharmacokinetics (i.e., plasma AUC) with extended-release metformin 2000 mg administered once daily and immediate-release metformin 1000 mg administered twice daily.

Does the Agency concur?

**Response: Yes, we concur that no new additional preclinical studies with the extended-release formulation are required to support registration. We remind you to include appropriate support for any differences in the impurity/degradant profile of the new formulation in accordance with available ICH Q3 guidances.**

*Clinical Questions:*

2. The Sponsor proposes MK-0431A XR as an additional formulation in the Janumet (MK-0431A) product circular, with the prototype labeling, to be supported by the following data:
  - A clinical pharmacology study demonstrating bioequivalence between MK- 0431A XR and co-administration of corresponding doses of sitagliptin and a marketed metformin XR (Glumetza), and data from supporting clinical pharmacology studies (Multiple-Dose Safety, Tolerability and Pharmacokinetic Study with MK-0431A XR FDC tablets; Food-Effect Study; Drug-Drug Interaction Study);
  - Reference to existing clinical data demonstrating similar safety and efficacy profiles of extended- and immediate-release metformin products; Reference to existing clinical data demonstrating safety and efficacy of sitagliptin and metformin as monotherapy, co-administration of sitagliptin and immediate release metformin, and administration of Janumet (MK-0431A).

Does the Agency concur?

**Response: There are no data supporting metformin pharmacokinetic comparability or clinical equivalency between MK-0431A XR and Janumet because there are no such bridging data between Glumetza, a metformin reference for MK-0431A XR, and a generic metformin formulation, a metformin reference for Janumet. Therefore, you should provide metformin pharmacokinetic comparability or clinical equivalency data between MK-0431A XR and Janumet.**

*Clinical Pharmacology Questions:*

3. Assuming that the Agency agrees with the proposed, bioequivalence-based registration strategy for MK-0431A XR (question 2 above), the Sponsor considers the following components of the Clinical Pharmacology Program to be sufficient to support registration of MK-0431A XR FDC tablet:
  - Completed FDC Probe Formulation Biocomparison Study-Fed (PN 112)
  - Definitive BE Study
  - Multiple-Dose Safety, Tolerability and Pharmacokinetic Study with MK-0431A XR FDC tablets
  - Food-Effect Study with a High-Fat Meal
  - Sitagliptin/Metformin Drug-Drug Interaction Study (PN 012)

Does the Agency concur?

**Response: In addition to what you have proposed, you should submit the following to support registration of MK-0431A XR:**

- Dosage form equivalence study comparing two tablets of 50-mg/500-mg and one tablet of 100-mg/1000-mg
- Biowaiver request for the 50-mg/1000-mg dose strength
- Metformin pharmacokinetic comparability or clinical equivalency data between MK-0431A XR and Janumet (see response #2).

4. Since Glumetza is an approved XR metformin product, the Sponsor believes that Glumetza is an appropriate comparator for the proposed Bioequivalence Study. Does the Agency concur?

**Response: Yes**

5. Recommendations for documentation of relative bioavailability (BA) and bioequivalence (BE) for modified-release products in the FDA document, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General Considerations" (March 2003) indicate that administration in such a study should occur "... according to the dosage recommendations in the labeling. According to the Glumetza product label, it is recommended that Glumetza be taken with food, preferably in the evening. In the Sponsor's Probe Formulation Study (PN 112), each treatment was administered 5 minutes after consumption of a high-fat breakfast. The Sponsor also plans to conduct the proposed Definitive Bioequivalence Study with this same administration regimen.
- a. The Sponsor considers the proposed administration regimen for the BE Study to be consistent with the product labeling for "with food." Does the Agency concur?

**Response: Yes**

- b. The Sponsor believes the proposed BE Study can be conducted with administration of treatments with the morning meal, as opposed to with dinner, as indicated in the Glumetza product label, considering that the same conditions will be applied to each treatment. Does the Agency concur?

**Response: Yes**

6. The Sponsor believes that the design of the proposed bioequivalence study will support registration of the MK-0431A XR FDC tablets. Does the Agency concur?

**Response: The design of the proposed bioequivalence study is acceptable. However, please see response #3 for additional recommendations to support registration of the MK-0431A XR fixed-dose combination tablets.**

7. The Sponsor considers the previously conducted drug-drug interaction study between sitagliptin and immediate-release metformin (MK-0431 PN 012) to be sufficient to support registration of the MK-0431A XR FDC tablets. Does the Agency concur?

**Response: Yes**

8. The modified-release technology used in the proposed MK-0431A XR FDC tablets does not differ amongst the three proposed tablet strengths. The Sponsor believes that a food-effect study on only the highest doses of each of the respective components of MK-0431A, i.e., MK-0431A XR 100-mg/2000-mg after consumption of a high-fat meal should be sufficient to support registration. Does the Agency concur?

**Response: Yes**

9. Although the proposed Bioequivalence Study will be conducted at tablet strengths rather than the recommended clinical doses, the Sponsor believes that a dose proportionality study is not required to support registration of the MK-0431A XR FDC tablet since the AUC for sitagliptin exhibits linear pharmacokinetics at doses that include 50- and 100-mg [PN 033 CSR synopsis in Annex 18]; and bioequivalence to Glumetza, based on AUC similarity for the metformin component of the FDC tablet, will be demonstrated in the proposed Bioequivalence Study. Does the Agency concur?

**Response: You should demonstrate dosage form equivalence between two tablets of 50 mg/500 mg and one tablet of 100 mg/1000 mg.**

If you have any questions, contact Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

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

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 101964

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MERCK AND CO INC

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MK-0431A XR  
(SITAGLIPTIN/METFORMIN HCL)  
extended release TABLETs

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/s/  
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MARY H PARKS  
03/05/2009