CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202343Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 202-343/JUVISYNC (sitagliptin and simvastatin fixed-dose combination [FDC])

PMR/PMC Description: A randomized,,double-blind, active-controlled clinical trial to study the effect of sitagliptin and simvastatin FDC versus sitagliptin on glycemic control in type 2 diabetic patients on background metformin therapy.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	04/30/2012
Study/Trial Completion:	01/29/2015
Final Report Submission:	07/29/2015
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Meta-analyses in the published literature have shown increases in fasting plasma glucose and hemoglobin A1C in patients receiving statin therapy, including simvastatin. The applicant conducted a meta-analysis of clinical trial data with simvastatin in diabetic patients showing that there was no clinically significant worsening of glycemic control. However, this involved a limited number of subjects and was not a rigorous appraisal of this safety concern. The applicant is being required to further assess this safety signal in a dedicated clinical trial. It is understood that the individual components in this FDC are already available and are frequently being co-administered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to conclusively demonstrate the effect of simvastatin on glycemic control in type 2 diabetic patients being treated with sitagliptin and simvastatin FDC on a background of metformin therapy versus type 2 diabetic patients being treated with sitagliptin.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, active-controlled clinical trial in ≥ 200 type 2 diabetic subjects per treatment arm on background metformin therapy randomized to sitagliptin and simvastatin FDC or sitagliptin alone for ≥ 16 weeks to assess the effect of simvastatin on glycemic control. Glycemic control should be assessed by the change in HbA1c (primary endpoint), change in fasting plasma glucose, and change in 2-hour postprandial glucose.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

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/s/

AMY G EGAN
10/06/2011

M E M O R A N D U M

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

DATE: September 7, 2011

TO: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
Office of Drug Evaluation

FROM: Sripal R. Mada, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader – Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-343, (b) (4)® (Sitagliptin/Simvastatin) Tablets, 100/10 mg, 100/20 mg, 100/40 mg, from Merck Sharp & Dohme Corp.

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following studies:

Study: 255: "A Single-Dose Study to Evaluate Definitive Bioequivalence of MK-0431D and Co-administration of Sitagliptin and Simvastatin"

Study: 153: "A 2-Part Single-Dose Study to Evaluate a Probe Formulation of MK-0431D and Evaluate Definitive Bioequivalence of MK-0431D and Co-administration of Sitagliptin and Simvastatin"

CLINICAL INSPECTION:

The inspection of clinical portion was conducted at **Icon Development Solutions (Icon), San Antonio, TX.**

Following the inspection at Icon (June 14-24, 2011), Form FDA 483 was issued (**Attachment 1**). The firm's response (dated June

28, 2011) was received (**Attachment 2**). The Form FDA 483 observations, Icon's response to Form FDA 483 and our evaluations follow:

1. Failure to retain reserve samples for Study 153 Part 1.

Icon stated that they did not retain reserve samples, according to the study protocol. Icon stated that after dispensing the study drug into unit dosing containers, they returned the remaining drug product to the sponsor. Note that the lot number for drug product used in Study 153 Part 2 differed from product used in Study 153 Part 1.

In response to Form FDA 483, Icon explained that Study 153 Part 1 was initially planned and was later amended to Study 153 Part 2 for final BE evaluation.

DBGC is of the opinion that because Icon did not retain reserve samples for Study 153 Part 1, the authenticity of the drug products used in Study 153 Part 1 cannot be confirmed.

2. Failure to randomly select reserve samples for Study 153 Part 2. Retention samples that were retained were pre-identified by the sponsor as "Replacement Kits." In addition, these kits were returned to the sponsor upon completion of the study. Further, the reserve samples were subsequently returned by the sponsor resulted in broken chain of custody.

During the inspection, Icon revealed that they did not randomly select drug kits for dosing and reserves. The sponsor pre-identified kits #1001 to 1100 as "replacement kits." Icon dosed subjects with kits #0401 to 0500.

In the response to Form FDA 483, Icon acknowledged their error in returning the reserve samples (pre-identified as replacement kits) from Protocol 153 Part 2 to the sponsor. Although this error was quickly identified, the return of these samples to the sponsor broke the chain of custody. However, in contradiction of the findings of the inspection, the Principal Investigator (PI) stated that she randomly selected bottles to be used for dosing, and considered all remaining drug products as reserve samples. She stated that no bottles were pre-identified as retention samples.

Icon failed to meet the regulatory requirements for retention of reserve samples for bioavailability or study (21 CFR 320.38 and 320.63). The sponsor is not an "independent third party" as specified by the regulation.

Icon failed to randomly select drug products for dosing and reserves, and failed to maintain custody of the unused drug products. Therefore, the authenticity of drug products cannot be verified for Study 153 Part 2.

3. **Failure to randomly select reserve samples for Study 255. Retention samples that were retained were pre-identified by the sponsor as Replacement Kits.**

During the inspection, Icon revealed that they did not randomly select drug kits for dosing and reserves. The sponsor pre-identified kits #1001 to 1100 as "replacement kits." Icon dosed subjects with kits #001 to 100.

In response to Form FDA 483, Icon stated that they received 100 kits for randomized subjects and 100 kits for replacement subjects in six containers with two of each test and reference product. However, the purpose of the "replacement subjects" kits is unclear. The Principal Investigator (PI) stated that she randomly selected bottles to be used for dosing, and considered all remaining drug products as reserve samples. She stated that no bottles were pre-identified as retention samples.

Icon failed to randomly select drug products for dosing and reserve. Therefore, the authenticity of drug products cannot be verified for Study 255.

4. **Source study records show employees performed certain key study tasks of the study, however; were not listed on the "Site Signature Log" as being delegated by you to perform those key delegated study tasks.**

In the response to Form FDA-483, Icon acknowledged this observation and identified the delegation process in use is deficient. Icon developed corrective actions instituted on May 25, 2010.

5. **Failure to follow SOP CPU132, Maintenance and Organization of the "Investigator File," as during review of the study files it was discovered that not all significant study related e-mails were included in**

the "General Correspondence" section of the study file.

In response to Form FDA 483, Icon acknowledged this observation and stated they will re-train all staff on SOP CPU132, to be completed by August 31, 2011. The inspection audited the available e-mails and suggested that they be transferred to the study file.

ANALYTICAL INSPECTION:

The inspection of analytical portion was conducted at (b) (4) (b) (4)

Following the inspection at (b) (4), Form FDA 483 was issued (**Attachment 3**). The firm's response dated July 11, 2011 was received on July 11, 2011, and the response dated July 21 was received on July 28, 2011 (**Attachment 4**). The Form FDA 483 observations, (b) (4) responses to Form FDA 483, and our evaluations follow:

1. **Failure to provide adequate security for electronic source records. Specifically,**
   (a) **A common access procedure is used to access the computer workstation and the "Analyst" software used for analytical data integration.**
   (b) **Technical writers who do not work in the bioanalytical laboratory were given inappropriate permission to edit chromatograms in the "Analyst" software.**

DBGC explained to (b) (4) that these practices were not recommended during the conduct of any bioequivalence studies. This objectionable practice is related to DBGC's concern discussed below under Form FDA-483, Item 4, regarding modifying chromatographic integration parameters. The observation tends to confirm a complaint received by OSI that unauthorized individuals at (b) (4) had edited various records of clinical trials. Currently, (b) (4) has updated their operating procedures to restrict the common computer access procedure and not granting permission to technical writers edit chromatograms in future studies.

2. **Failure to conduct long term freezer stability and freeze/thaw stability at -20^{0}C for samples containing MK-0431, simvastatin and simvastatin hydroxy acid. Specifically, subjects in studies #255-00 and 153-01**

were treated with both MK-0431 and simvastatin and the analyses determined the plasma concentrations of MK-0431, simvastatin and simvastatin hydroxy acid.

3. **Failure to evaluate long term freezer stability of simvastatin and simvastatin hydroxy acid in plasma at -20^{0}C and -80^{0}C.**

(b) (4) acknowledged the above observations. (b) (4) had previously prepared freeze/thaw and long-term frozen storage stability test samples containing MK-0431, simvastatin and simvastatin hydroxy acid, and stored them at -20^{0}C. These samples were analyzed during the inspection.

In response to Form FDA 483, (b) (4) submitted stability data for freeze/thaw and long-term frozen storage (Attachment). The results are acceptable and adequate to cover sample handling conditions during the study.

(b) (4) also submitted stability data at -20°C for long-term stability of simvastatin and simvastatin hydroxy acid alone in plasma for 7 days and 9 days, respectively. (b) (4) submitted stability data at -80°C for simvastatin and simvastatin hydroxy acid alone in plasma for 122 days, adequate to cover the study sample storage time (77 days).

The newly submitted data are acceptable, and (b) (4) response is adequate.

4. **Integration parameters from most analytical runs in the validation and production for studies # 255-00 and 153-01 were modified and were different from the method SOP. These changed integration parameters were not applied to all samples in the respective runs.**

Integration parameters for many chromatograms in validation and analytical runs were modified. The reasons for modifying integration parameters were not documented in records or an audit trial.

In the response to Form FDA 483, (b) (4) reintegrated all chromatograms generated during method validation and production runs, using a revised uniform automatic integration process. Also, (b) (4) compared the re-integrated chromatographic data with original data in summary tables (see **Attachment 4**). DBGC's review of the comparative data found no significant differences.

However, the OCP reviewer should re-evaluates the bioequivalence statistics using the uniformly re-integrated data.

5. **Failure to demonstrate lack of carry-over during the simvastatin assay validation. Although two of six blank samples in validation run #5 contain simvastatin peaks >20% of LLOQ, the run was accepted for the evaluation of precision and accuracy.**

In response to Form FDA-483, [redacted] stated that the interfering peak was an artifact not caused by instrumental carryover. Their source was not identified.

[redacted] response is adequate, in that the interferences do not significant affect measurements of Cmax and AUC.

Conclusions:

Following the inspection, DBGC recommends the following:

- The analytical data generated at [redacted] are acceptable for review. However, the OCP reviewer should re-evaluate bioequivalence statistics using the uniformly re-integrated data.

- The studies fail to meet the regulatory requirements for retention of reserve samples for bioavailability or study (21 CFR 320.38 and 320.63). The Final Rule for Retention of Bioavailability and Bioequivalence Testing Samples (Federal Register, Vol. 58, No. 80, Pages 25918-25928, 1993) clarifies that:

  "The study sponsor should provide to the testing facility batches of the test product and reference standard packages such that the reserve samples can be randomly selected to ensure that they are in fact representative of the batches provided by the study sponsor…"

  Since, Icon did not randomly select reserve samples and maintain custody of them; DBGC cannot verify the authenticity of the study drugs tested (see **Clinical Form FDA-483 items 1, 2 and 3**).

DBGC is of the opinion that studies 255 and 153 (Part 1 and 2) are not acceptable for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.
Bioequivalence Branch, DBGC, OSI

Final Classifications:

VAI – (b) (4)

OAI – Icon Development Solutions, San Antonio, TX
FEI: 3007158681

(DBGC is considering regulatory letters to Icon Development Solutions and Merck Sharp & Dohme Corp for the regulatory violations involving reserve samples).

cc:
OSI/Ball
OSI/DBGC/Salewski/Dejernett/Matthews
OSI/DBGC/BB/Mada/Yau/Haidar
OCP/DCP2/Sahajwalla/Lee/Vaidyanathan/Chung
ODE2/DMEP/Parks/Chiang
HFR-SW1540/Martinez
HFR-SW350/Kuchenthal
Draft: SRM 09/02/2011
Edit: MFS 09/02/2011; MKY 09/07/2011
DSI: BE6185; O:\Bioequiv\EIRCover\202343.mer.juv.doc
Complaint: 3299/Chu
FACTS: 1266778

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/s/

SRIPAL R MADA
09/07/2011

MARTIN K YAU
09/07/2011

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

PATIENT LABELING REVIEW

Date:	**September 1, 2011**
To:	Mary Parks, M.D., Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)** Robin Duer, RN, BSN, MBA Senior Patient Labeling Reviewer **Division of Risk Management**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	(b) (4) (sitagliptin and simvastatin)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 202343
Applicant/Sponsor:	Merck & Co., Inc.
OSE RCM #:	2011-302

1 INTRODUCTION

On December 3, 2010 Merck Sharp & Dohme Corp., a subsidary of Merck & Co., Inc. (Merck), submitted a New Drug Application (NDA) for (b) (4) a fixed-dose combination tablet containing sitagliptin phosphate and simvastatin. (b) (4) is indicated as (b) (4)

This review is written in response to a request by the Division of Metabolic and Endocrine Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for (b) (4) (sitagliptin and simvastatin) Tablets.

2 MATERIAL REVIEWED

- Draft (b) (4) (sitagliptin and simvastatin) Medication Guide (MG) received on December 7, 2010, revised by the review division throughout the review cycle and sent to DRISK on August 18, 2011.
- Draft (b) (4) (sitagliptin and simvastatin) Prescribing Information (PI) received December 7, 2010, revised by the Review Division throughout the current review cycle and received by DRISK on August 18, 2011.
- Approved JANUMET (sitagliptin/metformin hydrochloride) comparator labeling dated May 13, 2011.
- Approved JANUVIA (sitagliptin) comparator labeling dated April 14, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)

- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
09/01/2011

LASHAWN M GRIFFITHS
09/01/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: August 29, 2011

To: Pooja Dharia, Regulatory Project Manager,
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Kendra Jones, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 202343 (b) (4) ™ (sitagliptin and simvastatin) Tablets

DDMAC labeling comments for (b) (4)

DDMAC has reviewed the proposed Prescribing Information (PI) and Medication Guide (Med Guide) for (b) (4) accessed from the eRoom on August 27, 2011.

General Comment

Comments regarding the PI and the Med Guide are provided in the marked version below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the MedGuide, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
08/29/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Date:	June 20, 2011
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products
Through:	Lubna Merchant, PharmD, M.S., Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Anne C. Tobenkin, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s) and Strength:	(b) (4) (Sitagliptin and Simvastatin) Tablets 100 mg/10 mg, 100 mg/20 mg, 100 mg/40 mg
Application Type/Number:	NDA 202343
Applicant:	Merck
OSE RCM #:	2011-300

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the proposed container labels and carton and insert labeling for (b) (4) (Sitagliptin and Simvastatin) Tablets for NDA 202343 for areas of vulnerability that could lead to medications errors. The review responds to a request from the Division of Metabolism and Endocrinology Products (DMEP) to review the container labels and carton labeling for this Application. The proposed proprietary name is currently being evaluated under OSE review # 2011-1129.

2 MATERIAL REVIEWED

Using Failure Mode and Effects Analysis, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product labels submitted on December 7, 2010 to identify vulnerabilities that may lead to medication errors. See the Appendix for samples of the draft container labels and carton labeling.

Additionally, Merck, the Applicant for this NDA, standardized the label design for the container labels of their oral solid dosage forms. DMEPA reviewed and provided recommendations for the revised labels of the effected products included in a bundled supplement in OSE reviews # 2010-628 dated August 13, 2010 and # 2010-628-1 dated April 11, 2011. DMEPA considered these recommendations during the evaluation of the labels and labeling for this product to ensure consistency across the Merck products.

3 CONCLUSIONS AND RECOMMENDATIONS

Our Label Risk Assessment indicates that the presentation of information on the labels and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval, and thus we provide recommendations in the following sections that aim at reducing the risk of medication errors. We request the recommendations in Section 3.2 be communicated to the Applicant prior to the approval of this NDA.

Please copy the Division of Medication Error Prevention and Analysis on any communication to Merck. with regard to this review. If you have further questions or need clarifications, please contact Margarita Tossa, OSE Project Manager, at 301-796-4053.

3.1 COMMENTS TO THE DIVISION

A. Highlights Sections; Dosage and Administration and Dosage Forms and Strengths

Revise the strength statements so that they are expressed with the mg after each ingredient, for example, 100 mg/20 mg. Also, revise all strength statements throughout the insert to reflect this presentation.

3.2 COMMENTS TO THE APPLICANT

A. Physician Sample Carton Labeling (All strengths)

1. Revise the presentation of the established name so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).
2. Revise the strength presentation so that the unit of measure "mg" is on the same line as the numeric strengths and in the same size font to improve readability. Currently, the unit of measure appears as a superscript.
4. Revise the contents statement so that it reads;

   7 tablets per bottle
   Carton contains 2 bottles

5. The contents and sample statements should appear on more then one panel to ensure that this information is conveyed regardless of how it is stored on shelves.
6. Decrease the size of the graphic that appears around the proprietary name, (b) (4) so that there is no intervening matter between the proprietary name and the established name and also to decrease distraction from the drug name and strength.
7. Relocate and increase the prominence of the Med Guide statement so that it appears as the first statement underneath the statement of strength and above the 'Each tablet contains' statement (of note, this revised presentation also more closely mimics the (b) (4) container labels).

B. Container Labels, 7 tablets, 30 tablets, 1000 Tablets (All strengths)

1. Increase the prominence of the Med Guide statement by using bold font so that it is more readily visible to practitioners.

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/s/

ANNE C TOBENKIN
06/20/2011

LUBNA A MERCHANT
06/20/2011

CAROL A HOLQUIST
06/21/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 8, 2011
To:	Valerie Pratt, MD Medical Officer Division of Metabolism and Endocrinology Products Office of Drug Evaluation II
Thru:	Judy Staffa, Ph.D., R.Ph. Director Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology Laura Governale, Pharm.D, MBA Drug Utilization Data Analysis Team Leader Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology
From:	Tracy Pham, Pharm.D Drug Use Data Analyst Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology
Subject:	Outpatient utilization trend of simvastatin and sitagliptin products, April 2006 to March 2011
Drug Name(s):	Simvastatin and sitagliptin products
Application Type/Number:	Simvastatin: multiple Sitagliptin: NDA 021995 Simvastatin/Sitagliptin: NDA 202343
Applicant/sponsor:	Merck Sharp & Dohme Corp
OSE RCM #:	2011-1292

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information in this document has been cleared for public release.

CONTENTS

EXECUTIVE SUMMARY

This review analyzes the nationally projected outpatient utilization patterns for simvastatin and sitagliptin products from April 1, 2006 through March 31, 2011, with a focus on utilization patterns in patients aged 10-17 years old. Proprietary drug use databases licensed by the FDA were used to conduct this analysis. Data findings are as followed:

- The majority of simvastatin (72%) and sitagliptin (83%) products were sold to outpatient retail pharmacy settings in year 2010.
- Approximately 2.9 million patients had a prescription claim for sitagliptin products over the cumulative time period from April 2006 through March 2011. The majority of patients on sitagliptin products were aged 18 years and older. Patients aged 10-17 years old accounted for less than 1% (1,800 patients) of sitagliptin use. Sitagliptin 100mg (1,600 patients) had the highest proportion of use among patients aged 10-17 years old, followed by sitagliptin 50mg (236 patients) and sitagliptin 25mg (58 patients).
- Over the cumulative time period from April 2006 through March 2011, approximately 35.2 million patients had a prescription claim for simvastatin products. The majority of patients on simvastatin products were aged 18 years and older. Patients aged 10-17 years old accounted for less than 1% (26,000 patients) of simvastatin use. Simvastatin 20mg (13,000 patients) had the highest proportion of use among patients aged 10-17 years old, followed by simvastatin 40mg (9,000 patients) and simvastatin 10mg (7,000 patients).
- The use of sitagliptin and simvastatin as monotherapy or concurrent therapy among patients aged 10-17 years old were infrequent. For patients on sitagliptin 100mg, approximately 58 patients (4%) were on concurrent therapy with simvastatin 40mg. For patients on sitagliptin 50mg, approximately 15 patients (6%) were on concurrent therapy with simvastatin 20mg.

1 INTRODUCTION

The Division of Metabolism and Endocrinology Products (DMEP) requested drug utilization data on simvastatin and sitagliptin products to evaluate the extent of use of these products in the diabetic pediatric population. This review summarizes the outpatient utilization patterns for simvastatin and sitagliptin products in the U.S. from April 1, 2006 through March 31, 2011, with a focus on utilization patterns in patients aged 10-17 years old.

2 BACKGROUND

2.1 REGULATORY HISTORY

Sitagliptin is a dipeptidyl peptidase-4 inhibitor, approved under NDA 021995 in October 16, 2006, as an adjunct to diet and exercise to "improve glycemic control in adults with type 2 diabetes mellitus."[1] Sitagliptin is currently marketed as Januvia in three strengths: 25mg, 50mg, and 100mg. The use of sitagliptin in the pediatric population is currently being studied.[2]

Simvastatin is an HMG-CoA reductase inhibitor indicated as an adjunct to diet for the treatment of hyperlipidemia, the reduction in the risk of coronary heart disease and cardiovascular events, and the reduction of "elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls aged 10 to 17 years with heterozygous

[1] U.S. Food and Drug Administration: Drugs@FDA. Data collected in April 2011. Available at: http://www.accessdata fda.gov/drugsatfda_docs/label/2011/021995s017lbl.pdf

[2] U.S. Food and Drug Administration: Office of Surveillance and Epidemiology consult request. Date requested on 4/18/2011.

familial hypercholesterolemia."[3] It was initially approved under NDA 019766 in December 23, 1991, and marketed as Zocor. Currently, it is available in five strengths: 5mg, 10mg, 20mg, 40mg, and 80mg. The safety and effectiveness of simvastatin to reduce cardiovascular risks and lipid parameters in the general pediatric population is unknown. Moreover, simvastatin does not have an approved indication for use in the general diabetic population although the 2011 American Diabetes Association Standards of Medical Care in Diabetes suggested adding a statin in diabetic patients aged "10 years and older who, after medical nutrition therapy and lifestyle changes, have LDL cholesterol > 160mg/mL or LDL cholesterol > 130mg/mL and one or more CVD risk factors."[4]

On December 6, 2010, Merck Sharp & Dome Corporation submitted a New Drug Application (NDA 202343) for (b) (4) (sitagliptin and simvastatin) with three fixed-dose combination (FDC) strengths: 100/10 mg, 100/20 mg, and 100/40 mg. The application is currently under review in DMEP. In preparation for the Pediatric Review Committee (PeRC) meeting on August 10, 2011, and to determine if this new (b) (4) FDC product needs to be studied in the pediatric population, DMEP requested drug utilization data for simvastatin and sitagliptin products in the pediatric population aged 10 to 17 years old.

3 METHODS AND MATERIALS

3.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ (see Appendix 2 for full data description) was used to determine the various retail and non-retail channels of distribution for simvastatin and sitagliptin products. During year 2010, approximately 72% and 83% of simvastatin and sitagliptin products, respectively, were distributed to outpatient retail pharmacies; 16% and 10%, respectively, were to mail order pharmacies; and 12% and 8%, respectively, were to non-retail settings.[5] As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail order nor non-retail settings data were included in this analysis.

3.2 DATA SOURCES USED AND METHODS

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (see Appendix 2 for full data description).

Wolters Kluwer's Health Concurrent Product Analyzer (WKCPA) was used to obtain nationally projected estimates of the number of unique patients with a prescription claim for simvastatin products alone, for sitagliptin products alone, and for sitagliptin (100mg or 50mg) concurrent with simvastatin (10mg, 20mg, or 40mg), stratified by product strength and patient age (0-9, 10-17, and 18+ years), dispensed through outpatient retail pharmacies from the 12-month period ending in March 2007 to the 12-month period ending in March 2011 (April 1, 2006 to March 31, 2011). Files for patients who submitted a prescription claim were searched using national drug codes (NDC) for the selected sitagliptin and simvastatin products. Additionally, a lookback period of 90 days prior to the start of the study, April 1, 2006, was applied to check for claims within the study market to determine patient eligibility. Mail order prescription claims were not included in the analysis.

An episode of concurrent therapy was identified if the *days supplied*[6] for a prescription in the *base group* (sitagliptin 100mg or 50mg) overlapped with the days supplied for a dispensed prescription in the *concurrent*

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[3] U.S. Food and Drug Administration: Drugs@FDA. Data collected in April 2011. Available at: http://www.accessdata fda.gov/drugsatfda_docs/label/2010/019766s081lbl.pdf

[4] American Diabetes Association. "Standards of Medical Care in Diabetes – 2011." Diabetes Care 2011; 34 (Suppl. 1): S38-42.

[5] IMS Health, IMS National Sales Perspectives™. Year 2010. Extracted April 2011. File: 1104sisi.dvr

[6] *Days Supplied* - The number of *days supplied* is estimated by the dispensing pharmacist by dividing the number of tablets or capsules dispensed by the number of tablets or capsules consumed per day.

group (simvastatin 10mg, 20mg, or 40mg). Patients with overlapping therapy days from the *base group* and the *concurrent group* were identified as *concurrent patients* or patients on concurrent drug therapy.

We applied a conservative definition of concurrency by adding a 50% grace period to the total days supplied time window for a dispensed prescription in either the base group (sitagliptin) or the concurrent group (simvastatin). A grace period is typically added to the prescription total days supplied time window to allow for delays in prescription filling. For example, if the total days supplied for a prescription is 30 days, a 50% grace period would add 15 more days to the prescription days supplied time window for a total of 45 days of therapy. A longer days supplied time window in either group would increase the likelihood of meeting the definition of concurrent episode, and therefore, identify patients on concurrent drug therapy.

4 RESULTS

4.1 SITAGLIPTIN ALONE ANALYSIS (TABLE 1)

Over the cumulative time period from April 2006 through March 2011, approximately 2.9 million patients had a prescription claim for sitagliptin products from outpatient retail pharmacies. The number of patients with a prescription claim for sitagliptin products increased by almost 6-fold from 248,000 patients during the 12-month period ending in March 2007 to 1.4 million patients during the 12-month period ending in March 2011.

Patients aged 18 years and older (2.8 million patients) accounted for approximately 98% of the total patients who had a prescription claim for sitagliptin products over the cumulative time period. Less than 1% of the total patients were aged 10-17 years old (1,800 patients) and aged 0-9 years old (847 patients).

The number of pediatric patients aged 10-17 years with a prescription claim for sitagliptin products increased by almost 4-fold from 183 patients during year ending March 2007 to 678 patients during year ending March 2011. Similar to adults, the majority of these pediatric patients had a prescription claim for sitagliptin 100mg with approximately 1,600 patients (88% of patients aged 10-17 years old) over the cumulative time period from April 2006 through March 2011. Prescription claims for sitagliptin 50mg and sitagliptin 25mg followed with approximately 236 patients (13% of patients aged 10-17 years old) and 58 patients (3% of patients aged 10-17 years old), respectively, in this age group.

4.2 SIMVASTATIN ALONE ANALYSIS (TABLE 2)

Over the cumulative time period from April 2006 through March 2011, approximately 35.2 million patients had a prescription claim for simvastatin products from outpatient retail pharmacies. The number of patients with a prescription claim for simvastatin products increased by almost 3-fold from 7.4 million patients during year ending in March 2007 to 20.6 million patients during year ending in March 2011.

Patients aged 18 years and older (34.4 million patients) accounted for approximately 98% of the total patients who had a prescription claim for simvastatin products over the cumulative time period. Less than 1% of the total patients were aged 10-17 years old (26,000 patients) and aged 0-9 years old (16,000 patients).

The number of pediatric patients aged 10-17 years with a prescription claim for simvastatin products increased by approximately 3-fold from 4,000 patients during year ending in March 2007 to 12,000 patients during year ending in March 2011. Among this age group, nearly half of patients had a prescription claim for simvastatin 20mg with approximately 13,000 patients (48% of patients aged 10-17 years old) over the cumulative time period from April 2006 through March 2011. Prescription claims for simvastatin 40mg and simvastatin 10mg followed with approximately 9,000 patients (33% of patients aged 10-17 years old) and 7,000 patients (26% of patients aged 10-17 years old) patients, respectively, in this age group.

4.3 CONCURRENCY ANALYSIS (TABLE 3)

Table 3 shows projected number of patients aged 10-17 years old who received sitagliptin 100mg or 50mg concurrent with simvastatin 10mg, 20mg, or 40mg from outpatient retail pharmacies, from the 12-month period ending in March 2007 to the 12-month period ending in March 2011.

4.3.1 Sitagliptin 100mg Concurrent with Simvastatin 10mg, 20mg, or 40mg

Over the cumulative time period from April 2006 through March 2011, nearly 1,600 pediatric patients aged 10-17 years old had a prescription claim for sitagliptin 100mg. The greatest number of concurrent patients occurred with simvastatin 40mg with 58 patients, followed by simvastatin 20mg with 41 patients, and simvastatin 10mg with 15 patients. Stated in terms of percentages, approximately 4%, 3%, and 1% of pediatric patients with a prescription claim for sitagliptin 100mg were on concurrent therapy with simvastatin 40mg, 20mg, or 10mg, respectively. Conversely, less than 1% of pediatric patients with a prescription claim for simvastatin 10mg, 20mg, or 40mg were on concurrent therapy with sitagliptin 100mg throughout the study period.

4.3.2 Sitagliptin 50mg Concurrent with Simvastatin 10mg, 20mg, or 40mg

Over the cumulative time period from April 2006 through March 2011, around 236 pediatric patients aged 10-17 years old had a prescription claim for sitagliptin 50mg. The greatest number of concurrent patients occurred with simvastatin 20mg with 15 patients, followed by simvastatin 10mg with 10 patients, and simvastatin 40mg with 8 patients. Stated in terms of percentages, approximately 3%, 6%, and 4% of pediatric patients with a prescription claim for sitagliptin 50mg were on concurrent therapy with simvastatin 40mg, 20mg, or 10mg, respectively. Conversely, less than 1% of pediatric patients with a prescription claim for simvastatin 10mg, 20mg, or 40mg were on concurrent with sitagliptin 50mg.

5 DISCUSSION

From our analysis, the use of sitagliptin and simvastatin as monotherapy or concurrent therapy among patients aged 10-17 years old was infrequent, and therefore, below the acceptable counts to allow reliable conclusions about national trends. For this reason, these results should be interpreted with caution. Despite the low usage, the number of patients with a prescription claim for sitagliptin alone and simvastatin alone does appear to have increased over the study period.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for year 2010 showed that most of simvastatin and sitagliptin products were distributed to outpatient retail pharmacies. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

When examining concurrency, several assumptions are made: (1) a patient is taking the prescription(s) as recommended; and (2) the days supply for a prescription is recorded to reflect how the patient is actually taking the prescription. Patients who receive prescriptions with the instructions of “as needed” will tend to have a days supply assigned by the pharmacist that assumes the patient will take the maximum dose possible. This may lead to an underestimate of the length of time that these as needed medications will actually last for a patient.

We focused our analysis on only the outpatient retail pharmacy settings, therefore these estimates may not apply to other settings of care in which these products are used (e.g., mail order pharmacies and non-retail settings). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

Due to the possibility of double counting patients who are receiving treatment over multiple periods in the study, unique patient counts may not be added across time periods. Summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

6 CONCLUSIONS

Over the cumulative time period from April 2006 through March 2011, approximately 2.9 million patients and 35.2 million patients had a prescription claim for sitagliptin alone and simvastatin alone, respectively. The use

of sitagliptin and simvastatin as monotherapy among patients aged 10-17 years old was less than 1% of the total patient count for each product. Of these, sitagliptin 100mg and simvastatin 20mg had the highest proportion of use among this age group. Concurrent therapy with sitagliptin and simvastatin was also low among this age group. Of these, sitagliptin 100mg and simvastatin 40mg had the highest number of patients on concurrent therapy.

APPENDIX 1: TABLES

Table 1. Projected number of patients with a prescription claim for sitagliptin by age and product strength in the U.S. outpatient pharmacies, April 2006 through March 2011

	4/2006-3/2007		4/2007-3/2008		4/2008-3/2009		4/2009-3/2010		4/2010-3/2011		Cumulative 4/2006-3/2011	
	N	%	N	%	N	%	N	%	N	%	N	%
Total Sitagliptin	**248,418**	***100.00%***	**975,689**	***100.00%***	**1,279,612**	***100.00%***	**1,373,936**	***100.00%***	**1,417,891**	***100.00%***	**2,875,179**	***100.00%***
0-9 years	**88**	***0.04%***	**288**	***0.03%***	**300**	***0.02%***	**316**	***0.02%***	**265**	***0 02%***	**847**	***0.03%***
100mg	88	*100.00%*	261	*90.63%*	241	*80.33%*	250	*79.11%*	220	*83.02%*	713	*84.12%*
50mg	0	*0.00%*	27	*9.38%*	72	*24.00%*	72	*22.78%*	50	*18.87%*	162	*19.13%*
25mg	0	*0.00%*	5	*1.74%*	0	*0.00%*	7	*2.22%*	0	*0.00%*	12	*1.42%*
10-17 years	**183**	***0.07%***	**580**	***0.06%***	**667**	***0.05%***	**648**	***0.05%***	**678**	***0 05%***	**1,795**	***0.06%***
100mg	176	*96.17%*	549	*94.66%*	611	*91.60%*	543	*83.86%*	561	*82.74%*	1,581	*88.08%*
50mg	11	*6.01%*	40	*6.90%*	59	*8.85%*	106	*16.37%*	93	*13.72%*	236	*13.15%*
25mg	0	*0.00%*	0	*0.00%*	0	*0.00%*	34	*5.25%*	44	*6.49%*	58	*3.23%*
18+ years	**245,447**	***98.80%***	**963,001**	***98.70%***	**1,258,617**	***98.36%***	**1,348,887**	***98.18%***	**1,390,931**	***98.10%***	**2,821,185**	***98.12%***
100mg	225,988	*92.07%*	857,736	*89.07%*	1,084,229	*86.14%*	1,137,861	*84.36%*	1,144,893	*82.31%*	2,400,982	*85.11%*
50mg	17,177	*7.00%*	109,525	*11.37%*	184,513	*14.66%*	224,595	*16.65%*	255,457	*18.37%*	514,045	*18.22%*
25mg	4,815	*1.96%*	21,795	*2.26%*	31,255	*2.48%*	36,520	*2.71%*	43,346	*3.12%*	94,352	*3.34%*
Unspecified	**2,700**	***1.09%***	**11,820**	***1.21%***	**20,029**	***1.57%***	**24,086**	***1.75%***	**26,017**	***1 83%***	**51,352**	***1.79%***

Source: Wolters Kluwer Health's Concurrent Product Analyzer (WKCPA)®. April 2006 through March 2011. Extracted May 2011. File: WKLX 2011-1292 sitagliptin simvastatin alone age strength 5-5-11.xls

Table 2. Projected number of patients with a prescription claim for simvastatin by age and product strength in the U.S. outpatient pharmacies, April 2006 through March 2011

	4/2006-3/2007		4/2007-3/2008		4/2008-3/2009		4/2009-3/2010		4/2010-3/2011		Cumulative 4/2006-3/2011	
	N	%	N	%	N	%	N	%	N	%	N	%
Total Simvastatin	**7,406,235**	***100.00%***	**11,109,457**	***100.00%***	**16,045,029**	***100.00%***	**18,824,498**	***100.00%***	**20,566,555**	***100.00%***	**35,179,871**	***100.00%***
0-9 years	**3,000**	***0.04%***	**4,092**	***0.04%***	**5,615**	***0.03%***	**6,594**	***0.04%***	**6,581**	***0.03%***	**16,236**	***0.05%***
40mg	1,218	*40.60%*	1,633	*39.91%*	2,227	*39.66%*	2,782	*42.19%*	2,737	*41.58%*	6,854	*42 21%*
20mg	1,322	*44.07%*	1,657	*40.49%*	2,354	*41.92%*	2,522	*38.25%*	2,483	*37.73%*	6,863	*42 27%*
10mg	367	*12 23%*	551	*13.45%*	690	*12.29%*	809	*12.27%*	863	*13.11%*	2,174	*13.39%*
80mg	218	*7 27%*	376	*9.19%*	544	*9.69%*	749	*11.36%*	701	*10.65%*	1,678	*10.33%*
5mg	71	*2.37%*	118	*2.88%*	119	*2.12%*	163	*2.47%*	156	*2.37%*	392	*2.41%*
10-17 years	**4,037**	***0.05%***	**6,287**	***0.06%***	**8,692**	***0.05%***	**11,075**	***0.06%***	**12,274**	***0.06%***	**26,322**	***0.07%***
20mg	1,899	*47 05%*	2,717	*43.22%*	3,724	*42.85%*	4,920	*44.42%*	5,620	*45.79%*	12,616	*47.93%*
40mg	1,292	*32 01%*	2,060	*32.77%*	2,818	*32.42%*	3,357	*30.31%*	3,817	*31.10%*	8,747	*33.23%*
10mg	848	*21 00%*	1,510	*24.01%*	2,188	*25.17%*	2,806	*25.33%*	3,121	*25.42%*	6,905	*26.23%*
80mg	143	*3.54%*	246	*3.91%*	412	*4.74%*	650	*5.87%*	796	*6.49%*	1,507	*5.72%*
5mg	154	*3 82%*	209	*3.32%*	259	*2.98%*	299	*2.70%*	367	*2.99%*	857	*3.26%*
18+ years	**7,287,210**	***98.39%***	**10,927,276**	***98.36%***	**15,742,607**	***98.12%***	**18,435,405**	***97.93%***	**20,126,151**	***97.86%***	**34,391,318**	***97 76%***
40mg	3,089,334	*42.39%*	4,727,921	*43.27%*	6,955,593	*44.18%*	8,066,403	*43.75%*	8,778,543	*43.62%*	16,022,258	*46.59%*
20mg	3,163,718	*43.41%*	4,699,698	*43.01%*	6,522,208	*41.43%*	7,590,969	*41.18%*	8,183,641	*40.66%*	15,848,341	*46.08%*
80mg	778,969	*10.69%*	1,185,142	*10.85%*	1,872,566	*11.89%*	2,309,539	*12.53%*	2,540,043	*12.62%*	4,406,174	*12.81%*
10mg	726,838	*9.97%*	1,041,745	*9.53%*	1,457,315	*9.26%*	1,731,293	*9.39%*	1,868,302	*9.28%*	3,781,529	*11.00%*
5mg	64,191	*0 88%*	82,159	*0.75%*	108,228	*0.69%*	122,009	*0.66%*	130,604	*0.65%*	290,544	*0.84%*
Unspecified	**111,989**	***1.51%***	**171,803**	***1.55%***	**288,116**	***1.80%***	**371,424**	***1.97%***	**421,549**	***2.05%***	**745,996**	***2.12%***

Source: Wolters Kluwer Health's Concurrent Product Analyzer (WKCPA)®. April 2006 through March 2011. Extracted May 2011. File: WKLX 2011-1292 sitagliptin simvasta in alone age strength 5-5-11.xls

Table 3. Projected number of patients aged 10-17 years on concurrent therapy with sitagliptin (100mg or 50mg) and simvastatin (10mg, 20mg, or 40mg) products, cumulative April 2006 through March 2011

Cumulative 4/2006-3/2011						
Base Group	**Concurrent Group**	**Patients (Base Group)**	**Patients (Concurrent Group)**	**Concurrent Patients**	***Concurrent Patient % (Base Group)***	***Concurrent Patient % (Concurrent Group)***
sitagliptin 100mg	**simvastatin 10mg**	1,581	6,905	15	0.95%	*0.22%*
	simvastatin 20mg	1,581	12,616	41	2.59%	*0.32%*
	simvastatin 40mg	1,581	8,747	58	3.67%	*0.66%*
sitagliptin 50mg	**simvastatin 10mg**	236	6,905	10	4.24%	*0.14%*
	simvastatin 20mg	236	12,616	15	6.36%	*0.12%*
	simvastatin 40mg	236	8,747	8	3.39%	*0.09%*

Source: Wolters Kluwer Health's Concurrent Product Analyzer (WKCPA)®. April 2006 through March 2011. Extracted May 2011. Files: WKLX 2011-1292 sitagliptin simvastatin alone age strength 5-5-11.xls; WKLX 2011-1292 sitagliptin simvastatin concurrency age 10-17 strength 5-5-11.xls

APPENDIX 2: DATABASES DESCRIPTION

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Wolters Kluwer SOURCE Lx®

Wolters Kluwer Health's Source® Lx database a longitudinal patient data source which capture adjudicated claims across the United States from a mix of prescription claims from commercial plans, Medicare Part D plans, Cash and Medicaid claims. The database contains approximately 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

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

/s/

TRACY M PHAM
06/08/2011
Drug use data were cleared for public release.

LAURA A GOVERNALE
06/08/2011
drug use data cleared

JUDY A STAFFA
06/08/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202343 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Sitagliptin/Simvastatin Dosage Form: Tablet Strengths: 100 mg /10 mg, 100 mg/20 mg, 100 mg/40 mg		
Applicant: Merck Agent for Applicant (if applicable):		
Date of Application: 12/6/10 Date of Receipt: 12/7/10 Date clock started after UN:		
PDUFA Goal Date: 10/7/11	Action Goal Date (if different):	
Filing Date: 02/05/11	Date of Filing Meeting: 02/01/11	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): Indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		X 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 103183	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	X			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 021995	Sitagliptin	NCE	10/16/11

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	This is an electronic submission.

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		This is being requested by OSE PM Margarita Tossa.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		A REMS is being requested in the 74-day letter.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) X Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***			X	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 06/24/10	X			

If yes, distribute minutes before filing meeting				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 02/01/11

BLA/NDA/Supp #: 202343

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Sitagliptin/Simvastatin

DOSAGE FORM/STRENGTH: 100 mg/10 mg, 100 mg/20 mg, 100 mg/40 mg Tablets

APPLICANT: Merck, Sharp & Dohme, a division of Merck & Co.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate

BACKGROUND: (b) (4) (sitagliptin/simvastatin) is a fixed-dose combination of two approved products: Sitagliptin, dipeptidyl peptidase IV (DPP-4) inhibitor that has been developed for the treatment of patients with type 2 diabetes mellitus (T2DM) and simvastatin an HMG-CoA reductase inhibitor for the treatment of hypercholesteremia. Both products are owned by Merck. The product will initially be available in only the following doses: 100-mg sitagliptin/10-mg simvastatin, 100-mg sitagliptin/20-mg simvastatin, and 100-mg sitagliptin/40-mg simvastatin, in order to avoid confusion and to have the fixed-dose combination available to the majority of patients with T2DM who use both sitagliptin and simvastatin.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pooja Dharia	Y
	CPMS/TL:	Enid Galliers	Y
Cross-Discipline Team Leader (CDTL)	Ilan Irony		Y
Clinical	Reviewer:	Valerie Pratt	Y
	TL:	Ilan Irony	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		

	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sang Chung	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Lee Ping Pian	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Patricia Brundage	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	John Hill/Ted Carver	Y
	TL:	Su Tran	Y
Quality Microbiology *(for sterile products)*	Reviewer:	John Duan	Y
	TL:	Angelica Dorantes	Y
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	X Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES X NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☐ YES Date if known: X NO ☐ To be determined Reason:

○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	x Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division Director

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Filing Meeting	02/01/11
Filing Date	02/05/11
74 day letter	02/19/11
Midcycle	
Wrap Up	
Team Meetings	
Labeling Meetings	
Primary reviews due	09/02/11
Secondary reviews due	09/09/11
PDUFA Goal Date	10/07/11

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): Review Classification: X Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

POOJA DHARIA
02/17/2011