CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-995

CHEMISTRY REVIEW(S)

ONDQA Division Director's CMC Memorandum on NDA 21-995

Date: October 15, 2006
From: Chi-wan Chen, Acting Director, Division of Pre-Marketing Assessment I, Office of New Drug Quality Assessment
To: DA 21-995 File

Applicant: Merck and Co., Inc.
Drug Name: Januvia (Sitagliptin) tablets, 25, 50, 100 mg
Indication: Type 2 diabetes mellitus

The CMC portion of this NDA was submitted on December 16, 2005, under the ONDQA Pilot Program to explore science- and risk-based approaches to assuring product quality. An expanded pharmaceutical development section was submitted. Several quality-by-design (QbD) elements were presented with respect to product design and process understanding.

Drug Substance

The following critical process parameters (CPPs) for the drug substance manufacturing process were identified:

The major issues identified and resolved during the review are:

1. The applicant proposed no measurement of even though the has been shown to have an impact on drug product processing (e.g.,

   - A batch made at site was and incurred a . The applicant agreed to include in their process description.
   - While the applicant has demonstrated a higher than usual level of understanding of the , the data provided does not provide sufficient assurance over the range of operation proposed in the application. A test was added to the specification sheet to ensure the desired is obtained.

2. No specific designation of critical quality attributes (CQAs) or design space was discussed in the process development section, and the process description for the commercial scale production was vague. The applicant revised the process description and provided a table capturing established design space and initial control space with a few identified CQAs. The revised version contains much more information than a typical process description and provides additional value to reviewers for post-approval changes and for field inspectors.

Drug Product

The application included detailed studies on Process risks associated with scale-up were proactively identified, which include

The process development studies were focused on defining a robust operating space that effectively minimized the inherent process risks. The applicant claimed that none of the process parameters were found to be critical. They defined a critical step or operation as "one that requires process conditions or parameters to be carefully controlled within a predetermined operating range" to assure quality. The applicant established a design space for

The applicant proposed a non-traditional approach to the drug product control strategy. Assay by are tested on , in-process only, though the criteria are included in the specification. The remaining attributes in the drug product specification includes

will be used for stability testing.

The major issues identified and resolved during the review are:

1. Although was conducted to assess the potential risks related to drug substance or excipient variability, the applicant proposed to monitor the . They did not investigate and understand the effects of material attributes on process or product performance and relied instead on th to ensure and on pharmacopeial standards for the excipients. And the applicant did not intend to monitor or control during commercial production.

   At our request and after the PAI of the drug product facility in ne applicant agreed to control the variability in excipients, including , against a set of quality specifications as defined in their quality standard, and include key attributes for all excipients in their drug product design space and control space table.

2. No specific designation of critical quality attributes (CQAs) or design space is discussed in the process development section. The applicant revised the process description and provided a table capturing established design space and initial control space with a few input variables, rather than product attributes, as CQAs. The applicant has identified which design spaces for the unit operations are dependent upon scale or equipment. The revised version contains much more information than a typical process description and provides additional value to reviewers for post-approval changes and for field inspectors.

3. was proposed, but no in-process control for was considered. The applicant addressed FDA's concern by incorporating additional controls to help prevent or minimize These additional controls are:

4. The proposed acceptance criterion for ssay is abel claim (LC) for the mean of a pre-determined number of ablets without an acceptance limit for the SD or a tolerance limit for the number of outliers allowed. The sample size is typically ablets for a tablet batch of the 100-mg strength sampled during the The applicant has agreed to include an acceptance limit for the standard deviation (SD) of the individual assay concentrations to ensure that greater than of the individual ablets assay values, when converted to %LC, are within LC.

5. The proposed acceptance criterion for [redacted] s [redacted] LC. Typically [redacted] ablets for a [redacted] tablet batch of the 100-mg strength were sampled during the [redacted]

- The applicant has agreed to change the acceptance limits to ensure that the [redacted]
- The applicant also agreed to add a [redacted] test [redacted]

The revised procedure and criteria are more scientifically sound and provide an increased level of quality assurance.

6. The proposed [redacted] was found unacceptable by Office of Clinical Pharmacology [redacted] The applicant agreed to replace [redacted] with dissolution for product release and to add dissolution to future stability testing.

7. The proposed established name did not correspond to the labeled strength. The applicant was advised of the FDA policy that the name and the strength should match. They agreed to drop "phosphate" from the established name at the next printing in January, 2007.

As a footnote, the applicant proposed a CMC regulatory agreement outlining the regulatory mechanisms for managing changes related to process, equipment, scale, site, and design and control spaces for the drug substance and drug product post-approval. The agreement will not be approved at this time since FDA has not established a regulatory pathway to allow us to approve such an agreement.

Recommendation

The applicant has provided sufficient scientific information to demonstrate product knowledge and process understanding of the drug substance and product, and made necessary changes to their control strategy to increase the level of assurance in product quality. Other traditional aspects of the NDA, including demonstration of stability and establishment of retest period (36 months) and shelf life (30 months), are satisfactory. The application is recommended for approval from the chemistry, manufacturing, and control standpoint.

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

/s/

Chi Wan Chen
10/16/2006 05:35:28 PM
CHEMIST

NDA 21-995

Januvia™ (sitagliptin phosphate) Tablets

Merck And Co., Inc.

Stephen Moore, PhD
Christine Moore, Ph.D.
Vibhakar Shah, Ph.D.

ONDQA/ DPA I DMEP

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Chemistry Review Data Sheet

1. NDA 21-995

2. REVIEW #: 1

3. REVIEW DATE: 16-OCT-2006

4. REVIEWER: Stephen Moore, Ph.D., Christine Moore, Ph.D. and Vibakhar Shah, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 65,495 (MK-0431)	
IND 70,934 (MK-0431A)	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-DEC-2006
Amendments	13-JUN-2006
	23-JUN-2006
	20-JUL-2006
	21-SEP-2006
	12-OCT-2006
	16-OCT-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck and Co., Inc.
Address:	Summeytown Pike, P.O. Box 4 BLA-20 West Point, PA 19486 USA
Representative:	Steven A. Aurecchia, M.D. Director Regulatory Affairs
Telephone:	484-344-4662

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Januvia
b) Non-Proprietary Name (USAN):	sitagliptin phosphate
c) Code Name/# (ONDQA only):	MK-0431
d) Chem. Type/Submission Priority:	
· Chem. Type:	Type 1 (New molecular entity)
· Submission Priority:	S

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

10. PHARMACOL. CATEGORY: Hypoglycemic

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 25, 50 and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

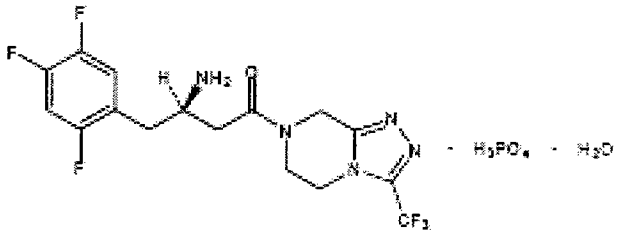
14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note20]:
_____SPOTS product – Form Completed
___x__Not a SPOTS product

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

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

Structural formula:



Molecular formula: $C_{16}H_{15}F_6N_5O \cdot H_3O_4P \cdot H_2O$

Molecular weight: 523.32.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	Colorcon	[redacted]	1	Adequate	13-JUL-2006	
[redacted]	III	Lyondell	[redacted]	4	N/A	N/A	

	III	4	N/A	N/A	
	III	4	N/A	N/A	
	III	4	N/A	N/A	
	III	4	N/A	N/A	
	III	4	N/A	N/A	
	III	4	N/A	N/A	
	III	4	N/A	N/A	
	III	4	N/A	N/A	
	II	1	Adequate	15-JUN-2006	
	II	1	Adequate	15-JUN-2006	

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

Chemistry Review Data Sheet

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	12-OCT-2006	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

The Chemistry Review for NDA 21-995

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application can be approved with respect to chemistry, manufacturing and controls (CMC).

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

The following statements regarding CMC should be included in the action letter:

1. As indicated in our Information Request (IR) letter dated 07-SEP-2006 and teleconference on October 13, 2006, your proposed CMC Regulatory Agreement submitted as part of the CMC Pilot Program is under review. Your proposal outlines the regulatory mechanisms for managing changes related to process design and control spaces post-approval. While a mutually accepted CMC Agreement is not a condition for the approval of this application, it will have implications for post-approval changes. Therefore, you are reminded that, until the CMC Agreement is approved, the existing regulations and guidances should be followed, as appropriate for the post-approval CMC changes.

2. We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

II. Summary of Chemistry Assessments

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

Drug Product:

The drug product consists of film coated tablets of 25, 50 and 100 mg strengths packaged in bottles. The active ingredient is stigaliptin phosphate in the form of a monohydrate. The strengths, however, are expressed as sitagliptin free base. The tablets contain as inactive ingredients microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide. The tablet strengths are weight multiples. The tablets have been formulated for immediate release (IR). Information on a 200 mg tablet is also provided, however, this tablet does not appear in the labeling and is not intended to be marketed.

The applicant indicates that a Quality by Design (QbD) approach was used to develop a robust formulation and drug product manufacturing process. [redacted] The excipients were selected to provide a chemically and physically stable formulation with optimized performance.

The tablets are manufactured using [redacted] followed by [redacted] The same blend is used for all tablet strengths. Tablet core weights and [redacted] tablet core assays are performed in-process, although the weights and assay measurements are not paired on the same tablet cores. Tablets are then film coated for appearance and taste masking in a [redacted]

The application includes detailed studies on [redacted] and identification of a [redacted] The applicant indicates that the drug product manufacturing process exhibits no Critical Process Parameters

(CPPs). Failure Modes Effects Analysis (FEMA) was conducted to assess the potential risks related to drug substance or excipient variability.

The applicant proposes a "streamlined" approach to quality testing of the drug product. The testing includes

The stability of the drug substance was studied under both accelerated and long term conditions. will be monitored in the stability protocol.

The applicant proposes outlines for the regulatory mechanisms for managing changes related to process design and control spaces for the drug product post-approval. An agreement has not yet been reached regarding these items.

Drug Substance:

The drug substance is sitagliptin phosphate in the form of a monohydrate. The drug substance is a chiral compound with a single asymmetric carbon. Its chemical name is 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. The drug substance in a BCS Class III (high solubility, low permeability) /borderline Class I (high solubility, high permeability) compound.

The drug substance is chemically

The applicant indicates that the drug substance process development included process optimization using Quality by Design (QbD) concepts, employing both design of experiments and first principles of chemical engineering unit operations. The applicant further indicates that the experiments provided in-depth understanding of the process and an increased assurance that the process will consistently provide final drug substance with the appropriate crystal morphology, particle size and degree of hydration.

Critical process parameters (CPPs) for the drug substance manufacturing process were identified as (1) the

Potential impurities in the drug substance are described. The impurities may form in the drug substance due to the presence of the corresponding impurities in the The maximum level of in drug substance lots used in safety studies was

The applicant proposes a "streamlined" approach to quality testing of the drug substance. The testing includes and will be tested in-process only, however the criteria are retained inthe specification. Based on development, the drug substance specification will not include testing for , however, these are controlled in-process. Also based on development, no testing is performed for . The stability of the drug substance was studied under long term, accelerated and stress conditions. The

The applicant proposes outlines for the regulatory mechanisms for managing changes related to process design and control spaces for the drug substance post-approval. An agreement has not yet been reached regarding these items.

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

Januvia (sitagliptin phosphate) is an orally active, highly potent, selective competitive reversible inhibitor of dipeptidyl peptidase 4 (DPP-4) [1] and a member of a new therapeutic class of drugs intended to treat type 2 diabetes mellitus (T2DM).

Each film-coated tablet of JANUVIA contains 32.13, 64.25, or 128.5 mg of sitagliptin phosphate, which is equivalent to 25, 50, or 100 mg, respectively, of free base. Tablets contain the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide.

The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin or a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (e.g., thiazolidinedione).

Tablets JANUVIA are supplied in bottles and blister packages. Storage is at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. The expiration dating period is 30 months.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has satisfactorily addressed all outstanding CMC deficiencies in the chemistry amendments filed to this NDA. All manufacturing facilities have been given an acceptable CGMP compliance status.

III. Administrative

This NDA was submitted electronically as a 505(b)(1) application. A Quality Overall Summary is included in the application. The CMC information in this NDA was accepted for review under the CMC pilot program (FR Vol. 70, No. 134, pp. 40719-40720, July 14, 2005). This program proposes innovative approaches to ensuring product quality.

The CMC section of this application was reviewed by a team approach. The review team members selected for the quality assessment and their individual responsibilities are listed below:

Review Team	Assessment Responsibility
Stephen Moore, Ph.D.	Team Liaison/Lead Drug substance section excluding its manufacturing process
Vibhakar Shah, Ph.D.	Drug product section excluding its manufacturing process

[1] DPP-4 inhibitors enhance the levels of active incretin hormones. These hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the intestine in response to a meal, and are part of an endogenous system involved in maintaining glucose homeostasis. When blood glucose concentrations are elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production. However, when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by the incretin hormones are not observed. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. MK-0431 prevents this hydrolysis, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, the drug increases insulin secretion and decreases glucagon levels. In patients with T2DM and hyperglycemia, these changes in insulin and glucagon levels lead to lower fasting and postprandial glucose concentrations.

Christine Moore, Ph.D.	Manufacturing processes including their development both for the drug substance and the drug product

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

Stephen Moore, Ph.D./ONDQA/Pharmaceutical Assessment Lead
Christine Moore, Ph.D./ONDQA/Branch Chief
Vibakhar Shah, Ph.D./ONDQA/Reviewer
Chi-Wan Chen, Ph.D./ONDQA/Deputy Director

C. CC Block

Lina Aljuburi, M.S., Regulatory Project Manager

237 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-2

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/s/

Stephen Moore
10/16/2006 05:03:17 PM
CHEMIST
Stephen Moore for Vibhakar Shah, Chemist

Christine Moore
10/16/2006 05:08:22 PM
CHEMIST

Chi Wan Chen
10/16/2006 05:14:39 PM
CHEMIST

INITIAL QUALITY ASSESSMENT
Office of New Drug Quality Assessment
Division of Metabolism and Endocrinology Products
NDA 21-995

Applicant: Merck and Co., Inc.
Stamp Date: 16-DEC-2005
PDUFA Date: 16-OCT-2006

Pharmacological Category: Hypoglycemic
Proposed Proprietary Name: Januvia Tablets
Established Name: (sitagliptin phosphate tablets)
Dosage Form and Strength: 25, 50 and 100 mg tablets
Route of Administration: oral
Indication(s): Treatment of Type 2 diabetes

PAL: Stephen Moore, Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing
Review Team Recommendation: The CMC review team was pre-selected by ONDQA office and primary reviews started immediately: Stephen Moore (drug substance characterization), Christine Moore (drug substance development and process) and Vibhakar Shah (drug product).

Time goals:

Initial Quality Assessment in DFS: JAN-2006
Chemistry filing memo in DFS: 14-FEB-2006
Filing decision "Day 45": Filed 14-FEB-2006 (no CMC filing issues stated at internal filing meeting 06-FEB-2006)
Filing review issues "Day 74": No CMC filing review issues. Filing letter issued by clinical division 27-FEB-2006
Chemistry Review (DR/IR) letter: 17-MAY-2006
Mid-cycle meeting "Month 5": 17-MAY-2006
Final Chemistry Review "Month 8" in DFS: 16-AUG-2006
PDUFA: 16-OCT-2006

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	Not applicable
CDRH	Not Applicable
EA	To be assessed by Primary Reviewer(s)
EES	EER sent to Office of Compliance on 24-JAN-2006
ODS/DMETS	Labeling consult request will be sent as part of DMEP's request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Not Applicable
Pharm/Tox	Not Applicable

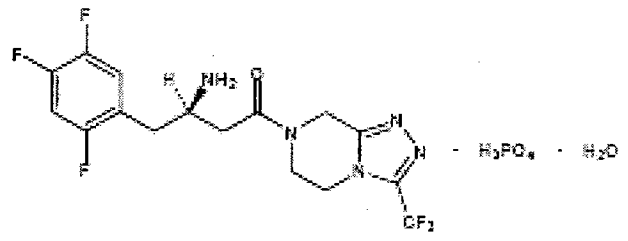
SUMMARY:

Submission type: This NDA was submitted electronically as a 505(b)(1) application with full clinical trials information. The active ingredient, sitigliptin phosphate, is classified as a new chemical entity (NCE). A Quality Overall Summary is included in the application. The CMC information in this NDA was accepted for review under the Quality by Design (QbD) pilot program (FR Vol. 70, No. 134, pp. 40719-40720, July 14, 2005). This program proposes innovative approaches to ensuring product quality.

Clinical indication(s): Januvia (sitagliptin phosphate) is proposed as an orally active, highly potent, selective competitive reversible inhibitor of dipeptidyl peptidase 4 (DPP-4) and a member of a new therapeutic class of drugs intended to treat type 2 diabetes mellitus (T2DM). DPP-4 inhibitors enhance the levels of active incretin hormones. These hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the intestine in response to a meal, and are part of an endogenous system involved in maintaining glucose homeostasis. When blood glucose concentrations are elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production. However, when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by the incretin hormones are not observed. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. MK-0431 prevents this hydrolysis, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, MK-0431 increases insulin secretion and decreases glucagon levels. In patients with T2DM and hyperglycemia, these changes in insulin and glucagon levels lead to lower fasting and postprandial glucose concentrations.

Pre-submission CMC issues and/or agreements: Investigational studies were performed under INDs 65,495 (MK-0431) and 70,934 (MK-0431A). No CMC issues were discussed at the EOP2 meeting held on 06-JUN-2004. The applicant presented its QbD approach in the Pre-NDA CMC meeting held on 01-NOV-2005. The Agency agreed to next meet with the applicant during the review cycle, once the review team has made its initial assessment of the NDA.

Drug Substance: The chemical name for sitagliptin phosphate is: 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. The empirical formula is C16H15F6N5O•H3O4P•H2O and the molecular weight is 523.32. MK-0431 has the following structural formula:



The drug substance in a BCS Class III (high solubility, low permeability) /borderline Class I (high solubility, high permeability) compound.

The drug substance is chemically [redacted] process. The process performed by Merck

[redacted]

The applicant indicates that the drug substance process development included process optimization using Quality by Design (QbD) concepts, employing both design of experiments and first principles of chemical engineering unit operations. The applicant further indicates that the experiments provided in-depth understanding of the process and an increased assurance that the process will consistently provide final drug substance with the appropriate [redacted]

Critical process parameters (CCPs) for the drug substance manufacturing process were identified as [redacted]

Potential impurities in the drug substance are described. The [redacted] may form in the drug substance due to the presence of the corresponding [redacted] impurities in the [redacted] The maximum level of [redacted] in drug substance lots used in safety studies was [redacted]

The applicant proposes a "streamlined" approach to quality testing of the drug substance. Based on development, the applicant proposes that the drug substance specification will not include testing for certain attributes (see list of critical issues). The stability of the drug substance was studied under both accelerated and long term conditions.

Drug Product: Firm coated tablets are supplied in 25, 50 and 100 mg strengths expressed as sitagliptin free base. Information on a 200 mg tablet is also provided, however, this tablet does not appear in the labeling. The tablets contain as inactive ingredients microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide. The tablet strengths are weight multiples. The tablets have been formulated for immediate release (IR).

The applicant indicates that a QbD approach was used to develop a robust formulation and drug product manufacturing process. [redacted] The excipients were selected to provide a chemically and physically stable formulation with optimized performance.

The tablets are manufactured using [redacted] The same [redacted] is used for all tablet strengths. Tablets are film coated.

The applicant indicates that the drug product manufacturing process exhibits no CCP. Failure Modes

Effects Analysis (FEMA) was conducted to assess the potential risks related to drug substance or excipient variability.

The applicant proposes a "streamlined" approach to quality testing of the drug product. Based on development, the applicant proposes that the drug product specification will not include testing for certain attributes (see list of critical issues). Noteworthy, a disintegration test is proposed instead of dissolution. The stability of the drug substance was studied under both accelerated and long term conditions.

Manufacturing sites to request CGMP status:

Name and address	CFN #	Responsibility
Merck Sharp & Dohme Quimica de Puerto Rico, Inc. Road #2, Kilometer 56.7 Barceloneta, PR 00617	2623436	Manufacture, packaging and release testing of drug substance
Merck & Co., Inc. 4663 Merck Road Wilson, NC 27893, USA	1036761	Stability testing of the commercial drug substance and primary and secondary packaging of drug product
Merck Sharp & Dohme (Italia) S.p.A. Via Emilia, 21 27100 Pavia, Italy		Manufacturing and Release Testing of drug product
Merck Sharp & Dohme Ltd. Shotton Lane, Cramlington Northumberland NE23 3JU, England	9611927	Stability Testing of drug product

Drug Master Files (DMF):

DMF	TYPE	HOLDER	ITEM REFERENCED	LOA	PREVIOUS REVIEW(S)	CURRENT REVIEW
[redacted]	IV	[redacted]	[redacted]	28-JUL-2005	Similar materials have been reviewed, but not these particular materials	Review needed

	III	[redacted]	29-JUL-2005	DMF previously reviewed.
	III	[redacted]	08-SEP-2005	DMF previously reviewed. Adequate information in NDA
	III	[redacted]	29-JUL-2005	DMF previously reviewed. Adequate information in NDA
	III	[redacted]	03-AUG-2005	DMF previously reviewed. Adequate information in NDA
	III	[redacted]	03-AUG-2005	DMF previously reviewed. Adequate information in NDA
	III	[redacted]	28-JUL-2005	DMF previously reviewed. Adequate information in NDA

	III		09-JUN-2005	DMF previously reviewed. Adequate information in NDA
	III		29-JUL-2005	DMF previously reviewed. Adequate information in NDA
	III		28-JUL-2005	DMF previously reviewed. Adequate information in NDA
	II		07-NOV-2005	No previous review.
	II		03-NOV-2005	No previous review.

DMF review needed.

DMF review needed.

NDA FILABLILITY CHECKLIST:

Is the CMC section of the application filable? Yes.

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		

4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		CFN not available for Pavia, Italy facility.
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?			Not applicable

CRITICAL ISSUES:

1. The review team will evaluate whether the applicant has satisfactorily identified the critical process parameters (CCP) for the drug substance and drug product manufacturing processes.
2. The review team will evaluate whether the applicant has satisfactorily identified the critical quality attributes (CQA) for the drug substance and drug product.
3. The review team will evaluate whether the applicant has sufficiently identified possible sources of variability in the drug substance and drug product manufacturing processes and how associated risks are mitigated.
4. The review team will evaluate whether the drug substance and drug product manufacturing descriptions are sufficiently detailed.
5. The applicant proposes acceptance specifications for the [redacted] and [redacted] hat only include identity. The review team will evaluate whether the raw material acceptance specifications are sufficient.
6. The applicant proposes not to test for the [redacted] distribution in-process or on the final drug substance. The review team will evaluate whether the level of process understanding, process controls and/or drug substance specification are sufficient to justify the reduced testing.
7. The applicant proposes to test for the [redacted] in-process, but not on the final drug substance. The review team will evaluate whether the drug substance specification is sufficient. In such cases, the review will also evaluate whether addition of a specification with a footnote indicating that the test is performed in-process would be appropriate. The latter would provide a means for quality monitoring for shelf life, stability and/or surveillance.
8. The review team will discuss the impurities and their levels with the Pharm/Tox reviewer(s).

9. The applicant proposes not to test for [redacted] in-process. The review team will evaluate whether the level of process understanding and/or in-process controls for [redacted] are sufficient to justify the omission of an in-process control for [redacted]
10. The applicant proposes to test for [redacted] in-process rather than [redacted] The review team will evaluate whether this surrogate test is sufficient.
11. The applicant proposes not to include a specification for [redacted] on the final drug product. The review team will evaluate whether the drug product specification is sufficient (see also #5).
12. Where and how the design space could be captured in the application will be discussed with the applicant.

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

/s/

Stephen Moore
6/5/2006 02:27:57 PM
CHEMIST

Blair Fraser
6/5/2006 03:22:46 PM
CHEMIST