

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-044**

**CHEMISTRY REVIEW(S)**

**Janumet™**  
**(Sitagliptin Phosphate (+) Metformin Hydrochloride)**  
**Tablets**  
**NDA 22-044**

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

**Applicant:** Merck & Co., Inc.  
UG2CD-48  
PO Box 1000  
North Wales, PA 19454-1099

**Indication:** Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

**Presentation:** The drug product is supplied in two strengths (50 mg sitagliptin/500 mg metformin hydrochloride or 50 mg sitagliptin/1000 mg metformin hydrochloride) as immediate release film-coated tablets packaged in — bottles (60, 180 and 1000-count) and in unit dose — blister packages (50 count as 10-unit doses per foil).

**EER Status:** Acceptable 24-Jan-2007

**Consults:** Methods Validation – Agency revalidation not recommended.  
EA – Categorical exclusion granted under 21 CFR §25.31(b) for both drugs.  
Labeling – Under review (multi disciplinary approach).

**Original Submission:** 31-May-2006

**Amendments:** 24-Jul-2006  
05-Jan-2007  
05-Feb-2007  
05-Feb-2007

**Post-Approval Agreements:** None

**Drug Substances:**

**Sitagliptin Phosphate Monohydrate**

Sitagliptin is a highly selective and potent inhibitor of the enzyme dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors act by enhancing the levels of active incretin hormones. Sitagliptin is synthesized and present in the drug product as its phosphate

— monohydrate. Sitagliptin phosphate monohydrate has a 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, a molecular formula of  $C_{16}H_{15}F_6N_5O \cdot H_3O_4P \cdot H_2O$ , and a molecular weight of 523.32 g/mole. Sitagliptin phosphate monohydrate is a white to off-white solid, melting point \_\_\_\_\_ °C, and a pKa of — According to the Biopharmaceutics classification system (BCS) sitagliptin is a Class III (high solubility, low permeability)/borderline Class I (high solubility, high permeability) drug. Sitagliptin phosphate monohydrate is the drug substance of Januvia™ Tablets, which is described in and referred to Merck's approved NDA 21-995.

The release specifications include appearance, identity, assay, related impurities, moisture content, particle size distribution, residual metals, and chiral purity. The proposed regulatory methods have been validated. Residual metals and enantiomeric purity will be tested in-process only. However the criteria are retained in the specification. Based on development, no testing is performed for Polymorphic Form and Solvent \_\_\_\_\_ Content. The reference standard, a re-purified commercial lot, has been developed, characterized, and purity data provided.

Bulk sitagliptin phosphate monohydrate, packed in \_\_\_\_\_ is stable for long-term up to — years when stored at room temperature (25 °C/60 % RH).

### Metformin HCl

Metformin is a biguanide class of antihyperglycemic agent that acts primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Metformin HCl has a chemical name of 1,1-Dimethylbiguanide hydrochloride, a molecular formula of  $C_4H_{11}N_5 \cdot HCl$ , and a molecular weight of 165.62 g/mole. Metformin is a class 3 (high solubility, low permeability) BCS drug.

CMC information on the drug substance, metformin HCl, is described in the Type II DMF \_\_\_\_\_; detailed information on its characterization, manufacture, in-process controls, analytical procedures and their validation, and stability is included.

The release specifications include description, identification, loss on drying, residue on ignition, heavy metal, assay, related impurities, residual solvents and particle size. These specifications comply with the USP monograph for metformin hydrochloride. The drug substance specification differs from the USP monograph in (1) additional particle size criteria and (2) more stringent limits on impurities. The reference standard for metformin HCl is commercially available from USP.

Bulk metformin HCl, packed in \_\_\_\_\_, is stable long-term up to — years at room temperature (25 °C/60 % RH).

**Conclusion:** Drug substance information is acceptable.

**Drug Product:**

The drug product is a fixed dose combination tablet, composed of a fixed dose of sitagliptin and a variable dose of metformin hydrochloride, and is available as two strengths with the following description:

- The 50/500 tablets contain 50 mg sitagliptin free base /500 mg metformin HCl, are light pink film-coated, oblong (17.3 mm x 8.4 mm) biconvex tablets debossed "575" on one side, blank on the other, and weigh 706.2 mg.
- The 50/1000 tablets contain 50 mg sitagliptin free base /1000 mg metformin HCl, are red film-coated, oblong (21.2 mm x 10.3 mm) biconvex tablets debossed "577" on one side, blank on the other, and weigh 1333 mg.

Each film-coated tablet of Janumet™ contains the following inactive ingredients: microcrystalline cellulose \_\_\_\_\_, polyvinylpyrrolidone \_\_\_\_\_, sodium lauryl sulfate \_\_\_\_\_, and sodium stearyl fumarate \_\_\_\_\_. The film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and black iron oxide. All excipients, including film coating components, meet compendial requirements.

The manufacturing process includes

The specification for the drug product includes appearance, identification ( \_\_\_\_\_ ), assay, degradation products (individual unspecified and total degradation products), dissolution (both actives are measured in the same media by the same HPLC method), and uniformity of dosage units (mass and active content). The proposed regulatory methods have been validated. The drug product reference materials are the same as those used for sitagliptin phosphate monohydrate and metformin hydrochloride drug substances.

Stability data indicate that there are no significant changes in terms of appearance, assay, related compounds, dissolution, disintegration, hardness and moisture, when tablets are stored at either 25 °C/60 % RH or at 30 °C/65 % RH in \_\_\_\_\_ bottles with closure and in \_\_\_\_\_ blister packages. Photostability studies indicate that the tablets are stable when exposed to light.

Based on 12 months of stability data at either 25 °C/60 % RH or 30 °C/65 % RH for tablets packaged in \_\_\_\_\_ bottles and blister packages, and 6 months at 40 °C/75 % RH, the requested expiration dating period of \_\_\_\_\_ is acceptable under the proposed storage conditions: "Store at 20 – 25 °C (68 – 77 °F); excursion permitted to 15 – 30 °C (59 – 86 °F) [see USP Controlled Room Temperature]."

**Conclusion:** Drug product information is acceptable.

**Additional Items:**

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

The applicant agrees to place at least one batch of each strength annually in the post-approval stability program.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for **approval**, pending agreement on product labeling.

Blair A. Fraser, Ph.D.  
Director  
DPA I/ONDQA

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

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Blair Fraser  
3/4/2007 12:49:28 PM  
CHEMIST

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**NDA 22-044**

**Janumet™**  
(Sitagliptin Phosphate (+) Metformin Hydrochloride)  
Tablets

**Merck & CO., Inc.**

**Xavier Ysern, PhD**  
**CDER/OPS/ONDQA/DPA I**

**(NDA Clinical Review Division: DMEP)**



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## Chemistry Review Data Sheet

1. NDA: 22-044  
2. REVIEW #: 1  
3. REVIEW DATE: 22-FEB-2007  
4. REVIEWER: Xavier Ysern, PhD  
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 65,495 MK-0431 (Sitagliptin)	12-AUG-2002
NDA 21-995 MK-0431 (Sitagliptin)	16-DEC-2005 (approved 16-OCT-2006)
IND 70, 934 MK-0431A (Sitagliptin/Metformin HCl)	23-MAR-2005

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submissions Reviewed</u>	<u>Document Date</u>
Original: 31-MAY-2006	
Amendments: 24-JUL-2006 (Labeling)	
05-JAN-2007 (Additional Stability Data)	
05-FEB-2007 (Validation Summary Report)	
05-FEB-2007 (Labeling)	

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Merck & Co., Inc.  
Address: UG2CD-48  
PO Box 1000  
North Wales, PA 19454-1099  
Representative: Steven A. Aurecchia, MD Director, Regulatory Affairs  
Telephone: 267 305 6669

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Janumet™  
b) Non-Proprietary Name (USAN): Sitagliptin Phosphate (+) Metformin Hydrochloride fixed dose combination tablets  
c) Code Name/# (ONDC only): --  
d) Chem. Type/Submission Priority (ONDC only):  
• Chem. Type: 4 (New Combination)  
• Submission Priority: S (Standard Review, Substantially Equivalent)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of Type 2 Diabetes Mellitus  
Sitagliptin: dipeptidyl peptidase-4 (DPP-4) inhibitor

11. DOSAGE FORM: Tablet



# CHEMISTRY REVIEW



12. STRENGTH/POTENCY: 50/500 and 50/1000 mg/mg sitagliptin/metformin hydrochloride

13. ROUTE OF ADMINISTRATION: Oral

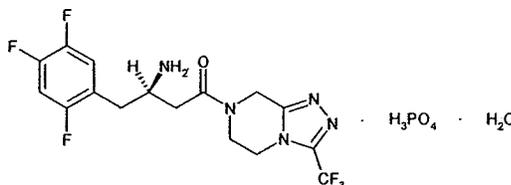
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

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

Sitagliptin Phosphate Monohydrate

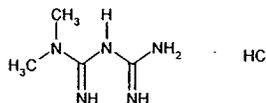
$C_{16}H_{15}F_6N_5O \cdot H_3O_4P \cdot H_2O$   
MW = 407.32 + 98.00 + 18.00 = 523.32  
CAS 654671-77-9



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

Metformin Hydrochloride

$C_4H_{11}N_5 \cdot HCl$   
MW = 129.17 + 36.46 = 165.63  
CAS 657-25-9 (base) 1115-70-4 (hydrochloride)  
*N,N*-Dimethylimidodicarbonimidic



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code <sup>1</sup>	Status <sup>2</sup>	Date Review	LOA	Comments
Type II			1	Adequate	07-APR-2005	10-DEC-2004	Reviewed by Mouna P. Selvam, HFD-625
Type III			4	N/A		26-OCT-2004	
			4	N/A		16-JUN-2005	
			4	N/A		29-OCT-2004	
			4	N/A		05-APR-2006	
			4	N/A		27-OCT-2004	
			4	N/A		20-JAN-2006	
			4	N/A		13-APR-2006	
			4	N/A		13-JUN-2003	
			4	N/A		04-APR-2006	
			4	N/A		23-MAR-2006	
			4	N/A		01-NOV-2004	
Type IV			1	Adequate	08-JAN-2007	24-FEB-2006	X. Ysern
			1	Adequate	08-JAN-2007	24-FEB-2006	X. Ysern

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I 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")

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



# CHEMISTRY REVIEW



## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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## 18. STATUS:

### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--		
EES	Acceptable	24-JAN-2007	S. Adams (HFD-322) EER Summary Report attached
Pharm/Tox	--		
Biopharm	--		
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories not recommended		This Review
OPDRA	--		
EA	Acceptable		This Review
Microbiology	N.A.		

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## The Chemistry Review for NDA 22-044

The Executive Summary

## I. Recommendations

## A. Recommendation and Conclusion on Approvability

From the CMC point of view this application can be APPROVED. Based on the submitted stability data, an expiry of \_\_\_\_\_ is granted under the recommended storage conditions: Store at 20-25 °C (68-77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

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

None.

## II. Summary of Chemistry Assessments

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

The drug product, Janumet™ Tablets is a combination product with two active components: sitagliptin and metformin. These two active components are hypoglycemic agents that differ in both chemical class and mode of action. Sitagliptin is a highly selective and potent inhibitor of the enzyme dipeptidyl peptidase 4 (DPP-4). Sitagliptin mechanism of action is well understood, DPP-4 inhibitors act by enhancing 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. Metformin belongs to the biguanide class. Biguanides act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Due to their complementary mechanisms of action, concurrent administration of sitagliptin (Januvia™ (sitagliptine) tablets) and metformin (Glucophage or generic metformin hydrochloride tablets) is prescribed. Janumet™ Tablets has been developed as an immediate release product containing a fixed dose of sitagliptin phosphate and a variable dose of metformin hydrochloride proposed to be commercialized in two dosage strengths different strengths: 50/500 and 50/1000 (mg/mg, Sitagliptin free base/Metformin Hydrochloride) immediate release film-coated tablets for oral administration. The combination drug product will facilitate patient compliance.

*Drug Substances*

Sitagliptin has \_\_\_\_\_ and it is synthesized as its phosphate salt monohydrate, sitagliptin phosphate monohydrated. 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. Sitagliptin phosphate monohydrate is a white to off-white solid, melting point \_\_\_\_\_ °C, pKa value of \_\_\_\_\_. According to the Biopharmaceutics classification system (BCS) sitagliptin is a Class III (high solubility, low permeability)/borderline Class I (high solubility, high permeability) drug. Sitagliptin phosphate monohydrate is the drug substance of Januvia™ Tablets, which is described and referred to approved NDA 21-995.

Metformin, a \_\_\_\_\_, is a \_\_\_\_\_, to metformin hydrochloride. Metformin hydrochloride is a white to off-white crystalline compound. The pKa of metformin is \_\_\_\_\_. Metformin is a class 3 (high solubility, low permeability) BCS drug. Metformin hydrochloride is the drug substance of approved metformin immediate and modified release tablet formulations, including generic versions, and also in combination with other active components. Metformin hydrochloride drug substance employed for Janumet™ Tablets is supplied by \_\_\_\_\_, as described in their approved DMF \_\_\_\_\_.



The two drug substances have the following in common: (1) both are synthesized as salts to improve their stability, (2) their quality is controlled by specifications which are consistent with their respective approved drug substances, sitagliptin phosphate monohydrate and metformin hydrochloride, (3) no evidence of polymorphism, and (4) high stability, showing almost no degradation at room temperature (storage condition) for its proposed retest conditions.

#### Drug Product

The drug product, Janumet™ (Sitagliptin Phosphate (+) Metformin Hydrochloride) Tablets, has been developed as an immediate release product containing a fixed dose of sitagliptin phosphate and a variable dose of metformin hydrochloride. Janumet™ Tablets are proposed to be commercialized in two dosage strengths: 50/500 and 50/1000 (mg/mg, Sitagliptin free base/Metformin Hydrochloride) immediate release film-coated tablets for oral administration. In addition to the two drug substances, sitagliptin phosphate in the form of monohydrate and metformin hydrochloride, each film-coated tablet of Janumet™ contains the following inactive ingredients: microcrystalline cellulose \_\_\_\_\_, polyvinylpyrrolidone \_\_\_\_\_, sodium lauryl sulfate \_\_\_\_\_, 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 black iron oxide. All excipients, including film coating components, meet compendial requirements.

Excipient selection throughout pharmaceutical development was initially guided by the experience knowledge gained from the MK-0431 development program (Januvia™ (sitagliptin) Tablets, Merck's approved NDA 21-995) and from the knowledge literature on commercial metformin tablets. Early formulations showed dissolution of the drug substances relatively slow when compared to the MK-0431 tablet. The addition of the disintegrant \_\_\_\_\_, used in the MK-0431 tablet formulation, did not significantly enhance the dissolution rate. Addition of a surfactant, sodium lauryl sulfate, significantly and favorably impacted \_\_\_\_\_. Sodium stearyl fumarate was selected due to \_\_\_\_\_ relative to similar formulations with magnesium stearate as the \_\_\_\_\_.

Through development the formulation and manufacturing process parameters were simultaneously optimized. The manufacturing process includes \_\_\_\_\_

Drug product specifications include appearance, identification (actives by \_\_\_\_\_), assay, degradation products (individual unspecified and total degradation products), dissolution (both actives are measured in the same media by the same \_\_\_\_\_ method), and uniformity of dosage units (mass and active content). Justification for the lack of testing for water content, microbial limits and hardness are fully justified by manufacturing process development. The two active components are very stable in the drug product formulation. The criteria of acceptance for any unspecified sitagliptin and metformin degradation products are no more than (NMT) \_\_\_\_\_% and NMT \_\_\_\_\_%, respectively. The total maximum amount of allowed degradation products is NMT \_\_\_\_\_% for either sitagliptin or metformin degradation products. The different strengths are distinguished by tablet size, color and marking.

The stability of the drug product has been inferred from the product characterization study (two lots, one of each strength) and from the formal stability study (six batches, three of each strength). Although the formal stability study is still ongoing, in both studies, 52 weeks stability data have been provided at 25 °C/60 % RH and 30 °C/65 % RH storage conditions, and up to 26 weeks for batches stored at 40 °C/75 % RH. Stability studies protocols include bracketing. Bracketing for the \_\_\_\_\_ bottle presentations included the worst-case (least protective) and best-case (most protective) conditions of bottle size and fill. Based on the provided stability information an expiry dating of \_\_\_\_\_ is granted under the proposed storage conditions: "Store at 20 - 25 °C (68 - 77 °F); excursions permitted to 15 - 30 °C (59 - 86 °F) [see USP Controlled Room Temperature]."

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

Janumet™ Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin. Two Janumet™ doses are available for oral administration as tablets: 50 mg sitagliptin/500 mg metformin hydrochloride and 50 mg sitagliptin/1000 mg metformin hydrochloride.

The dosage of antihyperglycemic therapy with Janumet™ Tablets should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin. Janumet™ should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin.

Janumet™ Tablets are supplied in bottles (50, 60, 180, and 1000 count) and blister packages (10 count per foil). Storage is at 20-25 °C (68-77 °F) [see USP Controlled Room Temperature]. The expiration dating period is —

**C. Basis for Approvability or Not-Approval Recommendation**

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by the expected compliance to their proposed specifications, to assure their quality throughout their granted shelf life. Based on the evaluation of the provided CMC information, from the chemistry viewpoint this NDA can be approved.

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

See appended electronic signature page.

**B. Endorsement Block**

Xavier Ysern, PhD/ ONDQA/ DPA I Reviewer  
Blair Fraser, PhD/ ONDQA/ DPA I Division Director

**C. CC Block**

Lina Aljubari, MS/DMEP/ Regulatory Project Manager

79 Page(s) Withheld

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 22044/000	Action Goal:	
Stamp:	31-MAY-2006	District Goal:	30-JAN-2007
Regulatory Due:	31-MAR-2007	Brand Name:	JANUMET (PHOSPHATE METFORMIN)
Applicant:	MERCK	Estab. Name:	MIN HCL FIXED DOSE
	1000	Generic Name:	SITAGLIPTIN
	NORTH WALES, PA 19454		PHOSPHATE/METFORMIN
N HCL			
Priority:	4S		TABS
Org Code:	510	Dosage Form:	(TABLET)
/MG		Strength:	50/500, 50/1000 M

Application Comment: DRUG NAME: SITAGLIPTIN PHOSPHATE/METFORMIN HCL  
 REFER TO NDA 21-995 FOR INFO ON SITAGLIPTIN. BOTH NDA 21-995 AND NDA 22-044 INITIALLY GOT "NME" DESIGNATION; THE FIRST ONE APPROVED KEEPS "NME" AND THE SECOND ONE APPROVED BECOMES TYPE 6 NDA. (on 20-JUN-2006 by S. TRAN ( ) 301-796-1764)

FDA Contacts:	L. ALJUBURI	301-796-1168	, Project Manager
	X. YSERN	301-796-2410	, Review Committee
	S. TRAN	301-796-1764	, Team Leader

Overall Recommendation: ACCEPTABLE on 24-JAN-2007 by S. ADAMS (HFD-322) 301-27-9051

Establishment: CFN 9613092

FEI

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DMF No: \_\_\_\_\_

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

File: CSN OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
SUBMITTED TO OC TRANS	20-JUN-2006				
SUBMITTED TO DO ADAMSS	20-JUN-2006	GMP			
ASSIGNED INSPECTION T ADAMSS	22-JUN-2006	GMP			
INSPECTION SCHEDULED IRIVERA	07-SEP-2006		09-NOV-2006		
INSPECTION PERFORMED S.DUNNI	09-NOV-2006		09-NOV-2006		JAM

The inspection of this active pharmaceutical ingredient (API) manufacturer was made in

response to a FACTS inspection request from HFD-322 regarding the manufacturing of

Metformin Hydrochloride, as well as a general GMP inspection of this facility.

The previous FDA inspection of this site was conducted on 06/03-07/2002 and was classified as VAI. That inspection was a pre-approval inspection for \_\_\_\_\_

\_\_\_\_\_ and Metformin Hydrochloride. That inspection disclosed six

objectionable conditions in the areas of Materials, Production, and the Laboratory

Control systems. The firm's management committed to follow-up and implement corrective

actions as soon as possible.

There was one objectionable condition noted during the current inspection and a F  
A-483

ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

was issued. The observation was that although the Metfomin Hydrochloride API has an expiry time of five years, effective 4/13/06, the firm had reduced the long term stability test duration from five years to three years.

Based upon the results of the inspection, the firm should remain acceptable for the manufacturing of Metformin Hydrochloride (API).

DO RECOMMENDATION 24-JAN-2007  
ADAMSS

ACCEPTABLE

ADEQUATE FIRM RESPONSE  
INSPECTION

OC RECOMMENDATION 24-JAN-2007  
ADAMSS

ACCEPTABLE

DISTRICT RECOMMENDATION

-----  
-----  
Establishment: CFN 1036761 FEI 1036761  
MERCK AND CO INC  
4633 MERCK RD W  
WILSON, NC 278939613

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER  
FINISHED DOSAGE PACKAGER

Profile: CTL OAI Status: NONE

EMilestone Name Date Type Insp. Date Decision & Reason C

erator

SUBMITTED TO OC 20-JUN-2006  
TRANS

RECOMMENDATION 20-JUN-2006  
B. IOJ

ACCEPTABLE DA

BASED ON PROFILE

Profile: TCM

OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	C
erator					

SUBMITTED TO OC 20-JUN-2006  
TRANS

OC RECOMMENDATION 20-JUN-2006  
BROGIOJ

ACCEPTABLE DA

BASED ON PROFILE

Establishment: CFN 2650235 FEI 1000131917

MERCK CO INC

RD 2 KM 60.3 BO SAB HOYO

ARECIBO, PR 00688

DMF No:

AADA:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: NONE

EMilestone Name eator	Date	Type	Insp. Date	Decision & Reason	C
SUBMITTED TO OC TRANS	20-JUN-2006				
OC RECOMMENDATION BROGIOJ	20-JUN-2006			ACCEPTABLE  BASED ON PROFILE	DA

Establishment: CFN 2623436 FEI 2623436  
 MERCK SHARP AND DOHME QUIMICA  
 RD 2, KM 56.7  
 BARCELONETA, PR 00617

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

EMilestone Name eator	Date	Type	Insp. Date	Decision & Reason	C
SUBMITTED TO OC TRANS	20-JUN-2006				
OC RECOMMENDATION BROGIOJ	20-JUN-2006			ACCEPTABLE  BASED ON PROFILE	DA

Establishment: CFN

FEI

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM

OAI Status: NONE

EMilestone Name eator	Date	Type	Insp. Date	Decision & Reason	C
SUBMITTED TO OC TRANS	20-JUN-2006				
SUBMITTED TO DO BROGIOJ	20-JUN-2006	10D			DA
INSPECTION SCHEDULED MSOSA	28-AUG-2006		25-SEP-2006		
PECTION PERFORMED OSA	28-SEP-2006		28-SEP-2006		
DO RECOMMENDATION MSOSA	07-DEC-2006			ACCEPTABLE	
OC RECOMMENDATION RGUSONS	07-DEC-2006			INSPECTION ACCEPTABLE	F
				DISTRICT RECOMMENDATION	

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this page is the manifestation of the electronic signature.**  
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/s/

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Xavier Ysern  
2/27/2007 03:29:38 PM  
CHEMIST

Blair Fraser  
2/28/2007 05:52:58 AM  
CHEMIST