

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201281Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 201281/000
Start Date: 19-JAN-2011
Regulatory: 30-JAN-2012

Action Goal:
District Goal: 01-DEC-2011

Applicant: BOEHRINGER PHARMS
900 RIDGEBURY RD
RIDGEFIELD, CT 06877

Brand Name: Linagliptin + Metformin Fixed Dose Combi
Estab. Name: Linagliptin + Metformin Fixed Dose Combination Tablets
Generic Name:

Priority: 4
Org. Code: 510

Product Number; Dosage Form; Ingredient; Strengths
001; TABLET; LINAGLIPTIN; 2.5MG
001; TABLET; METFORMIN HYDROCHLORIDE; 500MG
002; TABLET; LINAGLIPTIN; 2.5MG
002; TABLET; METFORMIN HYDROCHLORIDE; 850MG
003; TABLET; LINAGLIPTIN; 2.5MG
003; TABLET; METFORMIN HYDROCHLORIDE; 1000MG

Application Comment: PLEASE SEE BELOW FOR ESTABLISHMENT COMMENTS (on 21-JAN-2011 by K. SHARMA ())

FDA Contacts: K. SHARMA Project Manager
S. TRAN Team Leader 301-796-1764

Overall Recommendation:	ACCEPTABLE	on 20-DEC-2011	by D. SMITH	()
	WITHHOLD	on 15-NOV-2011	by D. SMITH	()
	WITHHOLD	on 22-AUG-2011	by EES_PROD	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: ALTERNATE SITE OF TESTING (RELEASE NAD STABILITY) FOR DRUG PRODUCT (on 21-JAN-2011 by K. SHARMA ())

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	25-JAN-2011				SHARMAKH
OC RECOMMENDATION	26-JAN-2011			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: ALTERNATE SITE FOR TESTING (RELEASE AND STABILITY FOR THE DRUG PRODUCT) (on 18-FEB-2011 by K. SHARMA ())
Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-FEB-2011				SHARMAKH
SUBMITTED TO DO	22-FEB-2011	Product Specific			TOULOUSEM
ASSIGNED INSPECTION TO IB	24-FEB-2011	Product Specific			PHILPYE
INSPECTION PERFORMED	[REDACTED] (b) (4)				JOSE.CRUZ
<p>Inspection of this contract control-testing facility was conducted as requested by HFC-130 (DFFI), under FACTS assignment # 6757605, to cover the chemical testing activities related to Linagliptin / Metformin HCl Tablets 2.5 mg / 500 mg, 2.5 mg / 850 mg, 2.5 mg / 1000 mg in connection with review of NDA # 201-281.</p> <p>This is the first time this contract testing facility is inspected by FDA. Current inspection disclosed no objectionable conditions and no FDA-483 was issued. Two verbal observations were discussed with firm's management. The verbal observations were as follows: personnel training procedures have no requirement for the analysts' GMP training on a continued (yearly) basis, and sample intermediate-storage room not mapped-studied under conditions representative of routine sample storage conditions.</p> <p>→ firm's management committed to provide continued GMP training to analysts and to qualify the sample storage area under loaded conditions.</p>					
INSPECTION SCHEDULED	[REDACTED] (b) (4)				IRIVERA
DO RECOMMENDATION	19-SEP-2011			ACCEPTABLE INSPECTION	STOCKM
OC RECOMMENDATION	20-SEP-2011			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9610492 FEI: 3002806556
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
BINGER STREET 173
INGELHEIM AM RHEIN, GERMANY

DMF No: **AADA:**

- Responsibilities:**
- DRUG SUBSTANCE LABELER
 - DRUG SUBSTANCE MANUFACTURER
 - DRUG SUBSTANCE PACKAGER
 - DRUG SUBSTANCE STABILITY TESTER
 - FINISHED DOSAGE LABELER
 - FINISHED DOSAGE MANUFACTURER
 - FINISHED DOSAGE PACKAGER
 - FINISHED DOSAGE RELEASE TESTER
 - FINISHED DOSAGE STABILITY TESTER

Establishment Comment: IN ADDITION, ALSO RESPONSIBLE FOR TESTING OF EXCIPIENTS AND METFORMIN (on 02-DEC-2011 by S. PATWARDHAN (HF-01) 301-796-4085)
ALL ASPECTS OF MANUFACTURING, PACKAGING, LABELING AND TESTING (RELEASE AND STABILITY) FOR DRUG PRODUCT (on 21-JAN-2011 by K. SHARMA ())
ALL ASPECTS OF THE MANUFACTURING (b) (4) PACKAGING, LABELING, QUALITY CONTROL OPERATIONS, AND STABILITY TESTING FOR DRUG SUBSTANCE LINAGLIPTIN (on 21-JAN-2011 by K. SHARMA ())
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

TABLETS, PROMPT RELEASE NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	25-JAN-2011				SHARMAKH
OC RECOMMENDATION	26-JAN-2011			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	25-JAN-2011				SHARMAKH
SUBMITTED TO DO	26-JAN-2011	10-Day Letter			INYARDA
DO RECOMMENDATION	31-JAN-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	02-FEB-2011			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
SUBMITTED TO DO	04-DEC-2011	10-Day Letter			STOCKM
DO RECOMMENDATION	20-DEC-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

OC RECOMMENDATION

20-DEC-2011

ACCEPTABLE

SMITHDE

DISTRICT RECOMMENDATION

January 25, 2012 2:37 PM

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**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 1510690 FEI: 1510690
BOEHRINGER INGELHEIM ROXANE INCORPORATED
1809 WILSON RD
COLUMBUS, OH 432289579

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Establishment Comment: ALTERNATE PACKAGING AND LABELING FOR THE DRUG PRODUCT (on 13-APR-2011 by K. SHARMA ())

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	25-JAN-2011				SHARMAKH
REQUEST CANCELLED	26-JAN-2011			IRRELEVANT FACILITY/PROFILE	SHARMAKH
SUBMITTED TO OC	13-APR-2011				SHARMAKH
OC RECOMMENDATION	13-APR-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] (b) (4)
FEI: [REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: ALSO RESPONSIBLE FOR TESTING OF EXCIPIENTS (on 02-DEC-2011 by S. PATWARDHAN (HF-01) 301-796-4085)
DRUG PRODUCT RELEASE AND STABILITY TESTER (on 13-APR-2011 by K. SHARMA ())

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	25-JAN-2011				SHARMAKH
REQUEST CANCELLED	26-JAN-2011			IRRELEVANT FACILITY/PROFILE	SHARMAKH
SUBMITTED TO OC	13-APR-2011				SHARMAKH
OC RECOMMENDATION	13-APR-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: STABILITY TESTING FOR DRUG SUBSTANCE METFORMIN HYDROCHLORIDE (on 21-JAN-2011 by K. SHARMA ())

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	25-JAN-2011				SHARMAKH
SUBMITTED TO DO NEW FIRM	26-JAN-2011	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	31-JAN-2011	Product Specific			PHILPYE
INSPECTION SCHEDULED	[REDACTED] (b) (4)				IRIVERA
UNDER REVIEW	21-SEP-2011				STOCKM
DO RECOMMENDATION	07-NOV-2011			ACCEPTABLE INSPECTION	STOCKM
OC RECOMMENDATION	15-NOV-2011			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4)

FEI: (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: STABILITY TESTING FOR DRUG SUBSTANCE METFORMIN HYDROCHLORIDE (on 25-JAN-2011 by K. SHARMA ())

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	25-JAN-2011				SHARMAKH
SUBMITTED TO DO NEW FIRM	26-JAN-2011	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	31-JAN-2011	Product Specific			PHILPYE
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
INSPECTION PERFORMED	(b) (4)		(b) (4)		DEMERSON
UNDER REVIEW	21-SEP-2011				STOCKM
DO RECOMMENDATION	03-NOV-2011			ACCEPTABLE INSPECTION	STOCKM
OC RECOMMENDATION	07-NOV-2011			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER

Establishment Comment: MANUFACTURING, PACKAGING AND LABELING FOR DRUG SUBSTANCE (METFORMIN HYDROCHLORIDE) (on 21-JAN-2011 by K. SHARMA ())
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	25-JAN-2011				SHARMAKH
SUBMITTED TO DO NEW FIRM	26-JAN-2011	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	31-JAN-2011	Product Specific			PHILPYE
INSPECTION SCHEDULED	[REDACTED] (b) (4)				IRIVERA
UNDER REVIEW	21-SEP-2011				STOCKM
DO RECOMMENDATION	24-OCT-2011			ACCEPTABLE INSPECTION	STOCKM
OC RECOMMENDATION	24-OCT-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	02-DEC-2011				PATWARDHAN
OC RECOMMENDATION	04-DEC-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

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/s/

NIKOO N MANOCHEHRI KALANTARI
02/06/2012

Memorandum to NDA 201,281 File

From: Sheldon Markofsky (Chemistry Reviewer)

Date: December 22, 2011

Subject:

Office of Manufacturing & Product Quality **Acceptable**

Recommendation for the Facilities of NDA 201,281

The Office of Manufacturing & Product Quality (OMPQ) has determined that the relevant facilities employed for the manufacture and testing of the drug substances and the drug product (Linagliptin and Metformin Hydrochloride Tablets) are **Acceptable**. Therefore, from both a Chemistry and OMPQ point of view, this NDA (201281) can be approved

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

/s/

SHELDON B MARKOFSKY
12/22/2011

ALI H AL HAKIM
12/22/2011

Memorandum to NDA 201,281 File

From: Sheldon Markofsky (Chemistry Reviewer)

Date: November 8, 2011

Subject:

Office of Compliance "Withhold" Recommendation for NDA 201,281

The office of Compliance has recommended a "**Withhold**" for the approval of the [REDACTED] ^{(b) (4)} which is used for testing metformin HCl and the excipients that are employed for the Drug Product (Linagliptin and Metformin HCl Tablets). The Office of Manufacturing and Product Quality (OMPQ) stated that the "withhold" recommendation will not change prior to the PDUFA goal date for NDA 201,281.

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

/s/

SHELDON B MARKOFSKY
11/08/2011
Compliance "Withhold" recommendation Memo

ALI H AL HAKIM
11/08/2011
CMC recommendation is CR due to the Withhold Recommendation issued by office of compliance.



NDA 201-281

Trade*
(Linagliptin and Metformin hydrochloride) Tablets
* Boehringer Ingelheim has not yet finalized (selected) a trade name.

Boehringer Ingelheim Pharmaceuticals, Inc

Sheldon Markofsky, Ph.D.

Division of Metabolism and Endocrine Products (HFD-510)

and

**Office of New Drug Quality Assessment III
Branch VII**

File: n201281Rev2a

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 201-281
2. REVIEW #: 2
3. REVIEW DATE: 23-Sept-2011
4. REVIEWER: Sheldon Markofsky, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original)	19-Jan-2011
Initial Quality/ CMC Assessment	01-March-2011
Amendment ^a	12-April-2011
Amendment ^b	27-April-2011
Chemistry Review # 1	06-June-2011
Information Request Letter	06-June-2011

- a) The 4-12-11 amendment provided up-dated container/closure and manufacturing and testing facility information.
- b) The 4-27-11 amendment provided up-dated information on in-use stability studies.

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment ^a	01-July-2011
Amendment ^b	26-Aug-2011

- a) The 7-1-11 amendment provides responses to our IR letter of 6-6-2011.
- b) The 8-26 amendment updated the specifications for the container/closure systems.

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
 900 Ridgebury Road
 Address: PO Box 368
 Ridgefield, CT 06877-0368

Representative: Dawn Collette, Associate Director, DRA
 Telephone: 203-798-4268

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Not yet determined
 b) Non-Proprietary Name: Linagliptin and Metformin Hydrochloride Tablets
 c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type:1
 - Submission Priority: S

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

(The reference listed drug is Glucophage (metformin HCl tablets))

10. PHARMACOL. CATEGORY: Treatment of type 2 diabetes mellitus

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY:

2.5/500, 2.5/850, 2.5/1000 mg (linagliptin/metformin HCl)

13. ROUTE OF ADMINISTRATION: Oral

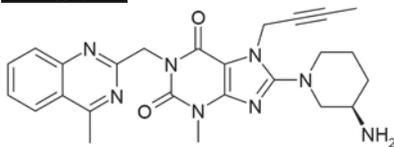
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Linagliptin

$C_{25}H_{28}N_8O_2$
472.54 g/mol.

INN: Linagliptin
 USAN: Linagliptin

Chemical names:

(Chemical Abstracts)

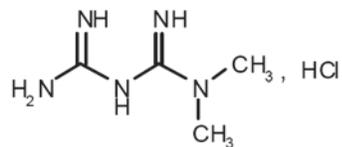
1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7- (2-butyn-1-yl)-3,7-dihydro-3 methyl-1-[(4-methyl-2- quinazoliny)methyl]-

(IUPAC) and (INN)

8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-yn-1-yl-3-methyl-1- [(4-methylquinazolin-2 yl)methyl]-3,7-dihydro-1H-purine- 2,6-dione

CAS Registry Number 668270-12-0
 Company Code Number BI 1356 BS

Metformin HCl



$C_4H_{11}N_5 \cdot HCl$
 165.62 g/mol

Chemical names:

Metformin Hydrochloride (INN and USAN names)

N,N-Dimethylimidodicarbonimidic diamide hydrochloride

N,N-Dimethylbiguanide hydrochloride

CAS Registry Number: 115-70-4

Deleted: 1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ₁	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	2-1-08 3-10-10	Reviewed by S. Markofsky & H.Khorshidi
	III			3	Adequate	9-15-00	Reviewed by Don Klein
	III			3	Adequate	3-24-10	Reviewed by R. Agarwal

Chemistry Review Data Sheet

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
PIND	105,055	PIND for Linagliptin/metformin HCl tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	WITHHOLD	8-22-11	
Pharm/Tox	Pending		David Carlson
Methods Validation	Acceptable	6-6-11	S. B. Markofsky
EA	Acceptable	6-6-11	S. B. Markofsky
Microbiology	N/A		
ONDQA Dissolution Review	Acceptable	9-19-11	Houda Mahayni

19. ORDER OF REVIEW: N/A (OGD Only)

The Executive Summary

The Chemistry Review for NDA 201-281

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved.

However, the Establishment Inspection work for the relevant manufacturing and testing facilities has not been completed: and one testing site has been given a WITHHOLD finding. Thus, the CMC recommendation for approval does not reflect any facility inspection issues.

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

None

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II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

1) Drug Product

The drug product, whose trade name has not yet been determined, consists of linagliptin / metformin hydrochloride immediate-release (film-coated) tablets. The combination of linagliptin, a dipeptidyl peptidase-4 inhibitor used to improve glycemic control, and metformin hydrochloride, an antihyperglycemic agent, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and metformin are appropriate. Linagliptin / metformin hydrochloride tablets are supplied in 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg strengths. The tablets of various strengths are oval, debossed on one side with the Boehringer Ingelheim company symbol, and on the other side with a symbol appropriate to its strength. The tablets are distinguished by a characteristic color as shown below.

Strength	Strength debossment symbol	Color	Oval Size
2.5 mg/500 mg,	D2/500	Light yellow	16 mm long
2.5 mg/850 mg,	D2/850	Light orange	19 mm long

2.5 mg/1000 mg, D2/1000	Light pink	21 mm long
-------------------------	------------	------------

The tablets are packaged in high density polyethylene (HDPE) bottles containing a desiccant and closed with plastic screw closures as summarized in the following table.

Bottle type	no. of film coated tablets	Bottle size	Intended use
14-count; (b) (4) induction foil seal	14	60 ml	physician samples only
60-count; (b) (4) induction foil seal	60	150 ml	one month' supply
180-count; (b) (4) induction foil seal	180	375 ml	three months' supply
2000-count; standard closure	2000	3750 ml	for mail order pharmacies

Adequate drug product specifications were provided for the Description of the dosage form, Identification of the active ingredients, (b) (4) and Uniformity of Dosage Units, Assay, Dissolution, and Degradation Products for both drug substances.

Besides linagliptin and metformin HCL, the drug product contains the following inactive ingredients: arginine, corn starch, copovidone, colloidal silicon dioxide, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, talc, yellow ferric oxide (2.5 mg/500 mg; 2.5 mg/850 mg tablets) and/or red ferric oxide (2.5 mg/850 mg; 2.5 mg/1000 mg tablets). All of the inactive ingredients are compendial.

2) Drug Substances

Linagliptin

Linagliptin is manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG in Germany. The firm (BI) referenced their approved NDA 201-280, (Linagliptin Tablets) for the CMC information related to the linagliptin drug substance. This information is captured in Chemistry Reviews 1 and 2 of NDA 201-280.

Linagliptin is a (b) (4) white to yellowish solid, (b) (4)

(b) (4) Boehringer Ingelheim classifies this drug substance as a Class III compound according to the Biopharmaceutical Classification System (BCS) because of its high solubility and low bioavailability. In this connection, linagliptin shows high BCS defined solubility (> 1 mg/ml) in aqueous media up to pH 8. Satisfactory stability data was provided to support a retest date of (b) (4) months for the drug substance for storage at 25°C/60 % R.H. Based on the Chemistry reviews of Boehringer Ingelheim's approved NDA 201-280 (Linagliptin Tablets), this drug substance (linagliptin) is adequate to support this NDA (201-281).

Metformin HCL

Metformin hydrochloride (USP) is manufactured by (b) (4). BI referenced DMF (b) (4) for the CMC information related to the metformin HCl drug substance, and based on the Chemistry reviews of this DMF, this drug substance (metformin HCl) is adequate to support this NDA (201-281).

Boehringer Ingelheim's specification and testing procedures also comply with the USP monograph for metformin HCl. In addition, tests are performed on certain (b) (4) to comply with the suppliers specification, described in DMF (b) (4) for this drug substance.

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

The individualized starting dose of the linagliptin / metformin hydrochloride tablets should be based on the patient's current regimen and be given twice daily with meals, with gradual dose escalation, as appropriate. The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. The stability studies support an expiration-dating period of 24 months for all strengths of the tablets when stored at room temperature [25°C (77°F)], with excursions permitted between 59 °F to 86°F (15°C to 30°C) packaged in all of the proposed commercial container closure systems. Consequently, a 24 month expiry is granted.

C. Basis for Approvability or Not-Approval Recommendation

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved, on the following basis:

- Adequate information was provided in the NDA for the synthesis, purification and controls of the drug substances
- Adequate manufacturing information to support the proposed to-be-marketed drug product
- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product
- Adequate stability package to support the recommended expiry period of the drug product

However, the Establishment Inspection work for the relevant manufacturing and testing facilities has not been completed: and one testing site has been given a WITHHOLD finding. Thus, the CMC recommendation for approval does not reflect any facility inspection issues.

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

III. Administrative

A. Reviewer's Signatures

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)

B. Endorsement Block (OGD only)

N/A

C. CC Block (OGD only)

N/A

(b) (4)

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/s/

SHELDON B MARKOFSKY
09/26/2011

ALI H AL HAKIM
09/26/2011

NDA 201-281

Trade*

(Linagliptin and Metformin hydrochloride) Tablets

* Boehringer Ingelheim has not yet finalized (selected) a trade name.

Boehringer Ingelheim Pharmaceuticals, Inc

Sheldon Markofsky, Ph.D.

Division of Metabolism and Endocrine Products (HFD-510)

and

**Office of New Drug Quality Assessment III
Branch VII**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 201-281
2. REVIEW #: 1
3. REVIEW DATE: 13-June-2011
4. REVIEWER: Sheldon Markofsky, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original)	19-Jan-2011
Initial Quality/ CMC Assessment	01-March-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA Original	19-Jan-2011
Amendment ^a	12-April-2011
Amendment ^b	27-April-2011

a) The 4-12-11 amendment provides up-dated container/closure and manufacturing and testing facility information.

b) The 4-27-11 amendment provides up-dated information on in-use stability studies.

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
 900 Ridgebury Road
 Address: PO Box 368
 Ridgefield, CT 06877-0368

Representative: Dawn Collette, Associate Director, DRA

Telephone: 203-798-4268

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Not yet determined
- b) Non-Proprietary Name: Linagliptin and Metformin Hydrochloride Tablets
- c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type:1
- Submission Priority: S

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

(The reference listed drug is Glucophage (metformin HCl tablets))

10. **PHARMACOL. CATEGORY:** Treatment of type 2 diabetes mellitus

11. **DOSAGE FORM:** Tablets

12. **STRENGTH/POTENCY:**

2.5/500, 2.5/850, 2.5/1000 mg (linagliptin/metformin HCl)

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** Rx OTC

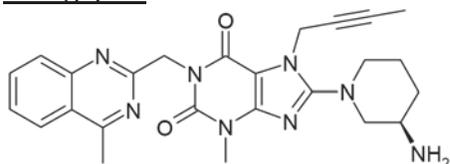
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

SPOTS product – Form Completed

Not a SPOTS product

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

Linagliptin



$C_{25}H_{28}N_8O_2$
472.54 g/mol.

INN: Linagliptin

USAN: Linagliptin

Chemical names:

(Chemical Abstracts)

1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7- (2-butyn-1-yl)-3,7-dihydro-3 methyl-1-[(4-methyl-2- quinazoliny)methyl]-

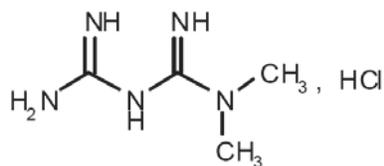
(IUPAC) and (INN)

8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-yn-1-yl-3-methyl-1- [(4-methylquinazolin-2 yl)methyl]-3,7-dihydro-1H-purine- 2,6-dione

CAS Registry Number 668270-12-0

Company Code Number BI 1356 BS

Metformin HCl



$C_4H_{11}N_5 \cdot HCl$

165.62 g/mol

Chemical names:

Metformin Hydrochloride (INN and USAN names)

N,N-Dimethylimidodicarbonimidic diamide hydrochloride

N,N-Dimethylbiguanide hydrochloride

CAS Registry Number: 115-70-4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	2-1-08 3-10-10	Reviewed by S. Markofsky & H.Khorshidi
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	9-15-00	Reviewed by Don Klein
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	3-24-10	Reviewed by R. Agarwal

Chemistry Review Data Sheet

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
PIND	105,055	PIND for Linagliptin/metformin HCl tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Pending		David Carlson
Methods Validation	Acceptable	6-13-11	S. B. Markofsky
EA	Acceptable	6-13-11	S. B. Markofsky
Microbiology	N/A		
ONDQA Dissolution Review	Pending		Houda Mahayni

19. ORDER OF REVIEW: N/A (OGD Only)

The Executive Summary

The Chemistry Review for NDA 201-281

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved, pending acceptable responses to our information Requests that will be sent to the applicant.

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 Substances

1) Drug Product

The drug product, whose trade name has not yet been determined, consists of linagliptin / metformin hydrochloride immediate –release (film-coated) tablets. The combination of linagliptin, a dipeptidyl peptidase-4 inhibitor used to improve glycemic control, and metformin hydrochloride, an antihyperglycemic agent, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and metformin are appropriate. Linagliptin / metformin hydrochloride tablets are supplied in 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg strengths. The tablets of various strengths are oval, debossed on one side with the Boehringer Ingelheim company symbol, and on the other side with a symbol appropriate to its strength. The tablets are distinguished by a characteristic color as shown below.

Strength	Strength debossment symbol	Color
2.5 mg/500 mg,	D2/500	Light yellow
2.5 mg/850 mg,	D2/850	Light orange
2.5 mg/1000 mg,	D2/1000	Light pink

The tablets are packaged in high density polyethylene (HDPE) bottles containing a desiccant and closed with plastic screw closures as summarized in the following table.

Bottle type	no. of film coated tablets	Bottle size	Intended use
14-count; [REDACTED] (b) (4) induction foil seal	14	60 ml	physician samples only
60-count; [REDACTED] (b) (4) induction foil seal	60	150 ml	one month' supply
180-count; [REDACTED] (b) (4) induction foil seal	180	375 ml	three months' supply
2000-count; standard closure	2000	3750 ml	for mail order pharmacies

Adequate drug product specifications were provided for the Description of the dosage form, Identification of the active ingredients, [REDACTED] (b) (4) and Uniformity of Dosage Units, Assay, and Degradation Products for both drug substances. However, the dissolution specifications for both drug substances in the tablets are still being negotiated.

Besides linagliptin and metformin HCL, the drug product contains the following inactive ingredients: arginine, corn starch, copovidone, colloidal silicon dioxide, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, talc, yellow ferric oxide (2.5 mg/500 mg; 2.5 mg/850 mg tablets) and/or red ferric oxide (2.5 mg/850 mg; 2.5 mg/1000 mg tablets). All of the inactive ingredients are compendial.

2) Drug Substances

Linagliptin

Linagliptin is manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG in Germany. The firm (BI) referenced their approved NDA 201-280, (Linagliptin Tablets) for the CMC information related to the linagliptin drug substance. This information is captured in Chemistry Reviews 1 and 2 of NDA 201-280.

Linagliptin is a [REDACTED] (b) (4) white to yellowish solid, [REDACTED] (b) (4)

[REDACTED] Boehringer Ingelheim classifies this drug substance as a Class III compound according to the Biopharmaceutical Classification System (BCS)

because of its high solubility and low bioavailability. In this connection, linagliptin shows high BCS defined solubility (> 1 mg/ml) in aqueous media up to pH 8. Satisfactory stability data was provided to support a retest date of (b) (4) months for the drug substance for storage at 25°C/60 % R.H. Based on the Chemistry reviews of Boehringer Ingelheim's approved NDA 201-280 (Linagliptin Tablets), this drug substance (linagliptin) is adequate to support this NDA (201-281).

Metformin HCL

Metformin hydrochloride (USP) is manufactured by (b) (4) BI referenced DMF (b) (4) for the CMC information related to the metformin HCl drug substance, and based on the chemistry reviews of this DMF, this drug substance (metformin HCl) is adequate to support this NDA (201-281).

Boehringer Ingelheim's specification and testing procedures also comply with the USP monograph for metformin HCl. In addition, tests are performed on certain (b) (4) to comply with the suppliers specification, described in DMF (b) (4) for this drug substance.

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

The individualized starting dose of the linagliptin / metformin hydrochloride tablets should be based on the patient's current regimen and be given twice daily with meals, with gradual dose escalation, as appropriate. The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. The stability studies support an expiration-dating period of 24 months for all strengths of the tablets when stored at room temperature [25°C (77°F)], with excursions permitted between 59 °F to 86°F (15°C to 30°C) packaged in all of the proposed commercial container closure systems. Consequently, a 24 month expiry is granted.

C. Basis for Approvability or Not-Approval Recommendation

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved, pending acceptable responses to our Information Requests that will be sent to the applicant. We anticipate that the outstanding CMC issues can be readily resolved.

III. Administrative

A. Reviewer's Signatures

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)

B. Endorsement Block (OGD only)

N/A

C. CC Block (OGD only)

N/A

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immediately following this page

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/s/

SHELDON B MARKOFSKY
06/15/2011

ALI H AL HAKIM
06/15/2011

ONDQA
IQA (Initial Quality/CMC Assessment)

Division of Metabolism and Endocrinology Products

NDA: 201281

Applicant: Boehringer Ingelheim Pharmaceuticals Inc.

Stamp Date: 19-JAN-2011

PDUFA Date: 19-NOV-2011

Proposed Proprietary Name: [none indicated]

Established Name: Linagliptin/metformin hydrochloride

Dosage form and strength: Tablet: immediate release
2.5/500, 2.5/850, 2.5/1000
(mg/mg linagliptin/
metformin hydrochloride)

Route of Administration: oral

Indications: Type 2 diabetes

CMC Lead: Su (Suong) Tran, ONDQA

ONDQA Fileability: Yes

ONDQA
 IQA (Initial Quality/CMC Assessment)

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	The ONDQA Biopharmaceutics Review Staff will review all dissolution-related information.
CDRH or CBER	<i>Not Applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
EES	EER was sent to Compliance on 25-JAN-2011 by ONDQA PM.
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>Not Applicable: This is not a sterile product.</i>
Pharm/Tox	Evaluation of the genotoxicity potential of identified impurities and degradants.
Quality by Design	<i>No design space is proposed (amendment dated 28-JAN-2011)</i>

This is an electronic NDA, filed as a 505(b)(2) application, with the reference listed drug being metformin HCl of Bristol-Myers Squibb. The supporting IND is IND 105055.

Reference is made to the pending NDA 201280 (linagliptin) by the same applicant for all CMC information on the drug substance linagliptin. Linagliptin is currently a New Molecular Entity (NME) and a small synthetic compound. It is xanthine-derived and an inhibitor of the dipeptidyl peptidase-4 enzyme. Reference is made to the DMF [REDACTED] (b)(4) all CMC information on the metformin HCl drug substance.

The drug product is an immediate release tablet, 2.5/500, 2.5/850, 2.5/1000 (mg/mg linagliptin/metformin hydrochloride) containing these excipients: arginine, corn starch, copovidone, colloidal silicon dioxide, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, talc, yellow ferric oxide (2.5 mg/500 mg; 2.5 mg/850 mg) and/or red ferric oxide (2.5 mg/850 mg; 2.5 mg/1000 mg).

The product will be packaged in bottles with desiccants, and will be stored at room temperature.

Maximum daily dose is 5 mg linagliptin and 2000 mg metformin HCl.

Has all information requested during the IND phases, and at the pre-NDA meetings been included?
 Yes. See the Quality Overall Summary.

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Drug substance:

Linagliptin

Linagliptin (INN) is a xanthine derivative with the chemical abstracts name 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidiny]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazoliny)methyl]. The molecular formula is $C_{25}H_{28}N_8O_2$ and the molecular mass is 472.54 g/mol. Linagliptin is a free base (b) (4)

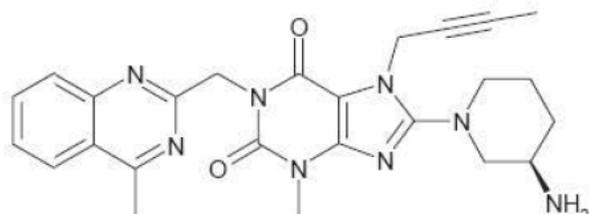


Figure 1 Molecular structure of linagliptin

Linagliptin is a white to yellowish solid substance with high solubility in aqueous media over the entire physiological pH range (> 1 mg/ml up to pH 8.0). In water a solubility of 0.9 mg/ml was determined; the resulting solution is slightly basic with an intrinsic pH of 9.4.

Linagliptin drug substance manufactured according to the proposed manufacturing process (b) (4)

(b) (4)

Physical appearance:	white to yellowish solid substance. (b) (4)
Melting temperature:	(b) (4)
Specific optical rotation $[\alpha]_D^{20}$:	(b) (4)
Dissociation constants:	pKa ₁ = 8.6 (primary amino group) pKa ₂ = 1.9 (quinazoline moiety)
Partition coefficient:	Log P = 1.7 (free base) Log D (pH 7.4) = 0.4
Hygroscopicity:	The solid drug substance is not or only slightly hygroscopic. (b) (4)
pH solubility profile:	Linagliptin shows high solubility (> 1 mg/ml) in aqueous media up to pH 8.0. The solubility in water is 0.9 mg/ml.
Solubility in organic solvents:	
methanol:	soluble
ethanol:	sparingly soluble
isopropanol:	very slightly soluble
acetone:	very slightly soluble

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Metformin hydrochloride

Metformin hydrochloride (Metformin HCl; 1,1-Dimethylbiguanide hydrochloride) is a widely used antidiabetic drug. It has been monographed in all major pharmacopeias, *e.g.*, USP, Ph. Eur. and JP.

The structural formula is given in [Figure 3](#):

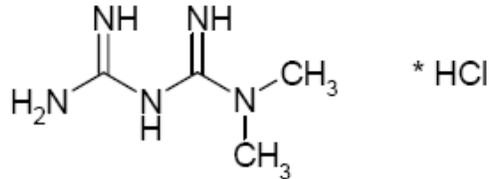


Figure 3 Molecular structure of metformin hydrochloride

The molecular weight of the hydrochloride is 165.62, and the formula is $C_4H_{11}N_5 \cdot HCl$.

Review comments:

- Reference is made to the pending NDA 201280 (linagliptin) by the same applicant for all CMC information on the drug substance linagliptin.
- Reference is made to the DMF (b) (4) all CMC information on the metformin HCl drug substance. The primary reviewer will evaluate any new information in the DMF submitted since the most recent review.

Drug product

Review comments: Composition is copied on the next page.

Linagliptin / metformin hydrochloride is presented as immediate release oval film coated tablets without breaking score. Three strengths have been developed, and they are differentiated by size, color of the film coating and by debossing:

- Linagliptin / metformin hydrochloride film coated tablets, 2.5 mg/500 mg, are oval, light yellow, one side debossed with the Boehringer Ingelheim company symbol, the other side debossed with 'D2/500'.
 - Linagliptin / metformin hydrochloride film coated tablets, 2.5 mg/850 mg, are oval, light orange, one side debossed with the Boehringer Ingelheim company symbol, the other side debossed with 'D2/850'.
 - Linagliptin / metformin hydrochloride film coated tablets, 2.5 mg/1000 mg, are oval, light pink, one side debossed with the Boehringer Ingelheim company symbol, the other side debossed with 'D2/1000'.
- **Established name and dosage strength.** The proposed established names of the product are "linagliptin" and "metformin hydrochloride", which are acceptable because they correlate with the dosage strengths as per current CDER policy on nomenclature.
 - **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The pivotal Bioequivalence (BE) studies 1288.1, 1288.2, and 1288.3 were conducted to demonstrate bioequivalence between the FDC tablets and the co-administered linagliptin and metformin hydrochloride. The metformin hydrochloride comparator was the EU Glucophage. An additional BE study (1218.57) was conducted to bridge the EU Glucophage to the US Glucophage (RLD). The FDC biobatches had the commercial formulation and were manufactured at the commercial manufacturing site, at full commercial scale using the commercial process. These batches are: 902832 for the 2.5/500 strength, 902831 for the 2.5/850 strength and 903235 for the 2.5/1000 strength. The primary stability batches consist of 3 batches of each of the dosage strengths and includes the biobatches.
 - **Excipients.** The reviewer will evaluate the control of (b)(4) in excipients because these residues interact with linagliptin resulting in specific degradants (see comments in Degradation Products).

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Table 3 Qualitative and quantitative composition of linagliptin / metformin hydrochloride film coated tablets

Ingredient	Function	linagliptin / metformin hydrochloride		
		2.5 mg / 500 mg [mg/ tablet]	2.5 mg / 850 mg [mg/ tablet]	2.5 mg / 1000 mg [mg/ tablet]
Linagliptin	Active ingredient	2.500	2.500	2.500
Metformin hydrochloride	Active ingredient	500.000	850.000	1000.000
Arginine	(b) (4)			
Corn starch				
Copovidone				
Colloidal silicon dioxide				
Magnesium stearate (b) (4)				
Titanium dioxide				
Yellow ferric oxide				
Red ferric oxide				
Propylene glycol				
Hypromellose (b) (4)				
Talc (b) (4)				
	Total weight (film coated tablet)	602.0	1016.0	1198.0

(b) (4)

ONDQA
IQA (Initial Quality/CMC Assessment)

Manufacturing process of the drug product

Linagliptin / metformin hydrochloride film coated tablets are manufactured using the following (b) (4) major unit operation steps:



The robustness of the manufacturing process has been demonstrated by numerous investigations on the influence of the operating parameters. They included



Commercial batch sizes are copied below:

Table 7 Approximate yields for (b) (4) batch size

Dosage strength	Approximate yield ((b) (4) and number of film coated tablets)
2.5 mg/500 mg	(b) (4)
2.5 mg/850 mg	(b) (4)
2.5 mg/1000 mg	(b) (4)

Review comments: Master batch records are included per 505(b)(2) requirements. The NDA includes reports of controlled experiments in support of the target operating values and ranges copied

ONDQA
IQA (Initial Quality/CMC Assessment)

below. The applicant stated in the 28-JAN-2011 amendment that no design space is proposed for this NDA.

Table 5 Resulting ranges in the manufacturing process

(b) (4)



Drug product specification

The drug product specification is copied on page 18 of this review.

Review comments:

- **Dissolution.** Dissolution information will be evaluated by the ONDQA Biopharm team.

(b) (4)



- **Uniformity of dosage units.** Content of uniformity of linagliptin is performed by RP-HPLC. Mass variation of metformin HCl is performed by weighing, as is done in other approved applications with the same dosage strengths.
- **Assay of arginine.** This is performed by HPLC with a proposed limit (b) (4) The reviewer will evaluate all available information (Pharmaceutical Development and Stability) to assess the adequacy of this proposed range. This excipient is a (b) (4) (b) (4)
- **Omitted tests.** The reviewer will evaluate all available information to assess the lack of the following in the drug product specification (the CMC reviews of NDA 201280 Linagliptin may be referenced for this same issues):

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Container closure systems for product distribution

Table 10 Summary of the container-closure-system

Bottle type	no. of film coated tablets	Bottle size	Intended use
14-count; (b) (4) induction foil seal	14	60 ml	physician samples only
60-count; (b) (4) induction foil seal	60	150 ml	one month' supply
180-count; (b) (4) induction foil seal	180	375 ml	three months' supply
2000-count; standard closure	2000	3750 ml	for mail order pharmacies

All parts of the container closure system comply with CFR requirements.

Review comment:

- The Pharmaceutical Development information includes the (b) (4)
[redacted]
- Moisture sensitivity. Water vapor transmission testing was conducted on the bottle system per USP <671>. In addition, the bottle system includes a desiccant to ensure adequate stability during the long term storage and in-use storage. The reviewer will make sure that adequate text appears in the labeling to indicate that the product is moisture-sensitive and that the desiccant should not be discarded from the bottle packaging during the patient's in-use storage period.
- The primary reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for solid oral drug products. Letters of authorization are provided for the following DMFs:

[redacted] (b) (4)

ONDQA
IQA (Initial Quality/CMC Assessment)

Stability of the drug product

Overview of stability studies

Boehringer Ingelheim provides results of long-term and accelerated stability studies as well as of in-use studies to cover the stability after opening the HDPE bottle (primary packaging). Stress stability data (light, humidity, heat) are also reported.

For the long-term and accelerated stability studies, a bracketing approach has been agreed upon with FDA in April 2009. It takes into consideration that a stability assessment shall be made for three dosage strengths and different bottle sizes (14 count, 60 count, 180 count) and allows reduction of the number of stability batches for the intermediate (2.5 mg/850 mg) strength and for the intermediate (60 count) bottle size. The stability studies follow that

agreement. The same bracketing approach has also been applied to a 2000 count bottle with respect to the dosage strength. Thus, a total of seven batches has been investigated.

All stability batches were full scale batches, manufactured with the commercial equipment at the commercial manufacturing site.

Review comments:

Stability data in the NDA include 12-month long-term and 6-month accelerated for the primary batches packaged in the commercial container closure systems. The bracketing design was previously reviewed in a CMC SPA. A sufficient amount of stability data is submitted for filing purposes. The reviewer will determine the final expiry based on all available data and per ICH stability guidelines.

Regulatory Briefing: Branch-level
per section 5.3 of IQP 5401 (copied below).

- 5.4 Branch-Level Briefings: ONDQA Regulatory Briefings that involve routine participation by reviewers and managers within a single branch. These briefings can be held to discuss NDAs that involve new formulations or new routes of administration, when the drug substance is already approved and there are no unique regulatory or scientific issues.

ONDQA
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GMP facilities: EER was sent to Compliance on 25-JAN-2011 by ONDQA PM.

Drug Substance – Linagliptin	
Establishment and Registration Number	Activity
<p>Boehringer Ingelheim Pharma GmbH & Co. KG Binger Strasse 173 55216 Ingelheim am Rhein GERMANY FEI Number: 3002806556 D-U-N-S® Number: 551147440</p> <p><u>Contact:</u> Dr. Antje Noerenberg Quality/Audit and Inspections Boehringer Ingelheim Pharma GmbH & Co.KG Telephone: +496132-778841 Facsimile: +496132-1758841 E-mail: antje.noerenberg@boehringer-ingelheim.com</p>	<p>All aspects of the manufacturing [REDACTED] ^{(b)(4)} packaging, labeling, quality control operations, and stability testing.</p>

1 pages has been withheld in full as B(4) CCI/TS immediately following this page

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Drug Product – Linagliptin / Metformin Hydrochloride Film-coated Tablets	
Establishment and Registration Number	Activity
<p>Boehringer Ingelheim Pharma GmbH & Co. KG Binger Strasse 173 55216 Ingelheim / Rhein GERMANY FEI Number: 3002806556 D-U-N-S® Number: 551147440</p> <p><u>Contact:</u> Dr. Harald Scheidecker Quality/SQA/ Audits Boehringer Ingelheim Pharma GmbH & Co.KG Telephone: +496132-772740 Facsimile: +496132-1752740 E-mail: harald.scheidecker@boehringer-ingelheim.com</p>	<p>All aspects of manufacturing, packaging, labeling and testing (release and stability)</p>

(b) (4)

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DRUG SUBSTANCE SPECIFICATION

Table 2 Specification and analytical procedures for linagliptin drug substance

Test Parameter	Acceptance Criterion	Analytical Procedure
Appearance	White to yellowish solid substance (white to yellowish powder)	Visual test
Identification		

(b) (4)



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The drug substance metformin HCl specification is the same as the USP monograph.

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DRUG PRODUCT SPECIFICATION

Table 8 Proposed Specifications

Parameter	Specification	Method(s)
Appearance	<p><u>2.5 mg/500 mg:</u> Light yellow, oval, biconvex film coated tablets, one side debossed with the company symbol and the other side debossed with "D2/500"</p> <p><u>2.5 mg/850 mg:</u> Light orange, oval, biconvex film coated tablets, one side debossed with the company symbol and the other side debossed with "D2/850"</p> <p><u>2.5 mg/1000 mg:</u> Light pink, oval, biconvex film coated tablets, one side debossed with the company symbol and the other side debossed with "D2/1000"</p>	visual
(b) (4)	(b) (4)	
Dissolution:		
linagliptin		
metformin hydrochloride		
Identification of linagliptin		
Identification of metformin hydrochloride		

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Parameter	Specification	Method(s)
Degradation of linagliptin		(b) (4)
Degradation of metformin hydrochloride		(b) (4)
Assay of linagliptin		(b) (4)
Assay of metformin hydrochloride		(b) (4)
Assay of arginine		(b) (4)
Uniformity of dosage units: Content uniformity of linagliptin		(b) (4)
Mass variation of metformin hydrochloride		(b) (4)

ONDQA
 IQA (Initial Quality/CMC Assessment)

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 201281	Established/Proper Name: Linagliptin/metformin hydrochloride
Applicant: Boehringer Ingelheim Pharmaceuticals Inc.	Stamp Date: 19-JAN-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

ONDQA
 IQA (Initial Quality/CMC Assessment)

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESSMENT				
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

ONDQA
 IQA (Initial Quality/CMC Assessment)

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?			See Biopharm filing memo
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		Review issue: whether data and analysis are adequate to support expiry
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	No design space being proposed.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		
G. microbiology				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Non-sterile solid oral dosage form.
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

Su (Suong) Tran
 CMC Lead, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}
 Ali Al Hakim
 Branch Chief, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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

/s/

SUONG T TRAN
03/01/2011

ALI H AL HAKIM
03/01/2011