CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208026Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
Approval

NDA 208026
Review #1
Review Date (see page 5)

Drug Name/Dosage Form	linagliptin and metformin hydrochloride extended release tablet
Strength	5 mg/1000 mg and 2.5 mg/1000 mg linagliptin/metformin hydrochloride
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Boehringer Ingelheim

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	7/27/2015
0003	8/6/2015
0008	1/27/2016
0009	2/17/2016
0010	3/11/2016
0013	4/6/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Product	Muthukumar Ramaswamy	New Drug Products II/ONDP
Biopharmaceutics	Mei Ou	Biopharmaceutics/ONDP
Process	Shujun Chen	Process Assessment II/OPF
Microbiology	Shujun Chen	Process Assessment II/OPF
Facility	Vipulchandra Dholakia	Inspectional Assessment/OPF

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	Currently adequate to support the approved NDA 201281 (linagliptin/metformin HCl, by the same applicant; reference is provided)		
	III			by M.Ramaswamy/D. Christodoulou Per MAPP "CMC Reviews of Type III DMFs for Packaging Materials" the referenced Type III DMFs need not be reviewed for solid dosage forms.		
	III					
	III					
	IV					

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21748	Glumetza(metformin HCl) Authorized reference from applicant (Salix)
NDA	201280	Tradjenta (linagliptin) Same applicant
NDA	201281	Jentaduo ((linagliptin/metformin HCl) Same applicant

2. CONSULTS: not applicable

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (including the Overall Manufacturing Inspection Recommendation) is for **APPROVAL**.

Labeling comments will be finalized during the multi-disciplinary review managed by OND.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

B. Recommendation on Post-Marketing Commitments, Agreements, and/or Risk Management Steps- not applicable

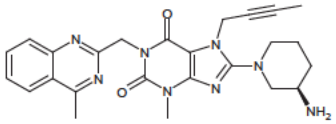
II. Summary of Quality Assessment

This is a 505(b)(1) application but not for an New Molecular Entity. The applicant has approved NDAs for the active ingredient linagliptin and full right of reference to the approved NDA for the active ingredient metformin HCl.

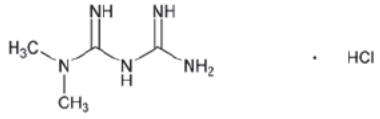
A. Drug Substance

Chemical Name or IUPAC Name/Structure:

Linagliptin is described chemically as 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-quinazolinyl)methyl]-, the empirical formula is C25H28N8O2 and the molecular weight is 472.54 g/mol. The structural formula is:



Metformin hydrochloride is N,N-dimethylimidodicarbonimidic diamide hydrochloride, with a molecular formula of C4H11N5•HCl and a molecular weight of 165.63. The structural formula is:



NDA 201280 Tradjenta (linagliptin), by the same applicant, is referenced for all CMC information on the drug substance linagliptin. The NDA is currently approved and the reference is adequate.

NDA 201281 Jentaduo ((linagliptin/metformin HCl), by the same applicant, is referenced for all CMC information on the drug substance metformin HCl. The NDA is currently approved and the reference is adequate.

B. Drug Product

The product is a film-coated tablet consist of immediate release saxagliptin and extended release metformin HCl, with two strengths: 5 mg/1000 mg and 2.5 mg/1000 mg linagliptin (immediate release)/metformin hydrochloride (extended release). (b) (4) . Polyethylene oxide is (b) (4)

2.5 mg/1000 mg - yellow oval tablet printed on one side in black ink with the BI logo and "D2" on the top line and "1000M" on the bottom line.
5mg/1000 mg - white oval tablet printed on one side in black ink with the BI logo and "D5" on the top line and "1000M" on the bottom line.

Excipients are
[Tablet core] polyethylene oxide, hypromellose, and magnesium stearate (b) (4).
[Coatings] hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, arginine, polyethylene glycol, ferric oxide yellow (2.5 mg/1000 mg), carnauba wax, ferrosoferric oxide, propylene glycol, and isopropyl alcohol.

The product manufacturing process (b) (4)

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form. It includes content for Arginine, (b) (4)

Container Closure: HDPE bottles with desiccant (b) (4)

Expiration Date & Storage Conditions: 24 months at room temperature

C. Summary of Drug Product Intended Use

Proprietary Name	[not finalized by GRMP goal; see CDTL's memo]
Non Proprietary Name of the Drug Product	linagliptin and metformin hydrochloride extended

	release tablet
Non Proprietary Name of the Drug Substance	linagliptin and metformin hydrochloride
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	chronic
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	not applicable

D. Biopharmaceutics Considerations

Three pivotal bioquivalence studies were conducted to compare the three dosage strengths to the co-administered single-entity products (details of these studies are found in the Clinical Pharmacology review). With the exception of printing ink (b) (4), the formulation is the same for the clinical batches, stability batches, and commercial product.

1. BCS Classification:
   - Drug Substance: Both of Linagliptin and Metformin HCl are considered as BCS III compounds (high solubility, low permeability)
   - Drug Product: BCS III

   Note: In Module 2.3.P and Module 3.2.P.2, the Applicant indicated that "Linagliptin is considered a Class III compound (high solubility, low permeability) according to the Biopharmaceutical Classification System (BCS)", "Metformin HCl is also considered a Class III compound (high solubility, low permeability) according to the Biopharmaceutical Classification System (BCS)".

2. Biowaivers/Biostudies
   - Biowaiver Requests: No Biowaiver request
   - PK studies: One BA study (study# 1288.8) and two BE studies (study# 1288.9 for 5mg/1000mg and study# 1288.11 for 2.5mg/1000mg) were submitted and reviewed by the Office of Clinical Pharmacology (OCP)
   - IVIVC: No IVIVC

E. Novel Approaches: not applicable

F. Any Special Product Quality Labeling Recommendations: not applicable

G. Life Cycle Knowledge Information (see Attachment)

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature: I concur with the reviewers' conclusions.

Suong T. Tran -S

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Date: 2016.04.18 10:18:54 -04'00'

Su (Suong) Tran, PhD

QUALITY ASSESSMENT

Reviewer's Assessment and Signature: Adequate

04/14/16
Muthukumar Ramaswamy, Ph.D.
Office of New Drug Products

Muthukumar Ramaswamy -S

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Date: 2016.04.14 20:42:27 -04'00'

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

Danae D. Christodoulou -S

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Date: 2016.04.15 08:21:03 -04'00'

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For NDA only

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

JENTADUETO® XR (Linagliptin and metformin hydrochloride extended-release) tablets

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Jentadueto XR Linagliptin and metformin hydrochloride	Adequate
Dosage form, route of administration	Extended release tablet, Oral	
Controlled drug substance symbol (if applicable)	Not applicable	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	2.5mg Linagliptin/ Metformin HCl extended release 5mg Linagliptin/ Metformin HCl extended release	2.5mg Linagliptin/ 1000 mg Metformin HCl extended release 5mg Linagliptin/ 1000 mg Metformin HCl extended release

Conclusion:

A 1999 Food and Drug Administration Draft Guidance for Industry states: "A dosage form is the way of identifying the drug in its physical form. In determining dosage form, FDA examines such factors as (1) physical appearance of the drug product, (2) physical form of the drug product prior to dispensing to the patient, (3) the way the product is administered, (4) frequency of dosing, and (5) how pharmacists and other health professionals might recognize and handle the product."

Among the several possible dosage form designation for the product, CMC Reviewer recommends Tablet, Extended Release as the most suitable designation for the dosage form. The proposed dosage form is to reduce the dosing frequency. It is also film coated. One of the coating layer contains Linagliptin for immediate release. This recommendation is consistent with the definition provided under USP <1151> Pharmaceutical dosage forms for Extended-release tablets. Extended-release tablets are formulated in such a manner as to make the drug substance available over an extended period of time following ingestion.

Tablet, Extended Release - A solid dosage form containing a drug which allows at least a reduction in dosing frequency as compared to that drug presented in conventional dosage form.

Tablet, Film Coated Extended Release - A solid dosage form that contains medicinal substances with or without suitable diluents and is coated with a thin layer of a water-insoluble or water-soluble polymer; the tablet is formulated in such manner as to make the contained medicament available over an extended period of time following ingestion.

Tablet multi-layer extended release (Tablet Multi-layer ER) - A solid dosage form containing medicinal substances that have been compressed to form a multiple-layered tablet or a tablet-within-a-tablet, the inner tablet being the core and the outer portion being the shell, which, additionally, is covered in a designated coating; the tablet is formulated in such manner as to allow at least a reduction in dosing frequency as compared to that drug presented as a conventional dosage form.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

JENTADUETO XR is a combination of Linagliptin and extended-release metformin hydrochloride. JENTADUETO XR tablets are available in the following dosage forms and strengths:

- 5 mg/1000 mg are white, oval-shaped coated tablets with one side printed in black ink with the Boehringer Ingelheim logo and "D5" on the top line and "1000M" on the bottom line.
- 2.5 mg /1000 mg are yellow, oval-shaped coated tablets with one side printed in black ink with the Boehringer Ingelheim logo and "D2" on the top line and "1000M" on the bottom line.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	tablet	
Strengths: in metric system	2.5mglinagliptin/1000 mg metformin HCl extended release	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	5 mg Linagliptin/1000 mg metformin hydrochloride extended-release tablet – description specified. 2.5 mg Linagliptin/1000 mg metformin hydrochloride extended-release tablet - description specified.	adequate .

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

JENTADUETO XR consists of an extended-release metformin core tablet that is spray-coated with four layers, one of which contains the immediate-release drug substance Linagliptin.

JENTADUETO XR is available for oral administration as tablets containing 5 mg Linagliptin and 1000 mg metformin hydrochloride extended-release (JENTADUETO XR 5 mg/1000 mg) or 2.5 mg Linagliptin and 1000 mg metformin hydrochloride extended-release (JENTADUETO XR 2.5 mg/1000 mg). Each coated tablet of JENTADUETO XR contains the following inactive ingredients: Tablet core: polyethylene oxide, hypromellose, and magnesium stearate. Coatings: hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, arginine, polyethylene glycol, ferric oxide yellow (2.5 mg /1000 mg), carnauba wax, ferrosoferric oxide, propylene glycol, and isopropyl alcohol.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	JENTADUETO XR Linagliptin and metformin HCl extended release	Established name not specified
Dosage form and route of administration	Tablet , extended release. oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	2.5 mg Linagliptin /1000mg metformin HCl 5mg Linagliptin /1000mg metformin HCl	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Tablet core: polyethylene oxide, hypromellose, and magnesium stearate. Coatings: hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, arginine, polyethylene glycol, ferric oxide yellow (2.5 mg /1000 mg), carnauba wax, ferrosoferric oxide, propylene glycol, and isopropyl alcohol.	Adequate
Statement of being sterile (if applicable)	Not Applicable	
Pharmacological/ therapeutic class	Specified	
Chemical name, structural formula, molecular weight	Specified	
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Specified	

Conclusion: Adequate information available for review.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

JENTADUETO XR (Linagliptin and metformin hydrochloride extended-release) tablets 5 mg/1000 mg are supplied as follows:
Bottles of 30 (NDC 0597-0275-33)
Bottles of 90 (NDC 0597-0275-81)

JENTADUETO XR (Linagliptin and metformin hydrochloride extended-release) tablets 2.5 mg/1000 mg are supplied as follows:
Bottles of 60 (NDC 0597-0270-73)
Bottles of 180 (NDC 0597-0270-94)

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from exposure to high humidity. Store in a safe place out of reach of children.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	2.5 mg/1000 mg and 5 mg/1000 mg	
Available units (e.g., bottles of 100 tablets)	2.5mg/1000mg (b) (4) 5 mg/1000 mg -	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not specified	Deficiency Shape, color, coating, scoring, imprinting not specified
Special handling (e.g., protect from light, do not freeze)	Protect from exposure to high humidity. Store in a safe place out of reach of children.	
Storage conditions	**Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)** [see USP Controlled Room Temperature].	

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		

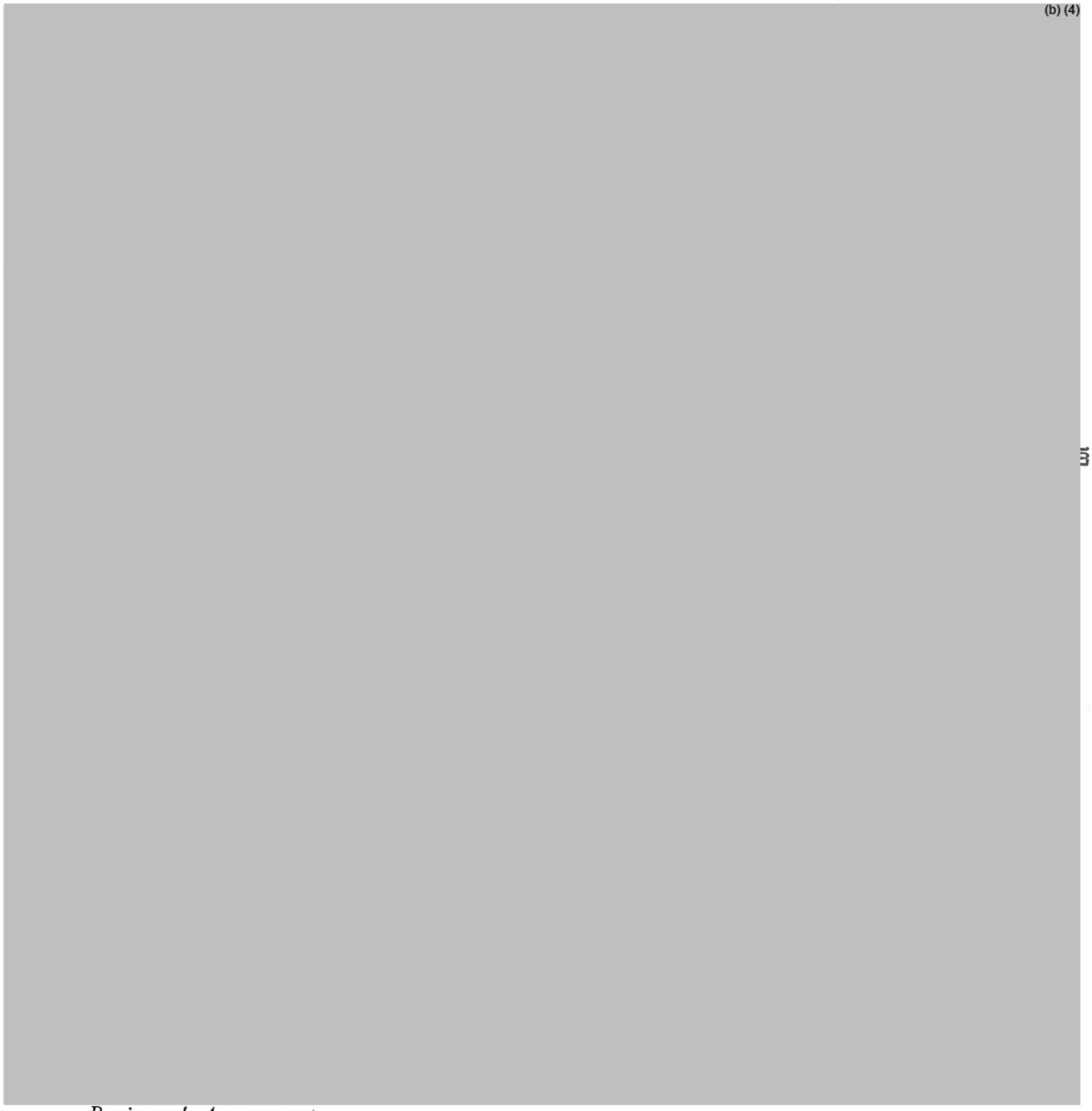
Conclusion: Add the following to section 16 (to be communicated to the applicant during labeling discussions):

Size , shape, color, and imprinting information for both strength tablets.

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Jentadueto XR– Proprietary name Linagliptin and metformin HCl extended release tablets	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	2.5mg/1000mg and 5 mg/1000 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral	adequate
Net contents* (21 CFR 201.51(a))	60 and 180 counts - 2.5mg/1000 mg ER tablets 30 and 90 counts - 5mg/1000 mg ER tablets	Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not specified	
Lot number per 21 CFR 201.18	Specified	
Expiration date per 21 CFR 201.17	Specified	
"Rx only" statement per 21 CFR 201.100(b)(1)	Specified	
Storage (not required)	Store at 25°C (77°F) excursions permitted to 15° to 30°C (59°-86°F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Specified	
Bar Code per 21 CFR 201.25(c)(2)***	Available	
Name of manufacturer/distributor (21 CFR 201.1)	Provided	
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
***Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Evaluation: Adequate

2) Carton Labeling

Carton label for professional sample (5mg 7ct and 2.5mg 14ct) available. *Carton Labels for commercial presentation are not provided.*

(b) (4)

QUALITY ASSESSMENT

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Jentadueto XR– Proprietary name Linagliptin and metformin HCl extended release tablets	Adequate information provided in the label
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	2.5mg/1000mg and 5 mg/1000 mg	
Net contents (21 CFR 201.51(a))	14 counts - 2.5mg/1000 mg ER tablets 14 counts - 5mg/1000 mg ER tablets	
Lot number per 21 CFR 201.18	specified	
Expiration date per 21 CFR 201.17	Specified	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Not specified	
Sterility Information (if applicable)	Not applicable	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Specified	
Storage Conditions	Store at 25°C (77°F) excursions permitted to	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Not specified	
Bar Code per 21 CFR 201.25(c)(2)**	Available	
Name of manufacturer/distributor	Provided	
"See package insert for dosage information" (21 CFR 201.55)	Yes	
"Keep out of reach of children" (optional for Rx, required for OTC)	Specified	
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not required	

Conclusion: Adequate information for the carton label used professional sample is provided in the NDA.

Carton label for commercial packaging is not available for review. This information will be discussed during labeling discussions.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Adequate.

04/14/16
Muthukumar Ramaswamy, Ph.D.
Office of New Drug Products

Muthukumar Ramaswamy -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000341660, cn=Muthukumar Ramaswamy -S
Date: 2016.04.14 20:43:21 -04'00'

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

Danae D. Christodoulou -S

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Date: 2016.04.15 08:22:25 -04'00'

II. List of Deficiencies To Be Resolved During Labeling Discussion

Label/Labeling Deficiencies: (To be resolved during labeling discussion)

a) Product identification (Size, shape, color, and imprinting) information is not specified for both strength tablets the package insert under Section16 - How supplied and Storage/handling instructions).

36 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ASSESSMENT OF THE BIOPHARMACUETICS

BACKGROUND

The Applicant, Boehringer Ingelheim Pharmaceuticals, Inc, submitted this **NDA 208026** on 07/27/2016 for their proposed drug product, Linaglipin/Metformin HCl Extended-Release Fixed Dose Combination (ER-FDC) Tablets, 2.5 mg/1000 mg and 5 mg/1000 mg. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.

This submission is a 505(b)(1) application. The Division of Biopharmaceutics (DB) focuses on the reviewing of:

- In vitro dissolution test and acceptance criteria of the proposed drug product;
- In vitro alcohol dose dumping studies of the proposed drug product.

BIOPHARMACEUTICS ASSESSMENT

1. The composition of proposed drug product formulation

The two strengths of the to-be-marketed (TBM) formulation and composition of the proposed drug product, Linaglipin/Metformin HCl ER-FDC Tablets, 2.5 mg/1000 mg and 5 mg/1000 mg, are shown in Table 1.

Table 1: Qualitative and Quantitative Composition of Linagliptin/Metformin HCl ER Coated Tablets, 2.5 mg/1000 mg and 5 mg/1000 mg
(from M.2.3.P Quality overview summary)

Ingredient	2.5 mg / 1000 mg [mg / tablet]	5 mg / 1000 mg [mg / tablet]	Function	Reference to Standards
(b) (4)				

Reviewer's Assessment:

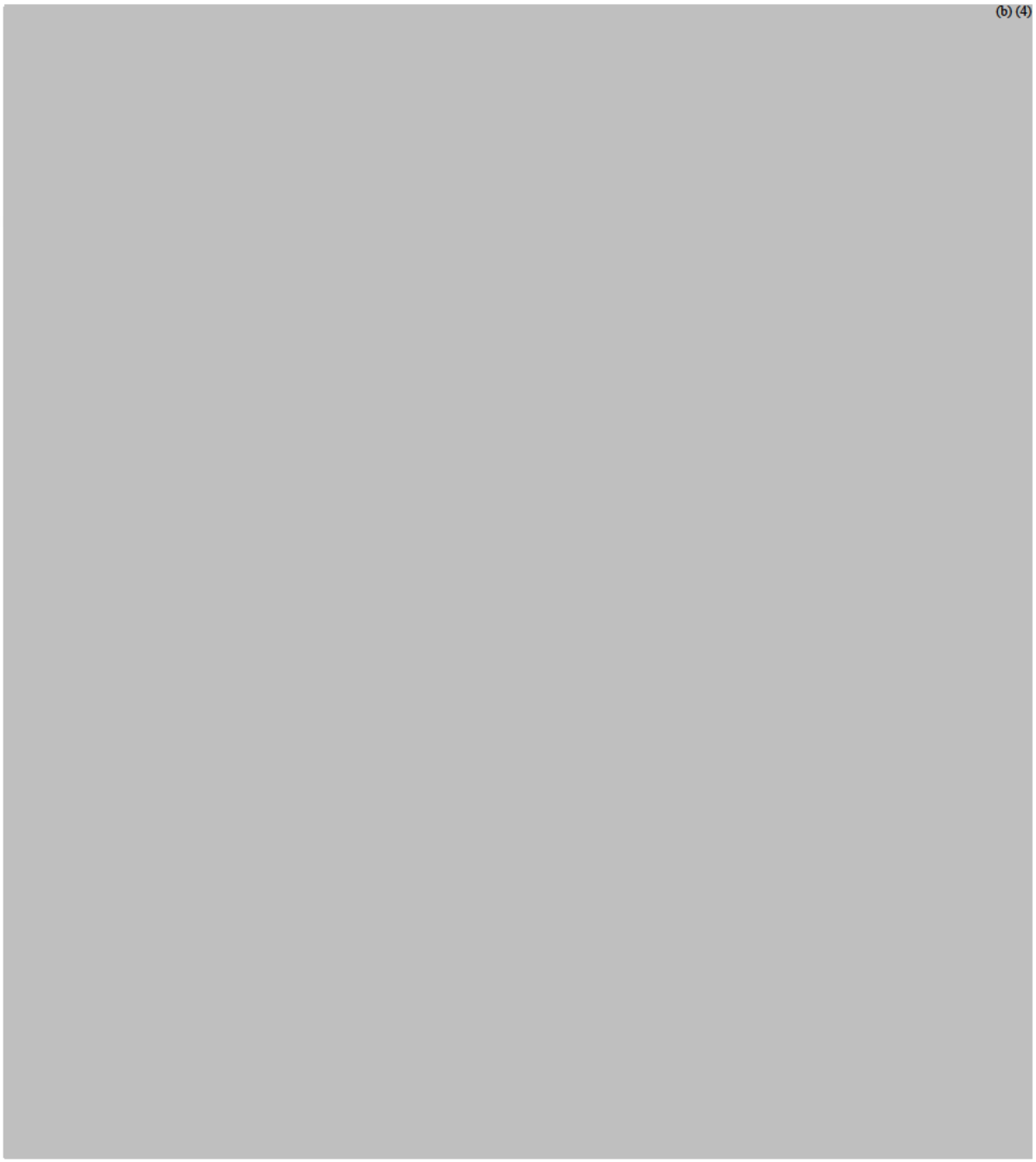
(b) (4)

Since this is an oral (b) (4) formulation, the SUPAC IR guidance (for solid oral dosage forms) would not be applied. The differences for the inactive ingredients between the two strengths are considered minor. The Applicant submitted two in vivo Bioequivalence (BE) studies (study# 1288.9 for 5 mg/1000 mg and study# 1288.11 for 2.5 mg/1000 mg), which are under reviewing by the Office of Clinical Pharmacology (OCP). No Biowaiver request was submitted for the DB to review.

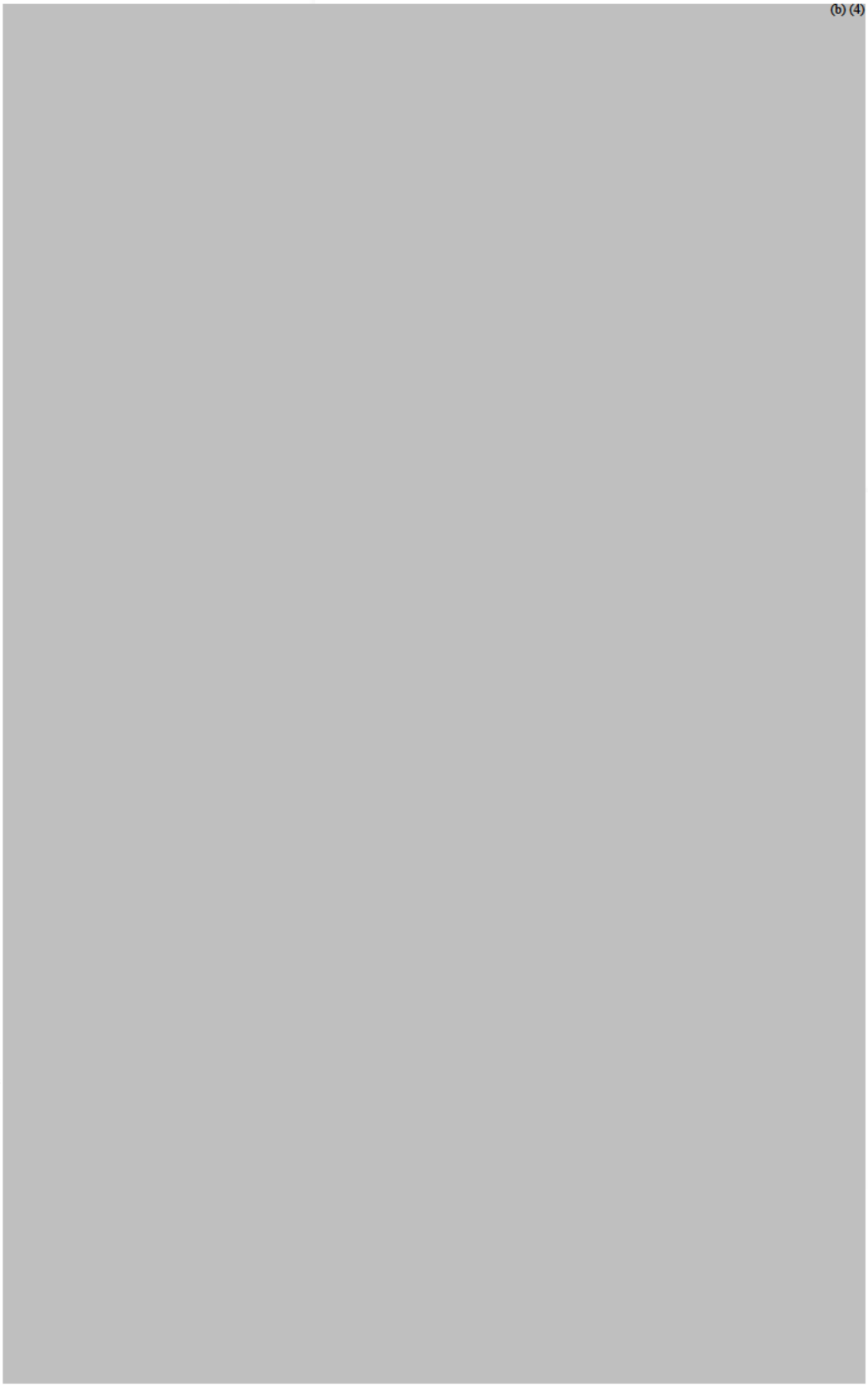
2. The proposed in vitro dissolution method

(1) In vitro dissolution method development

(b) (4)



(b) (4)



(b) (4)

[redacted]

Reviewer's Assessment:

The dissolution method development with the following conditions and the related data has been evaluated to support the proposed dissolution method and acceptance criteria (see M.3.2.P.5.6 Justification of Dissolution Specification for details):

- BCS classification of linagliptin and metformin HCl, including solubility and permeability;
- Selection of apparatus, rotation speed, and dissolution medium for linagliptin and metformin HCl release;
- Discriminating power of the method, including the manufacturing variables (such as (b) (4) [redacted] (b) (4)

The Biopharmaceutics review team considered the proposed dissolution QC method utilizes Apparatus 1 (baskets) at 100 rpm with dissolution medium of SGF without enzymes at pH 1.2 is suitable for the proposed drug product, Linaglipin/Metformin HCl Extended-Release Fixed Dose Combination (ER-FDC) Tablets, both strengths as 2.5 mg/1000 mg and 5 mg/1000 mg.

(2) In vitro dissolution method procedure and analytical method validation

The analytical procedure for dissolution of linagliptin of drug product (Method# 929888) was submitted in M.3.2.P.5.2, effective on 12/02/2014.

The analytical procedure for dissolution of metformin HCl of drug product (Method# 929887) was submitted in M.3.2.P.5.2, effective on 11/25/2014.

The method validation report of dissolution of linagliptin of drug product and related data (Study# 15-059-01) was submitted in M.3.2.P.5.3, which were validated in terms of linearity, accuracy, precision, specificity, and robustness, summarized in Table 6.

The method validation report of dissolution of metformin HCl of drug product and related data (Study# 15-074-01) was submitted in M.3.2.P.5.3, which were validated in terms of linearity, accuracy, precision, specificity, and robustness, summarized in Table 7.

Table 6: Dissolution method validation summary for Linagliptin of drug product (from M.3.2.P.5.2)

Validation Parameter	Method of Determination	Results	
Linearity	Performed at 8 concentrations from approx.10% up to 125% (5mg) or 250% (2.5 mg) of linagliptin potency	Correlation coefficient: 1.000 Y-intercept of 0.07% (2.5 mg) and 0.03% (5 mg) Slope of 349350.917 mV-sec/µg/mL (2.5 mg) and 348971.454 mV-sec/µg/mL (5 mg) Linear range from 5 % to 124 % (5 mg) and 10 % to 247 % (2.5 mg) of linagliptin potency	
Accuracy	Performed by analysing spiked placebo sample solutions in triplicate at approx. 20%, 80% and 140% for the 2.5 mg strength and approx. 20%, 80% and 150% for the 5 mg strength of the nominal sample solution concentration of linagliptin	2.5 mg/ 750 mg strength	Overall average recovery of 99% with individual recovery results ranging from 93.8% to 101.8%
		2.5 mg/ 1000 mg strength	Overall average recovery of 101% with individual recovery results ranging from 100.6% to 101.4%
		5 mg/ 1000 mg strength	Overall average recovery of 101% with individual recovery results ranging from 99.8% to 103.9%
Precision (repeatability)	One batch of each strength was prepared and tested 12 times by the proposed method	The RSD of the percent recoveries (n=12) should not be more than 6.0 % at 30 minutes. Results: 2.5 mg/750 mg: 2.6 % 2.5 mg/1000 mg: 4.0 % 5 mg/1000 mg: 3.2 %	
Precision (reproducibility)	One batch of each strength was prepared and tested 12 times by the proposed method	The RSD (n=12) should not be more than 6.0 % at 30 minutes for each analyst and the overall RSD for all analysts (n=36) should not be more than 6.0 % at 30 minutes.	
		Analyst 2	2.5 mg/ 750 mg: RSD = 1.2 % 2.5 mg/1000 mg: RSD = 3.7 % 5 mg/1000 mg: RSD = 3.3 %
		Analyst 3	2.5 mg/ 750 mg: RSD = 3.3 % 2.5 mg/1000 mg: RSD = 4.5 % 5 mg/1000 mg: RSD = 2.0 %
		Overall	2.5 mg/ 750 mg: RSD = 2.6 % 2.5 mg/1000 mg: RSD = 3.9 % 5 mg/1000 mg: RSD = 2.9 %
Specificity	Evaluation if degradants or other relevant peaks are separated from linagliptin (dissolution media, placebo & metformin solution)	In the chromatograms of the placebo solutions, dissolution media and CD 10085 solution, there were no significant interfering peaks present in the retention time window of linagliptin.	

Table 6: Dissolution method validation summary for Linagliptin of drug product (from M.3.2.P.5.2) (Continued)

Validation Parameter	Method of Determination	Results
Robustness (HPLC conditions)	One chromatographic method parameter was varied at a time. Different column batches were also used during the repeatability & reproducibility studies.	Linagliptin retention time, peak area, peak efficiency and tailing factor are evaluated with variations in column batch, mobile phase composition, detector wavelength, column temperature and flow rate. If significant performance deviations are noted then a precautionary statement is in the method. Results: Shifts in performance were observed when the mobile phase composition was changed.
Robustness (manual and automated sampling)	Twelve tablets were analyzed by the proposed method and sampled at 30 minutes.	The difference between the average results obtained at 30 minutes for the manual and automatic sampling should not be more than 5 %. 2.5 mg/1000 mg — 30 minutes Manual : 98.1 % (Analyst 1) Manual: 96.9 % (Analyst 2) Automated: 97.1 % Max. diff (%).: 1 %
Robustness (filter study)	One repeatability sample solution (2.5 mg/1000 mg and 5 mg/1000 mg strength) were analyzed. Three separate aliquots of each sample solution were collected using the same identified filter; non-filtered aliquots were also obtained by centrifugation.	The difference between the average recovery result of linagliptin of the filtered and centrifuged sample solutions should not be more than 2.0 % (absolute). Results: The difference between the average recovery result of linagliptin of the filtered and centrifuged sample solutions was 1 % at maximum.

Validation Parameter	Method of Determination	Results
Robustness (stability of analytical solutions)	A working standard solution and dissolution sample were stored at ambient and refrigerated conditions and compared to freshly prepared standards at various time points up to 6 days.	The standard and sample solutions are considered stable for a specified time as stored if recovery is within 98 % to 102 % of the initial result. Results: Standard: Clear flask, ambient: 99.3 – 99.9 % Refrigerated: 99.4 – 100.0 % Sample: Clear flask, ambient: 93.9 – 98.6 % Refrigerated: 98.5 – 99.7 % The standard solution is stable for 6 days when stored under ambient laboratory or refrigerated conditions.
		The sample solution is considered stable for a specified time as stored if the percent recovery is within 2.0 % (absolute) of the initial result. Results: The maximum difference in percent recovery observed versus the initial result after storage for up to 6 days is 1.7 % (ambient) and 1.4 % (refrigerated). The sample solution is stable for 6 days when stored under ambient laboratory or refrigerated conditions.

Table 7: Dissolution method validation summary for Metformin HCl of drug product (from M.3.2.P.5.2)

Validation Parameter	Method of Determination	Results	
Linearity	Performed at 7 concentrations from approx.10% (750 mg) up to 120% (1000 mg) of metformin potency	Correlation coefficient: 1.000 Y-intercept of 1.2 % (750 mg) and 1.1 % (1000 mg) Slope of 1,417,988.120 mV-sec/µg/mL (750 mg) and 1,420,513.832 mV-sec/µg/mL (1000 mg) Linear range from 10 % to 160 % (750 mg) and 7.5 % to 120 % (1000 mg) of metformin potency	
Accuracy	Performed by analysing spiked placebo sample solutions in triplicate at approx. 30%, 80% and 140% of the nominal sample solution concentration of metformin	2.5 mg/ 750 mg strength	Overall average recovery of 103.4 % with individual recovery results ranging from 100.1 % to 106.0 %
		2.5 mg/ 1000 mg strength	Overall average recovery of 102.4% with individual recovery results ranging from 100.1 % to 104.6 %
		5 mg/ 1000 mg strength	Overall average recovery of 102.7 % with individual recovery results ranging from 100.7 % to 105.3%
Precision (repeatability)	One batch of each strength was prepared and tested 12 times by the proposed method	The RSD of the percent recoveries (n=12) should not be more than 6.0 % at 2 hours, 4 hours and 12 hours.	
		Results:	2 hours / 4 hours / 12 hours
		2.5 mg/750 mg:	1.7 % / 1.1 % / 0.9 %
		2.5 mg/1000 mg:	1.6 % / 1.1 % / 1.2 %
		5 mg/1000 mg:	1.1 % / 1.1 % / 1.2 %
Precision (reproducibility)	One batch of each strength was prepared and tested 12 times by the proposed method	The RSD (n=12) should not be more than 6.0 % at 2 hours, 4 hours and 12 hours for each analyst and the overall RSD for all analysts (n=36) should not be more than 6.0 % at 2 hours, 4 hours and 12 hours.	
		Analyst 2	2 hours / 4 hours / 12 hours
		2.5 mg/750 mg:	1.4 % / 1.2 % / 1.0 %
		2.5 mg/1000 mg:	0.9 % / 1.0 % / 0.7 %
		5 mg/1000 mg:	1.2 % / 1.0 % / 0.9 %
		Analyst 3	2 hours / 4 hours / 12 hours
		2.5 mg/750 mg:	2.6 % / 1.9 % / 1.2 %
		2.5 mg/1000 mg:	1.8 % / 1.4 % / 1.4 %
		5 mg/1000 mg:	2.2 % / 2.5 % / 4.6 %
		Overall	2 hours / 4 hours / 12 hours
		2.5 mg/750 mg:	2.6 % / 1.6 % / 1.9 %
		2.5 mg/1000 mg:	1.6 % / 1.2 % / 1.9 %
		5 mg/1000 mg:	2.1 % / 2.1 % / 3.1 %

Table 7: Dissolution method validation summary for Metformin HCl of drug product (from M.3.2.P.5.2) (Continued)

Validation Parameter	Method of Determination	Results
Specificity	Evaluation if degradants or other relevant peaks are separated from metformin (dissolution media, placebo, metformin & metformin impurity E solution)	In the chromatograms of the placebo solutions, dissolution media and metformin impurity E, there were no significant interfering peaks present in the retention time window of metformin.
Robustness (HPLC conditions)	One chromatographic method parameter was varied at a time. Different column batches were also used during the repeatability & reproducibility studies.	Metformin retention time, peak area, peak efficiency and tailing factor are evaluated with variations in column batch, mobile phase composition, detector wavelength, column temperature and flow rate. If significant performance deviations are noted then a precautionary statement is in the method. Results: Shifts in performance were observed when the mobile phase composition and detector wavelength were changed.
Robustness (manual and automated sampling)	Twelve tablets were analyzed by the proposed method and sampled at 2 hours, 4 hours and 12 hours.	The difference between the average results (% dissolved) obtained at 2 hours, 4 hours and 12 hours for the manual and automatic sampling should not be more than 5 %.

2.5 mg/ 750 mg		2 hours	4 hours	12 hours
	Manual : (Analyst 1)	40.0 %	61.5	98.5 %
	Manual: (Analyst 2)	38.8 %	61.8	98.2 %
	Automated:	40.6 %	62.7	101.5 %
	Max. diff (%).:	2 %	1 %	3 %

5 mg/ 1000 mg		2 hours	4 hours	12 hours
	Manual : (Analyst 1)	38.1 %	59.8 %	100.7 %
	Manual: (Analyst 2)	36.8 %	57.9 %	97.3 %
	Automated:	37.5 %	58.4 %	97.4 %
	Max. diff (%).:	1 %	2 %	3 %

Robustness (filter study)	One repeatability sample solution (2.5 mg/750 mg and 5 mg/1000 mg strength) were analyzed. Three separate aliquots of each sample solution were collected using the same identified filter; non-filtered aliquots were also obtained by centrifugation.	The difference between the average recovery result of metformin of the filtered and centrifuged sample solutions should not be more than 2 % (absolute). Results: No difference between the average recovery result of metformin of the filtered and centrifuged sample solutions was observed.

Table 7: Dissolution method validation summary for Metformin HCl of drug product (from M.3.2.P.5.2) (Continued)

Validation Parameter	Method of Determination	Results
Robustness (stability of analytical solutions)	A working standard solution and dissolution sample were stored at ambient and refrigerated conditions and compared to freshly prepared standards at various time points up to 6 days.	The standard and sample solutions are considered stable for a specified time as stored if recovery is within 98 % to 102 % of the initial result. Results: Standard: Clear flask, ambient: 99.9 – 101.6 % Refrigerated: 99.9 – 101.4 % Sample: Clear flask, ambient: 98.4 – 101.1 % Refrigerated: 98.7 – 101.5 % The standard solution is stable for 6 days when stored under ambient laboratory or refrigerated conditions.
		The sample solution is considered stable for a specified time as stored if the percent recovery is within 2.0 % (absolute) of the initial result. Results: The maximum difference in percent recovery observed versus the initial result after storage for up to 6 days is 1.1 % (ambient) and 1.5 % (refrigerated) for the 2.5 mg/750 mg strength and 1.6 % (ambient) and 2.0 % (refrigerated) for the 5 mg/1000 mg strength The sample solution is stable for 6 days when stored under ambient laboratory or refrigerated conditions.

Reviewer's Assessment:

The submitted in vitro dissolution method procedure and analytical method validation reports are considered adequate.

3. The in vitro dissolution data and specifications

One biobatch of each strength of drug product was employed in the in vitro dissolution testing by using the proposed QC method [Apparatus 1 (baskets) at 100 rpm with dissolution medium of SGF without enzymes at pH 1.2]. The batch information is summarized in Table 8 below (from M.3.2.P.2 Pharmaceutical Development Comparative Dissolution, M.3.2.P.2 Clinical Trial Formulations and Batches, and M.3.2.P.5.6 Justification of Dissolution Specification). The mean and individual data of biobatch drug product (N=12 units/batch) were given in Table 9-12 below.

Table 8: Batch information of biobatch and stability batches of drug product for in vitro dissolution testing (from M.3.2.P.2 and M.3.2.P.5.6)

Drug Product	Strength	Batch No.	Purpose
Linaglipin/Metformin HCl Extended-Release Fixed Dose Combination (ER-FDC) Tablet	2.5 mg/1000 mg	BI41000640	BE Study 1288.11
Linaglipin/Metformin HCl Extended-Release Fixed Dose Combination (ER-FDC) Tablet	5 mg/1000 mg	BI41000138	BE Study 1288.9

Table 9: Linagliptin Dissolution Data in SGF Without Enzymes (pH 1.2) Linagliptin/Metformin HCl ER Coated Tablets, 2.5 mg/1000 mg, Batch BI41000640 (from M.3.2.P.2)

Replicate	% Linagliptin Released				
	10 minutes	15 minutes	20 minutes	30 minutes	45 minutes
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	61	89	98	102	103
RSD (%) (n=12)	10.7	4.4	3.0	2.4	2.1

Table 10: Linagliptin Dissolution Data in SGF Without Enzymes (pH 1.2) Linagliptin/Metformin HCl ER Coated Tablets, 5 mg/1000 mg, Batch BI41000138 (from M.3.2.P.2)

Replicate	% Linagliptin Released				
	10 minutes	15 minutes	20 minutes	30 minutes	45 minutes
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	63	85	92	95	95
RSD (%) (n=12)	11.9	4.3	2.6	1.9	1.7

Table 11: Metformin HCl Dissolution Data in SGF Without Enzymes (pH 1.2) Linagliptin/Metformin HCl ER Coated Tablets, 2.5 mg/1000 mg, Batch BI41000640 (from M.3.2.P.2)

Replicate	% Metformin HCl Released				
	2 hours	4 hours	6 hours	8 hours	12 hours
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	37	58	73	84	95
RSD (%) (n=12)	1.4	1.4	1.0	1.0	1.2

Table 12: Metformin HCl Dissolution Data in SGF Without Enzymes (pH 1.2) Linagliptin/Metformin HCl ER Coated Tablets, 5 mg/1000 mg, Batch BI41000138 (from M.3.2.P.2)

Replicate	% Metformin HCl Released				
	2 hours	4 hours	6 hours	8 hours	12 hours
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	36	58	73	85	99
RSD (%) (n=12)	1.7	0.6	0.8	0.9	1.8

Reviewer's Assessment:

The Biopharmaceutics review team profiled the mean dissolution data of the biobatch drug product based on the submission, given in Figure 1 and 2:

Figure 1: Mean Dissolution Profile of Linagliptin of drug product using Apparatus 1 at 100 rpm with SGF without enzymes at pH 1.2 (from M.3.2.P.2)

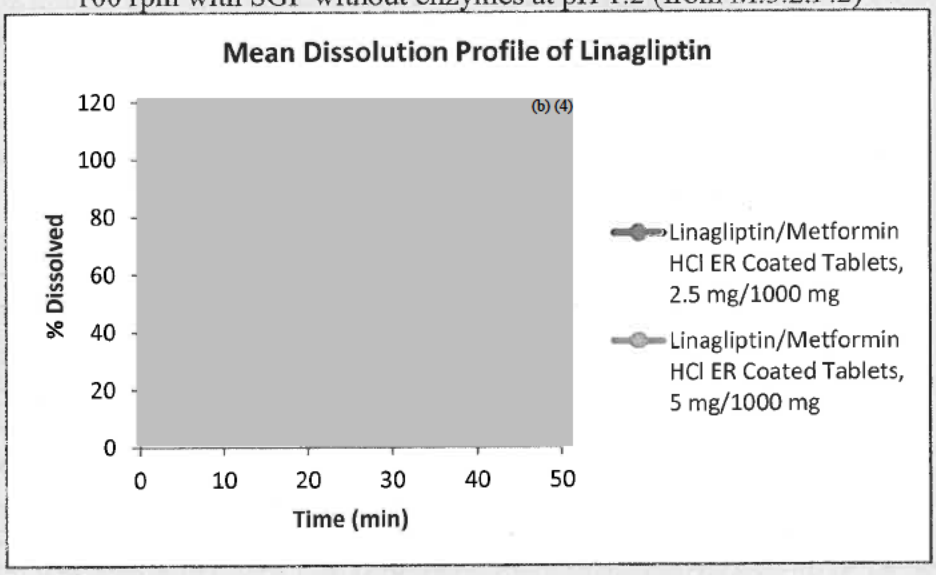
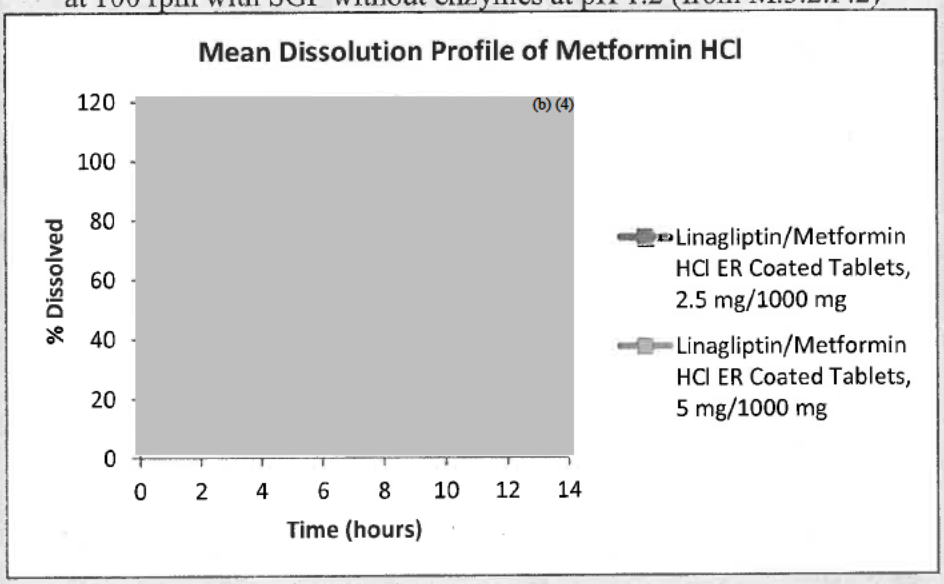


Figure 2: Mean Dissolution Profile of Metformin HCl of drug product using Apparatus 1 at 100 rpm with SGF without enzymes at pH 1.2 (from M.3.2.P.2)



The Biopharmaceutics review team also calculated the similarity factors (f2). The dissolution profiles of Meformin HCl between the proposed two strengths of drug product (2.5 mg/1000 mg versus 5 mg/1000 mg) are considered comparable with f2=79.5.

Because linagliptin dissolved (b)(4)% or more in 15 minutes, per *FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*, the dissolution profile comparison with f2 calculation is not needed between the lower strength (2.5 mg/1000 mg) and the higher strength (5 mg/1000 mg).

Based on the submitted data, the Biopharmaceutics review team considered that the proposed dissolution specification: *For Linagliptin: Not less than (b)(4)% (Q) at 30 minutes; For Metformin HCl: 2 hours: (b)(4)%, 4 hours: (b)(4)%, 12 hours: Not less than (b)(4)%* are too wide.

Therefore, the following Biopharmaceutics Information Request (IR) was conveyed to the Applicant on 12/21/2015:

Biopharmaceutics Information Request:

Your proposed Dissolution Acceptance Criteria are too wide for both of Linagliptin and Metformin HCl, therefore, they are not acceptable. Based on the submitted dissolution data of the clinical batches of Linagliptin/Metformin HCl ER Coated Tablets, 2.5 mg/1000 mg (Batch BI41000640), and 5 mg/1000 mg (Batch BI41000138), by using the proposed dissolution QC method (USP 1 basket with 100 rpm in SGF without enzyme, pH 1.2), the following data-driven acceptance criteria should be implemented:

Drug Substance	Time Point	Acceptance Criteria
Linagliptin	20 minutes	Not less than (b)(4)% (Q)
Metformin HCl	2 hours	(b)(4)%
	4 hours	%
	12 hours	Not less than (b)(4)%

Revise the sections of M.3.2.P.5.1 "Specifications", M.3.5.P.5.6 "Justification of Specification" and other related sections to reflect the new Dissolution Acceptance Criteria as quality control for Release and Stability for your drug product.

4. The Responses for the Biopharmaceutics IR:

On 01/25/2016, the Applicant provided responses for the IR above as:

- Keep the proposed dissolution specification for Linagliptin as NLT (b)(4)% (Q) at 30 minutes;
- Provided the summarized mean dissolution data of pivotal clinical batches in primary stability testing with different storage conditions up to 18 months;
- Accepted the recommended dissolution specification for Metformin HCl as proposed by FDA;
- Updated M.3.2.P.5, Specification document and 3.2.P.6, Justification of Dissolution Specification document for Metformin HCL.

Reviewer's Assessment:

The Biopharmaceutics review team still considered the overall dissolution data supported the recommended specification for Linagliptin as *NLT* (b)(4)*% (Q) at 20 minutes* for drug quality control.

With the concurrence with upper management, we will recommend the Applicant to set the proposed dissolution specification for Linagliptin [*NLT* (b)(4)*% (Q) at 30 minutes*] as interim specification. Also, we will recommend the Applicant to collect/generate additional dissolution data including both 20 and 30 min time points (N=12 units/batch) for all the commercial batches manufactured during the first year upon approval, analyze the new dissolution profile data, and report the complete dissolution profile data of Linagliptin in the first annual report for review/discussion. Based on the additional data, the dissolution specification of Linagliptin will be finalized for implementation for drug product quality control post approval.

5. In vitro alcohol dose dumping study

The in vitro alcohol dose dumping study and data were submitted in M.3.2.P.2 Pharmaceutical Development Comparative Dissolution. Testing was conducted on N=12 units/batch using dissolution QC method with various concentration of alcohol. This was to address the concern of dose dumping of the ER drug component, Metformin HCl, from the proposed drug product. The dissolution media is listed in Table 13. The detailed description of analytical method was submitted in M.3.2.P.5.2, the individual data was submitted in M.3.2.P.2. The dissolution profiles were provided in Figure 3 and 4 below.

Table 13: Dissolution Media used for the Alcohol Induced Dose Dumping Studies (from M.3.2.P.2)

Condition [Ethanol, %(v/v)]	Media Composition
0	0% ethanol (v/v) in SGF without enzymes
5	5% ethanol (v/v) in SGF without enzymes
10	10% ethanol (v/v) in SGF without enzymes
20	20% ethanol (v/v) in SGF without enzymes
40	40% ethanol (v/v) in SGF without enzymes

Figure 3: Metformin HCl Dissolution Profile from Linagliptin/Metformin HCl ER Tablets, 2.5 mg/750 mg, in the Presence of Different Concentrations of Alcohol (from M.3.2.P.2)

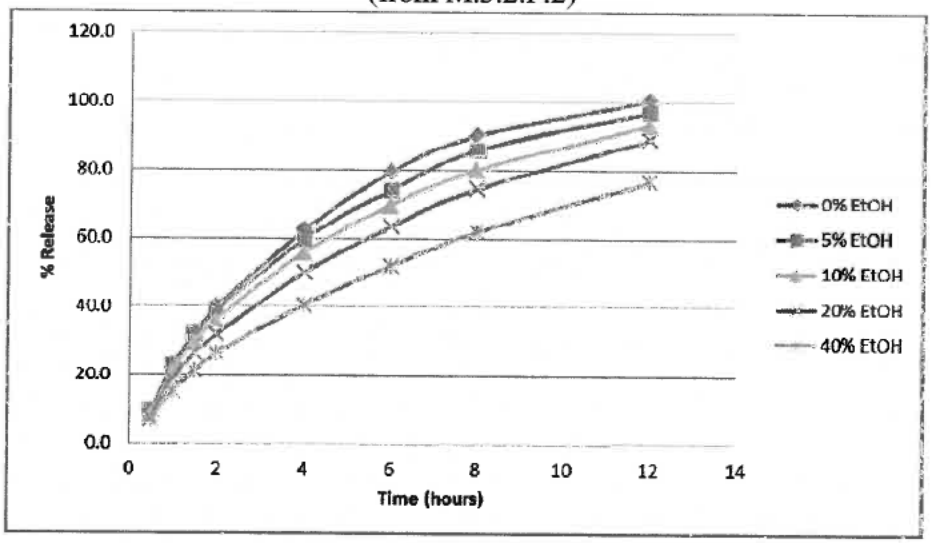
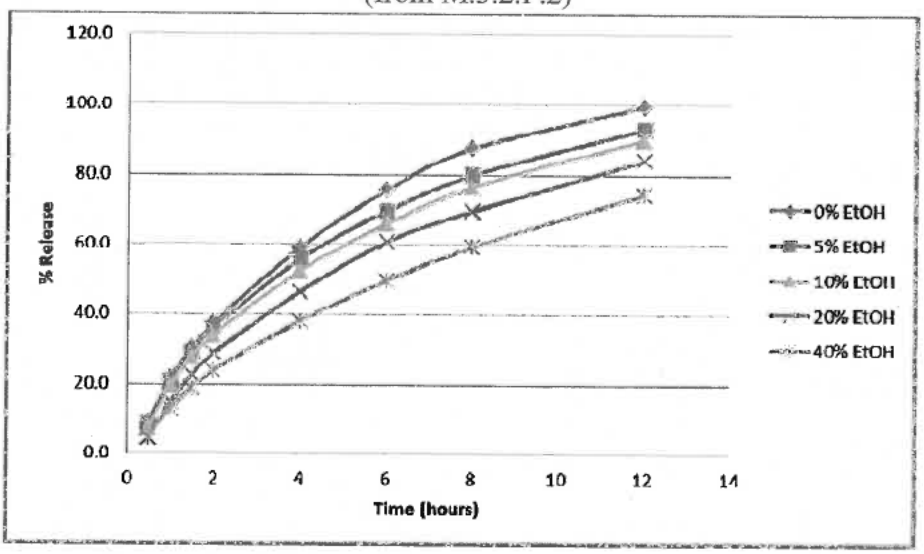


Figure 4: Metformin HCl Dissolution Profile from Linagliptin/Metformin HCl ER Tablets, 5 mg/1000 mg, in the Presence of Different Concentrations of Alcohol (from M.3.2.P.2)



Reviewer's Assessment:

It is observed that the dissolution rate of Metformin HCl decreased with the increased concentration of alcohol. Therefore, the proposed drug product is considered to have no in vitro alcohol dose dumping effects. The above results had been communicated to the OCP review team.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

From Biopharmaceutics perspective:

- The proposed in vitro dissolution method for the drug product, Linaglipin/Metformin HCl Extended-Release Fixed Dose Combination Tablets, 2.5 mg/1000 mg and 5 mg/1000 mg, is acceptable with adequate discriminating ability;
- The in vitro dissolution method validation for the proposed drug product is well established and acceptable;
- The proposed drug product showed no in vitro alcohol dose dumping effects;
- The recommended dissolution specification for Metformin HCl was accepted by the Applicant for drug product release and stability implementation;
- The proposed dissolution specification for Linaglipin [*NLT* (b)(4)*% (Q) at 30 minutes*] will be recommended as interim specification. Additional dissolution profile data of Linagliptin collecting at both 20 and 30 min time points (N=12 units/batch) for all commercial batches manufactured during the first year upon approval will be recommended. The generated new data will be recommended to be analyzed and reported in the first annual report for the Agency to review. Based on the additional data, the dissolution specification of Linagliptin will be finalized for implementation for the drug product quality control post approval.
- The in vitro dissolution method and interim specification for the proposed drug product are summarized as below:

Apparatus	I (Basket)
Medium	Simulated Gastric Fluid (SGF) without enzyme (pH 1.2)
Volume	900 mL
Rotation Speed	100 rpm
Temperature	37°C ± 0.5°C
Sampling Time	2, 4, 6, 8, and 12 hours
Interim Specification for Linagliptin	Not less than (b)(4)% (Q) at 30 minutes
Specification for Metformin HCl	2 hours: (b)(4)% 4 hours: % 12 hours: Not less than (b)(4)%

OVERALL COMMENTS:

This NDA 208026 for drug product, Linaglipin/Metformin HCl Extended-Release Fixed Dose Combination Tablets, 2.5 mg/1000 mg and 5 mg/1000 mg, is reviewed and found acceptable from the Biopharmaceutics perspective; therefore, this NDA 208026 is recommended for APPROVAL.

The following comments should be conveyed to the Applicant upon approval as:

- We acknowledge your acceptance of dissolution specification for Metformin HCl as we recommended as: *2 hours:* (b) (4) *%, 4 hours:* (b) (4) *%, 12 hours: Not less than* (b) (4) *%.*

- Based on your responses to the NDA submission (25 Jan 2016) and the totality of the submitted data, we recommend you to use the proposed dissolution specification for Linagliptin as: *NLT* (b) (4) *% (Q) at 30 minutes* as interim specification.

- We also recommend you to collect/generate additional dissolution data including both 20 and 30 minute time points (N=12 units/batch) for all commercial batches manufactured during the first year post-approval, analyze the dissolution data, and submit the results with complete dissolution information in the first annual report. Based on the additional data, the dissolution specification of Linagliptin will be reviewed and finalized for implementation for your drug product quality control post approval.

03/23/2016
Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Mei Ou -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mei Ou -S, 0.9.2342.19200300.100.1.1=2001622313
Date: 2016.03.24 08:46:14 -04'00'

Secondary Review Comments and Concurrence:

I concur. 03/23/16

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

Tienmien Chen -S
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ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

From 1/25/2016 Information Amendment:

For the solid oral dosage form linagliptin/metformin hydrochloride extended release (ER) coated tablets (dosage strengths 2.5 mg / 1000 mg and 5 mg / 1000 mg) we propose to omit microbiological testing from the drug product specifications since the product is not prone to microbial growth. The following upstream microbiological controls (items 1, 2, and 3) are established and justify omission of microbiological testing from the drug product specifications. In addition, data have been generated (item 4) demonstrating that the product is not prone to microbial growth. Some of these items were presented in Section 3.2.5.6 of the original application but each is further discussed in this response.

1. Raw material controls
2. Environmental monitoring
3. Validated equipment holding times (cleaned equipment)
4. Microbiological stability of the (b) (4) and processing time for the (b) (4)

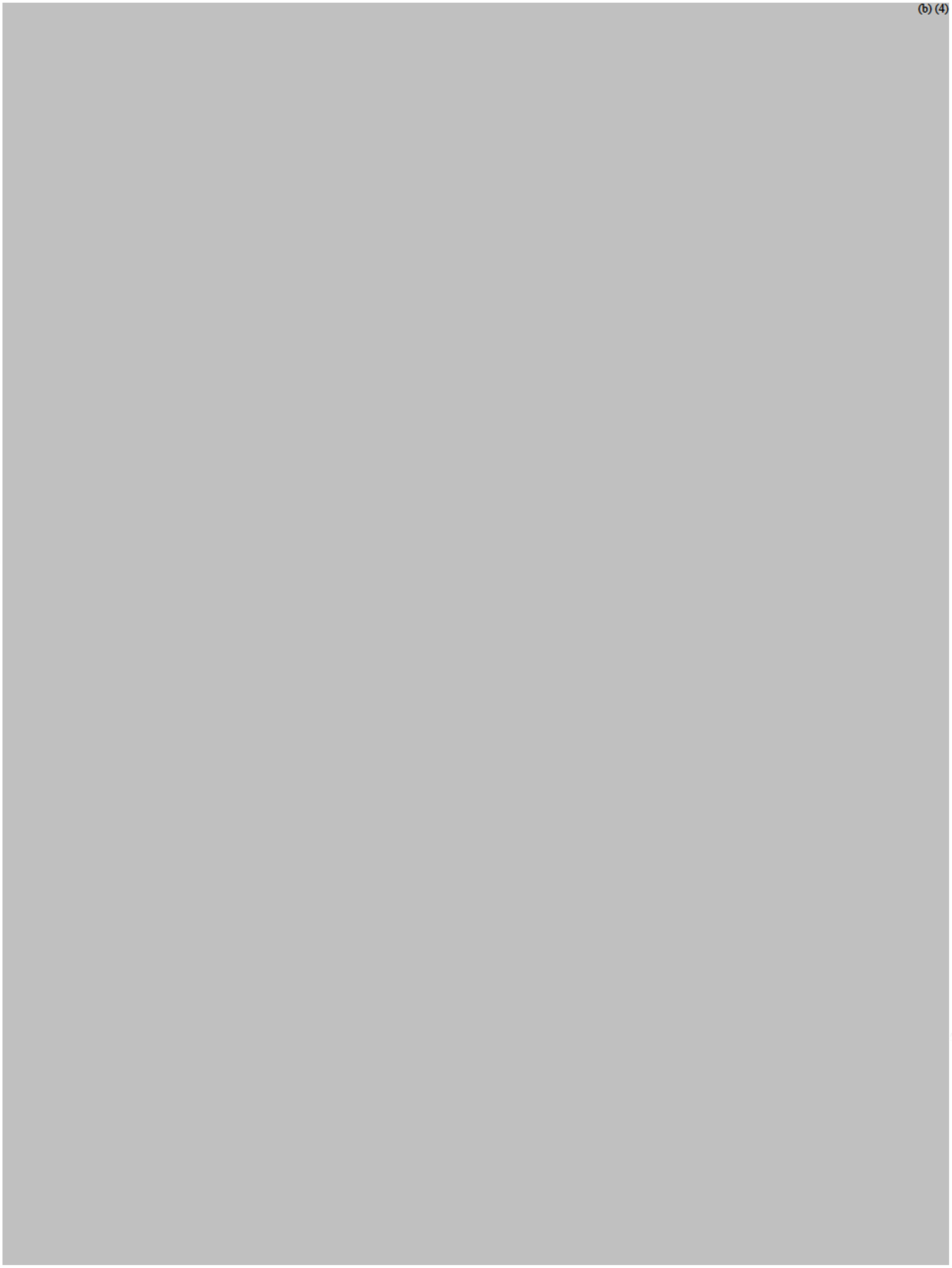
(b) (4)

[redacted]

Table 2 Specification for microbiological quality of Nonaqueous preparations for oral use according to USP <1111>

Test Parameter	Method Type	Acceptance Criteria for Non-aqueous Preparations for Oral Use
Total Aerobic Microbial Count	USP <61>	Not more than (b) (4) cfu/g
Total Combined Yeasts and Molds Count		Not more than (b) (4) cfu/g
Escherichia coli	USP <62>	Absent in 1 g or 1 mL

(b) (4)



We issued the following deficiency in IR #1 (12/21/2015):

Deficiency 8 (IR #1), 12/21/2015:

You propose waiving microbial limits release and stability testing for your drug product. Provide additional information in support of your proposal:

a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
   i. Define the maximum processing time for the (b) (4)
   ii. Define the maximum holding time for the (b) (4)

b. Describe the microbiological monitoring and acceptance criteria for the critical control points that you have identified. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

c. Describe activities taken when microbiological acceptance criteria are not met at the control points.

d. Provide results of microbial limits testing performed on the exhibit or stability batches of the drug product, at release and stability testing time points, including 24-month long-term stability data, to support your proposed shelf life of 24 months.

e. Test method suitability should be verified for compendial methods. Provide your product-specific method suitability study reports for both strengths of the drug product for the compendial microbial test methods, USP <61> and <62>.

f. The (b) (4) COAs you included as part of the executed BMRs for your two representative registration batches have the following microbiological specification:

   (b) (4) Plate Count: NMT (b) (4) cfu/mL

   This is not equivalent to the Total Aerobic Microbial Count (TAMU), Total Combined Yeasts and Molds (TCYM), and Absence of E. coli specifications in USP <1111>. (b) (4)

   (b) (4)

g. You propose a (b) (4)

   (b) (4)

(b) (4)

[redacted]

Reviewer's Assessment: N/A

As this is a low microbial risk simple solid oral drug, this information is not applicable.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment:

Refer to the Drug Product review.

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment:

Refer to the Drug Product review.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate.
Shujun Chen, Primary Reviewer, April 14, 2016

Secondary Review Comments and Concurrence:
Concur with Reviewer Evaluation and Conclusions, Ubrani V. Venkataram, 4/15/2016

OVERALL ASSESSMENT AND SIGNATURE:

Application Technical Lead Signature: I concur with the reviewers' conclusions.

Suong (Su) Tran, PhD

[See digital signature and date on page 5, Executive Summary]

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/s/

JONATHAN T DOW
06/06/2016