CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209803Orig1s000
209805Orig1s000
209806Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 209805
ADDENDUM TO Review #1

The recommendation from the Office of Pharmaceutical Quality (OPQ) is for Approval, including the Overall Manufacturing Inspection Recommendation dated 11/1/2017.

This current recommendation for Approval replaces the 8/23/17 recommendation for a Complete Response.

- The 8/23/17 Complete Response recommendation resulted from the 8/17/17 Facilities "Withhold" Recommendation for (b) (4) the proposed manufacturer of sitagliptin phosphate monohydrate.
- The 8/17/17 "Withhold" recommendation resulted from an inspection dated (b) (4) which was followed by (b) (4)

The facility was re-inspected by FDA on (b) (4) and the firm's response to deficiencies was found adequate by FDA.The GMP status of this facility was then changed to "Compliant".

Suong T. Tran -S

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/s/

SUONG T TRAN

11/13/2017

This addendum to the OPQ Integrated Quality Assessment, recommending "APPROVAL", replaces the OPQ recommendation dated 8/23/17.
This addendum is finalized in DARRTS because Panorama closed the project and no additional document can be uploaded. A request was sent to CDER Informatics2 weeks ago to re-open the project so that this addendum can be uploaded; to date, our request has been ignored.

QUALITY REVIEW

Recommendation:
(including the Facility Review/Overall Manufacturing Inspection Recommendation)

COMPLETE RESPONSE - to be re-evaluated at the end of September, 2017

NDA 209805

Review #1
Review Date (see last page)

Drug Name/Dosage Form	ertugliflozin and sitagliptin tablet (fixed ratio combination)
Strength	(b) (4) 5/100, 15/100 mg/mg ertugliflozin/sitagliptin
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Merck

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	12/19/16
0002	1/13/17
0003	1/23/17
0008	3/21/17
0010	4/25/17
0012	5/8/17
0014	5/10/17
0015	6/7/17
0018	6/23/17
0019	7/25/17
0021	7/28/17

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Erika Englund/Donna Christner	New Drug API/ONDP
Drug Product	Ravi Kasliwal/Danae Christodoulou	New Drug Products II/ONDP
Process/Microbiology	Huai Chang/Chengjiu Hu	Process Assessment II/OPF
Facility	Krishnakali Ghosh/Juandria Williams	Inspectional Assessment/OPF
Biopharmaceutics	Peng Duan/Haritha Mandula	Biopharmaceutics/ONDP
Environmental Assessment	James Laurenson/Michael Furness	ONDP

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   - **A. DMFs:** Adequate (see Chapter II)
   - **B. Other Documents:** NDA 21995 JANUVIA (sitagliptin) tablets, NDA 209805 (ertugliflozin/sitagliptin), and NDA 209806 (ertugliflozin/metformin HCl) by the same applicant
2. **CONSULTS:** n/a

Executive Summary

I. Recommendation and Conclusion on Approvability

The current OPQ recommendation is for Complete Response, including the overall manufacturing inspection recommendation. This recommendation will be re-evaluated at the end of (b) (4)

Summary of Complete Response issues:

(b) (4) is the proposed manufacturer of sitagliptin phosphate monohydrate. Major deficiencies were observed during the recent inspection conducted from (b) (4) (b) (4)

- This facility will be re-inspected by FDA in (b) (4) The applicant stated that the facility would be removed from the NDA upon failure of the re-inspection (no plan to remove the facility from the NDA until then).
- If this facility is removed from the NDA, the OPQ recommendation for the application would be changed because there is no other pending issue identified in our review. The NDA includes another manufacturer of sitagliptin phosphate monohydrate with an acceptable GMP profile.

Action letter language:

To be finalized at the end of (b) (4), pending the applicant's additional information to be submitted in September as discussed above.

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(1) NDA for ertugliflozin, a New Molecular Entity.
Ertugliflozin is processed with the conformer L-pyroglutamic acid (LPGA) to yield the ertugliflozin-LPGA co-crystal. As per FDA's guidance "Regulatory Classification of Pharmaceutical Co-Crystals", the ertugliflozin-LPGA co-crystal (b) (4) Therefore, the active ingredient/drug substance of the product is "ertugliflozin", to be reflected in the labeled established name and corresponding dosage strength.
Reference is made to the approved NDA 21995 JANUVIA (sitagliptin) tablets, same applicant, for CMC information on the drug substance sitagliptin phosphate, a small synthetic molecule.

The drug product is an immediate release oral tablet, in fixed ratio combinations with four strengths: (b) (4) 5/100, 15/100 mg/mg ertugliflozin/sitagliptin.

Bioequivalence studies were conducted to compare all four combination strengths to the concomitant administration of ertugliflozin tablets and JANUVIA tablets. The biobatches had the commercial formulation with the exception of colors and debossing and were manufactured at the R&D site (b) (4) The biowaiver request for the product manufactured at the commercial site (b) (4) is granted based on comparative dissolution profiles.

Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	[not finalized by GRMP goal; see CDTL's memo]
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	n/a

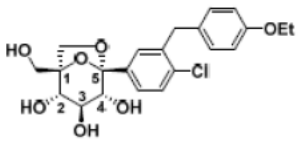
A. Quality Assessment Overview

Drug Substance: Ertugliflozin

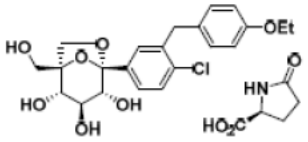
Ertugliflozin: (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol

Ertugliflozin L-PGA: (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid

Figure 2.3.S.1-1. Ertugliflozin and Ertugliflozin L-PGA Structures



Ertugliflozin



Ertugliflozin L-PGA

Molecular Formula

Ertugliflozin: $C_{22}H_{25}ClO_7$

Ertugliflozin L-PGA: $C_{27}H_{32}ClNO_{10}$

Molecular Weight

Ertugliflozin: 436.88 Daltons

Ertugliflozin L-PGA: 566.00 Daltons

Ertugliflozin is an unstable amorphous material that was developed as a 1:1 co-crystal with L-pyroglutamic acid (LPGA) in order to achieve better physical and chemical properties including stability. As per FDA's guidance "Regulatory Classification of Pharmaceutical Co-Crystals", the ertugliflozin-LPGA co-crystal (b) (4) and the active ingredient of the product is "ertugliflozin". Adequate CMC information is provided in the NDA on ertugliflozin, LPGA, and the co-crystal.

Ertugliflozin-LPGA is BCS 1, non-hygroscopic, and crystalline (b) (4)

(b) (4)

The drug substance specification includes standard quality attributes of a small synthetic molecule including chirality and LPGA content. Batch analysis data include batches from the commercial site "Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland" and the R&D site "Pfizer Sandwich, UK".

Particle size – This attribute is not critical to dissolution because the drug substance is BCS 1 (i.e., highly soluble). Therefore, acceptance criteria are established (b) (4)

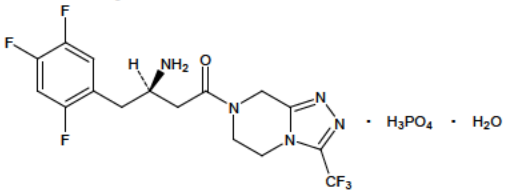
Impurities – (b) (4) have limits that exceed the ICH qualification thresholds; their limits are considered qualified by the Pharmacology Toxicology team. All specified impurities, including these three, were evaluated for mutagenicity and none was found positive (confirmed by the Pharmacology Toxicology team).

Polymorphism – Ertugliflozin-LPGA has the (b) (4) Free ertugliflozin has different physico-chemical properties and can be readily controlled by test methods (b) (4) Therefore, the lack of polymorph testing in the drug substance specification is acceptable.

A retest period (b) (4) is acceptable for Ertugliflozin-LPGA (b) (4) The retest period is based on stability data for (b) (4) batches, manufactured at "Pfizer Sandwich, UK" and the commercial site "Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland".

Drug Substance: Sitagliptin

Reference is made to the approved NDA 21995 JANUVIA (sitagliptin) tablets, same applicant, for CMC information on the drug substance sitagliptin phosphate, a small synthetic molecule.



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

$C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ molecular weight 523.32

Drug Product

The drug product is an immediate release oral tablet, in fixed ratio combinations with four strengths: (b) (4) 5/100, 15/100 mg/mg ertugliflozin/sitagliptin. The 5 mg or 15 mg ertugliflozin corresponds to 6.477 mg or 19.431 mg ertugliflozin-LPGA, respectively.

Excipients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, sodium stearyl fumarate, and magnesium stearate. The inert film coating contains hypromellose, hydroxypropyl cellulose, titanium dioxide, iron oxide red, ferrosoferric oxide/black iron oxide, and carnauba wax. There is no novel excipient, and there is no human/animal-derived excipient.

(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, including information on elemental impurities.

Degradants - No sitagliptin degradant was observed (b) (4)
The two specified ertugliflozin-related degradants (b) (4) have limits (b) (4) Both were evaluated for mutagenicity and found negative (confirmed by the Pharmacology Toxicology team). (b) (4) are degradants resulting from the interaction between ertugliflozin and the (b) (4) excipient in the formulation, (b) (4) Both were found negative for mutagenicity (confirmed by the Pharmacology Toxicology team).

Disintegration – The use of disintegration in lieu of dissolutionis acceptable based on ertugliflozin-LPGA and sitagliptin phosphate monohydrate being both highly soluble, and disintegration was shown to be more discriminating than dissolution to changes in tablet hardness and tensile strength.

Polymorphism is not part of the specification. (b) (4)

(b) (4) Therefore, polymorph testing is not necessary.

(b) (4)

Primary container closure system: The drug product is packaged in (b) (4) bottles/closures and aluminum blisters.

Expiration Date & Storage Conditions: The shelf life of the drug product is 24 months at room temperature.

The long-term expiry is based on 12-month long-term (25 C/60% RH) and 6-month accelerated (40 C/75% RH) data are provided in the NDA for three primary stability batches of each of the 5/100 and (b) (4) the 15/100 (b) (4) strengths. Stability batches were manufactured at the R&D site (b) (4), with ertugliflozin LPGA from the R&D site Pfizer Sandwich in the UK and with sitagliptin phosphate monohydrate from (b) (4) and were packaged in the commercial container closure systems, utilizing a reduced design to bracket the 30-count and 90-count bottles.

Environmental assessment (EA): Ertugliflozin-LPGA is categorically excluded from an an EA. The NDA includes an EA for sitagliptin phosphate monohydrate. Based on all available information in the application and literature, a finding of no significant impact is granted and an environmental impact statement will not be required for this active ingredient.

B. Special Product Quality Labeling Recommendation: not applicable

C. Life Cycle Knowledge Information/ Final Risk Assessment:

API	none
Drug product	page 45 of Chapter II
Process	none
Facilities	page 6 of Chapter VI
Biopharmaceutics	none

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

Suong T. Tran -S

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Suong (Su) Tran, Ph.D.
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LABELING

NDA 209805

R Regional Information

1.14 Labeling

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment:

The labels contain all the necessary information and are accurate from a CMC perspective and are consistent with other fixed dose combination drug product labels. However, since the product is moisture sensitive, I recommend that the following statement be placed on the 500 tablet bottle immediate container labels (for all strengths) from which a pharmacy dispenses individual patient dose.

"**Dispense into a USP tightly closed, moisture-resistant container**".

Also, the storage statement for the bottles should be revised from, "Protect from moisture. Store in a dry place" to "**Store in tightly sealed container in a dry place**" as a user may not be able to know what does protect from moisture means.

In the final labeling the word Trademark™ will be replace with the actual trademark of the drug product and the "FPO" will be replaced by the image of actual tablet with embossed side up. An example is provided and reproduced below.

(b) (4)

[redacted]

CARTON LABELING

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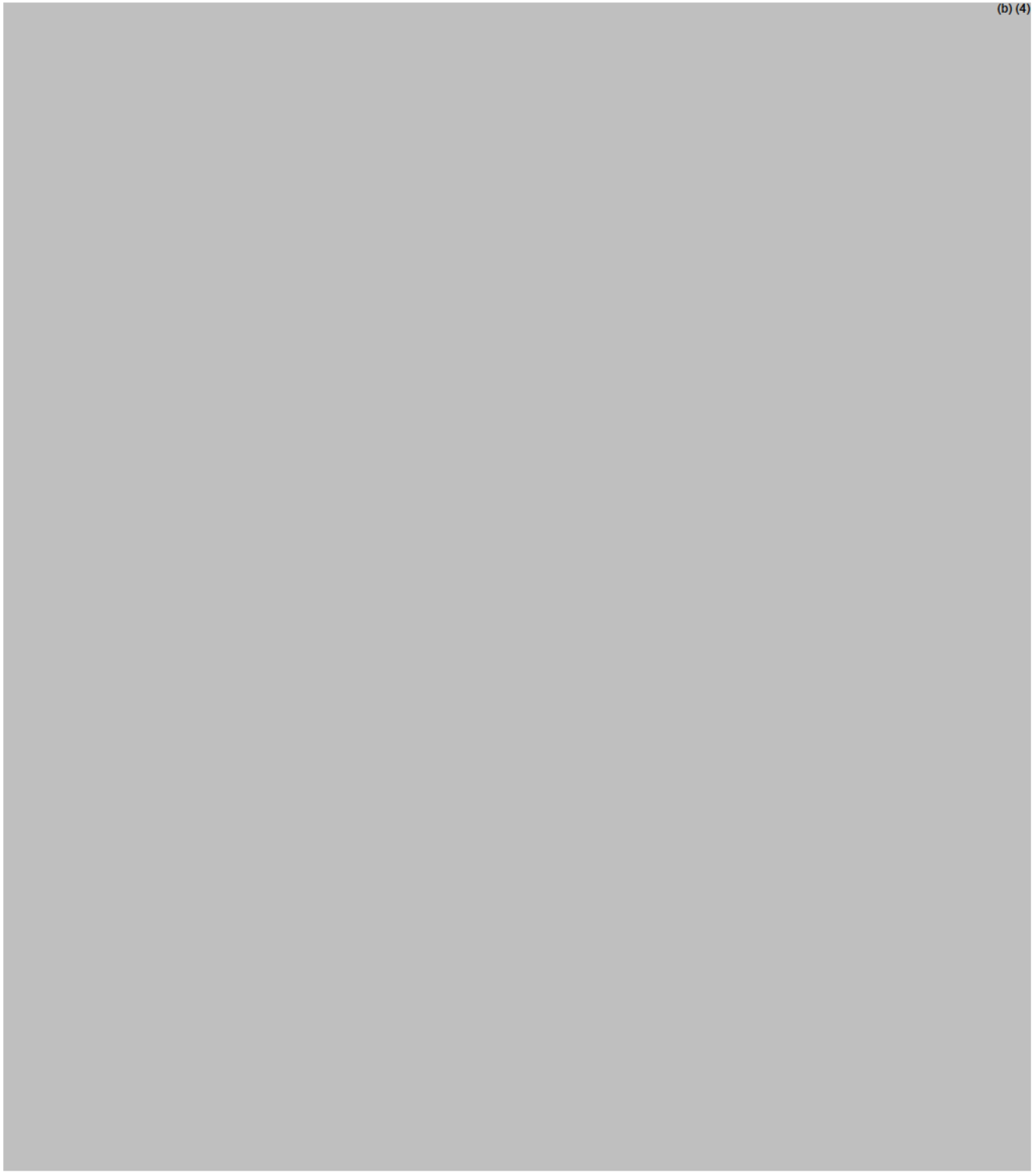
(b) (4)



Reviewer's Assessment:

The labels contain all the necessary information and are accurate from a CMC perspective,

except that the storage statement in the carton for 7 tablet HDPE sample bottles should be revised from, "Protect from moisture. Store in a dry place" to "**Store in tightly sealed container in a dry place**" as a user may not be able to know what does protect from moisture means.

- ***Package Insert:***

DOSAGE FORMS AND STRENGTHS

- (b) (4)
- TRADEMARK™ 5 mg/100 mg tablets are beige, almond-shaped, film-coated tablets debossed with "554" on one side and plain on the other side.
- TRADEMARK™ 15 mg/100 mg tablets are brown, almond-shaped, film-coated tablets debossed with "555" on one side and plain on the other side.

Reviewer's Assessment:

The dosage form and strength description is acceptable from a CMC point of view.

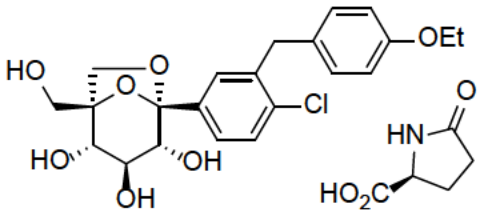
11 DESCRIPTION

TRADEMARK contains ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor, and sitagliptin phosphate, a DPP-4 inhibitor.

Ertugliflozin

The chemical name of ertugliflozin L-pyroglutamic acid is (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid. The molecular formula is $C_{27}H_{32}ClNO_{10}$ and the molecular weight is 566.00.

The chemical structure is:

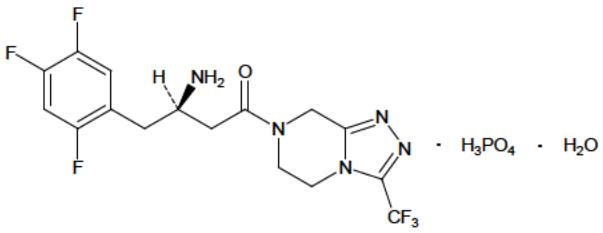


Ertugliflozin L-pyroglutamic acid is a white to off-white powder that is soluble in ethyl alcohol and acetone, slightly soluble in ethyl acetate and acetonitrile and very slightly soluble in water.

Sitagliptin

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

The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N, N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

TRADEMARK is available for oral use as film-coated tablets containing:

- (b) (4)
- 6.48 mg ertugliflozin L-pyroglutamic acid equivalent to 5 mg of ertugliflozin and 128.5 mg sitagliptin phosphate monohydrate equivalent to 100 mg sitagliptin (TRADEMARK 5/100)
- 19.43 mg ertugliflozin L-pyroglutamic acid equivalent to 15 mg of ertugliflozin and 128.5 mg sitagliptin phosphate monohydrate equivalent to 100 mg sitagliptin (TRADEMARK 15/100)

Inactive ingredients are microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, sodium stearyl fumarate, and magnesium stearate.

The film coating contains: hypromellose, hydroxypropyl cellulose, titanium dioxide, iron oxide red, ferrous or ferric oxide/black iron oxide, and carnauba wax.

(b) (4)

Reviewer's Assessment:

The other aspects of the description section are accurate from a CMC perspective.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRADEMARK (ertugliflozin and sitagliptin) tablets are available in the strengths listed below:

(b) (4)

(b) (4)

TRADEMARK tablets, 5 mg/100 mg, are beige, almond-shaped, film-coated tablets debossed with "554" on one side and plain on the other side. They are supplied as follows:

(b) (4)

NDC 0006-5367-03 unit-of-use bottles of 30
NDC 0006-5367-06 unit-of-use bottles of 90
NDC 0006-5367-07 bulk bottles of 500

TRADEMARK tablets, 15 mg/100 mg, are brown, almond-shaped, film-coated tablets debossed with "555" on one side and plain on the other side. They are supplied as follows:

(b) (4)

NDC 0006-5368-03 unit-of-use bottles of 30
NDC 0006-5368-06 unit-of-use bottles of 90
NDC 0006-5368-07 bulk bottles of 500

Storage of Bottles
Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (between 59-86°F). Protect from moisture. Store in a dry place.

(b) (4)

Reviewer's Assessment:

The "How Supplied" and "Storage" statements are accurate from a CMC perspective and are acceptable. However, as indicated previously the storage statement for the bottles should be revised from, "Protect from moisture. Store in a dry place" to "**Store in tightly sealed container in a dry place**" as a user may not be able to know what does protect from moisture means.

List of Deficiencies:

1. **Place statement "Dispense into a USP tightly closed moisture-resistant container", on the 500 tablet bottles immediate container labels (for all strengths).**
2. **Revise the storage statement for the bottles (immediate container labels, sample carton labels and package insert) from, "Protect from moisture. Store in a dry place" to "Store in tightly sealed container in a dry place" as a user may not be able to know what does protect from moisture means.**

Primary Labeling Reviewer Name and Date:

Ravindra K. Kasliwal, Ph.D. August 21, 2017
CMC Reviewer
Branch VI, DNDP-II
ONDP / OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur with primary reviewer's recommendations.

Suong T. Tran, Ph.D.
Team Lead
Branch VI, DNDP-II
ONDP/ OPQ

Su (Suong) Tran

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Ravindra Kasliwal

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CHAPTER III: Environmental Analysis

ENVIRONMENTAL ANALYSIS

R Regional Information

Summary: The applicant provided an environmental assessment (EA) for SIT and a claim for a categorical exclusion for ERT. For the EA for SIT, FDA concludes that (1) the EA contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment and (2) the proposed action does not appear to significantly affect the environment. A finding of no significant impact (FONSI) is recommended for SIT. For the categorical exclusion claim for ERT, the applicant cited the appropriate exclusion and provided the required statement of no extraordinary circumstances. FDA requested additional information to confirm the lack of extraordinary circumstances. The claim and supporting information were reviewed and the claim found to be acceptable.

Environmental Analysis

The applicant filed an NDA for the use of ertugliflozin (ERT) administered as a fixed-dose combination with sitagliptin (SIT) for the treatment of type 2 diabetes mellitus (T2DM). ERT/SIT is formulated as an immediate-release tablet for oral administration in four dose strengths (i.e., 5 mg or 15 mg ERT, each in combination with (b) (4) 100 mg SIT).

SIT EA

The applicant submitted an EA, dated March 16, 2016, for SIT, pursuant to 21 CFR 25, noting that the EA was compiled in accordance with Guidance for Industry: Environmental Assessments of Human Drug and Biologics Application (USFDA, 1998). Briefly, this EA noted the following:

1. Fate/Depletion. The physical/chemical characteristics of SIT suggest that sitagliptin has a low probability for bioaccumulation in the environment. In the human absorption-distribution-metabolism-excretion (ADME) study, SIT was confirmed to be primarily renally eliminated, indicating significant uptake. Approximately 85% was accounted for by the parent drug substance. SIT is not susceptible to hydrolysis, does not photolyze, and shows very little primary degradation in the aerobic and anaerobic sediment-water systems. Therefore, when calculating the expected introductory concentration (EIC), removal due to wastewater treatment was not taken into account.

2. Exposure. The EIC of SIT, assuming no degradation or adsorption, is (b) (4) µg/L. Metabolism in the body results in an EIC value of (b) (4) µg/L. In the aquatic environment, assuming no dilution or degradation, SIT has a maximum expected environmental concentrations (MEEC) of (b) (4) µg/L. The PEC for sediment was not provided. No air exposure is expected.

3. Toxicity. Chronic toxicity data in the aquatic environment were provided for three species. The most sensitive aquatic organism was *P. subcapitata* (green algae) with a 72-hour lowest no-observed-effect concentration (NOEC) of 840 µg/L. For sediment, two species were assessed, and *Lumbriculus variegatus* (blackworm) resulted in the lowest NOEC, (b) (4) mg/kg, based on survival.

4. Risk. This aquatic toxicity NOEC of 840 µg/L more than (b) (4) of magnitude greater than the EIC of (b) (4) µg/L, thus indicating negligible risk, especially given the conservative assumptions regarding the EIC. The sediment risk could not be calculated because only toxicity data were available.

The applicant concluded that no environmental issues were anticipated related to patient use of this product.

ERT Categorical Exclusion

The applicant submitted a claim for a categorical exclusion from an EA for ERT in accordance with 21 CFR Part 25.31(b), noting that the EIC will be below 1 ppb, and in particular (b) (4) ppb. The applicant stated that to the best of their knowledge, no extraordinary circumstances exist.

Reviewer's Assessment:

SIT EA

The main goals of this review of the SIT EA, per 21 CFR 25.15(a) and (b), are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) if so, whether the proposed action will significantly affect the environment.

The EA was found to be missing expected sediment concentration data with which to compare with the toxicity data and thus characterize the risk for sediments. Therefore, FDA requested that the applicant provide maximum and/or expected SIT concentrations in sediments to allow this comparison. In response, the applicant used the EIC value of (b) (4) ug/L to model a corresponding PEC sediment value of (b) (4) mg/kg. This value is (b) (4) lower than the designated NOEC of (b) (4) mg/kg, thus indicating negligible risk from SIT in sediments from this application. FDA examined the supporting calculations and agreed with the conclusion.

The remainder of the EA for SIT contains sufficient information to enable a determination of whether the proposed action may significantly affect the quality of the human environment. The data appeared to be accurate and objective. This assessment should be considered worst-case. Specifically, the calculation of the EIC does not take into consideration of (1) degradation during wastewater treatment or (2) dilution, degradation, or removal in surface water. FDA expects that a PEC would be more than an order of magnitude below the EIC. Therefore, FDA agrees that SIT poses no significant environmental risk via this application.

ERT Categorical Exclusion

Given the status of ERT as a new molecular entity, FDA conducted a literature search and also used a fish plasma model (FPM) based on Huggett et al. (2003) to screen for aquatic environmental risk. No additional literature was found, but the FPM showed that based on an EIC of (b) (4) µg/L, a therapeutic concentration of (b) (4) µg/mL (Cmax from p. 9 of module 2.6.6, Toxicology Written Summary), and a log D of (b) (4) (pH (b) (4); from www.chemspider.com), the effect ratio (ER) (b) (4), thus indicating the need for additional information. Therefore, to assist us in confirming that extraordinary circumstances do not exist for ERT, FDA ask the applicant to provide any readily available literature, data, and/or analysis for estimating or providing (1) a more realistic expected environmental concentration, (2) more relevant toxicity data (including from similar molecules), and/or (3) any other indicators of possible environmental risk.

The applicant responded by providing a Phase II, Tier A environmental fate and effects assessment of ERT, conducted as per the EMEA/CHMP/SWP/4447/00 entitled "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (June 1, 2006). This Environmental Risk Assessment (ERA) is based on a calculated PEC for surface water of (b) (4) µg/L, which is higher than the US EIC of (b) (4) µg/L, and still higher if dilution in surface water was accounted for as in the ERA PEC derivation. The PEC/PNEC risk quotients derived for surface water, ground water, micro-organisms, and sediment are all below the respective action criteria and, therefore, the applicant concludes that ERT will not present an environmental risk following patient use. FDA reviewed this ERA and agrees that ERT in this application does not present extraordinary circumstances.

References:

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Decision:

The EA for SIT is adequate for approval of the NDA. The EA contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and additional reports, and on the scientific validity of the conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA for SIT. Therefore, based on the information available to date, a FONSI is recommended for this portion of the application. For the categorical exclusion claim for ERT, the applicant cited the appropriate exclusion and provided the required statement of no extraordinary circumstances. FDA requested additional information to confirm the lack of extraordinary circumstances. The claim and supporting information were reviewed and the claim found to be acceptable.

Primary EA Reviewer Name and Date: James P. Laurenson, June 14, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): M. Scott Furness, June 16, 2017

James Laurenson

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Michael Furness

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Finding of No Significant Impact

NDA 209805 Ertugliflozin/Sitagliptin (ERT/SIT) Tablet, (b) (4) 5/100 mg, and 15/100 mg

Food and Drug Administration
Center for Drug Evaluation and Research

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

Merck & Co., Inc. (Merck) requests approval of NDA 209805 for the treatment of type 2 diabetes mellitus. The product is a tablet with ertugliflozin/sitagliptin in the following combinations doses: (b) (4) 5/100 mg, and 15/100 mg. Ertugliflozin is an oral, selective inhibitor of sodium glucose cotransporter-2 (SGLT2) and has been categorically excluded from an environmental assessment (EA). Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme and is the subject of this finding.

In support of its application, Merck prepared an EA, including an amendment, for sitagliptin (attached). This EA evaluates the potential environmental impact from the use and disposal of this product. The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and has carefully considered the potential environmental impact due to approval of this application. CDER conducted a literature search that did not result in any conflicting information. Based on the CDER review of the entirety of this information, FDA has determined that approval of the present application for sitagliptin is not expected to have a significant impact on the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

Attachments: March 24, 2016, Environmental Assessment; and June 5, 2017, Amendment

1. Date: 24 March 2016

2. Name of Applicant/Petitioner: Merck & Co., Inc.

3. Address: Sumneytown Pike
West Point, PA 19486

4. Description of Proposed Action:

a. Requested Approval

Merck & Co., Inc., is filing a New Drug Application pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin/sitagliptin (MK 8835A) (b) (4) 5/100mg and 15/100mg) packaged in high density polyethylene (HDPE) bottles with desiccant and closures with heat induction seal liner, and in aluminum foil blister and lidding. An EA has been submitted pursuant to 21 CFR part 25.

b. Need for Action

Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme developed by Merck & Co., Inc. for the treatment of type 2 diabetes mellitus. Sitagliptin is present in MK-0431 tablets in the form of sitagliptin phosphate monohydrate (sitagliptin phosphate, MK-0431).

c. Locations of Use

The product will be used in hospitals, clinics, and/or in homes throughout the United States.

d. Disposal Sites

At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, drug take-

back programs and recycling, although minimal quantities of unused drug could be disposed of in the sewer system.

5. Identification of Substances that are Subject of the Proposed Action:

a. Nomenclature

i. **Established Name (U.S. Adopted Name – USAN):** Sitagliptin (as sitagliptin phosphate)

ii. **Brand/Proprietary Name/Trade Name:** JANUVIA™

iii. **Chemical Names:**

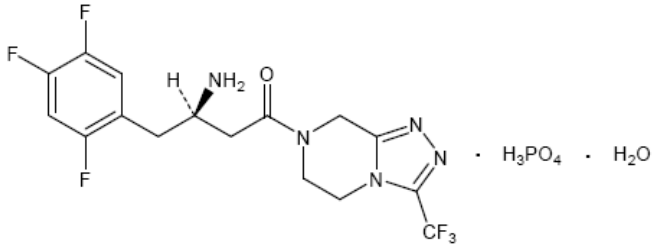
- **Chemical Abstracts (CA) Index Name (inverted form):** 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate

b. **Chemical Abstracts Service (CAS) Registration Number:** 65467-77-9

c. **Molecular Weight:** 523.32

d. **Molecular Formula:** $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$

e. **Structural (graphic) Formula:**



6. Environmental Issues:

Summary. The pharmacologic agent, sitagliptin, is used to treat Type 2 diabetes mellitus. Sitagliptin is also marketed singly or with metformin under the trademarks JANUVIA™ and JANUMET™. The Expected Introduction Concentration (EIC) for sitagliptin phosphate for all products, based on the latest production estimates for 2020 (Confidential/Appendix B) (b) (4) an Environmental Assessment (EA) was conducted as described by the Guidance for Industry. Based on the predicted EIC and the

low aquatic toxicity of sitagliptin, no environmental issues are anticipated related to patient use of this product.

Physical/Chemical Characteristics. A summary of physical/chemical data is given in Appendix A. The aqueous solubility of sitagliptin is 69.5 mg/g at 24.5°C (Module 3.2.S.2.1 of the Original New Drug Application). The compound has an octanol/water partition coefficient (K_{ow}) which is dependent on pH. At pH=5.0, the log K_{ow} = –1.08, at pH=7.0 the log K_{ow} = –0.03, and at pH=9.0 the log K_{ow} = 1.11 as determined according to OECD Guideline 107 [1]. The K_{ow} and water solubility data suggests that sitagliptin has a low probability for bioaccumulation in the environment.

Metabolism of the Drug Substance. In the human absorption-distribution-metabolism-excretion (ADME) study, sitagliptin phosphate derived radioactivity was confirmed to be primarily renally eliminated. The mean recovery of the orally administered radioactivity was approximately 87% of the orally administered dose in urine and 13% of the orally administered dose in feces. Of the dose excreted in the urine, approximately 85% of the radioactivity was accounted for by parent drug substance. The remainder of the radioactivity in the urine was comprised of six metabolites, each comprising less than or equal to 4% of the radioactivity of the total dose. Of the dose excreted in the feces, approximately 72% was accounted for by parent drug substance. Metabolite profiles in feces were similar to those in urine, except that two of the metabolites found in the urine were not detected in the feces.

Depletion Mechanisms. Sitagliptin is not susceptible to hydrolysis per OECD 111 in the aquatic environment ($t_{1/2}$ = 895 days, pH = 7 and 25°C) [2]. The compound does not photolyze (no potential for phototransformation between 295 and 800 nm) [3] and is not readily biodegradable per OECD 302B (7% loss after 28 days) [4].

Since sitagliptin is not readily biodegradable, a transformation study was conducted to assess potential biodegradation in aerobic and anaerobic aquatic sediment systems using the OECD 308 method [5]. Results of the OECD 308 study suggest that very little primary degradation of sitagliptin occurred in the aerobic and anaerobic sediment-water systems. The times of disappearance of 50 percent of the parent (DT50) from the aqueous layers were 6.5 to 20.9 days and 138.6 to 266.5 days in the aerobic and

anaerobic test systems, respectively. The results of the study also indicated that sitagliptin has the potential for sorption to sediments. The mass balance results from day 103 indicated that up to 78% of the dosed radioactivity was found in the extractable sediment fraction and up to 28% was found in the bound fraction. The mass balance data from day 103 is summarized in Appendix A.

Upon entering waste water treatment, the removal of sitagliptin phosphate due to hydrolysis, photolysis, and biodegradation is expected to be minimal. Therefore, when calculating the expected introductory concentration (EIC), removal due to waste water treatment was not taken into account. The K_{ow} and water solubility suggest that sitagliptin phosphate has a low probability for bioaccumulation.

EIC Calculation. The EIC was calculated in accordance with the formula given in the Guidance for Industry (b) (4) Detailed calculations and the resultant estimates are provided in Appendix B/Confidential. (b) (4)

Environmental Assessment. The primary route of exposure of sitagliptin is excretion to wastewater. Therefore, this environmental assessment focuses on exposures to aquatic and sediment-dwelling organisms.

Chronic aquatic toxicity studies to freshwater organisms were performed according to OECD Guidelines for testing. The 21-day EC_{50} (reproduction endpoint) for sitagliptin to the water flea, *Daphnia magna,* was greater than 9.8 mg/L using a flow-through life-cycle toxicity test according to OECD 211. The 21-day no-observable-effect concentration (NOEC) for *D. magna* was 9.8 mg/L (reproduction endpoint) [6]. The 33-day NOEC for sitagliptin to the fathead minnow, *Pimephales promelas*, was 9.2 mg/L in an early life stage toxicity test per OECD 210 [7]. There were no statistically significant treatment-related effects on hatching success, survival or growth at any concentration tested. Consequently, the lowest-observed-effect concentration for *P. promelas* was greater than 9.2 mg/L. In a study with *Pseudokirchneriella subcapitata* (freshwater green algae) per OECD 201, the 72 and 96–hour EC_{50} values, based on growth rate, were greater than 39 mg/L, the highest concentration tested. The 72- and 96-hour NOEC,

based on effects on cell density, yield, and growth rate, were 0.84 and 2.2 mg/L, respectively [8].

In order to evaluate if sitagliptin exhibited any anti-microbial effects, the Activated Sludge Respiration Inhibition Test (ASRIT) was carried out according to OECD 209 [9]. The data from the ASRIT study is useful in predicting if the drug substance will disrupt the microbial communities in the STP. The study determines if the drug substance has an effect on activated sludge microorganisms maintained in an aerobic environment. Based on the results of the ASRIT study, sitagliptin is considered non-toxic to unacclimated activated sludge with a 3-hour EC_{50} estimated to be greater than or equal to 150 mg/L.

Because greater than 10% of the compound was present in the sediment at the termination of the OECD 308 study, a sediment toxicity test was also completed. In order to assess the potential effects of sitagliptin to sediment organisms, a prolonged sediment toxicity test with *Chironomus riparius*, using spiked sediment, was undertaken according to the OECD 218 method [10]. The 28-Day EC_{50} value based on percent survival of *Chironomus riparius* midges exposed to sediment-incorporated ^{14}C-sitagliptin was greater than 1000 mg/kg. There were no treatment related effects observed on mean emergence rates in any of the treatment groups, but there were significant differences ($p<0.05$) between the negative control and the 1000 mg/kg treatment groups in comparisons of development time and development rate. Therefore, the 28-Day LOEC was 1000 mg/kg and the 28-Day NOEC was 500 mg/kg, based on development time and development rate.

In addition to the *Chironomus riparius study,* a prolonged sediment toxicity test with *Lumbriculus variegatus*, using spiked sediment, was undertaken according to the OECD 225 method [11]. The 28-Day EC_{50} value based on percent survival of *Lumbriculus variegatus* oligochaetes exposed to sediment-incorporated ^{14}C-sitagliptin was greater than 1000 mg/kg. There were differences in the mean number of worms observed in half of the treatment groups at test termination, however since the other half of the treatment groups were not significantly different from the negative control group, the significance is not believed to be treatment related. The 28-Day LOEC was 63 mg/kg and the 28-Day NOEC was 31 mg/kg, based on survival.

The aquatic and microbial effects studies are summarized in Appendix A.

As chronic toxicity data for three species are available, a Tier 3 assessment was performed. The most sensitive organism in chronic toxicity testing was *P. subcapitata* with a 72-hour NOEC of 0.84 mg/L.

The MEEC (Maximum Expected Environmental Concentration) as presented in Confidential Appendix B, (b) (4) As such, no environmental effects related to patient use of sitagliptin phosphate are anticipated.

7. Mitigation Measures:

No adverse environmental effects have been identified. Therefore, no mitigation measures are needed.

8. Alternatives to the Proposed Action:

No potential adverse environmental effects have been identified for the proposed action so no alternatives are necessary.

9. List of Preparers:

Lisa Ziv, M.S.

Director, Merck Global Safety & the Environment

B.S., James Madison University, Harrisonburg, VA, 1997

M.S., Environmental Management, Yale University, New Haven, CT, 2001

10. References:

[1] Wildlife International, Ltd., Determination of n-octanol/water partition coefficient of MK-0431 by the shake flask method, 2009. 03QQH9

[2] Wildlife International,Ltd, MK-0431: An evaluation of hydrolysis as a function of pH, 2005. 03QM3Y

[3] Wildlife International, Ltd, Phototransformation Potential of MK-0431, 2005. 03QM44

[4] Wildlife International, Ltd, MK-431: An evaluation of inherent biodegradability using the zahn-wellens/EMPA test, 2005. 03QM3Z

[5] Springborn Smithers Laboratories, [14C]MK-0431 - Aerobic and anaerobic transformation in aquatic sediments systems following OECD guideline 308, 2007. 03QM40

[6] Wildlife International, Ltd, MK-0431: A flow-through life-cycle toxicity test with the cladoceran (daphnia magna), 2006. 03QM43

[7] Wildlife International, Ltd, MK-0431: An early life-stage toxicity test with the fathead minnow (pimephales promelas), 2006. 03QM42

[8] Wildlife International, Ltd., Sitagliptin: A 96-hour toxicity test with the freshwater alga (pseudokirchneriella subcapitata) final report, 6-1-2009. 03QTY8

[9] Toxikon Corporation, MK-0431: Activated sludge, respiration inhibition test, 2004. 03QM3X

[10] Wildlife International, Ltd., [14C]-MK-0431: A prolonged sediment toxicity test with chironomus riparius using spiked sediment, 2008. 03QMD6

[11] Wildlife International, Ltd., [14C]-MK-0431: A prolonged sediment toxicity test with lumbriculus variegatus using spiked sediment, 2008. 03QQH7

11. Appendices:

(Attached)

APPENDIX A

Non-Confidential Information

APPENDIX A: DATA SUMMARY TABLE FOR SITAGLIPTIN **NON-CONFIDENTIAL**

PHYSICAL/CHEMICAL CHARACTERIZATION		
Water Solubility		69.5 mg/mL (24.5°C)
Dissociation Constant (pK_a)		7.02
Log Octanol/Water Partition Coefficient ($\log K_{ow}$)		$\log K_{ow}$ = -0.03 @ pH 7.0
Vapor Pressure		Not Applicable
Sorption/Desorption ($\log K_{oc}$)		Sludge $\log K_{oc}$ = 1.27
DEPLETION MECHANISMS		
Hydrolysis		Half-life @ pH 7 = 895 days
Aerobic Biodegradation		28 day recovery = 93%
Soil Biodegradation		Not anticipated
Photolysis		Does not photolyze between 295 and 800 nm
Metabolism		Very little metabolism (see text)
ENVIRONMENTAL EFFECTS		
Activated Sludge Inhibition		3-hour EC_{50} > 150 mg/L; NOEC = 150 mg/L
Sediment Toxicity (Midge)		28-day LOEC= 1000 mg/kg; NOEC = 500 mg/kg
Sediment Toxicity (Oligochaete)		28-day LOEC = 63 mg/kg; NOEC = 31 mg/kg
Chronic Aquatic Toxicity		
Organism	**Endpoint**	**Result**
Daphnia Magna (water flea)	Reproduction	NOEC = 9.8 mg/L
Pimephales promelas (fathead minnow)	Growth, Mortality, Reproduction	NOEC = 9.2 mg/L
Pseudokirchneriella subcapitata (green algae)	Growth	72-hour EC_{50} > 39 mg/L; NOEC = 0.84 mg/L 96-hour EC_{50} > 39 mg/L; NOEC = 2.2 mg/L

APPENDIX A

MASS BALANCE OF SITAGLIPTIN IN SEDIMENT-WATER SYSTEMS: DAY 103

PARAMETER	INTERVAL/RESULT (Material Balance)
Water Layer	**Through Day 103**
aerobic test systems	1.7% – 4.7%
anaerobic test systems	4.3%
Sediment extractable	**Through Day 103**
aerobic test systems	60.5% – 65.1%
anaerobic test systems	76.9% – 78.4%
Bound sediment residues	**Through Day 103**
aerobic test systems	26.6% – 28.7%
anaerobic test systems	13.5% – 14.6%
Volatile gases	**Through Day 103**
aerobic test systems	1.8% – 2.2%
anaerobic test systems	<0.1%
Total	**All intervals**
aerobic test systems	92.7% – 107.5%
anaerobic test systems	95.7% – 107.3%

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James Laurenson

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Michael Furness

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BIOPHARMACEUTICS

Product Background:

NDA: 209805

Drug Product Name / Strength: ertugliflozin/sitagliptin fixed-dose combination (FDC) (b) (4) 5/100 mg, (b) (4) and 15/100 mg

Route of Administration: Oral

Indication: Treatment of Type II diabetes

Applicant Name: Merck

Review Summary:

Ertugliflozin/sitagliptin FDC is administrated once daily for Type II diabetes. The composition for the proposed drug product is shown in Table 1.

Table 1. Final Market Formulations for Ertugliflozin/Sitagliptin Tablets

Strength		(b) (4)	5/100 mg	(b) (4)	15/100 mg
Component	Function		mg/tablet	%	mg/tablet	%
Ertugliflozin L-PGA*	Active		6.477	(b) (4)	19.43	(b) (4)
Sitagliptin phosphate monohydrate†	Active		128.5		128.5	
Microcrystalline Cellulose	(b) (4)		(b) (4)		(b) (4)	
Dibasic Calcium Phosphate Anhydrous						
Croscarmellose Sodium						
Sodium Stearyl Fumarate						
Magnesium Stearate						
(b) (4)		(b) (4)				
(b) (4)						
Carnauba Wax						
(b) (4)			-		-	
Coated Tablet Weight			411.8		411.8	

* 1.000 g of ertugliflozin L-PGA is equivalent to 0.772 g of the ertugliflozin free form. (b) (4)

† 1.285 g of sitagliptin phosphate monohydrate is equivalent to 1.000 g of the sitagliptin free form. (b) (4)

Concise Description Outstanding Issues Remaining:

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

{Assess method development, method robustness, and criteria; modeling approach}

The proposed dissolution method is shown in Table 2.

Table 2. Dissolution method summary

Apparatus	USP Apparatus I (baskets), with 10 mesh
Rotational Speed	100RPM
Dissolution medium	Acetate buffer pH 4.5 (USP)
Medium volume	900 mL
Medium Temperature	37 ± 0.5°C
Sampling Volume	1.5 mL (auto-sampling) 5 mL (manual sampling) with 3 mL discard
Sampling time	10, 15, 20, 30, 60 minutes
Clarification	(b) (4)

(b) (4)

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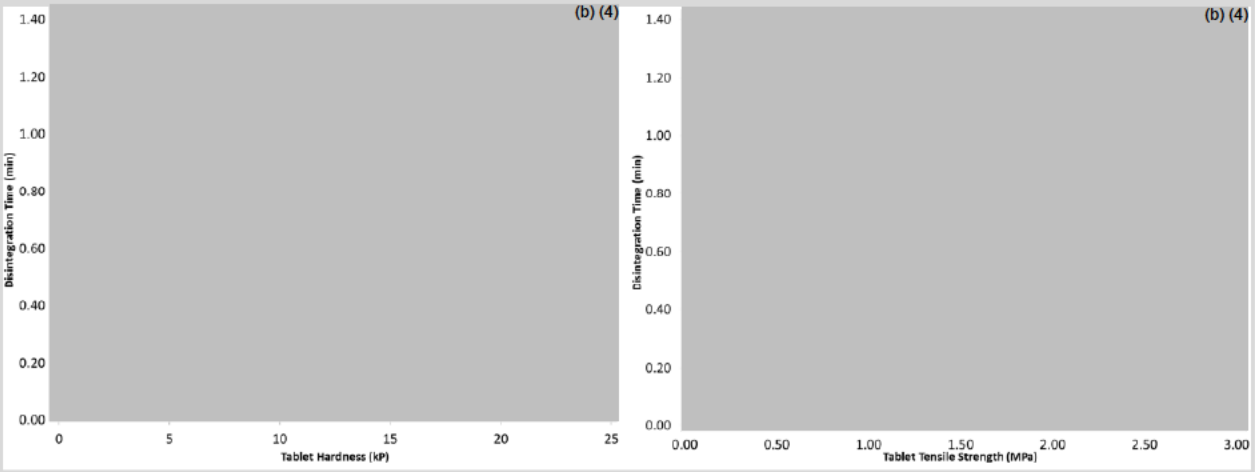
Figure 7. Disintegration Time as a Function of Tablet Hardness (Left) and Tablet Tensile Strength (Right) for Ertugliflozin/Sitagliptin Tablets



The Applicant submitted the validation report for the analytical method of dissolution. This validation report would be reviewed by the drug product reviewer.

2. Dissolution acceptance criterion

Although the Applicant proposed disintegration test in line of dissolution in release and stability control, the Applicant would continue to apply dissolution method to support potential future post-approval changes. As of that, the proposed dissolution method acceptance criterion for both ertugliflozin and sitagliptin in FDC tablets is NLT (b) (4)% (Q) in 15 min. Figure 8 shows the mean dissolution profiles of ertugliflozin (Figure 8A) and sitagliptin (Figure 8B) from different strengths of clinical/stability batches.

Figure 8A. Mean Dissolution Profiles for Ertugliflozin in Ertugliflozin/Sitagliptin Tablets Intended for Clinical/Stability Supplies in pH 4.5 Acetate Buffer using 100 RPM Apparatus (I) Baskets

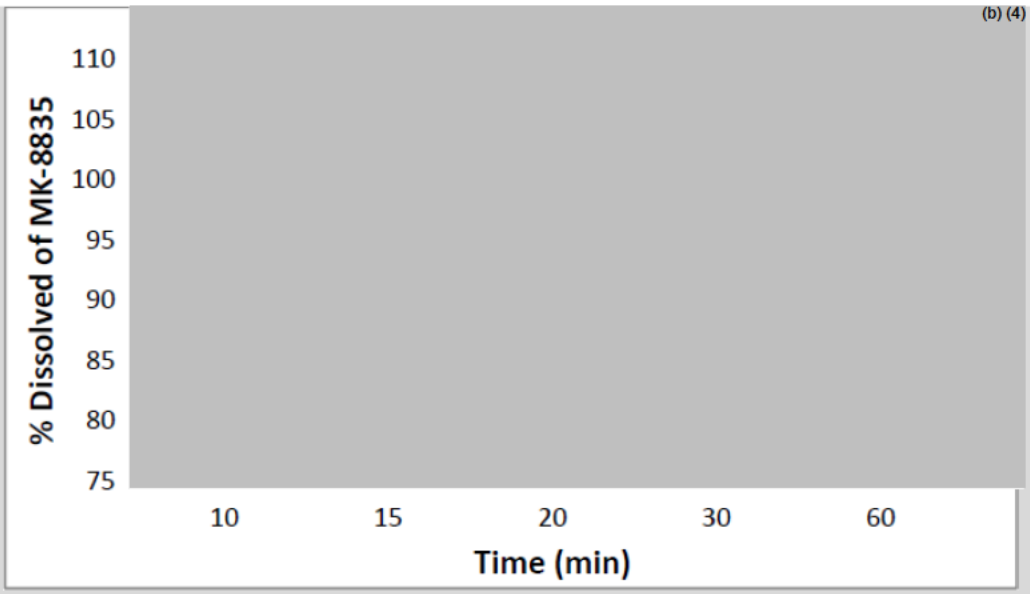
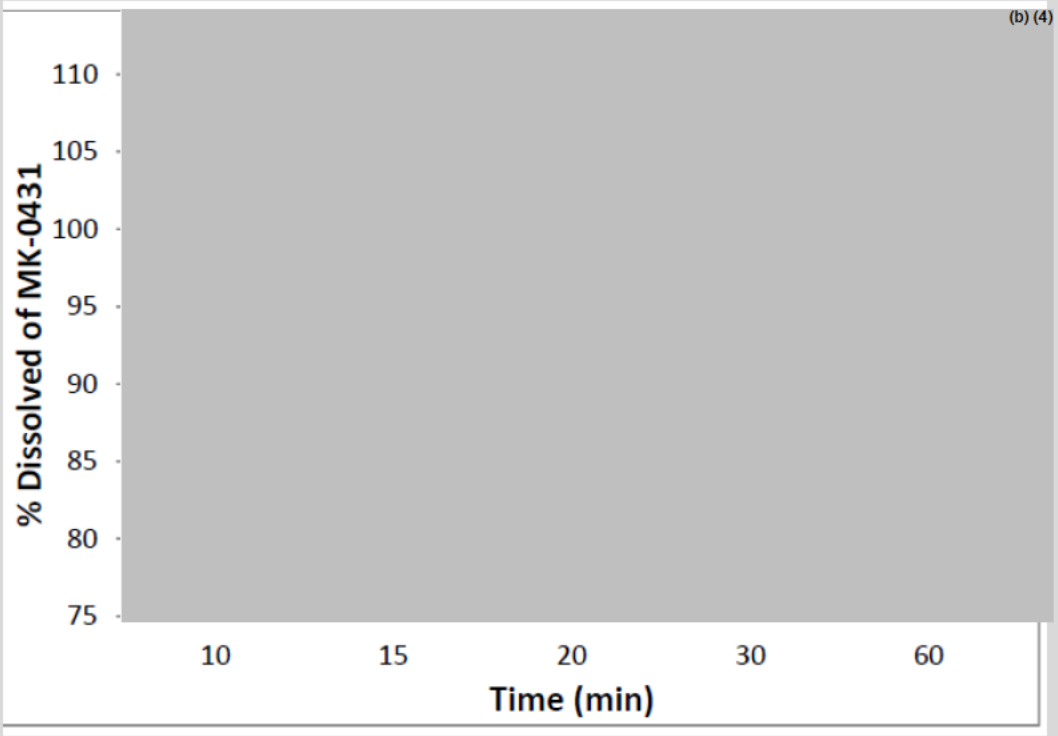


Figure 8B. Mean Dissolution Profiles for Sitagliptin in Ertugliflozin/Sitagliptin Tablets Intended for Clinical/Stability Supplies in pH 4.5 Acetate Buffer using 100 RPM Apparatus (I) Baskets



As shown in Figure 8, the dissolution of sitagliptin and ertugliflozin in different strengths of FDC tablets was very fast, and quickly reached more than 90% of release within 10 min. Furthermore, the RSD% for dissolution at each sampling time points for all tested units is low

(~1%-3.5%). Therefore, the proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 15 min is acceptable.

3. Acceptance criterion for disintegration

The proposed acceptance criterion for disintegration is ≤ (b) (4)min. Figure 9 shows the mean disintegration time (with range) for all clinical/stability batches in different strengths of FDC tablets. As shown in Figure 9, the disintegration time for all clinical/stability batches of different strengths of FDC tablets ranges from 0.7-1.7 min. Therefore, the proposed acceptance criterion for disintegration of NMT (b) (4)min is liberal. We recommend revising the acceptance criterion for disintegration to NMT (b) (4)min.

Figure 9. Mean disintegration time (minutes) with ranges in all clinical/stability batches of different strengths of FDC tablets

(b) (4)

An IR was conveyed to the Applicant as follows:

FDA Request:

We acknowledged your application of disintegration test in QC in lieu of dissolution test. However, the proposed acceptance criterion of NMT (b) (4)min for disintegration is liberal. We recommended the acceptance criterion for disintegration to be NMT (b) (4)min based on your data. We request that you acknowledge your acceptance of the recommended acceptance criterion for disintegration and implement the recommended acceptance criterion accordingly in submission.

In the response to IR dated June 23, 2017, the Applicant acknowledged our recommendation on the acceptance criterion of disintegration. They updated the specification for disintegration accordingly in the submission.

(b) (4)

[redacted]

Bridging of Formulations

Reviewer's Assessment:

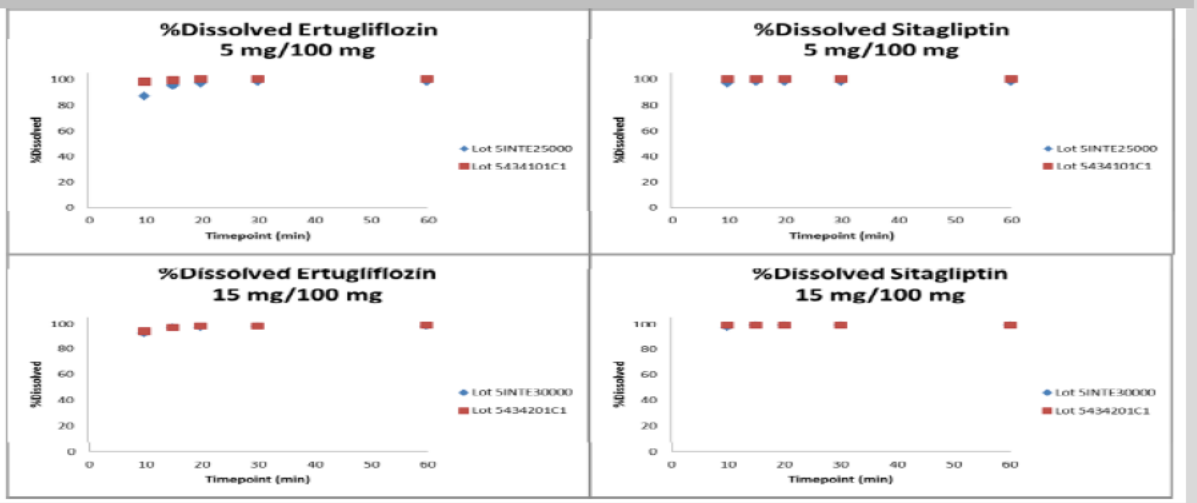
A BE study was performed to bridge the market formulation tablets (all four strengths) and the ertugliflozin and sitagliptin monotherapy tablets used in Phase III studies. The formulations used in BE study are the same as the final to-be-marketed (TBM) formulation except that they were not debossed. At our request, the Applicant provided the dissolution comparison data between the final commercial debossed tablets and the non-debossed tablets used in the pivotal BE studies. Figure 10 shows the mean dissolution profiles of debossed tablets and non-debossed tablets. Both tablet formulations were rapidly dissolving and superimposable for all

the strengths. And since the release of both components in FDC tablets reached more than 85% within 10 min, the calculation of f2 is not needed to demonstrate the dissolution similarity. Therefore, the dissolution of debossed tablets was similar as those of non-debossed tablets used in pivotal BE study, and the TBM formulations are appropriately bridged to the batches in BE study.

Furthermore, the proposed commercial manufacturing site for the FDC tablets is (b) (4) while the tablets used in BE study (non-debossed tablets) were manufactured in (b) (4) The dissolution similarity between two formulations (debossed vs. non-debossed) in Figure 10 manufactured at two different sites supported the change in manufacturing sites.

Figure 10. Average (N=12) dissolution profile comparison between debossed film coated tablets and tablets used in pivotal BE studies (blue dots represent debossed batches and red dots represent non-debossed batches in BE study)

(b) (4)



After the submission of NDA package, the Applicant notified the Agency that they need to change the source for sitagliptin drug substance from (b) (4) to MSD international GmbH, Singapore. As the request of the Agency, on Aug 9, 2017, the Applicant submitted a multi-point dissolution profile comparison for the following drug products:

1. Final commercial debossed tablets manufactured at the commercial site, (b) (4) using MSD International GmbH, Singapore sitagliptin drug substance (new source of drug substance) (post-change batches).

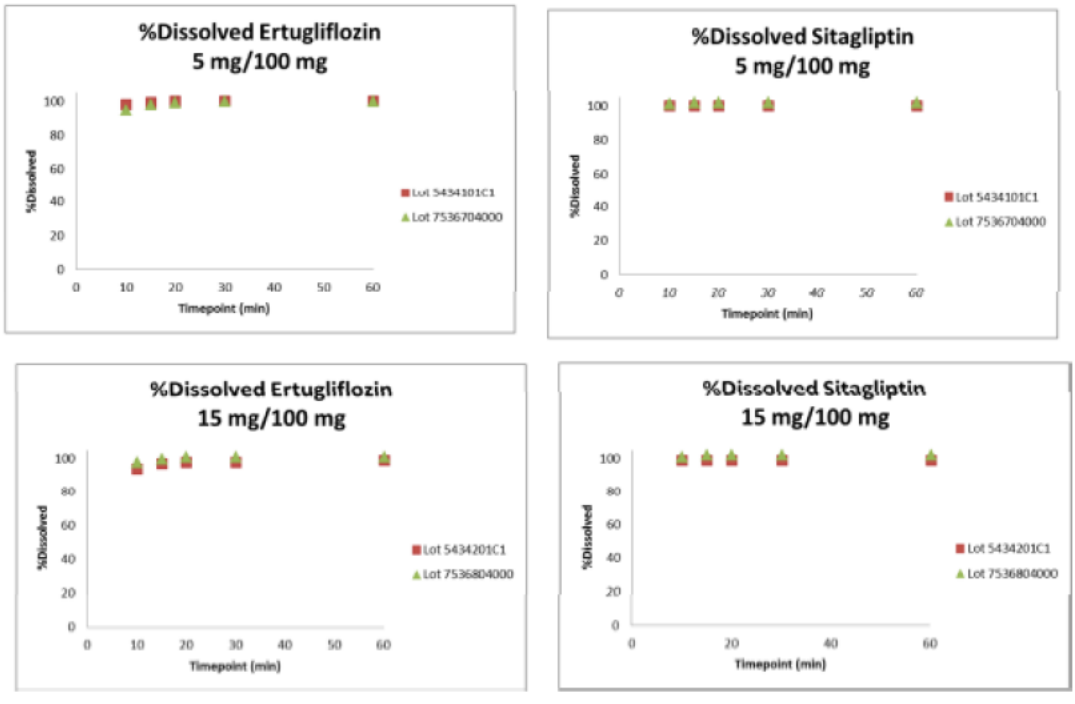
2. Non-debossed tablets manufactured at (b) (4) with (b) (4) sitagliptin phosphate drug substance (the old source of drug substance), used as both registration/exhibit batches and pivotal BE batches (pre-change batches).

The mean dissolution profiles of the two batches for each strength were shown in Figure 11. Red dots represent pre-change batch (old site, non-debossed, and old source of drug substance) and green triangles represent post-change batch (TBM site, debossed, and new source of drug substance). As shown in Figure 11, the dissolution profiles from pre-change and post-change batches are superimposable, and f2 calculation is not needed to demonstrate dissolution similarity, since the release of both components in FDC quickly reached more than 85% within 10 min.

Overall, the formulations are properly bridged.

Figure 11. Average (N=12) dissolution profile comparison between debossed commercial tablets manufactured with Singapore sitagliptin drug substance and non-debossed tablets with (b) (4) sitagliptin used in both registration stability and pivotal BE studies (red dots represent pre-change batch and green triangles represent post-change batch)

(b) (4)



Biowaiver Request

Reviewer's Assessment:

BE studies were conducted for all proposed strengths to compare 5 mg / 100 mg, 15 mg /100 mg, (b) (4) of ertuglizlozin / sitagliptin FDC to respective individual components. No biowaiver request is submitted.

List of Deficiencies: N/A

From Biopharmaceutics perspective, NDA 209805 is recommended for approval.

Primary Biopharmaceutics Reviewer Name and Date: Vincent (Peng) Duan, Ph.D. 8/11/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Haritha Mandula, Ph.D., 8/21/2017

Peng Duan

Digitally signed by Peng Duan
Date: 8/21/2017 01:14:53PM
GUID: 54579633000330547a76e69866efb4b3

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 8/21/2017 03:14:19PM
GUID: 508da6fb000282df41459408f32a1ce0

CHAPTER VIII: Microbiology

see Chapter V

ATTACHMENT I: Final Risk Assessments

See Executive Summary

Su (Suong) Tran

Digitally signed by Su (Suong) Tran
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QUALITY REVIEW

Recommendation: APPROVAL
(including the Facility Review/Overall Manufacturing Inspection Recommendation)

NDA 209803

Review #1
Review Date (see last page)

Drug Name/Dosage Form	ertugliflozin tablet
Strength	5 mg and 15 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Merck

SUBMISSION(S) REVIEWED NDA 209803	DOCUMENT DATE
0000	12/19/16
0003	1/13/17
0004	1/23/17
0009	3/21/17
0011	3/29/17
0015	4/25/17
0019	5/10/17
0023	6/23/17
0025	7/28/17
0027	8/1/17
0029	8/9/17

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Erika Englund/Donna Christner	New Drug API/ONDP
Drug Product	Elise Luong/Danae Christodoulou	New Drug Products II/ONDP
Process/Microbiology	Chaoying Ma/Chengjiu hu	Process Assessment II/OPF
Facility	Allison Aldridge/B.J. Ryan	Inspectional Assessment/OPF
Biopharmaceutics	Hansong Chen/Haritha Mandula	Biopharmaceutics/ONDP

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   A. **DMFs:** Adequate (see Chapter II)
   B. **Other Documents:** NDA 209805 (ertugliflozin/sitagliptin) and NDA 209806 (ertugliflozin/metformin HCl) by the same applicant
2. **CONSULTS:** not applicable

Executive Summary

I. Recommendation and Conclusion on Approvability

The final OPQ recommendation is for Approval, including the overall manufacturing inspection recommendation.

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(1) NDA for ertugliflozin, a New Molecular Entity.

Ertugliflozin is processed with the conformer L-pyroglutamic acid (LPGA) to yield the ertugliflozin-LPGA co-crystal. As per FDA's guidance "Regulatory Classification of Pharmaceutical Co-Crystals", the ertugliflozin-LPGA co-crystal (b) (4) . Therefore, the active ingredient/drug substance of the product is "ertugliflozin", to be reflected in the labeled established name and corresponding dosage strength.

The drug product is an immediate release oral tablet, 5 mg or 15 mg based on ertugliflozin (6.477 mg or 19.431 mg ertugliflozin-LPGA, respectively). The two strengths (b) (4) differ in tablet weight and size.

The commercial 15 mg batch H000007589/J95389 was used in BE study P023/1037 to compare it to the phase 3 clinical 10 mg+5 mg tablets. The biobatch was manufactured at the drug product commercial site Pfizer in Freiburg, Germany. (b) (4) The commercial 5 mg has the same formulation as the phase 3 clinical 5 mg and primary stability batches with the difference of debossing, color and shape. Ertugliflozin-PLGA is BCS 1. A biowaiver request is granted for the commercial 5 mg based on the two strengths (b) (4) having similar dissolution profiles.

Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	[not finalized by GRMP goal; see CDTL's memo]
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	n/a

B. Quality Assessment Overview

Drug Substance

Ertugliflozin (PF-04971729, MK-8835 free form) is the active moiety, and ertugliflozin L-PGA (PF-04971729 (b) (4) MK-8835) represents the cocrystal of ertugliflozin and L-pyroglutamic acid.

r-INN: Ertugliflozin

USAN: Ertugliflozin

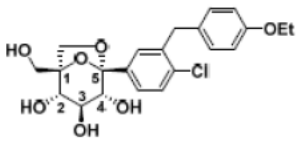
Chemical Names

IUPAC:

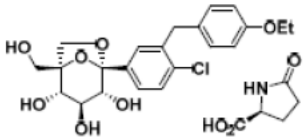
Ertugliflozin: (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol

Ertugliflozin L-PGA: (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid

Figure 2.3.S.1-1. Ertugliflozin and Ertugliflozin L-PGA Structures



Ertugliflozin



Ertugliflozin L-PGA

Molecular Formula

Ertugliflozin: $C_{22}H_{25}ClO_7$

Ertugliflozin L-PGA: $C_{27}H_{32}ClNO_{10}$

Molecular Weight

Ertugliflozin: 436.88 Daltons

Ertugliflozin L-PGA: 566.00 Daltons

Ertugliflozin is an unstable amorphous material that was developed as a 1:1 co-crystal with L-pyroglutamic acid (LPGA) in order to achieve better physical and chemical properties including stability. As per FDA's guidance "Regulatory Classification of Pharmaceutical Co-Crystals", the ertugliflozin-LPGA co-crystal (b) (4) and the active ingredient of the product is "ertugliflozin". Adequate CMC information is provided in the NDA on ertugliflozin, LPGA, and the co-crystal.

Ertugliflozin-LPGA is BCS 1, non-hygroscopic, and crystalline (b) (4)

(b) (4)

(b) (4)

The drug substance specification includes standard quality attributes of a small synthetic molecule including chirality and LPGA content. Batch analysis data include batches from the commercial site "Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland" and the R&D site "Pfizer Sandwich, UK".

Particle size – This attribute is not critical to dissolution because the drug substance is BCS 1 (i.e., highly soluble). (b) (4)

Impurities – (b) (4) have limits that exceed the ICH qualification thresholds; their limits are considered qualified by the Pharmacology Toxicology team. All specified impurities, including these three, were evaluated for mutagenicity and none was found positive (confirmed by the Pharmacology Toxicology team).

Polymorphism – Ertugliflozin-LPGA has the (b) (4) Free ertugliflozin (without LPGA) is amorphous and has different physico-chemical properties and can be readily controlled by test methods (b) (4) Therefore, the lack of polymorph testing in the drug substance specification is acceptable.

A retest period of (b) (4) is acceptable for Ertugliflozin-LPGA when stored (b) (4) The retest period is based on stability data for (b) (4) batches, manufactured at "Pfizer Sandwich, UK" and the commercial site "Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland".

Drug Product

The drug product is an immediate release oral tablet, 5 mg or 15 mg based on ertugliflozin (6.477 mg or 19.431 mg ertugliflozin-LPGA, respectively). The two strengths (b) (4) differ in tablet weight and size.

Excipients: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, and magnesium stearate. The inert film coating contains hypromellose, lactose monohydrate, macrogol, triacetin, titanium dioxide and iron oxide red. There is no novel excipient, and there is no human/animal-derived excipient.

(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, including information on elemental impurities.

Degradants – The two specified ertugliflozin-related degradants (b) (4) have limits (b) (4) Both were evaluated for mutagenicity and found negative (confirmed by the Pharmacology Toxicology team).

Disintegration – The use of disintegration in lieu of dissolutionis acceptable based on ertugliflozin-LPGA being BCS 1 with dissolution greater than 85% in 15 minutes in 0.1N HCl, pH 4.5, and pH 6.8, and an adequate correlation is demonstrate betweej disintegration and dissolution.

Polymorphism is not part of the specification. (b) (4) Therefore, polymorph testing is not necessary.

(b) (4)

Primary container closure system: The drug product is packaged in (b) (4) bottles/closures and aluminum blisters.

Expiration Date & Storage Conditions: The shelf life of the drug product is 24-month at room temperature.

The long-term expiry is based on 12-month long-term (25 C/60% RH) and 6-month accelerated (40 C/75% RH) data for three primary stability batches of each strength. Primary batches were manufactured at the commercial site Pfizer in Freiburg, Germany (with the drug substance from the R&D sitePfizer Sandwich, UK), and packaged in the commercial container closure systems with the exception of the closures: the commercial product will be (b) (4) closures while the stability studies used (b) (4) closures. However, this difference is not critical because both types of closures use the

same product-contact seal liner. A bracketing design was used in the stability studies to bracket the 30-count bottles of both strengths.

C. Special Product Quality Labeling Recommendation: not applicable

D. Life Cycle Knowledge Information/ Final Risk Assessment:

API	page 49 of Chapter I
Drug product	page 50 of Chapter II
Process	none
Facilities	none
Biopharmaceutics	page 47 of Chapter VII (IR to be sent post-approval)

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

Suong T. Tran -S

Digitally signed by Suong T Tran -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2017.08.18 10:37:32 -04'00'

Suong (Su) Tran, Ph.D.
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BIOPHARMACEUTICS

Product Background:
The Applicant, Merck Sharp & Dohme Corp., developed Ertugliflozin (MK-8835/ PF-04971729) tablets, 5 mg and 15 mg, and seek approval under NDA 209803 through 505 (b) (1) pathway. Ertugliflozin (MK-8835/ PF-04971729) tablets, 5 mg and 15 are indicated as an adjunct to diet and exercise for the treatment of Type 2 DM.

NDA/ANDA: NDA 209803

Drug Product Name / Strength: Ertugliflozin Intermediate Release tablets, 5 mg and 15 mg

Route of Administration: Oral

Applicant Name: Merck Sharp & Dohme Corp.

Review Summary:

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, dissolution specification, biowaiver request, DOE study, and formulation bridging.

The Applicant developed a dissolution method for the proposed product, which is acceptable. However, the initially proposed dissolution specification of "NLT (b) (4)% (Q) in (b) (4) minutes" is liberal. The following dissolution specification has been set as agreed upon with the Applicant: NLT (b) (4)% in 15 minutes.

The Applicant proposed to use the disintegration test in lieu of the dissolution test as quality control. The provided data show that the proposed products meet the requirements of ICH Q6A; therefore, it is acceptable to use disintegration testing to replace dissolution testing. The following disintegration specification has been set as agreed upon with the Applicant:

5 mg: NMT (b) (4) minutes

However, the Applicant did not accept the following disintegration specification for 15 mg strength as recommended, and stated that they need more data for a proper reevaluation.

15 mg: NMT (b) (4) minutes

Therefore, the applicant's proposed disintegration specification for 15 mg (NMT (b) (4) minutes) is only acceptable on an interim basis, which will be reevaluated after more data are available.

The Applicant used sufficient data to bridge Phase 3 tablets and Commercial tablets.

In addition, the Applicant provided sufficient data to request a biowaiver for the lower strength (5 mg). The waiver for the lower strengths is granted.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 209803 for Ertugliflozin (b) (4) Release tablets, 5 mg and 15 mg is ADEQUATE for approval with the following comments which could be addressed in the first annual report one year post NDA approval:

Biopharmaceutics Comments to the Applicant:

Your proposed disintegration specification for 15 mg (NMT (b) (4) minutes) is acceptable on an interim basis for release and stability testing until one year from approval. Generate and submit additional disintegration data for all 15 mg commercial batches up to one year post-approval to the agency for review in the first annual report. Your disintegration specification for 15 mg will be revaluated and may be revised based on this new analysis.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED NDA 209803	DOCUMENT DATE
0000	12/19/16
0003	1/13/17
0004	1/23/17
0009	3/21/17
0011	3/29/17
0015	4/25/17
0019	5/10/17
0023	6/23/17
0025	7/28/17
0027	8/1/17
0028	8/15/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None. Please refer to Biopharmaceutics comments to the applicant/Post approval Commitments

Your proposed disintegration specification for 15 mg (NMT (b) (4) minutes) is acceptable on an interim basis for release and stability testing until one year from approval. Generate and submit additional disintegration data for all 15 mg commercial batches up to one year post-approval to the agency for review in the first annual report. Your disintegration specification for 15 mg will be revaluated and may be revised based on this new analysis.

BCS Designation

Reviewer's Assessment: The Applicant reported that ertugliflozin is a BCS Class I drug, which has high solubility and high permeability.

Solubility: The amorphous ertugliflozin free form solubility was determined to be 0.64 - 0.74 mg/mL throughout the physiological pH range. The data in Table 1 show that the solubility of ertugliflozin is pH-independent.

Table 1. Aqueous solubility of ertugliflozin

Aqueous solution	solubility
unbuffered water (pH 5.6)	0.76 mg/mL
simulated gastric fluid with no enzymes (SGN) (pH 1.2)	0.74 mg/mL
PBS phosphate buffered saline (PBS) (pH 6.5)	0.64 mg/mL

The highest therapeutic dose (15 mg) of ertugliflozin L-PGA is completely soluble in 250 mL or less of aqueous media over the pH range of 1.2-6.8 at 37 ± 1°C.

Permeability: The Applicant did not determine the permeability of ertugliflozin. Instead, the Applicant conducted a single-dose study (B1521043) to assess the absolute bioavailability and fraction absorbed of ertugliflozin in healthy male subjects using a ^{14}C-microdose approach. Following oral administration of a single 15 mg dose of ertugliflozin in healthy volunteers, absolute bioavailability and fraction absorbed were approximately 100%. Therefore, the Applicant concluded that ertugliflozin is considered to be highly permeable.

Dissolution: In vitro dissolution: the ertugliflozin tablets display rapid in vitro dissolution characteristics (>85% dissolved in 15 minutes) over the pH range (1.2 – 6.8). See the Biopharm review below for details.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

I. Dissolution method

The Applicant developed the following method for the proposed product

Table 2. The proposed dissolution method for Ertugliflozin (MK-8835/ PF-04971729) tablets, 5 mg and 15 mg

	NDA 209803
Apparatus	USP apparatus 2 (paddles) with peak vessels
Speed	50 rpm
Dissolution media	pH 4.5 acetate buffer
Volume	900 mL
Time (min)	15, 30, 45 and 60 min
Temperature	37 ± 0.5 °C
Specifications	NLT (b) (4) % (Q) in (b) (4) minutes

(b) (4)

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(b) (4)

VI. Dissolution data and specification

The Applicant used the following batches for Phase 3 studies, pivotal bioequivalence study, and primary stability studies.

Table 6. Batch Information –Clinical and Primary Stability

Batch number	Strength	Formulation ID number	Date of Manufacture	Manufacturing site	Use of Batch
2011C0030	5 mg	D1100056	Mar 2011	Montreal	Clinical
2011C0084	5 mg	D1100056	May 2011	Montreal	Clinical
2011C0085	5 mg	D1100056	May 2011	Montreal	Clinical
2011C0095	5 mg	D1100056	Aug 2011	Montreal	Clinical
2011C0096	5 mg	D1100056	Aug 2011	Montreal	Clinical
H000964473	5 mg	D1100056	Jul 2013	Freiburg	Clinical

G30728					
H000964473 **H07089**	5 mg	D1100056	Sep 2013	Freiburg	Clinical
H000964473 H07092	5 mg	D1100056	Sep 2013	Freiburg	Clinical
H000007585 J47624	5 mg	D1100056	Jun 2014	Freiburg	Clinical
H000007586 J47630	5 mg	D1100056	Jun 2014	Freiburg	Clinical
L86050S	5 mg	D1100056	Apr 2015	Freiburg	Clinical
N54057	5 mg	D1100056	Mar 2016	Freiburg	Clinical
N54058	5 mg	D1100056	Mar 2016	Freiburg	Clinical
2011C0029	10 mg	D1005706	Feb 2011	Montreal	Clinical
2011C0031	10 mg	D1005706	Mar 2011	Montreal	Clinical
2011C0032	10 mg	D1005706	Mar 2011	Montreal	Clinical
2011C0039	10 mg	D1005706	Mar 2011	Montreal	Clinical
2011C0040	10 mg	D1005706	Mar 2011	Montreal	Clinical
2011C0041	10 mg	D1005706	Mar 2011	Montreal	Clinical
H000964493 G30325	10 mg	D1005706	Jul 2013	Freiburg	Clinical
H000964493 **H06829**	10 mg	D1005706	Sep 2013	Freiburg	Clinical
H000964493 H06839	10 mg	D1005706	Sep 2013	Freiburg	Clinical
H000007587 J47640	10 mg	D1005706	Jun 2014	Freiburg	Clinical
L86051	10 mg	D1005706	Apr 2015	Freiburg	Clinical
N54070	10 mg	D1005706	Apr 2016	Freiburg	Clinical
N54071	10 mg	D1005706	Apr 2016	Freiburg	Clinical
J95374	5 mg	D1400153	Oct 2014	Freiburg	Primary stability
J95377	5 mg	D1400153	Oct 2014	Freiburg	Primary stability
J95386	5 mg	D1400153	Oct 2014	Freiburg	Primary stability
J95387	15 mg	D1400154	Sep 2014	Freiburg	Primary stability
J95389	15 mg	D1400154	Oct 2014	Freiburg	Primary stability and clinical
J95390	15 mg	D1400154	Oct 2014	Freiburg	Primary stability

Batch J95389 (15 mg), Batch H06829 (10 mg), and Batch H07089 (5 mg) were used for the pivotal bioequivalent (BE) study.

The Applicant provided the complete dissolution data for all primary stability batches. In addition, the Applicant provided mean dissolution data for all clinical batches, which are listed in Table 7.

Mean dissolution data and specification

Table 7. Mean dissolution data of Phase 3 batches in pH 4.5 acetate buffer

Batch number /Time (min)	5	15	30	45
5 mg 2011C0030	74	101	101	101
5 mg 2011C0084	83	103	103	103
5 mg 2011C0085	85	101	101	101
5 mg 2011C0095	76	99	100	100
5 mg 2011C0096	82	102	103	103
5 mg H000964473 G30728	74	101	100	101
5 mg H000964473 **H07089**	82	96	96	96
5 mg H000964473 H07092	82	96	96	97
5 mg H000007585 J47624	90	95	95	95
5 mg H000007586 J47630	89	96	96	97
5 mg L86050S	88	98	98	98
5 mg N54057	88	94	95	95
5 mg N54058	85	96	97	98
10 mg 2011C0029	85	98	100	101
10 mg 2011C0031	85	100	101	100
10 mg 2011C0032	87	98	99	98
10 mg 2011C0039	90	100	100	100
10 mg 2011C0040	83	99	100	100
10 mg 2011C0041	81	100	100	100
10 mg H000964493 G30325	82	98	100	99
10 mg H000964493 **H06829**	79	96	97	97
10 mg H000964493 H06839	77	96	96	97
10 mg H000007587 J47640	88	97	97	97
10 mg L86051	88	99	99	99
10 mg N54070	90	98	98	99
10 mg N54071	91	98	99	100

Table 8. Mean dissolution data of commercial batches in pH 4.5 acetate buffer

Batch number/Time (min)	5	10	15	20	30	45	60
5 mg J95374	90	97	99	99	100	100	100
5 mg J95377	90	99	100	100	101	101	101
5 mg J95386	95	100	99	100	100	100	100

15 mg J95387	69	94	98	99	99	100	100
15 mg **J95389**	85	95	98	98	98	98	98
15 mg J95390	78	96	99	100	100	100	101

The Applicant proposed the following dissolution specification for their proposed product:

NLT (b) (4)% (Q) in (b) (4)minutes

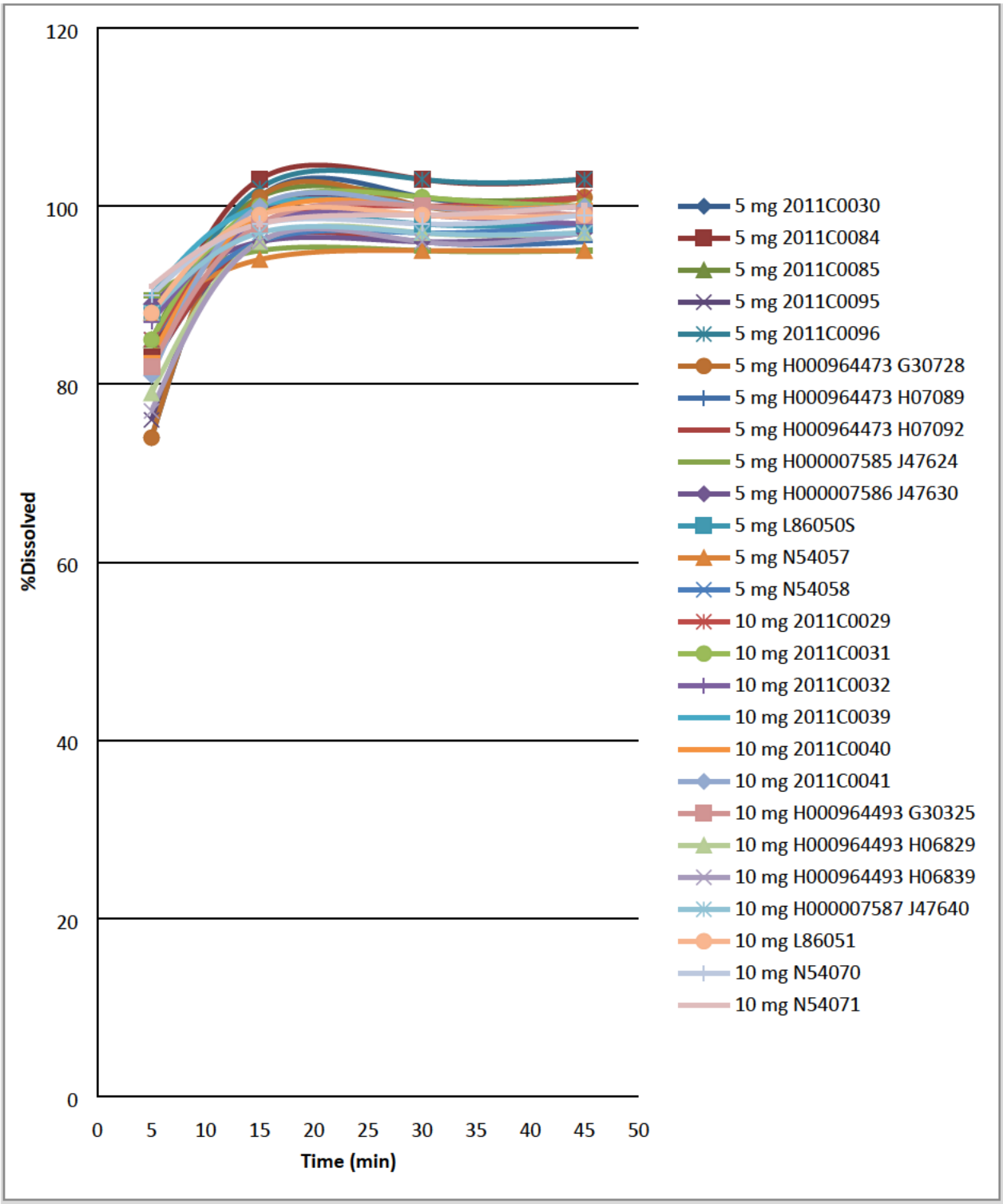
The data listed in Tables 5 and 6 show that all batches have at least 96% of mean dissolution at 15 minutes.

Therefore, the Applicant's proposed specification is liberal. Based on the data provided, the specification can be tightened to "NLT (b) (4)% (Q) in 15 minutes".

An IR was sent to the Applicant to accept the following specification:

NLT (b) (4)% (Q) in 15 minutes.

Figure 8. Mean dissolution profile comparison between clinical batches



VI. Disintegration testing

The Applicant used USP <701> method to conduct disintegration testing.

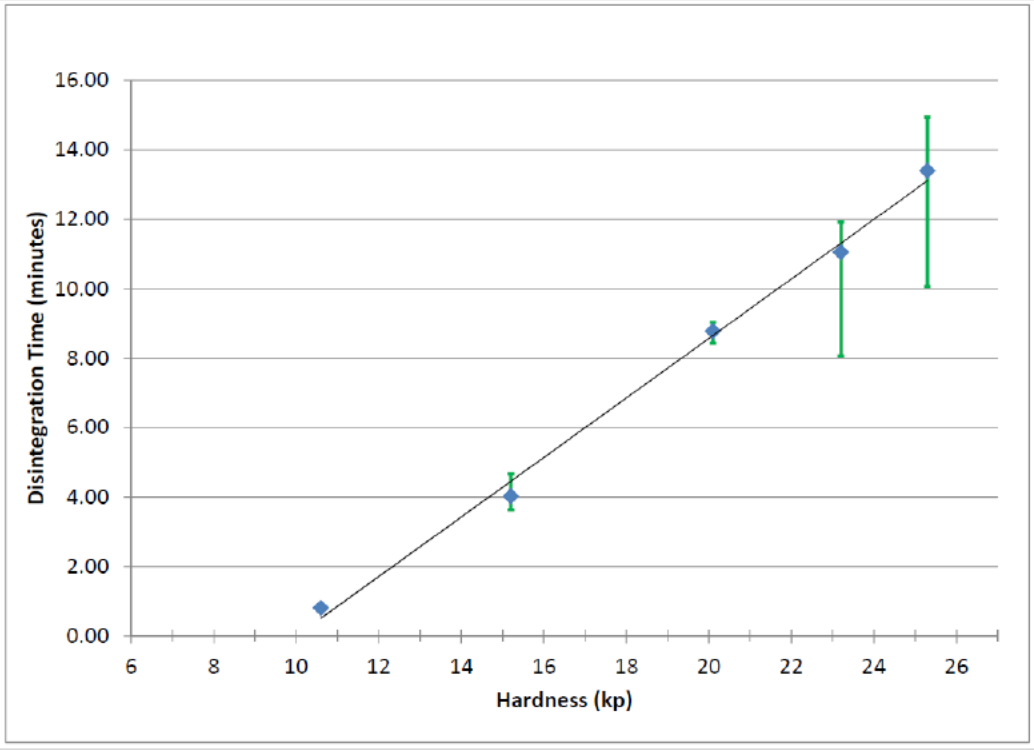
In this submission, the Applicant proposed to use disintegration in lieu of dissolution as the drug product quality control for ertugliflozin tablets due to the following reasons:

- The proposed product is immediate release tablets.
- The proposed drug (15 mg) has high solubility at 37 ±0.5°C throughout the physiological pH range (the highest therapeutic dose (and highest dose strength) of ertugliflozin (15 mg) is completely soluble in 250 mL or less of aqueous media over the pH range of 1.2-6.8 at 37±1°C).
- The proposed product is very rapidly dissolving, which can achieve ≥ 85% dissolution in pH 1.2, pH 4.5, and pH 6.8.
- A linear relationship has been demonstrated between disintegration and dissolution results.

Discriminatory power of disintegration test

The Applicant studied the discriminating power of the disintegration test. The disintegration tests were conducted on 15 mg triangle tablets manufactured with different hardness. The results show that there is a linear relationship between mean disintegration time and tablet hardness (Figure 9).

Figure 9. Disintegration Results for 15 mg Ertugliflozin Tablets Manufactured at Different Hardness Values. Mean Disintegration Values (n=6) are Plotted with Bars Showing the Minimum and Maximum Values



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VII. Disintegration data and specification

The Applicant provided the maximum disintegration time for the clinical batches and primary stability batches.

Table 9. Maximum disintegration time of Phase 3 batches

Batch number	Maximum disintegration Time (min)
5 mg 2011C0030	4
5 mg 2011C0084	4
5 mg 2011C0085	3
5 mg 2011C0095	2
5 mg 2011C0096	2
5 mg H000964473 G30728	2
5 mg H000964473 **H07089**	2
5 mg H000964473 H07092	2
5 mg H000007585 J47624	≤ 1
5 mg H000007586 J47630	≤ 1
5 mg L86050S	≤ 1
5 mg N54057	≤ 1
5 mg N54058	≤ 1
10 mg 2011C0029	2
10 mg 2011C0031	3
10 mg 2011C0032	2
10 mg 2011C0039	2
10 mg 2011C0040	2
10 mg 2011C0041	2
10 mg H000964493 G30325	≤ 1
10 mg H000964493 **H06829**	4
10 mg H000964493 H06839	3
10 mg H000007587 J47640	≤ 1
10 mg L86051	≤ 1
10 mg N54070	≤ 1
10 mg N54071	≤ 1

Table 10. Maximum disintegration time of primary stability batches

Batch number/Time (min)	Maximum disintegration Time (min)
5 mg J95374	≤ 1
5 mg J95377	≤ 1

5 mg J95386	≤ 1
15 mg J95387	4
15 mg **J95389**	5
15 mg J95390	5

Table 11. Summary of Disintegration Ranges (minutes)

Specification	Not more than (b) (4) minutes			
Method	USP <701>			
		5 mg	10 mg	15 mg
Range	Release	NMT (b) (4)	NMT (b) (4)	(b) (4)
	Stability in Bottles			
	25 °C/60% RH[1]	NMT 1 - 1	NA	4 - 6
	40 °C/75% RH[2]	NMT 1	NA	1 - 4
	Stability in Blisters			
	30 °C/75% RH[1]	NMT 1 - 1	NA	2 - 4
	40 °C/75% RH[2]	NMT 1	NA	2 - 3

NA = not applicable
NMT = not more than
1 Stability data range includes data from 3 months through 12 months.
2 Stability data range includes data from 3 months through 6 months.

Table 12. Complete disintegration data for 15 mg batch J95389, 10 mg batch H06829 and 5 mg batch H07089.

Lot	Individual Values (min)						Mean (min)	SD	RSD (%)
15 mg Batch J95389	4	4	4	5	3	4	4	0.6	15.8
10 mg Batch H06829	3	3	3	3	3	4	3	0.4	12.9
5 mg Batch H07089	2	2	2	2	1	2	2	0.4	22.3

The Applicant proposed the following disintegration specification for their proposed product:

NMT (b) (4) minutes

The data listed in Tables 9, 10, and 11 show that all batches have no more than (b) (4) minutes disintegration time for release, and no more than 1 minute for stability test of 5 mg strength and no more than 6 minutes for stability testing of 15 mg strength.

In addition, the DOE study conducted for 5 mg strength concludes that the primary factor that affects the disintegration time is tablet hardness. (b) (4)

The Applicant also conducted two univariate studies to investigate how tablet hardness affects disintegration time. The results showed that there is a linear relationship between 15 mg tablet hardness and disintegration time. (b) (4)

Therefore, the Applicant's proposed disintegration specifications are liberal. Based on the data provided, the specifications can be tightened as follows:

5 mg: NMT (b) (4) minutes

15 mg: NMT (b) (4) minutes

An IR was sent to the Applicant to accept the above specifications.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: N/A

(b) (4)

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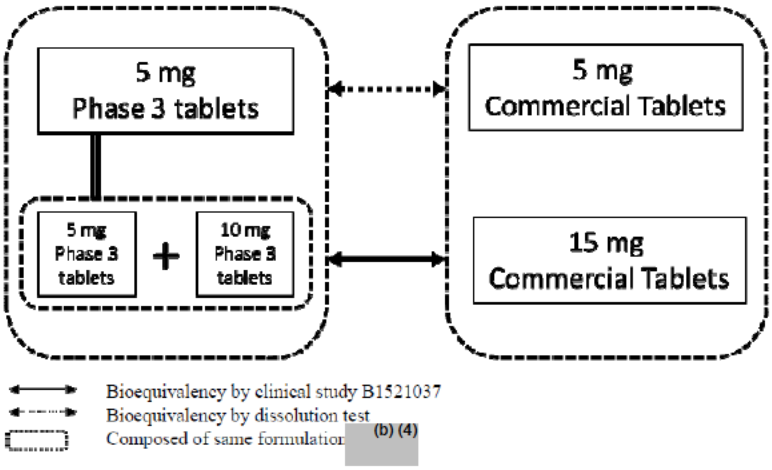
(b) (4)

Bridging of Formulations

Reviewer's Assessment:

The Applicant used White Film-coated Clinical Tablets (5 mg and 10 mg) for Phase 3 studies. For commercial use, the Applicant developed Pink/Red Film-coated Registration IR Tablets. To bridge the formulation changes, the Applicant conducted a pivotal BE study B1521037 to demonstrate bioequivalence between 15 mg commercial image tablet of ertugliflozin and ertugliflozin 15 mg dose (5 mg + 10 mg) used in Phase 3 studies under fasted conditions.



The Applicant also used multimedia dissolution profile comparison to bridge Phase 3 tablets and commercial tablets.

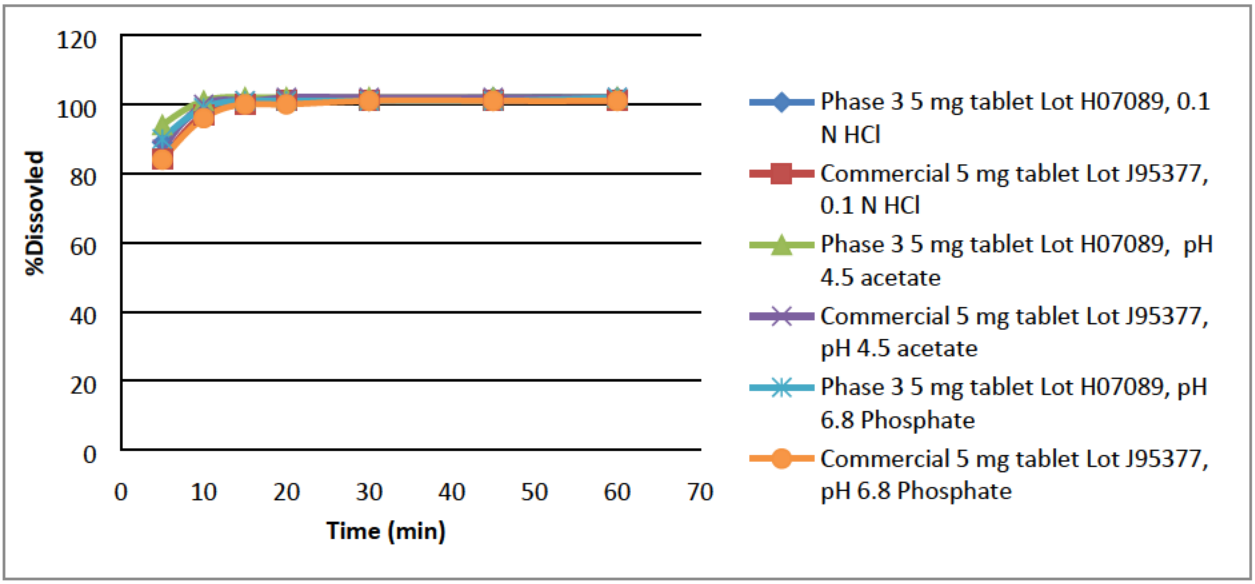
5 mg Phase 3 tablets vs. 5 mg commercial tablets

Table 18. Mean dissolution data of 5 mg Phase 3 tablets and 5 mg commercial tablets in multi-media

Lot number/time (min)	5	10	15	20	30	45	60
Phase 3 5 mg tablet Lot H07089, 0.1 N HCl	89	99	101	101	101	102	102
Commercial 5 mg tablet Lot J95377, 0.1 N HCl	84	97	100	101	101	101	101
Phase 3 5 mg tablet Lot H07089, pH 4.5 acetate	94	101	102	102	102	102	102
Commercial 5 mg tablet Lot J95377, pH 4.5 acetate	87	100	101	102	102	102	102

Phase 3 5 mg tablet Lot H07089, pH 6.8 Phosphate	90	99	101	101	101	101	102
Commercial 5 mg tablet Lot J95377, pH 6.8 Phosphate	84	96	100	100	101	101	101

Figure 15. Mean dissolution profile comparison of 5 mg Phase 3 tablets and 5 mg commercial tablets in multi-media



The dissolution data in Table 18 show that both batches have a mean dissolution of >85% in 15 minutes; therefore, they are considered to be similar on dissolution profiles in respective media without further f2 calculation.

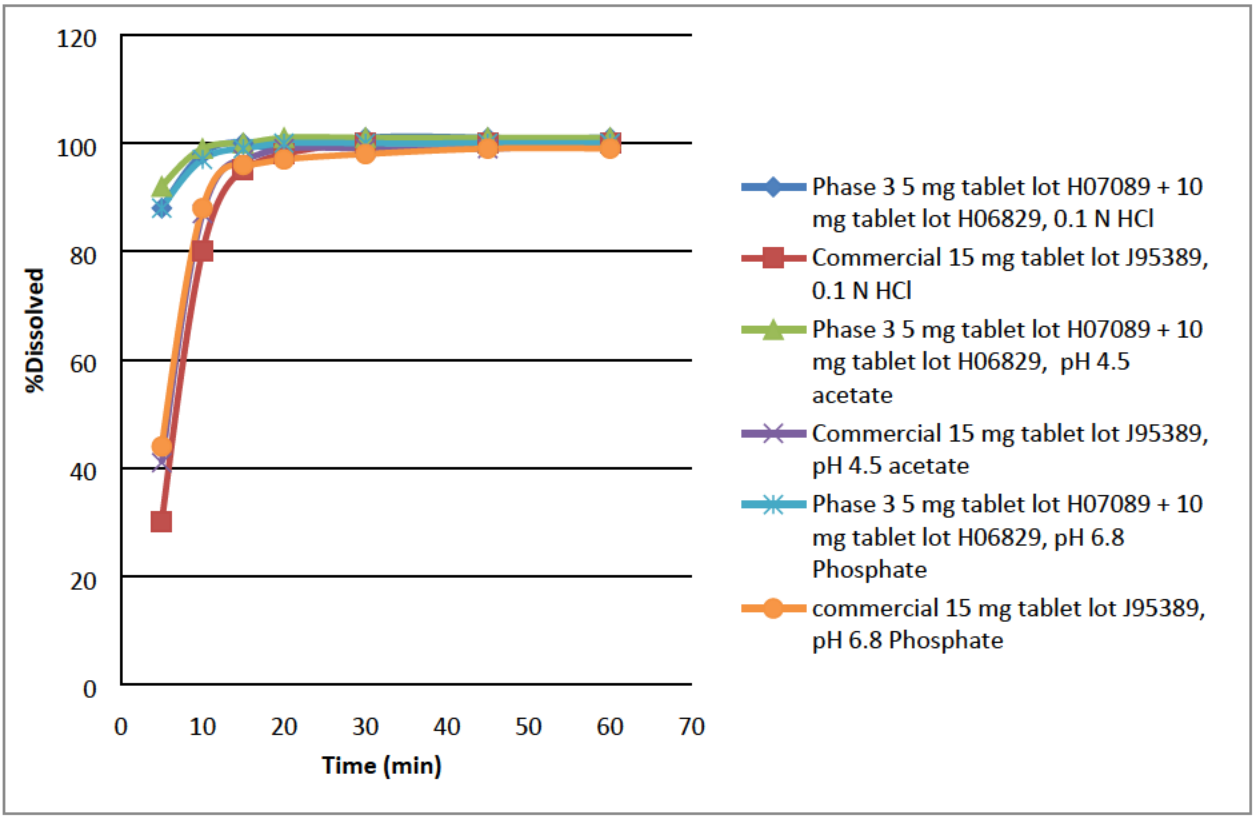
5 mg Phase 3 tablets + 10 mg Phase 3 tablets vs. 15 mg commercial tablets

Table 19. Mean dissolution data of Phase 3, 5 mg tablet lot H07089 (D1100056) + 10 mg tablet lot H06829 (D1005706) and commercial 15 mg tablet lot J95389 in multi-media

Lot number/time (min)	5	10	15	20	30	45	60
Phase 3 5 mg tablet lot H07089 + 10 mg tablet lot H06829, 0.1 N HCl	88	98	100	99	101	101	101
Commercial 15 mg tablet lot J95389, 0.1 N HCl	30	80	95	98	100	100	100
Phase 3 5 mg tablet lot H07089 + 10 mg tablet lot H06829, pH 4.5 acetate	92	99	100	101	101	101	101
Commercial 15 mg tablet lot J95389, pH 4.5 acetate	41	87	97	99	99	99	100
Phase 3 5 mg tablet lot H07089 + 10 mg tablet lot H06829, pH 6.8 Phosphate	88	97	99	100	100	100	100
commercial 15 mg tablet lot J95389, pH 6.8	44	88	96	97	98	99	99

Phosphate							

Figure 16. Mean dissolution profile comparison of Phase 3, 5 mg tablet lot H07089 + 10 mg tablet lot H06829 and commercial 15 mg tablet lot J95389 in multi-media



The dissolution data in Table 19 show that Phase 3 5 mg tablet lot H07089 + 10 mg tablet lot H06829 and commercial 15 mg tablet lot J95389 have a mean dissolution of >85% in 15 minutes; therefore, they are considered to be similar on dissolution profiles in respective media without further f2 calculation.

Biowaiver Request

Reviewer's Assessment:

The Applicant conducted a pivotal bioequivalence study to assess the comparative bioavailability between 15 mg commercial tablet and Phase 3, 15 mg dose (administered as one 10 mg tablet and one 5 mg tablet):

Study: P023/B1521037

Study title: "A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 15 mg Commercial Image Tablet vs Ertugliflozin Phase 3 Tablets in Healthy Subjects"

The results are pending Clinpharm Review conclusion (for additional details, please refer to clinical pharmacology review). The Applicant requested the biowaiver for the lower strengths 5 mg.

A. Formulation of the test products

Table 20. Qualitative and Quantitative Composition of the Drug Products

Component	Reference to Standard	Function	15 mg Quantity (mg/tablet)	5 mg Quantity (mg/tablet)
Ertugliflozin L-PGA	In-house	Active	19.431a	6.477
Microcrystalline Cellulose	USP/NF	(b) (4)		
Lactose Monohydrate	USP/NF			
Sodium Starch Glycolate	USP/NF			
Magnesium Stearate	USP/NF			
(b) (4)				
Total Finished Tablet			312.000	104.000

a Equivalent to 15 mg or 5 mg activity based on a theoretical potency factor of 0.772 for Ertugliflozin L-PGA.

(b) (4)

(b) (4)

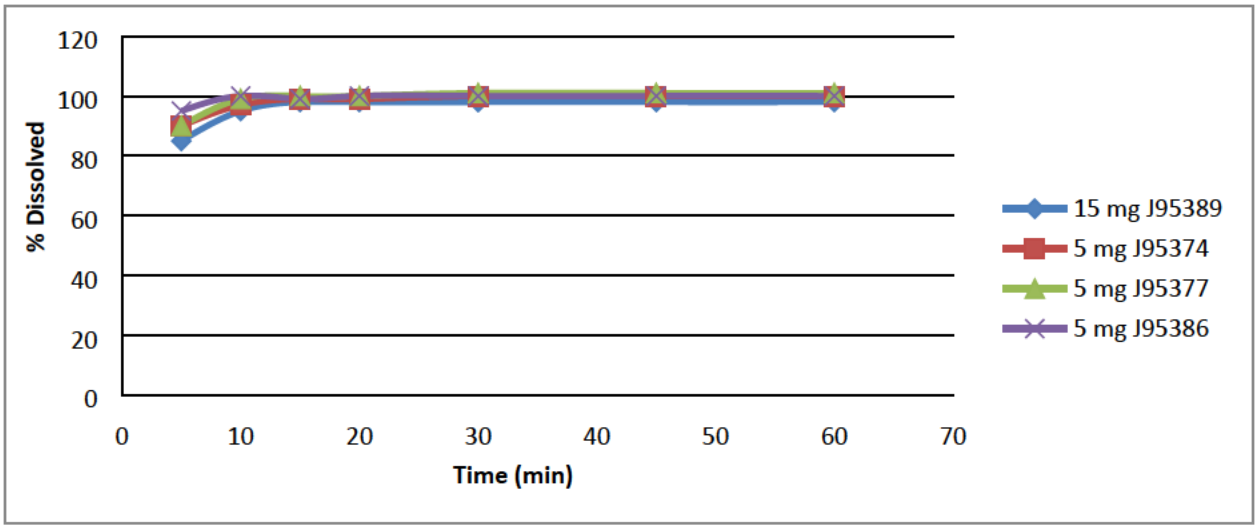
B. Comparative dissolution assessment

Biobatch J95389 (15 mg) and all three batches of 5 mg strength have at least 85% dissolution at 15 minutes. Therefore, it can be concluded that the lower strength (5 mg) is similar to the higher strength (15 mg) Biobatch J95389 on dissolution profiles without further f2 calculation.

Table 21. Mean dissolution data between the higher strength Biobatch and lower strength in pH 4.5 acetate buffer

Batch number/Time (min)	5	10	15	20	30	45	60
15 mg **J95389**	85	95	98	98	98	98	98
5 mg J95374	90	97	99	99	100	100	100
5 mg J95377	90	99	100	100	101	101	101
5 mg J95386	95	100	99	100	100	100	100

Figure 15. Mean Comparative Dissolution Profiles of Biobatch and lower strength



C. Biowaiver

The Biowaiver can be granted for the lower strength 5 mg based on the following reasons:

1) The lower strength product is in the same dosage form, but in different strength
2) The lower strength (5 mg) batch and the higher strength (15 mg) are (b) (4) similar in its active and inactive ingredients
3) The lower strength meets an appropriate in vitro dissolution test
4) Each lower strength (5 mg) batch and the higher strength (5 mg) biobatch have similar dissolution profiles (f2 was not calculated due to very rapid dissolution)

Appendix I Dissolution Data of primary stability batches (Batches J95374, J95377, J95386, J95387, J95389, and J95390)

Strength	Batch	Time (min)	Individual Results (% Dissolved)						Mean (%)	SD	RSD (%)
5 mg	J95374	5	91	89	91	90	90	86	90	1.9	2.1
		10	97	97	99	97	98	95	97	1.3	1.4
		15	98	98	100	98	100	97	99	1.2	1.2
		20	99	99	101	99	100	98	99	1.2	1.2
		30	99	99	101	99	101	99	100	1.0	1.0
		45	99	99	101	99	101	99	100	1.0	1.0
		60	99	99	101	99	101	99	100	1.0	1.0
5 mg	J95377	5	92	91	91	90	88	86	90	2.3	2.5
		10	99	100	100	99	97	97	99	1.4	1.4
		15	100	101	101	101	98	99	100	1.3	1.3
		20	100	101	101	102	98	100	100	1.4	1.4
		30	100	101	102	102	99	100	101	1.2	1.2
		45	100	102	102	102	99	100	101	1.3	1.3
		60	100	102	102	102	99	100	101	1.3	1.3
5 mg	J95386	5	96	93	95	94	95	96	95	1.2	1.2
		10	100	97	101	102	99	98	100	1.9	1.9
		15	99	98	101	100	100	98	99	1.2	1.2
		20	99	98	101	100	101	98	100	1.4	1.4
		30	99	99	101	100	100	99	100	0.8	0.8
		45	99	99	101	100	101	99	100	1.0	1.0
		60	99	99	101	100	101	99	100	1.0	1.0
15 mg	J95387	5	65	69	77	58	76	67	69	7.1	10.3
		10	94	93	96	92	94	92	94	1.5	1.6
		15	98	98	99	98	97	97	98	0.8	0.8
		20	99	98	99	99	98	98	99	0.5	0.6
		30	99	99	100	100	99	99	99	0.5	0.5
		45	99	99	100	101	99	99	100	0.8	0.8
		60	99	99	100	101	99	99	100	0.8	0.8
15 mg	J95389	5	86	85	85	85	87	82	85	1.7	2.0
		10	95	97	96	94	95	95	95	1.0	1.1
		15	97	99	98	96	98	97	98	1.0	1.1
		20	97	99	99	96	98	98	98	1.2	1.2
		30	98	100	99	97	98	98	98	1.0	1.1
		45	98	100	99	97	98	98	98	1.0	1.1
		60	98	100	99	97	98	98	98	1.0	1.1
15 mg	J95390	5	63	84	85	73	85	77	78	8.8	11.2
		10	96	96	95	96	97	97	96	0.8	0.8
		15	101	98	98	100	99	100	99	1.2	1.2
		20	102	98	98	100	99	100	100	1.5	1.5
		30	102	99	99	101	99	101	100	1.3	1.3
		45	102	99	99	101	99	101	100	1.3	1.3
		60	102	100	99	101	100	101	101	1.0	1.0

Appendix II Dissolution Data of Bridging lots in multimedia

Phase 3, 5 mg tablet lot H07089 (D1100056)

0.1 N HCl

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	89	99	101	101	101	102	101
2	88	100	102	102	102	103	103
3	89	99	101	101	101	102	102
4	87	97	98	99	99	99	99
5	89	98	100	101	101	101	101
6	87	98	100	101	101	101	101
7	90	99	101	102	102	102	102
8	88	99	101	102	102	102	102
9	91	101	103	103	103	103	103
10	90	99	101	101	101	101	102
11	90	99	100	101	101	101	101
12	88	98	100	101	101	101	101
Mean	*89*	*99*	*101*	*101*	*101*	*102*	*102*
SD	*1.3*	*1.0*	*1.2*	*1.0*	*1.0*	*1.1*	*1.1*
% RSD	*1.4*	*1.0*	*1.2*	*1.0*	*1.0*	*1.1*	*1.1*

Acetate, pH 4.5

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	94	101	102	102	102	102	102
2	95	102	103	104	104	104	104
3	96	102	103	103	103	103	103
4	96	104	105	105	105	105	105
5	95	101	103	103	103	103	103
6	91	100	101	101	101	101	101
7	94	101	101	102	102	102	102
8	94	102	103	103	103	103	103
9	93	99	100	100	100	100	100
10	95	102	103	103	103	103	103
11	95	101	102	102	102	102	102
12	92	99	100	101	100	101	101
Mean	*94*	*101*	*102*	*102*	*102*	*102*	*102*
SD	*1.5*	*1.4*	*1.5*	*1.4*	*1.5*	*1.4*	*1.4*
% RSD	*1.6*	*1.4*	*1.4*	*1.3*	*1.5*	*1.3*	*1.3*

Phosphate, pH 6.8

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	89	98	100	101	101	101	101
2	88	99	102	102	102	103	103
3	90	98	100	101	101	101	102
4	89	98	100	101	101	101	101
5	90	99	101	101	101	101	101
6	90	100	102	103	103	103	103
7	90	98	101	101	102	101	102
8	88	97	99	100	100	100	100
9	93	98	99	99	99	100	100
10	92	100	102	102	102	103	103
11	91	100	102	102	102	102	102
12	87	97	100	100	100	100	100
Mean	*90*	*99*	*101*	*101*	*101*	*101*	*102*
SD	*1.7*	*1.1*	*1.2*	*1.1*	*1.1*	*1.2*	*1.2*
% RSD	*1.9*	*1.1*	*1.1*	*1.1*	*1.1*	*1.1*	*1.2*

Commercial 5 mg tablet lot J95377 (D1400153)

0.1 N HCl

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	81	97	99	101	101	101	101
2	87	97	98	99	99	99	99
3	85	97	99	101	101	101	101
4	85	98	100	101	101	101	102
5	86	97	99	100	100	100	101
6	84	97	99	100	101	101	101
7	82	98	101	102	102	102	102
8	80	96	100	101	101	102	102
9	86	96	99	99	100	100	100
10	84	97	100	100	101	101	101
11	85	97	100	101	101	101	101
12	82	98	101	102	102	102	102
Mean	*84*	*97*	*100*	*101*	*101*	*101*	*101*
SD	*2.2*	*0.7*	*0.9*	*1.0*	*0.8*	*0.9*	*0.9*
% RSD	*2.6*	*0.7*	*0.9*	*1.0*	*0.8*	*0.9*	*0.9*

Acetate, pH 4.5

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20min**	**30 min**	**45 min**	**60 min**
1	87	99	101	101	101	102	101
2	85	99	102	102	102	102	102
3	88	101	102	102	102	102	102
4	81	103	106	105	105	105	105
5	88	100	102	102	102	102	102
6	86	99	101	101	101	101	102
7	90	99	100	100	100	100	100
8	90	100	101	102	102	102	102
9	91	99	100	100	100	100	100
10	88	100	102	103	102	102	103
11	89	99	100	101	101	101	101
12	86	99	100	101	101	101	101
Mean	*87*	*100*	*101*	*102*	*102*	*102*	*102*
SD	*2.7*	*1.2*	*1.7*	*1.4*	*1.3*	*1.3*	*1.4*
% RSD	*3.1*	*1.2*	*1.7*	*1.3*	*1.3*	*1.3*	*1.3*

Phosphate, pH 6.8

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	84	95	99	99	100	101	100
2	83	96	100	101	101	102	102
3	82	96	100	100	101	101	102
4	84	97	101	102	102	102	102
5	84	97	100	101	102	102	102
6	80	95	99	100	100	101	101
7	83	96	100	101	102	102	102
8	83	96	99	101	101	101	101
9	83	98	100	101	102	102	102
10	85	96	99	100	100	101	101
11	89	97	99	99	100	100	100
12	82	95	99	100	100	100	100
Average	*84*	*96*	*100*	*100*	*101*	*101*	*101*
SD	*2.2*	*0.9*	*0.7*	*0.9*	*0.9*	*0.8*	*0.9*
% RSD	*2.6*	*1.0*	*0.7*	*0.9*	*0.9*	*0.7*	*0.9*

Phase 3, 5 mg tablet lot H07089 (D1100056) + 10 mg tablet lot H06829 (D1005706)

0.1 N HCl

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	88	99	101	101	101	102	102
2	88	99	101	102	102	102	102
3	89	99	100	101	100	101	101
4	86	99	100	100	101	101	101
5	87	98	100	100	101	101	101
6	87	98	100	101	101	101	101
7	86	98	100	100	100	100	100
8	89	98	100	100	101	101	101
9	88	98	100	100	100	101	101
10	87	97	99	85	99	99	99
11	89	97	100	100	101	101	101
12	86	97	99	99	100	100	100
Mean	*88*	*98*	*100*	*99*	*101*	*101*	*101*
SD	*1.2*	*0.8*	*0.6*	*4.5*	*0.8*	*0.8*	*0.8*
% RSD	*1.3*	*0.8*	*0.6*	*4.5*	*0.8*	*0.8*	*0.8*

Acetate, pH 4.5

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	90	99	100	101	101	101	101
2	93	100	101	101	101	101	102
3	94	100	101	102	102	102	102
4	94	99	100	100	100	100	100
5	94	100	101	101	101	101	101
6	93	100	101	102	102	102	102
7	91	100	101	101	101	101	102
8	91	98	99	99	99	99	99
9	89	98	99	99	99	100	100
10	93	99	99	100	100	100	100
11	89	99	100	100	100	100	100
12	91	99	100	100	101	101	101
Mean	*92*	*99*	*100*	*101*	*101*	*101*	*101*
SD	*1.9*	*0.8*	*0.8*	*1.0*	*1.0*	*0.9*	*1.0*
% RSD	*2.1*	*0.8*	*0.8*	*1.0*	*1.0*	*0.9*	*1.0*

Phosphate, pH 6.8

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	86	97	99	100	100	100	100
2	88	97	98	99	98	99	99
3	89	98	100	100	100	101	101
4	87	97	98	99	99	100	100
5	85	97	98	99	99	99	99
6	86	96	98	99	100	100	100
7	88	97	99	100	100	100	100
8	87	97	99	100	100	100	100
9	89	97	99	99	100	100	100
10	90	99	100	101	101	101	101
11	88	98	100	100	101	101	101
12	89	98	99	100	100	100	100
Mean	*88*	*97*	*99*	*100*	*100*	*100*	*100*
SD	*1.5*	*0.8*	*0.8*	*0.7*	*0.8*	*0.7*	*0.7*
% RSD	*1.7*	*0.8*	*0.8*	*0.7*	*0.8*	*0.7*	*0.7*

Commercial 15 mg tablet lot J95389 (D1400154)

0.1 N HCl

	% Dissolved						
Tablet #	5 min	10 min	15 min	20 min	30 min	45 min	60 min
1	33	82	95	98	100	100	100
2	21	72	94	99	101	101	102
3	30	82	95	99	100	101	101
4	34	85	96	99	100	99	100
5	19	68	95	100	102	103	103
6	25	79	96	99	101	102	102
7	31	81	94	98	100	100	100
8	30	82	95	98	99	100	100
9	32	80	95	99	100	101	101
10	36	84	95	98	99	100	100
11	31	81	94	97	98	98	98
12	34	83	93	97	98	98	98
Mean	*30*	*80*	*95*	*98*	*100*	*100*	*100*
SD	*5.3*	*5.0*	*0.9*	*0.9*	*1.2*	*1.5*	*1.5*
% RSD	*17.9*	*6.2*	*0.9*	*0.9*	*1.2*	*1.5*	*1.5*

Acetate, pH 4.5

	% Dissolved						
Tablet #	5 min	10 min	15 min	20 min	30 min	45 min	60 min
1	50	91	97	96	97	96	97
2	36	89	97	98	99	99	99
3	45	90	96	98	98	98	99
4	50	90	96	97	97	98	98
5	37	86	96	99	99	100	100
6	41	87	96	98	95	98	99
7	41	89	98	99	99	100	100
8	36	84	99	100	101	101	101
9	37	85	98	100	100	101	101
10	39	87	99	100	100	101	101
11	44	89	97	99	99	99	100
12	32	80	99	101	101	102	102
Mean	*41*	*87*	*97*	*99*	*99*	*99*	*100*
SD	*5.7*	*3.1*	*1.2*	*1.4*	*1.8*	*1.7*	*1.4*
% RSD	*13.9*	*3.6*	*1.3*	*1.4*	*1.8*	*1.7*	*1.4*

Phosphate, pH 6.8

	% Dissolved						
Tablet #	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
1	48	88	96	97	99	99	99
2	43	87	96	97	98	98	99
3	48	88	94	96	97	97	97
4	34	88	96	97	98	98	99
5	41	89	97	99	100	100	100
6	37	89	97	99	100	100	101
7	56	91	96	97	98	98	99
8	42	87	96	98	99	99	99
9	43	87	95	97	98	99	99
10	50	88	95	97	97	98	99
11	41	87	95	97	98	99	99
12	42	88	96	98	99	99	100
Mean	*44*	*88*	*96*	*97*	*98*	*99*	*99*
SD	*5.9*	*1.2*	*0.9*	*0.9*	*1.0*	*0.9*	*0.9*
% RSD	*13.6*	*1.3*	*0.9*	*0.9*	*1.0*	*0.9*	*0.9*

Appendix III. Information Request

1. Information Request 1

On 2/24/2017, the FDA sent an Information Request (IR) to the Applicant. On 3/21/2017, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this reviewer's assessment of the Applicant's response.

IR 1 Item 1

1) Submit the complete dissolution data (individual, mean, SD, RSD, profiles) for the following batches that could not be located in the submission.
   i. Batches included in Figure 3.2.P.2.2-7 of Module 3.2.P.2.2. Drug Product (batch number unavailable)
   ii. Batches included in Figure 3.2.P.2.2-8 of Module 3.2.P.2.2. Drug Product (batch number unavailable)
   iii. Batches included in Figure 3.2.P.2.2-17 of Module 3.2.P.2.2. Drug Product (J95374, J95277, J95386, J95387, J95389, and J95390)

The Applicant's Response to IR 1 Item 1

The Applicant provided the requested information in the response to IR 1.

Reviewer's comment

The Applicant's response is adequate. The data are listed in Appendixes I and II for details, which were reviewed under Section VI. Dissolution data and specification of Dissolution Method and Acceptance Criteria and Bridging of Formulations.

IR 1 Item 2

2) Submit the complete disintegration data (individual, mean, SD, RSD) for the following batches that could not be located in the submission:
   i. 15 mg Batch No J95389
   ii. 10 mg Batch No H06829
   iii. 5 mg Batch No H07089

The Applicant's Response to IR 1 Item 2

The Applicant provided the requested information in the response to IR 1.

Reviewer's comment

The Applicant's response is adequate. The data were reviewed under Section VII. Disintegration data and specification.

2. Information Request 2

On 5/23/2017, the FDA sent another Information Request (IR) to the Applicant. On 6/23/2017, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this reviewer's assessment of the Applicant's response.

IR 2 Item 1

1) In section 3.2.P.2.2., you reported the development of the dissolution method. However, you did not provide detailed information to demonstrate how you optimized the parameters of the method. Submit the complete dissolution data (individual, mean, SD, RSD, and profiles) for the following figures:
   Figure 3.2.P.2.2-9
   Figure 3.2.P.2.2-10
   Figure 3.2.P.2.2-11
   Figure 3.2.P.2.2-12
   Figure 3.2.P.2.2-13

The Applicant's Response to IR 2 Item 1

The Applicant provided the requested information in the response to IR 2.

Reviewer's comment

The Applicant's response is adequate. The data were reviewed under Section II. Dissolution Method Development for Ertugliflozin IR Tablets, 15 mg, and 5 mg of Dissolution Method and Acceptance Criteria.

IR 2 Item 2

2) In section 3.2.P.2.2. Drug Product, you reported that the proposed dissolution method has discriminatory power towards changes in composition and components of the proposed product and changes in manufacturing process. However, you did not provide detailed information to support your conclusion. Submit the complete dissolution data (individual, mean, SD, RSD, and profiles) for the following figures:
Figure 3.2.P.2.2-14
Figure 3.2.P.2.2-15
Figure 3.2.P.2.2-16 a
Figure 3.2.P.2.2-16 b

The Applicant's Response to IR 2 Item 2

The Applicant provided the requested information in the response to IR 2.

Reviewer's comment

The Applicant's response is adequate. The data were reviewed under Section III. The Discriminatory Power of the Proposed Dissolution Method of Dissolution Method and Acceptance Criteria.

IR 2 Item 3

3) In section 3.2.P.2.2. Drug Product, you summarized discriminatory power of the disintegration test and the relationship between dissolution (b) (4) and disintegration. However, you did not provide detailed information to support your statement. Submit the complete dissolution data (individual, mean, SD, RSD, and profiles) for the following figures:
Figure 3.2.P.2.2-18
Figure 3.2.P.2.2-19
Figure 3.2.P.2.2-20
Figure 3.2.P.2.2-21

The Applicant's Response to IR 2 Item 3

The Applicant provided the requested information in the response to IR 2.

Reviewer's comment

The Applicant's response is adequate. The data were reviewed under Section III. The Discriminatory Power and Section VI. Disintegration testing of the Proposed Dissolution Method of Dissolution Method and Acceptance Criteria.

IR 2 Item 4

4) Submit the complete dissolution validation report.

The Applicant's Response to IR 2 Item 4

The Applicant provided the requested information in the response to IR 2.

Reviewer's comment

The Applicant's response is adequate. The data were reviewed under Section V. Validation of Analytical procedures for Dissolution of the Proposed Dissolution Method of Dissolution Method and Acceptance Criteria.

IR 2 Item 5

5) In section 3.2.P.5.4. Batch Analyses, you reported the mean dissolution data and ranges for clinical batches. Clarify the dissolution method that was used for this testing (specifically, clarify whether (b) (4) Buffer was used as the dissolution medium).

The Applicant's Response to IR 2 Item 5

The Applicant provided the requested information in the response to IR 2.

Reviewer's comment

The Applicant's response is adequate. The data were reviewed.

IR 2 Item 6

6) In Section 3.2.P.2.3. Manufacturing Process Development, you conducted a Design of Experiments study with the 5 mg strength to demonstrate how some parameter changes affect tablet disintegration time and dissolution. However, the data provided are not sufficiently detailed. Submit the detailed study design, results, and data analysis.

The Applicant's Response to IR 2 Item 6

The Applicant provided the requested information in the response to IR 2.

Reviewer's comment

The Applicant's response is adequate. The data were reviewed under Section Application of dissolution/IVIVC in QbD.

IR 2 Item 7

7) In Section 3.2.P.2.3. Manufacturing Process Development, you reported that "The impact of tablet hardness on disintegration time, dissolution and friability was studied for the 15 mg strength tablet in separate univariate studies." Submit the detailed report of the univariate studies (including study designs, results, and data analysis).

The Applicant's Response to IR 2 Item 7

The Applicant provided the requested information in the response to IR 2.

Reviewer's comment

The Applicant's response is adequate. The data were reviewed under Section Application of dissolution/IVIVC in QbD.

3. Information Request 3

On 8/14/2017, the FDA sent another Information Request (IR) to the Applicant. On 8/15/2017, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this reviewer's assessment of the Applicant's response.

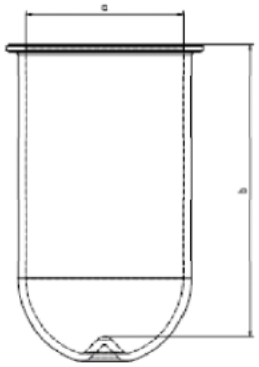
IR 3 Item 1

1) We acknowledge that you used peak vessels to conduct dissolution tests. Generally, we do not recommend using peak vessels as dissolution vessels because they are not compendial vessels. However, it can be accepted based on the justification that you provided: peak vessels are designed to prevent cone formation in the "dead zone" at the base of the dissolution vessels of USP Apparatus II. Provide detailed information about peak vessels (such as volume, diameter, verticality, height, manufacturer, and so on) to the Agency for review and record. In the future, you should use the same peak vessels to conduct dissolution tests for any post approval change of your proposed product.

The Applicant's Response to IR 3 Item 1

The Applicant stated that peak vessels from Sotax were used for release testing of 5 mg (formulation D1400153) and 15 mg (formulation D1400154) registration stability, tech transfer and validation batches which were provided in Section 3.2.P.5.4. Representative Certificates of Compliance provided by Sotax containing dimensions of the peak vessel are provided. In the future, the Applicant will use Sotax peak vessels for post approval changes.

For SOTAX AT Dissolution Testing Systems



Dimensions:	Inside Ø	a	100 mm	± 0.3 mm
	Height	b	186.9 mm	± 0.7 mm
	With hemispherical bottom			
Material:	(b) (4)	glass		

Reviewer's comment

The response is adequate.

IR 3 Item 2

2) You proposed the following dissolution specification for future post-approval change:
NLT (b) (4)% (Q) in (b) (4) minutes
Based on the data provided, the proposed dissolution specification is liberal. The specification should be tightened as follows:
NLT (b) (4)% (Q) in 15 minutes
We request you to acknowledge your acceptance of the above specification and update the relevant parts of your NDA accordingly.

The Applicant's Response to IR 3 Item 2

The Applicant stated that they agree to tighten the dissolution specification as requested. An updated Section 3.2.P.2.2 will be submitted later.

Reviewer's comment

The response is adequate.

IR 3 Item 3

3) You proposed the following disintegration specification for your proposed products:
NMT (b) (4) minutes

Based on the data provided, the proposed disintegration specification is liberal. The specification should be tightened as follows:
5 mg: NMT (b) (4) minutes
15 mg: NMT (b) (4) minutes
We request you to acknowledge your acceptance of the above specifications and update the relevant parts of your NDA accordingly.

The Applicant's Response to IR 3 Item 3

The Applicant stated that they agree to tighten the disintegration specification for 5 mg as requested. An updated Section 3.2.P.5.1 and Section 3.2.P.5.6 will be submitted.
However, the Applicant stated that they do not accept the FDA recommended specification at this time, because there are only 7 batches of 15 mg that have manufactured, which are not enough for a proper setting of an appropriate specification.
The Applicant request to maintain a disintegration criterion of NMT (b) (4) minutes and commits to critically review the disintegration acceptance criterion for 15 mg tablets using the tolerance interval approach after 13 additional batches (total of 20 batches) are available and adjust the acceptance criteria if appropriate.

Reviewer's comment
The response is adequate. The disintegration specification for 15 mg will be addressed in the post-approval commitment.

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

The following information needs to be conveyed to the Applicant:

Your proposed disintegration specification for 15 mg (NMT (b) (4) minutes) is acceptable on an interim basis for release and stability testing until one year from approval. Generate and submit additional disintegration data for all 15 mg commercial batches up to one year post-approval to

the agency for review in the first annual report. Your disintegration specification for 15 mg will be revaluated and may be revised based on this new analysis.

Lifecycle Management Considerations

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, Pharm.D., Ph.D., 5/5/2017, 8/8/2017, 8/14/2017

Biopharmaceutics reviewer

Division of Biopharmaceutics

ONDP/OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Haritha Mandula, Ph.D. 8/16/2017
Acting Biopharmaceutics Lead

Division of Biopharmaceutics

ONDP/OPQ

Hansong Chen

Digitally signed by Hansong Chen
Date: 8/16/2017 10:08:58PM
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Haritha Mandula

Digitally signed by Haritha Mandula
Date: 8/16/2017 10:13:22PM
GUID: 508da6fb000282df41459408f32a1ce0

CHAPTER VIII: Microbiology

see Chapter V

ATTACHMENT I: Final Risk Assessments

See Executive Summary

Su (Suong) Tran

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QUALITY REVIEW

Recommendation: APPROVAL
(including the Facility Review/Overall Manufacturing Inspection Recommendation)

NDA 209806

Review #1
Review Date (see last page)

Drug Name/Dosage Form	ertugliflozin and metformin HCl tablet (fixed ratio combination)
Strength	5 mg and 15 mg 2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg/mg ertugliflozin/metformin HCl
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Merck

SUBMISSION(S) REVIEWED NDA 209806	DOCUMENT DATE
0000	12/19/16
0002	1/13/17
0003	1/23/17
0008	3/21/17
0010	4/25/17
0013	5/10/17
0016	6/21/17
0017	6/23/17
0019	7/26/17
0020	7/28/17
0022	8/2/17
0023	8/4/17

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Erika Englund/Donna Christner	New Drug API/ONDP
Drug Product	Elise Luong/Danae Christodoulou	New Drug Products II/ONDP
Process/Microbiology	Hong Yang/Yong Hu	Process Assessment II/OPF
Facility	Michael Klapal/Juandria Williams	Inspectional Assessment/OPF
Biopharmaceutics	Kalpana Paudel/Haritha Mandula	Biopharmaceutics/ONDP

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   - **A. DMFs:** Adequate (see Chapter II)
   - **B. Other Documents:** NDA 209805 (ertugliflozin/sitagliptin) and NDA 209806 (ertugliflozin/metformin HCl) by the same applicant
2. **CONSULTS:** n/a

Executive Summary

I. Recommendation and Conclusion on Approvability

The final OPQ recommendation is for Approval, including the overall manufacturing inspection recommendation.

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(2) NDA for ertugliflozin, a New Molecular Entity, and metformin hydrochloride, relying on FDA's findings of safety and effectiveness for the listed GLUCOPHAGE (metformin hydrochloride).

Ertugliflozin is processed with the conformer L-pyroglutamic acid (LPGA) to yield the ertugliflozin-LPGA co-crystal. As per FDA's guidance "Regulatory Classification of Pharmaceutical Co-Crystals", the ertugliflozin-LPGA co-crystal (b) (4) Therefore, the active ingredient/drug substance of the product is "ertugliflozin", to be reflected in the labeled established name and corresponding dosage strength.

Reference is made to DMF (b) (4) for all CMC information on metformin HCl. The DMF is currently adequate.

The drug product is an immediate release oral tablet, fixed ratio combinations of ertugliflozin and metformin HCL: 2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg/mg.

Two pivotal BE studies (P027/1041 and P050/1058) were conducted to compare the 7.5/1000 (batch WL00061877/15-003858) and 2.5/500 (batch WL00061881/15-004639) strengths to the concomitant administration of ertugliflozin tablets and Glucophage tablets. The biobatches were manufactured at the drug product commercial site and have the commercial formulation with the exception of colors and debossing. Ertugliflozin-PLGA is BCS 1 and metformin HCl is BCS3. A biowaiver is granted for the 2.5/1000 and 7.5/500 strengths based on the four strengths having similar dissolution profiles (b) (4)

Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	[not finalized by GRMP goal; see CDTL's memo]
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	n/a

A. Quality Assessment Overview

Drug Substance

Ertugliflozin (PF-04971729, MK-8835 free form) is the active moiety, and ertugliflozin L-PGA (PF-04971729 (b) (4) MK-8835) represents the cocrystal of ertugliflozin and L-pyroglutamic acid.

r-INN: Ertugliflozin

USAN: Ertugliflozin

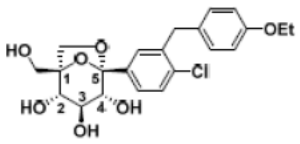
Chemical Names

IUPAC:

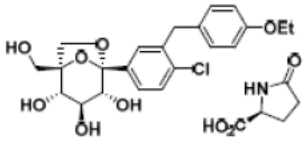
Ertugliflozin: (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol

Ertugliflozin L-PGA: (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid

Figure 2.3.S.1-1. Ertugliflozin and Ertugliflozin L-PGA Structures



Ertugliflozin



Ertugliflozin L-PGA

Molecular Formula

Ertugliflozin: $C_{22}H_{25}ClO_7$

Ertugliflozin L-PGA: $C_{27}H_{32}ClNO_{10}$

Molecular Weight

Ertugliflozin: 436.88 Daltons

Ertugliflozin L-PGA: 566.00 Daltons

Ertugliflozin is an unstable amorphous material that was developed as a 1:1 co-crystal with L-pyroglutamic acid (LPGA) in order to achieve better physical and chemical properties including stability. As per FDA's guidance "Regulatory Classification of Pharmaceutical Co-Crystals", the ertugliflozin-LPGA co-crystal (b) (4) and the active ingredient of the product is "ertugliflozin". Adequate CMC information is provided in the NDA on ertugliflozin, LPGA, and the co-crystal.

Ertugliflozin-LPGA is BCS 1, non-hygroscopic, and crystalline (b) (4)

(b) (4)

(b) (4)

The drug substance specification includes standard quality attributes of a small synthetic molecule including chirality and LPGA content. Batch analysis data include batches from the R&D site "Pfizer Sandwich, UK" and the commercial site "Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland".

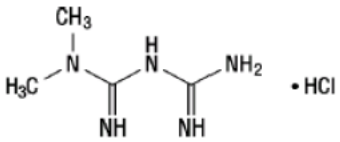
Particle size – This attribute is not critical to dissolution because the drug substance is BCS 1 (i.e., highly soluble). Therefore, acceptance criteria are established as (b) (4)

Impurities – (b) (4) have limits that exceed the ICH qualification thresholds; their limits are considered qualified by the Pharmacology Toxicology team. All specified impurities, including these three, were evaluated for mutagenicity and found negative (confirmed by the Pharmacology Toxicology team).

Polymorphism – Ertugliflozin-LPGA has the (b) (4) Free ertugliflozin is amorphous and has different physico-chemical properties and can be readily controlled by test methods (b) (4) Therefore, the lack of polymorph testing in the drug substance specification is acceptable.

A retest period of (b) (4) is acceptable for Ertugliflozin-LPGA when stored (b) (4) The retest period is based on stability data for (b) (4) batches, manufactured at the R&D site "Pfizer Sandwich, UK" and the commercial site "Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland".

Drug substance: Metformin hydrochloride



$C_4H_{11}N_5$•HCl molecular weight:165.63

Reference is made to DMF [redacted] (b) (4) for all CMC information on metformin HCl. The DMF is currently adequate.

Drug Product

The drug product is an immediate release oral tablet, fixed ratio combinations of ertugliflozin and metformin HCL: 2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg/mg. [redacted] (b) (4)

Excipients: povidone, microcrystalline cellulose, crospovidone, sodium lauryl sulfate, and magnesium stearate. The inert film coating contains hypromellose, hydroxypropyl cellulose, titanium dioxide, iron oxide red, and carnauba wax. There is no novel excipient, and there is no human/animal-derived excipient.

[redacted] (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, including information on elemental impurities.

Degradants – The two specified ertugliflozin-related degradants [redacted] (b) (4) Both were evaluated for mutagenicity and found negative (confirmed by the Pharmacology Toxicology team).

Disintegration – The use of disintegration in lieu of dissolutionis acceptable based on ertugliflozin-LPGA being BCS 1 and metformin HCl being BCS 3, and an adequate correlation is demonstrate betweej disintegration and dissolution.

Polymorphism is not part of the specification. [redacted] (b) (4)

[redacted] (b) (4). Therefore, polymorph testing is not necessary.

[redacted] (b) (4)

Primary container closure system: The drug product is packaged in [redacted] (b) (4) bottles/closures and aluminum blisters.

Expiration Date & Storage Conditions: The shelf life of the drug product is 24 months at room temperature.

The long-term expiry is based on 12-month long-term (25 C/60% RH) and 6-month accelerated (40 C/75% RH) data are provided in the NDA for three primary stability batches of each of the 2.5/1000 and 7.5/500 strengths and one batch of each of the 7.5/1000 and 2.5/500 strengths. Stability batches were manufactured at the commercial drug product site MSD in Las Piedras Puerto Rico, with ertugliflozin LPGA from the R&D site "Pfizer Sandwich, UK", and were packaged in the commercial container closure systems, utilizing a reduced design to bracket the 60-count and 180-count bottles.

B. Special Product Quality Labeling Recommendation: not applicable

C. Life Cycle Knowledge Information/ Final Risk Assessment:

API	page 49 of Chapter I
Drug product	none
Process	none
Facilities	none
Biopharmaceutics	none

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

Suong T. Tran -S

Digitally signed by Suong T Tran S
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Date: 2017 08 18 10:43:51 04'00'

Suong (Su) Tran, Ph.D.
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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 209806

The proposed drug products ertugliflozin and metformin fixed dose combination (FDC) are immediate release (IR) tablets. Four strengths of film-coated, FDC tablets of ertugliflozin and metformin for bid administration have been developed and proposed for commercialization in the US. The Applicant seeks approval of this NDA via the 505(b)(2) regulatory pathway for the treatment of type 2 diabetes mellitus.

Drug Product Name/Strength: Ertugliflozin/Metformin HCl/ 2.5/500 mg/mg, 2.5/1000 mg/mg, 7.5/500 mg/mg, 7.5/1000 mg/mg

Route of Administration: Oral

Applicant Name: Merck Sharp & Dohme Corp.

Review Recommendation: **ADEQUATE**

Review Summary:

The Applicant has proposed disintegration in lieu of dissolution testing for ertugliflozin/metformin tablets for quality control purposes. The Applicant has also developed and validated a dissolution method for ertugliflozin/metformin tablets to support relevant post-approval changes. The disintegration and the dissolution methods were deemed inadequate pending the Applicant's response to the following deficiency comment during the initial Filing review:

1. Provide detailed batch information (i.e., Batch/Lot Number, Manufacturing Date, Site, and Batch Size, Expiration Date, Testing Date, etc.), and the complete dissolution data (individual, mean, SD, RSD, profiles) summarized in Appendix 1, Table A1 of Module 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods.

2. Provide complete disintegration data (individual, mean, SD, RSD) for the above batches.

3. Provide the detailed protocol/SOP for the disintegration method.

On 03/21/2017, the Applicant responded to the above three deficiencies and the responses were reviewed and found acceptable with some remaining issues to be addressed as listed below.

The following deficiencies were sent to the Applicant in the first IR cycle.

1. Based on the disintegration data submitted, we recommend a specification of NMT (b) (4) minutes. Provide acknowledgement of the above recommended specification and update the drug product specification tables and other relevant parts of your ANDA accordingly.

2. Provide dissolution method development report for justification of the selection of dissolution method conditions for ertugliflozin/metformin tablet.

On 06/23/2017, the Applicant responded to the above deficiencies. The Applicant provided justification based on the additional data and rationale, that a disintegration acceptance criterion of NMT (b) (4) is appropriate to control product quality and ensure consistent product performance for the patient. Dissolution method development report was also provided and was found to be adequate. The Applicant's response is acceptable.

List Submissions being reviewed (table): Dissolution method and acceptance criteria; Biowaiver request

Application 209806 - Sequence 0000 - 0000 (1) 12/19/2016 ORIG-1 /Multiple Categories/Subcategories

Application 209806 - Sequence 0008 - 0008 (9) 03/21/2017 ORIG-1 /Quality/Response To Information Request

Application 209806 - Sequence 0017 - 0017 (18) 06/23/2017 ORIG-1 /Quality/Response To Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment:

The Applicant states that based upon the solubility and permeability in accordance with the US BCS guidance and EU BE Guideline, ertugliflozin and metformin are classified as BCS 1 and 3, respectively. Metformin HCl is highly soluble over the entire physiological pH range. Oral BA in humans is 50% to 60% of an administered dose and it is categorized as a BCS Class 3 (high solubility-low permeability) compound.

Solubility:

Ertugliflozin L-pyroglutamic acid (L-PGA) is a cocrystal of the active compound ertugliflozin with L-pyroglutamic acid. (b) (4)

The solubility of amorphous ertugliflozin was determined to be 0.64-0.74 mg/mL

throughout the gastrointestinal pH range. As ertugliflozin is non-ionizable under physiological conditions, the solubility is pH-independent. The highest dose, 15 mg, is soluble in <250 mL of aqueous media within the gastrointestinal pH range and thus meets the high solubility of the BCS.

Metformin HCl is highly soluble over the entire physiological pH range.

Permeability: N/A

Dissolution: Please see below.

Dissolution Method and Acceptance Criteria

1. Composition of proposed drug product:

The quantitative composition and function of each component of the 4 strengths of the ertugliflozin/metformin FDC proposed commercial tablets are listed in the Table 1. The proposed four strengths of the FDC products (b) (4)

Table 1: Composition of ertugliflozin/metformin FDC commercial tablets

Strength		2.5/500 mg	7.5/500 mg	2.5/1000 mg	7.5/1000 mg
Component	Function	Amount – mg/tablet (% w/w)			
Ertugliflozin L-PGA[a]	Active	3.238 (b) (4)	9.713 (b) (4)	3.238 (b) (4)	9.713 (b) (4)
(b) (4)	(b) (4)				(b) (4)
Microcrystalline Cellulose					
Crospovidone					
Sodium Lauryl Sulfate					
Magnesium Stearate					
(b) (4)					
Carnauba Wax					
(b) (4)		-	-	-	-
Coated Tablet		691.1 (b) (4)	691.1 (b) (4)	1373.3 (b) (4)	1373.3 (b) (4)

Source: [Table 3.2.P.2.2.1.4.4.2-8835B-tablet: 12].
Abbreviations: FDC=fixed-dose combination; L-PGA=L-pyroglutamic acid; US=United States.
a. 1.000 g of ertugliflozin L-PGA is equivalent to 0.772 g of the ertugliflozin free form. (b) (4)
(b) (4)

2. Disintegration of Ertugliflozin / Metformin HCl Tablets:

The Applicant has proposed disintegration testing in lieu of dissolution testing for ertugliflozin/metformin tablets for quality control purposes. The Applicant notes that dissolution testing will be performed on shelf-life to support relevant post-approval changes only. However, the protocol/SOP for the disintegration method was not provided. The Applicant was asked to provide the protocol/SOP for the disintegration method. The disintegration method provided by the Applicant is presented below. The Applicant noted that disintegration testing is performed according to USP <701>.

Instrument Parameters

Apparatus:	Basket-rack with a 1000 mL low-form beaker, supporting six cylindrical glass tubes
Temperature:	37 ± 2°C
Speed Rate:	29 - 32 cycles/minute
Stroke Distance:	53 - 57 mm
Basket Travel:	Minimum 15 mm below the surface of the fluid Minimum 25 mm from the bottom of the vessel

The proposed disintegration acceptance criteria for Release and Shelf-Life are ≤ (b) (4) minutes. In the protocol it is mentioned that all tablets should have completely disintegrated within (b) (4) minutes. If 1 or 2 tablets fail to disintegrate completely within (b) (4) minutes, repeat the test on 12 additional tablets. Not less than 16 of the total 18 tablets have disintegrated completely within (b) (4) minutes.

The Applicant was also asked to provide complete disintegration data (individual, mean, SD, RSD) to justify the disintegration acceptance criteria. In response, the Applicant provided a summary of the requested individual disintegration results as provided in the table below.

(b) (4) **Batch No. Drug Product Lot# West Point Drug Product Lot#**	0000475957 WL00061877	0000475997 WL00061849	0000481095 WL00061853	0000481103 WL00061881
Strength	7.5/1000	7.5/500	2.5/1000	2.5/500
Disintegration Time	Disintegration Time (min)			
Tablet 1	11.5	9.9	11.8	8.9
Tablet 2	11.8	10.6	12.2	8.9
Tablet 3	11.3	10.7	11.3	8.9
Tablet 4	11.5	10.1	11.6	8.3
Tablet 5	11.8	10.0	12.2	9.3
Tablet 6	10.8	9.7	11.8	8.6
Average	11.4	10.2	11.8	8.8
SD	0.4	0.4	0.3	0.3
RSD	3.3	3.9	2.7	3.9

Based on the data, the Applicant was asked to tighten the disintegration specification to (b) (4) However, on June 23, 2017, in response to the IR, the Applicant provided justification based on

the additional data and rationale, that a disintegration acceptance criterion of NMT (b) (4) is appropriate to control product quality and ensure consistent product performance for the patient. The Applicant's response is found to be acceptable. Please see the details in List of Deficiencies.

3. In vitro dissolution method and acceptance criteria:

The Applicant has proposed the below mentioned dissolution method for ertugliflozin and metformin. As mentioned earlier, the dissolution testing will be used to support relevant post-approval changes. The dissolution method details can be found in Sec. 3.2.P.5.2.5 and 3.2.P.5.2.6.

Table 2: Dissolution method conditions for ertugliflozin and metformin

Apparatus:	No. 1 (baskets, 10 mesh)
Rotation Speed:	100 rpm
Medium Volume:	900 mL
Medium Temperature:	37 ± 0.5°C
Sampling Time:	15 minutes
Dissolution Medium	50mM Acetate Buffer pH 4.5

The proposed dissolution acceptance criterion is as follows.

Q = (b) (4)% in 15 minutes

(b) (4)

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(b) (4)

6. Dissolution Profile Data Comparisons:

Please see details in Biowaiver section below.

Reviewer's Assessment: Initial assessment

- The Applicant has proposed disintegration in lieu of dissolution testing for ertugliflozin/metformin tablets for quality control purposes. The Applicant mentioned that disintegration testing is performed according to USP <701>. However, the protocol/SOP for the disintegration method was not provided. The Applicant was asked to provide the detailed protocol/SOP for the disintegration method as well as the individual disintegration data during the filing review. The Applicant has provided the

requested data. The method is acceptable. See details above. However, the Applicant was asked to tighten the disintegration acceptance criteria from NMT (b) (4) minutes to (b) (4) minutes in the first IR cycle based on the data. In response to the IR, the Applicant provided justification and data. Based on the additional data and rationale a disintegration acceptance criterion of NMT (b) (4) is deemed appropriate to control product quality and ensure consistent product performance for the patient. The Applicant's response is found to be acceptable. Please see additional details in List of Deficiencies.

- The Applicant has developed and validated a dissolution method for the ertugliflozin/metformin tablet to support relevant post-approval changes. The Applicant was asked to provide dissolution method development report for the justification of the selection of dissolution method conditions in the first IR cycle. In response, the Applicant noted that the document is available in M3.3.1. The Applicant has provided justification for the choice of dissolution apparatus, dissolution medium, and rotational speed. The report also provided tabulated dissolution data for all batches tested and released as intended clinical supplies and primary stability batches, including individual results, mean and standard deviation at each sampling timepoint. The Applicant notes that these batches are representative of the commercial product and were used for setting the dissolution acceptance criterion for Ertugliflozin/ Metformin Tablets. The report is found to be adequate.

- Applicant's proposed dissolution acceptance criteria is, *Q*=(b) (4)*% in 15 minutes*. To justify the specification, the Applicant was asked to provide detailed batch information and the complete dissolution data during the filing review. The Applicant has provided the data and profiles as requested. The profiles are presented below in biowaiver section. Based on the data, the proposed dissolution acceptance criterion is acceptable.

- The Applicant has provided data to show that the dissolution method was able to discriminate differences in hardness despite the fast dissolution profiles.

- The comparative dissolution profile data for the two middle strengths of the drug product vs. the proposed highest and lowest strengths are reviewed and considered acceptable. Comparative dissolution profile data showed very rapid dissolution (>85% dissolved in 15 min) for all strengths in all dissolution media. See biowaiver section below.

- The analytical method validation report for ertugliflozin and metformin are reviewed and considered acceptable.

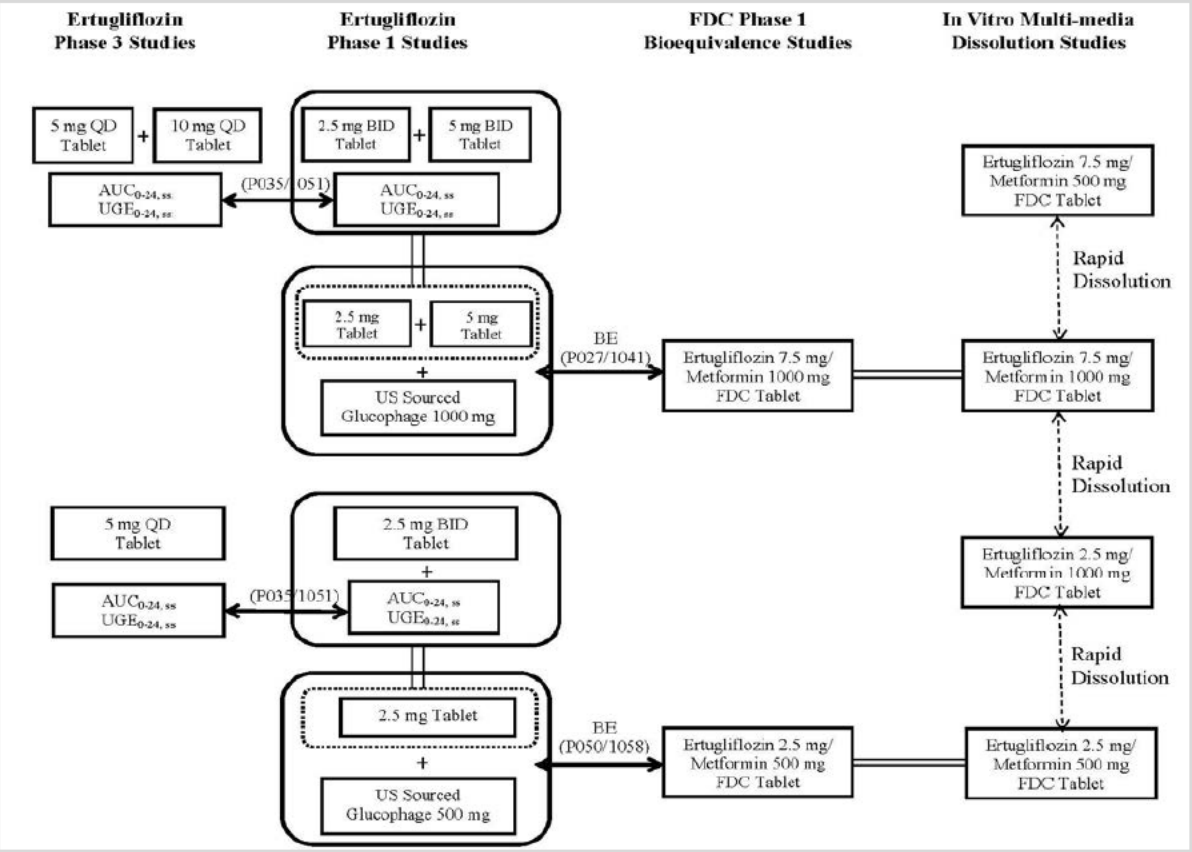
- The critical quality attribute of dissolution has been demonstrated to be robust with respect to the manufacturing process at both the pilot and commercial scales (b) (4)

Bridging of Formulations

Reviewer's Assessment:

Co-administration of the ertugliflozin and US-sourced Glucophage® tablets was bridged to the proposed commercial ertugliflozin/metformin tablets by a combination of BE study data and in vitro dissolution data (Please see Figure below). 2 pivotal BE studies (Study P027/1041 and Study P050/1058), conducted using the highest and lowest strengths of ertugliflozin/metformin proposed commercial tablets, are bioequivalent per the Applicant to respective doses of ertugliflozin and metformin co-administered as individual components. These studies will be reviewed by the Office of Clinical Pharmacology (please refer to their review for additional details). All 4 ertugliflozin/metformin tablet strengths developed for the US dissolve rapidly (>85% release in 15 minutes). Thus, ertugliflozin 2.5 mg/metformin 500 mg, ertugliflozin 2.5 mg/metformin 1000 mg, ertugliflozin 7.5 mg/metformin 500 mg and ertugliflozin 7.5 mg/metformin 1000 mg tablets are all considered bioequivalent to respective strengths of ertugliflozin and US sourced Glucophage® co-administered. Please see details in Biowaiver section below.

Pivotal BE Studies and In Vitro Multi-Media Dissolution, Bridging the Co administered Tablet Formulations of Ertugliflozin and US Sourced Glucophage with the Proposed Commercial Ertugliflozin/Metformin Tablets



Biowaiver Request

Reviewer's Assessment:

Four dose strengths of the Ertugliflozin/Metformin FDC (i.e., 2.5 mg or 7.5 mg ertugliflozin, each in combination with 500 mg or 1000 mg metformin), have been developed to support US registration. Table below lists the 4 different strengths of Ertugliflozin/Metformin Tablets.

Ertugliflozin/Metformin Tablet Strength

Ertugliflozin (mg)	Metformin (mg)
2.5	500
2.5	1000
7.5	500
7.5	1000

The Applicant requested a waiver from the requirement of a bioequivalence study for its middle two strengths (ertugliflozin 7.5 mg/metformin 500 mg and ertugliflozin 2.5 mg/metformin 1000 mg) of the ertugliflozin/metformin FDC. As per the FDA written communication dated 6/8/2015 (Type C guidance from the Agency), the Applicant has carried out 2 bioequivalence studies (Study P027/1041 and Study P050/1058) on the highest and the lowest strengths (ertugliflozin 7.5 mg/metformin HCl 1000 mg, ertugliflozin 2.5 mg/metformin HCl 500 mg) comparing the drug products with the respective strengths of single-entity metformin (US-sourced Glucophage®) co-administered with ertugliflozin. Per the communication, a waiver of *in vivo* testing requirements may be considered for the two middle strengths (ertugliflozin 2.5 mg/metformin HCl 1000 mg and ertugliflozin 7.5 mg/metformin HCl 500 mg) given that the Applicant provide supporting comparative dissolution profile data and similarity factor (f2) for the two middle strengths vs. the proposed highest and lowest strengths. The Applicant has provided these data.

Comparative dissolution profile data for the other 2 strengths (ertugliflozin 7.5 mg/metformin 500 mg and ertugliflozin 2.5 mg/metformin 1000 mg) vs the highest and lowest strength FDCs showed very rapid dissolution (>85% dissolved in 15 min) for all strengths in all dissolution media and are provided in Sec. 2.7.1 to support the waiver of BE studies for these 2 FDC strengths. The dissolution method conditions in multimedia and the data are provided below.

Multi-Media Dissolution Method Conditions for Ertugliflozin/Metformin FDC Formulations

Apparatus	USP I
Dissolution Media	USP SGF without enzymes, pH 1.2[a] acetate buffer, pH 4.5 phosphate buffer, pH 6.8
Rotation Speed (rpm)	100
Media Volume (mL)	900

Source: [Sec. 3.2.P.5.6.2.4-8835B-tablet].

Abbreviations: EDTA=ethylenediaminetetraacetic acid; FDC=fixed-dose combination; rpm=rotations per minute; SGF=simulated gastric fluid; USP=United States Pharmacopeia.

a. SGF contained 1 mM EDTA to eliminate adventitious ertugliflozin oxidation.

Summary of Dissolution Results for Ertugliflozin/Metformin Tablets Dissolved in pH 1.2, pH 4.5, and pH 6.8 Media at 10, 15, and 20 minutes (N=12) for the US

pH media	Strength (mg/mg)	Ertugliflozin % claim			Metformin % claim		
		10 minutes	15 minutes	20 minutes	10 minutes	15 minutes	20 minutes
6.8	7.5/1000	74	97	98	76	98	99
	7.5/500	82	98	98	84	100	100
	2.5/1000	70	95	98	73	98	101
	2.5/500	86	98	98	89	101	101
4.5	7.5/1000	73	96	98	75	99	101
	7.5/500	82	98	98	84	100	100
	2.5/1000	67	93	98	69	95	99
	2.5/500	85	98	98	87	100	100
1.2 (SGF without enzymes)[a]	7.5/1000	74	96	98	74	99	101
	7.5/500	83	99	99	86	100	100
	2.5/1000	70	93	97	73	97	101
	2.5/500	82	96	97	89	100	100

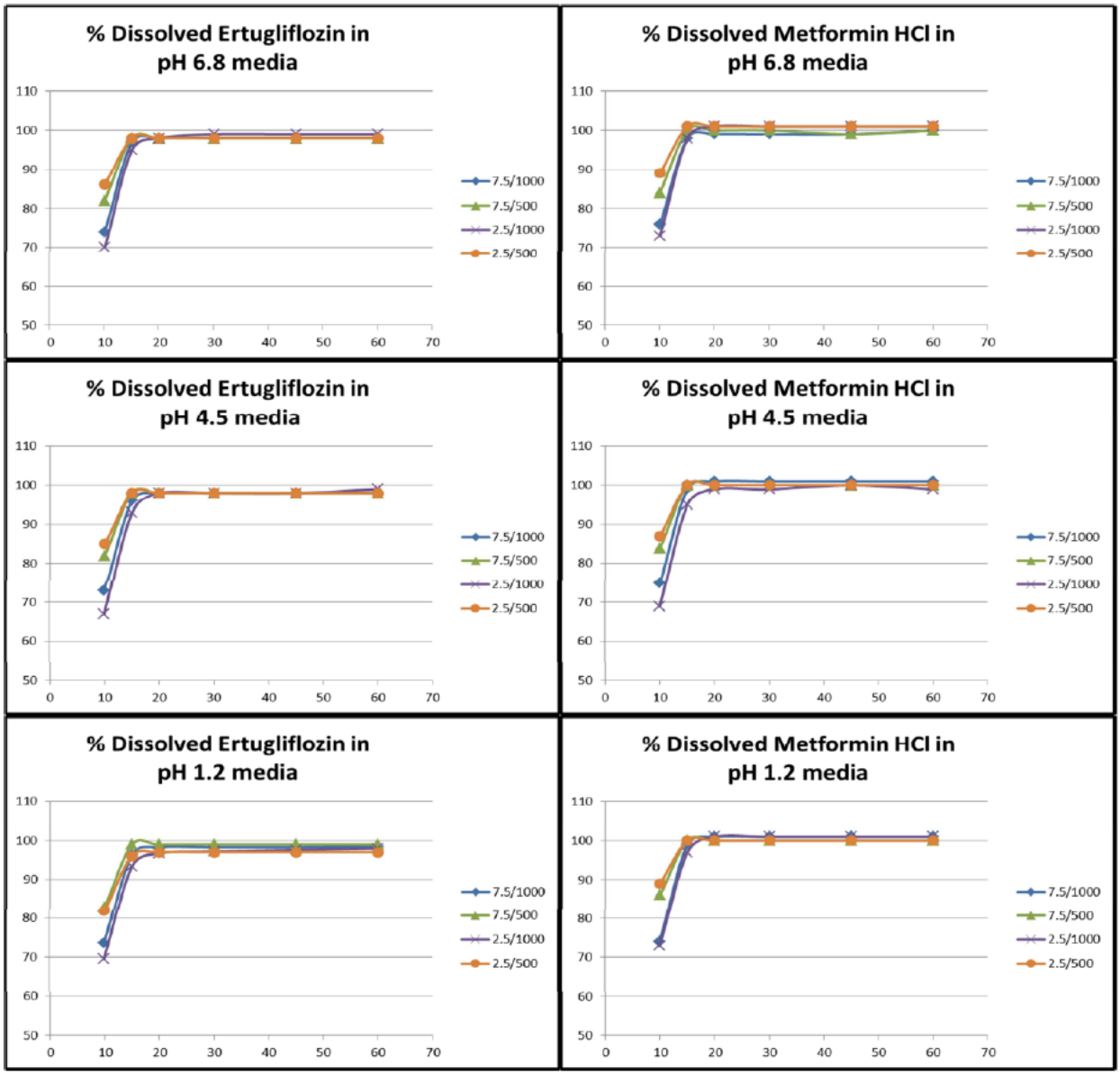
Source: [Table 3.2.P.5.6.2.4-8835B-tablet: 1].

Abbreviations: EDTA=ethylenediaminetetraacetic acid; N=number of individual units; SGF=simulated gastric fluid; US=United States.

a. Simulated gastric fluid media contained 1 mM EDTA to eliminate adventitious ertugliflozin oxidation.

The Applicant was asked to provide detailed batch information and the complete dissolution data (individual, mean, SD, RSD, profiles) for the mean data in the above table during the filing review. The Applicant has provided detailed batch information, complete set of dissolution data and dissolution profiles (average, n=12) in each media as requested. The profiles are presented below.

Multimedia Dissolution Profiles of Ertugliflozin/Metformin HCl Tablets



Based on the above data, the biowaiver request to waive the requirement of a bioequivalence study for the middle two strengths (ertugliflozin 7.5 mg/metformin 500 mg and ertugliflozin 2.5 mg/metformin 1000 mg) of the ertugliflozin/metformin FDC is acceptable if the BE study is found acceptable. BE study will be reviewed by clinical pharmacology.

List of Deficiencies: None

Review of Information Request from Filing review

The following deficiencies were sent to the Applicant during the filing review cycle.

1. Provide detailed batch information (i.e., Batch/Lot Number, Manufacturing Date, Site, and Batch Size, Expiration Date, Testing Date, etc.), and the complete dissolution data

(individual, mean, SD, RSD, profiles) summarized in Appendix 1, Table A1 of Module 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods.

2. Provide complete disintegration data (individual, mean, SD, RSD) for the above batches.

3. Provide the detailed protocol/SOP for the disintegration method.

Reviewer's comments
On 03/21/2017, the Applicant responded to the above deficiencies and provided complete disintegration and dissolution data and dissolution profiles in each media. Applicant's responses to the deficiencies are adequate. Please see the details in respective sections above. However, the Applicant was asked to tighten the disintegration acceptance criteria, and to provide the dissolution method development report.

Information Request 1 (First IR cycle)

The following deficiencies were sent to the Applicant in the first IR cycle.

1. Based on the disintegration data submitted, we recommend a specification of NMT (b) (4) minutes. Provide acknowledgement of the above recommended specification and update the drug product specification tables and other relevant parts of your ANDA accordingly.

Reviewer's comments
On 06/23/2017, the Applicant responded to the above deficiency. The Applicant noted that based on the historical disintegration performance of ertugliflozin/metformin tablets, reduction in the disintegration acceptance criterion to NMT (b) (4) min is inconsistent with available data and may place the drug product at high risk of unnecessary batch rejection and result in potential disruption to patient supply.

The Applicant noted that the nature of the USP disintegration test, which allows no greater than 2 tablets to exceed specifications, is more restrictive to individual tablet variation than USP Dissolution testing, which leverages average values for Stage 2 and Stage 3 testing. The Applicant also noted that the current stability data is limited, and during Formal stability study (FSS), individual tablet results of (b) (4) min have been observed. A statistical analysis of the 95 percent one-sided confidence limit trends for the currently available 18 month FSS disintegration results was performed by the Applicant. Stability data in Sec 3.2.P.8.1 and sec 3.2.P.8.3 have been updated with the 18 month time point data and are included to support this response. Results for the largest bracketing strength 2.5/1000 mg tablets are shown in the table below. From this dataset, analysis indicates that individual tablet values for the largest 2.5/1000 mg tablets may range up to (b) (4) min over the duration of the 36 month study.

Statistical Analysis of 18 month FSS Disintegration Results – One Sided 95% Confidence Limit

Condition	Package	Strength	Batch	Intercept (min)	Slope [a] (min/month)	Slope P-value	Time Point (month)	Predicted Mean (min)	One-Sided 95% Confidence Limit on the Mean (min)		One-Sided 95% Prediction Limit on the Individual (min)	
									Lower	Upper	Lower	Upper
25C/60%RH	Bottle_14ct,75cc	2.5 mg/1000 mg	0000481090	10.7	0.020	0.183	24	11.2	10.6	11.7	9.1	13.2
							36	11.4	10.5	12.3	9.2	13.6
			0000481095	10.9			24	11.4	10.8	12.0	9.3	13.5
							36	11.6	10.7	12.5	9.4	13.8
			0000481098	11.1			24	11.6	11.0	12.2	9.5	13.7
							36	11.8	10.9	12.7	9.6	14.0
25C/60%RH	Bottle_500ct,40oz	2.5 mg/1000 mg	0000481090	10.6	0.011	0.639	24	10.9	10.1	11.7	8.9	12.9
							36	11.0	9.7	12.4	8.8	13.3
			0000481095	10.4	0.061	0.012	24	11.9	11.1	12.7	9.9	13.8
							36	12.6	11.2	13.9	10.3	14.8
			0000481098	10.9	0.013	0.594	24	11.2	10.4	12.0	9.2	13.1
							36	11.3	10.0	12.7	9.1	13.6
30C/75%RH	Blister	2.5 mg/1000 mg	0000481090	10.6	0.069	0.000	24	12.3	11.8	12.7	10.5	14.0
							36	13.1	12.4	13.8	11.3	14.9
			0000481095				24	12.3	11.8	12.7	10.5	14.0
							36	13.1	12.4	13.8	11.3	14.9
			0000481098				24	12.3	11.8	12.7	10.5	14.0
							36	13.1	12.4	13.8	11.3	14.9

[a] Batch data were combined where ICH-Q1E criteria for poolability were met

The Applicant noted that from an efficacy perspective, disintegration times up to (b) (4) min are expected to provide suitable product performance. As BCS 1 / BCS 3 compounds, ertugliflozin and metformin HCl are highly soluble, and dissolution is disintegration mediated. (b) (4) By demonstrating full disintegration within a (b) (4) min period, availability of the active compounds at the appropriate levels is thus assured. Based on this data and rationale, the applicant believes a disintegration acceptance criterion of NMT (b) (4) is appropriate to control product quality and ensure consistent product performance for the patient. The Applicant's response is acceptable.

2. Provide dissolution method development report for justification of the selection of dissolution method conditions for ertugliflozin/metformin tablet.

Reviewer's comments

On 06/23/2017, the Applicant responded to the above deficiency. The Applicant referred to the 3.3. Literature References section of the original marketing application where the 3.3.1 Dissolution Method Development Report is provided.

Primary Biopharmaceutics Reviewer Name and Date: **Kalpana Paudel, 05/11/2017; 08/07/2017**

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Haritha Mandula, Ph.D., 08/17/2017

Kalpana Paudel

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Haritha Mandula

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Date: 8/18/2017 09:45:04AM
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CHAPTER VIII: Microbiology

see Chapter V

ATTACHMENT I: Final Risk Assessments

See Executive Summary

Su (Suong) Tran

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