CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210192Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 210192
Review #1

Drug Name/Dosage Form	JULUCA (dolutegravir and rilpivirine) Tablets
Strength	50 mg / 25 mg (Fixed Dose Combination)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ViiV Healthcare
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	June 1, 2017	All
Amendment	July 6, 2017	Product Quality
Amendment	Aug 21, 2017	Product Quality
Amendment	Sept 22, 2017	Product Quality
Amendment	Oct 13, 2017	Container Labels
Amendment	Oct 31, 2017	Labeling

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gene Holbert	Benjamin Stevens
Drug Product	Yushi Feng	Balajee Shanmugam
Process	Ying Wang	Steven Frisbee
Microbiology	Ying Wang	Steven Frisbee
Facility	Aditi Thakur	Christina Capacci-Daniel
Biopharmaceutics	Parnali Chatterjee	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Amendments	Adequate	Oct 2, 2017 (G. Holbert)	
Various	Type III *(if applicable)*	See DP review				
	Type IV *(if applicable)*	See DP review				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 204790		Dolutegravir Tablets
NDA 202022		Janssen's Rilpivirine NDA
IND 67699		Janssen's Rilpivirine IND

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Method Verification	NA			
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for approval from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

JULUCA is a two-drug combination of dolutegravir, a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, a HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults

Proposed Indication(s) including Intended Patient Population	Treatment of HIV infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL), on a stable antiretroviral regimen for at least 6 months, with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine.
Duration of Treatment	Chronic dosing unless resistance developes
Maximum Daily Dose	One tablet taken orally once a day with a meal
Alternative Methods of Administration	None

B. Quality Assessment Overview

The manufacturing processes and quality controls for the two drug substances are cross referenced to NDA 204790 (dolutegravir sodium) and DMF (b) (4) (rilpivirine hydrochloride). A review of recent amendments to DMF (b) (4) was conducted. This DMF is acceptable, and recommendations for updating the controls on elemental impurities were conveyed to the holder. Upon request, ViiV submitted the drug substance specifications for both actives ingredients to NDA 210192, and these specifications are identical to those in the cross-referenced documents. There is appropriate control of quality for both active ingredients. See Drug Substance Review section for additional details.

The drug product is a fixed dose combination, immediate release tablet for oral administration containing 52.6 mg dolutegravir sodium (equivalent to 50 mg dolutegravir free acid) and 27.5 mg rilpivirine hydrochloride (equivalent to 25 mg rilpivirine free base). The product is a (b) (4) tablet, (b) (4)

(b) (4) All excipients are compendial and conform to the current USP/NF standards, except the colorant in the film coat.

(b) (4)

- (b) (4)
- (b) (4)

The container closure system used for DTG/RPV Tablets is a high density polyethylene (HDPE) bottle, as used for TIVICAY and EDURANT, closed with (b) (4) child resistant (CR) closures with a (b) (4) desiccant (b) (4) The proposed drug product specification is adequate to ensure the quality of the drug product. The tests and acceptance criteria are appropriately justified.

Drug product stability data were presented for 3 (b) (4) batches for up to 12 months at 25°C/60% RH and 30°C/75% RH and up to 6 months at 40°C/75% RH with all results comply with the proposed specification. This supports the (b) (4) in the commercial packaging when stored at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Additional statements in the Prescribing Information are: "Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant." See Drug Product Review and Labeling Review sections for additional details.

(b) (4) (b) (4) Quality by design (QbD) approach has been utilized and Critical Process Parameters (CPP) have been identified for most unit operations where applicable. (b) (4) (b) (4) Manufacturing process are extensively developed, adequately described and controlled. See Process Review section for additional details.

The dissolution method and acceptance criteria are appropriate for this product:

- USP Apparatus 2 (Paddle) at 75 rpm; 900 mL of 1.0% w/v Tween 20 in 0.01 M HCl, pH 2.0
- Q= (b) (4)% in 45 minutes for dolutegravir
- Q= (b) (4)% in 30 minutes for rilpivirine

(b) (4)

Based on a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. All manufacturing facilities for NDA 210192 are found to be acceptable. See Facilities Review section for additional details.

C. Special Product Quality Labeling Recommendations (NDA only)

The current PI and bottle label are acceptable, and there are no additional product quality labeling recommendations at this time. See Labeling Review for additional details.

D. Final Risk Assessment (see Attachment)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 210192

Stephen Miller

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LABELING
210192

IQA Review Guide Reference

{For NDA Only}

I. Package Insert (SDN 23, eCTD Sequence 0011, Submitted on 10/13/2017)

1. *Highlights of Prescribing Information*

Product Title

JULUCA (dolutegravir and rilpivirine) tablets, for oral use

Dosage Forms and Strengths (DFS) Heading

Each tablet contains: 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride).

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	ADEQUATE
Dosage form, route of administration	ADEQUATE
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	ADEQUATE

2. *Section 2 Dosage and Administration*

The recommended dosage of JULUCA is one tablet taken orally once daily with a meal *[see Clinical Pharmacology (12.3)]*. One tablet of JULUCA contains 50 mg of dolutegravir and 25 mg of rilpivirine.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	ADEQUATE

3. ***Section 3 Dosage Forms and Strengths***

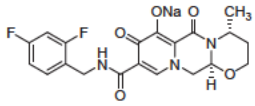
JULUCA tablets are pink, oval, biconvex tablets debossed with "SV J3T" on one side. Each film-coated tablet contains 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride).

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	ADEQUATE
Strengths: in metric system	ADEQUATE
Active moiety expression of strength with equivalence statement (if applicable)	ADEQUATE
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	ADEQUATE

4. ***Section 11 Description***

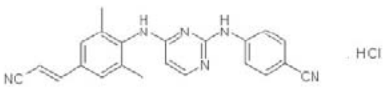
JULUCA is a fixed-dose combination tablet containing dolutegravir (as dolutegravir sodium), an INSTI, and rilpivirine (as rilpivirine hydrochloride), an NNRTI.

The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6 \cdot HCl$ and its molecular weight is 402.88g per mol. Rilpivirine hydrochloride has the following structural formula:



Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

JULUCA tablets are for oral administration. Each film-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride) and the inactive ingredients croscarmellose sodium, D-mannitol, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, povidone K29/32 and K30, silicified microcrystalline cellulose, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients iron oxide red, iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	ADEQUATE
Dosage form and route of administration	ADEQUATE
Active moiety expression of strength with equivalence statement (if applicable)	ADEQUATE
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	ADEQUATE (only abbreviation provided)
Chemical name, structural formula, molecular weight	ADEQUATE
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	ADEQUATE

5. ***Section 16 How Supplied/Storage and Handling***

Each JULUCA tablet contains 50 mg of dolutegravir and 25 mg of rilpivirine, and is a pink, oval, film-coated, biconvex tablet debossed with "SV J3T" on one side.

Bottle of 30 tablets with child-resistant closure (contains a desiccant) NDC 49702-242-13.

Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Store at 20•C to 25•C (68•F to 77•F); excursions permitted 15•C to 30•C (59•F to 86•F) [See USP Controlled Room Temperature].

Manufactured for:

ViiV Healthcare
Research Triangle Park, NC 27709

by:

GlaxoSmithKline
Research Triangle Park, NC 27709

JLC:XPI

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	ADEQUATE
Available units (e.g., bottles of 100 tablets)	ADEQUATE
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	ADEQUATE
Special handling (e.g., protect from light)	ADEQUATE
Storage conditions	ADEQUATE
Manufacturer/distributor name (21 CFR 201.1(h)(5))	ADEQUATE

6. ***Additional CMC-related labeling information***

Section 17 PATIENT COUNSELING INFORMATION

Storage

Instruct patients to store JULUCA in the original bottle to protect from moisture and keep the bottle tightly closed. Do not remove desiccant. *[See How Supplied/Storage and Handling (16).]*

PATIENT INFORMATION

How should I store JULUCA?

- Store JULUCA at room temperature between 68°F to 77°F (20°C to 25°C).
- Store JULUCA tablets in the original bottle. Keep the bottle tightly closed and protected from moisture.
- The bottle of JULUCA contains a desiccant to help keep your medicine dry (protect it from moisture). Keep the desiccant in the bottle. Do not remove the desiccant.

Keep JULUCA and all medicines out of the sight and reach of children.

Reviewer's Assessment of Package Insert: ADEQUATE

II. Labels:

1. ***Container and Carton Labels (SDN 23, eCTD Sequence 0011, Submitted on 10/13/2017)***

(b) (4)

2. ***Carton Label***

   No additional secondary packaging component (e.g., a carton) is described for this product. The container closure labeling submitted in Section 1.14.1.1 Draft Carton and Container Labels includes only a draft bottle label, no carton label.

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ADEQUATE	N/A
Dosage strength	ADEQUATE	N/A
Net contents	ADEQUATE	N/A
"Rx only" displayed prominently on the main panel	ADEQUATE	N/A
NDC number (21 CFR 207.35(b)(3)(i))	ADEQUATE	N/A
Lot number and expiration date (21 CFR 201.17)	ADEQUATE	N/A
Storage conditions	ADEQUATE	N/A
Bar code (21CFR 201.25)	ADEQUATE	N/A
Name of manufacturer/distributor	ADEQUATE	N/A
And others, if space is available	N/A	N/A

Reviewer's Assessment of Labels: ADEQUATE

List of Deficiencies: none

Overall Assessment and Recommendation:

Adequate. This labeling is recommended for approval from CMC perspective.

Primary Labeling Reviewer Name and Date:

Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
Oct 19, 2017

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

Yushi Feng

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Balajee Shanmugam

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BIOPHARMACEUTICS

NDA: 210192
Drug Product Name / Strength: JULUCA® (dolutegravir and rilpivirine) Tablets; 50 mg dolutegravir/25 mg rilpivirine
Route of Administration: Oral
Applicant Name: ViiV Healthcare Company (ViiV Healthcare)

Background: ViiV Healthcare Company (ViiV Healthcare) is seeking approval for JULUCA® (dolutegravir and rilpivirine) Tablets, 50 mg/25 mg fixed-dose combination (FDC) tablets (GSK3365791) to be administered orally for the treatment of human immunodeficicny virus type I (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA<50 copies/mL) (b) (4) via the 505 (b) (1) path.
In the current submission, the Applicant conducted pivotal bioequivalence (BE) study 201676 under fed conditions to compare the pharmacokinetic (PK) profile of the proposed FDC drug product (b) (4) with individual dolutegravir and rilpivirine drug products. This BE study was conducted as a bridge to Phase III efficacy studies that were conducted with individual dolutegravir and rilpivirine drug products and not with the proposed FDC drug product.

REVIEW SUMMARY:
This Biopharmaceutics Review evaluated the overall dissolution data supporting; **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criteria, **3)** the bridging of the formulations (b) (4) (b) (4) (b) (4) and **4)** risk assessment of the potential of dolutegravir and rilpivirine (b) (4)

Based on the review of the provided information/data, Biopharmaceutics has the following recommendations:

1) ***Proposed Dissolution Method:*** A (b) (4) dissolution method was developed for the proposed fixed-dose combination drug product. (b) (4) The proposed dissolution method described below is acceptable.

ACCEPTABLE Dissolution Method for JULUCA® (Dolutegravir/50 mg and Rilpivirine/25 mg) Tablets, 50 mg/25 mg	
Apparatus/Speed	USP Apparatus 2 (Paddle) at 75 rpm
Dissolution Media/ Volume	1.0% w/v Tween 20 in 0.01 M HCl, pH 2.0 /900 mL
Bath temperature	37.0±0.5°C

2) ***Proposed Dissolution Acceptance Criteria***: The dissolution data provided for the proposed drug product supports the dissolution acceptance criteria as proposed by the Applicant and are therefore acceptable for batch release and stability testing of the proposed drug product.

Dissolution Acceptance Criteria	Dolutegravir (DTG) Q= (b) (4)% in 45 minutes Rilpivirine (RPV) Q= (b) (4)% in 30 minutes

3) ***Bridging of the Formulations:*** The Applicant conducted an in vivo bioequivalence study to support the bridge between the FDC (b) (4) and the individual dolutegravir and rilpivirine drug products (reviewed by OCP) and provided adequate in vitro dissolution data to support the bridge between the FDC used in the BE study and the TBM FDC (b) (4) (b) (4)

4) ***Biopharmaceutics Risk Assessment:***

(b) (4)

(b) (4) The Applicant provided solubility and dissolution data as well as control strategies to mitigate the risks to the proposed drug product. However, the solubility and dissolution data provided are limited, (b) (4)

(b) (4)

➢ ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 210192 for JULUCA® (Dolutegravir/50 mg and Rilpivirine/25 mg) Tablets, 50 mg/25 mg is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Parnali Chatterjee, PhD ***10/18/2017***

Secondary Biopharmaceutics Reviewer Name and Date:

I concur with Dr. Chatterjee's assessment and recommendation
Elsbeth Chikhale, PhD ***10/27/2017***

***OVERALL BIOPHARMACEUTICS RECOMMENDATION*:**

Based on the review of the overall information, from the Biopharmaceutics perspective NDA 210192 for JULUCA® (dolutegravir and rilpivirine) Tablets, 50 mg/25 mg, is recommended for **APPROVAL.**

BIOPHARMACEUTICS ASSESSMENT

➢ LIST SUBMISSIONS BEING REVIEWED:

Submissions Reviewed	Reference ID
Original NDA Submission 210192 (DTG/RPV)	\\cdsesub1\evsprod\nda210192\0000\m1\us\102-cover-letters\cover.pdf

➢ DRUG PRODUCT:

The proposed drug product is a fixed-dose combination (FDC), immediate-release, (b) (4) tablet containing 52.6 mg dolutegravir sodium (equivalent to 50 mg dolutegravir drug substance as free acid) and 27.5 mg rilviprine hydrochloride (equivalent to 25 mg rilpivirine drug substance as free base) for once daily oral administration with a meal.

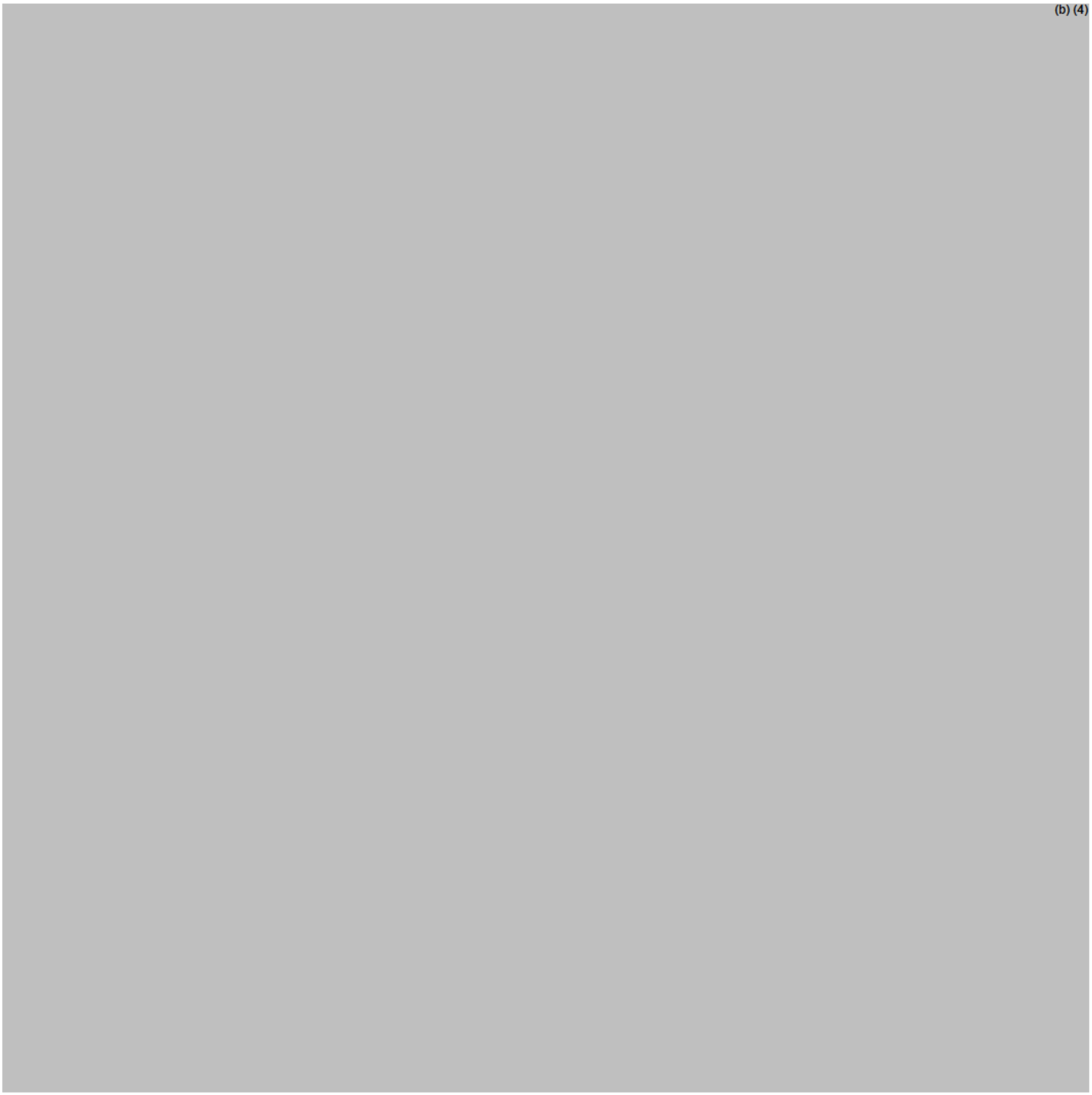
The Applicant developed the proposed FDC product of JULUCA® Tablets, 50 mg/25 mg, containing 50 mg dolutegravir and 25 mg rilpivirine based on information available regarding the development of the commercial formulations for TIVICAY Tablets, 50 mg for dolutegravir that was developed by GlaxoSmithKline and EDURANT Tablets, 25 mg, which was developed by Janssen Pharmaceuticals.

The proposed FDC dolutegravir and rilpivirine tablets, 50 mg/25 mg were (b) (4)

The qualitative and quantitative composition of the proposed drug product is given in **Table I**.

Table I. Qualitative and Quantitative Composition of
JULUCA® (dolutegravir/rilpivirine) Tablets, 50 mg/25 mg

(b) (4)



- ***BCS DESIGNATION***

The Applicant did not request an official BCS designation. The active ingredients in the proposed drug product are dolutegravir Na (b) (4) and rilpivirine HCl (b) (4) which are (b) (4)

- ***Solubility:***

In order to evaluate the aqueous solubility of the proposed drug substances, the Applicant conducted (b) (4) (b) (4) s (see **Table IIa and IIb**). The (b) (4) solubility of RPV HCl in simulated biofluids is given in **Table IIc**.

(b) (4)

Reviewer's Assessment DTG solubility:

From **Table IIa**, it can be seen that the DTG Na (b) (4) (see **Figure Ia**).

(b) (4)

[redacted]

(b) (4)

Reviewer's Assessment RPV solubility:

RPV HCl is practically insoluble in wate (b) (4)

(b) (4)

(b) (4)

- ***Permeability:***

(b) (4)

Reviewer's Assessment:

(b) (4)

(b) (4)

hich should be discussed in the CMC (drug substance, drug product, and/or process) review chapter(s).

- ***DISSOLUTION INFORMATION:***

Because dissolution testing is a critical quality attribute (CQA), the Applicant utilized the

(b) (4)

- ***PROPOSED DISSOLUTION METHOD:***

(b) (4)

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Parnali Chatterjee

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Elsbeth Chikhale

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

Final Risk Table for Dolutegravir and Rilpivirine Tablets

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability		L	(b) (4)	Acc	
Physical stability (solid state)		M		Acc	(b) (4)
Content uniformity		M		Acc	
Microbial limits		L		Acc	
Dissolution – BCS Class II & IV		M		Acc	The dissolution method has limited discriminating ability (b) (4) (b) (4) The dissolution test may not be able to reject batches with unacceptable (b) (4) and other CMC drug product tests.
(b) (4)		L		Acc	
		L		Acc	

Stephen Miller

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