CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209195Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209195
Review 2

Drug Name/Dosage Form	VOSEVI (Sofosbuvir, Velpatasvir and Voxilaprevir) Tablets
Strength	400 mg / 100 mg / 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	Dec 8, 2016	All
Amendment	Feb 7, 2017	Quality
Amendment	Feb 8, 2017	Labeling
Amendment	Mar 16, 2017	Quality
Amendment	Apr 28, 2017	Labeling
Amendment	May 3, 2017	Labeling
Amendment	July 7, 2017	Labeling
Amendment	July 13, 2017	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sithamalli (Mouli) Chandramouli	Ben Stevens
Drug Product & Labeling	Shrikant (Suresh) Pagay	Balajee Shanmugam
Process & Microbiology	Ying Wang	Upinder Atwal
Facility	Christina Capacci-Daniel	Derek Smith
Biopharmaceutics	Min Li	Kimberly Raines
Environmental Assessment	James Laurenson	M. Scott Furness
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
	Type II	None				
	Type III	See DP review				
	Type IV	See DP review				
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	204671	Information on sofosbuvir drug substance
NDA	208341	Information on velpatasvir DS and SDD

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Laboratory (OTR)	NA	No method verification was requested by the product quality team for this NDA		
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. This document (Review #2) contains the final evaluation of all manufacturing facilities, a copy of the final bottle label, the Final Risk Assessment, and the summary of all product quality aspects of the NDA. See Review #1 (June 7, 2017) for details of other product quality evaluations.

II. Summary of Quality Assessments

A. Product Overview

This (b) (4) tablet contains an NME (voxilaprevir, and inhibitor of the HCV NS3/4A protease) in combination with two other antivirals (the polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir). The indication is treatment of chronic infection with Hepatitis C virus in adult patients. (b) (4) (b) (4). This product was granted Breakthrough Therapy Designation and the NDA received a priority review because of this this unmet medical need.

Proposed Indication(s) including Intended Patient Population	Treatment of adult patients with chronic HCV infection (see package insert for details)
Duration of Treatment	Typically 12 weeks
Maximum Daily Dose	The dose is one tablet per day
Alternative Methods of Administration	None

B. Quality Assessment Overview

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 209195 are found to be acceptable. For details, see the Facility evaluation within this review (Product Quality Review #2).

Voxilaprevir (VOX) is the new molecular entity in this NDA, and the applicant references their approved NDAs, NDA 204671 for Sofosbuvir and NDA 208341 for Velpatasvir. (b) (4)

(b) (4)

(b) (4)

A retest period of (b) (4) months when VOX drug substance is stored below (b) (4) is acceptable, and is supported by stability studies including 12-month data at (b) (4) The July 13, 2017 amendment updates Module 3 documents to reflect revisions to the control strategy for VOX drug substance which were agreed-upon during this NDA review. Additionally, the SOF drug substance specification was updated in the July 13 amendment to reflect changes that were approved in NDA 204671 Supplement-008. Copies of both specifications are included in this review. For details, see the Drug Substance evaluation within Product Quality Review#1 (June 7, 2017).

The SOF/VEL/VOX tablets are beige, capsule-shaped, film-coated, and debossed with "GSI" on one side and "3" on the other side. (b) (4)

(b) (4)

(b) (4) A single package size will be commercialized: 28 tablets in an HDPE bottle with desiccant, polyester filler, child-resistant cap, (b) (4). The expiration dating period is 24 months when stored below 30°C, and is supported by 12-15 months of stability data, including the long-term condition of 30°C/75%RH.

(b) (4)

(b) (4)

- All clinical and developmental batches of tablets had mean VOX dissolution values above (b) (4)% at 60 minutes. (b) (4) (b) (4). This includes the results from long-term, accelerated, and stress stability studies.

Based on the dissolution results from clinical and developmental batches of SOF/VEL/VOX tablets, a dissolution acceptance criteria was proposed with the primary acceptance criterion set as Q(b) (4)% at 30 minutes for all three actives. A secondary acceptance criterion NLT (b) (4)% is included for mean VOX dissolved at 60 minutes (n=6) (b) (4) (b) (4). The in vitro dissolution data from clinical/stability batches supports the proposed acceptance criteria. The commercial batches have the same formulation and batch size as the Phase 3 clinical batch and therefore no bridging of formulations is necessary. For details, see the Biopharmaceutics evaluation within Product Quality Review#1 (June 7, 2017).

C. Special Product Quality Labeling Recommendations (NDA only)

The following recommendation was conveyed to the OND PM so that it could be included as the labeling is finalized:

Please delete: (b) (4) located below storage statement on the bottle label.

D. Final Risk Assessment (see Attachment)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209195

APPEARS THIS WAY ON ORIGINAL

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Sofosbuvir, Velpatasvir and Voxilaprevir 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**		Acc	
Physical stability (b) (4)	Vox and Vel both (b) (4) (b) (4) low solubility	**M**	See bulleted overview in Exec Summary	Acc	
Content uniformity	Based on (b) (4) drug load for Vel and Vox	**M**	Controls on process parameters and input materials; (b) (4) monitored in VOX specification	Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV		**M**	Method is discriminatory and AC are appropriate.	Acc	

Stephen Miller

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APPEARS THIS WAY ON ORIGINAL

Recommendation: Pending

NDA 209195
Review 1

Drug Name/Dosage Form	VOSEVI (Sofosbuvir, Velpatasvir and Voxilaprevir) Tablets
Strength	400 mg / 100 mg / 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
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Amendment	Apr 28, 2017	Labeling
Amendment	May 3, 2017	Labeling

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DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
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Biopharmaceutics	Min Li	Kimberly Raines
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	Type IV	See DP review				
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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NDA	208341	Information on velpatasvir DS and SDD

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Laboratory (OTR)	NA	No method verification was requested by the product quality team for this NDA		
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

At this time a recommendation cannot be made from the product quality perspective because the evaluation of the manufacturing facilities is on-going. Specifically, of the 17 facilities involved in the manufacturing, testing and packaging of this product, 2 facilities are scheduled to be inspected between June 12 and June 23, 2017. These two foreign facilities manufacture voxilaprevir drug substance (b) (4) (b) (4).

II. Summary of Quality Assessments

A. Product Overview

This (b) (4) tablet contains an NME (voxilaprevir, and inhibitor of the HCV NS3/4A protease) in combination with two other antivirals (the polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir). The indication is treatment of chronic infection with Hepatitis C virus in adult patients, (b) (4) (b) (4). This product was granted Breakthrough Therapy Designation and the NDA received a priority review because of this this unmet medical need.

Proposed Indication(s) including Intended Patient Population	Treatment of adult patients with chronic HCV infection (see package insert for details)
Duration of Treatment	Typically 12 weeks
Maximum Daily Dose	The dose is one tablet per day
Alternative Methods of Administration	None

B. Quality Assessment Overview

Voxilaprevir (VOX) is the new molecular entity in this NDA, and the applicant references their approved NDAs, NDA 204671 for Sofobuvir and NDA 208341 for Velpatasvir. (b) (4) (b) (4)

A retest period of (b) (4) months when VOX drug substance is stored below (b) (4) is acceptable, and is supported by stability studies including 12-month data at (b) (4).

The SOF/VEL/VOX tablets are beige, capsule-shaped, film-coated, and debossed with "GSI" on one side and "3" on the other side. (b) (4)

(b) (4)

(b) (4) A single package size will be commercialized: 28 tablets in an HDPE bottle with desiccant, polyester filler, child-resistant cap, (b) (4).

The expiration dating period is 24 months when stored below 30°C, and is supported by 12-15 months of stability data, including the long-term condition of 30°C/75%RH (b) (4)

(b) (4)

- All clinical and developmental batches of tablets had mean VOX dissolution values above (b) (4)% at 60 minutes, consistent with VOX remaining in the (b) (4) state. This includes the results from long-term, accelerated, and stress stability studies.

There are 17 facilities involved in the manufacturing, testing and packaging of this product. There are two facilities scheduled to be inspected between June 12 and June 23, 2017:

(b) (4)

Al

Based on the dissolution results from clinical and developmental batches of SOF/VEL/VOX tablets, a dissolution acceptance criteria was proposed with the primary acceptance criterion set as Q=(b) (4) at 30 minutes for all three actives. A secondary acceptance criterion NLT (b) (4)% is included for mean VOX dissolved at 60 minutes (n=6) (b) (4) (b) (4). The in vitro dissolution data from clinical/stability batches supports the proposed acceptance criteria. The commercial batches have the same formulation and batch size as the Phase 3 clinical batch and therefore no bridging of formulations is necessary.

C. Special Product Quality Labeling Recommendations (NDA only)

The following recommendation was conveyed to the OND PM so that it could be included as the labeling is finalized:

Please delete: (b) (4) located below storage statement on the bottle label.

D. Final Risk Assessment (see Attachment)

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 209195

Date: June 4, 2017

APPEARS THIS WAY ON ORIGINAL

LABELING

NDA 209195

I. Package Insert

1. *Highlights of Prescribing Information*

[TRADENAME] (sofosbuvir, velpatasvir, and voxilaprevir) tablets, for oral use

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	**Satisfactory (S)**
Dosage form, route of administration	S
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	S-under Indications and Usage

2. *Section 2 Dosage and Administration*

Tablets: 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg voxilaprevir (3)

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)	S: no additional instructions required; however, section 17 provides patient advice to take tablets with food, do not skip dose etc.

3. *Section 3 Dosage Forms and Strengths*

Each [TRADENAME] tablet contains 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir. The tablets are beige, capsule-shaped, film-coated, and debossed with "GSI" on one side and "3" on the other side.

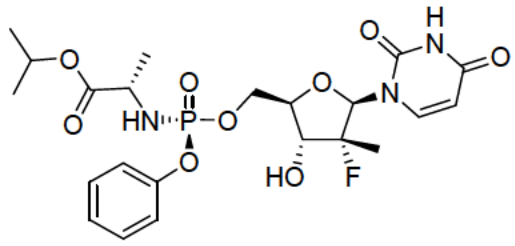
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	S
Strengths: in metric system	S
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including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

4. *Section 11 Description*

[TRADENAME] is a fixed-dose combination tablet containing sofosbuvir, velpatasvir, and voxilaprevir for oral administration. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor, velpatasvir is an NS5A inhibitor, and voxilaprevir is an NS3/4A protease inhibitor.

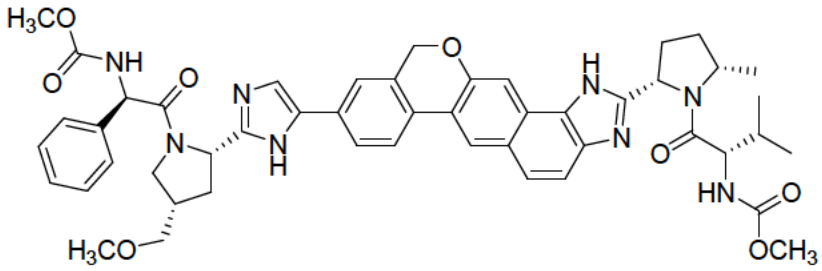
Each tablet contains 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg of voxilaprevir. The tablets include the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: ferrosoferric oxide, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Sofosbuvir: The IUPAC name for sofosbuvir is (*S*)-Isopropyl 2-((*S*)-(((2*R*, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl) methoxy)-(phenoxy) phosphorylamino) propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



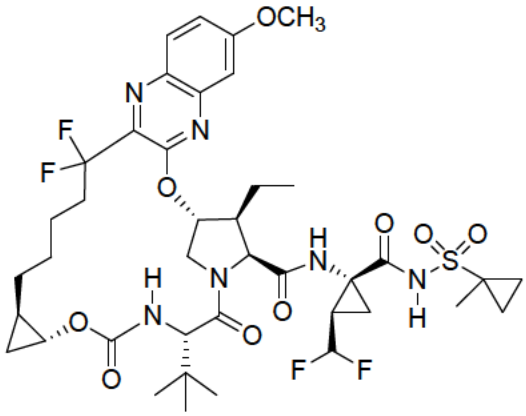
Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2–7.7 at 37 ºC and is slightly soluble in water.

Velpatasvir: The IUPAC name for velpatasvir is Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-*d*]imidazol-9-yl}-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular formula of $C_{49}H_{54}N_8O_8$ and a molecular weight of 883.0. It has the following structural formula:



Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2.

Voxilaprevir: The IUPAC name for voxilaprevir is (1*aR*,5*S*,8*S*,9*S*,10*R*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropanesulfonyl) carbamoyl] cyclopropyl}-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1*a*,3,4,5,6,9,10,18,19,20,21,22,22*a*-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide. It has a molecular formula of $C_{40}H_{52}F_4N_6O_9S$ and a molecular weight of 868.9. It has the following structural formula:



Voxilaprevir is a white to light brown solid. It is slightly hygroscopic to hygroscopic. Voxilaprevir is practically insoluble (less than 0.1 mg/mL) below pH 6.8.

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	S
Dosage form and route of administration	S
Active moiety expression of strength with equivalence statement (if applicable)	NA
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>)	NA
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	S
Chemical name, structural formula, molecular weight	S
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	S

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

Each [TRADENAME] tablet contains 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir. The tablets are beige, capsule-shaped, film-coated, and debossed with "GSI" on one side and "3" on the other side. Each bottle contains 28 tablets (NDC 61958-2401-1), polyester coil, silica gel desiccant, and is closed with a child-resistant closure.

Store below 30 °C (86 ºF). Dispense only in original container. (b) (4)

(b) (4)

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

Reviewer's Assessment of Package Insert: Adequate

II. Labels:

(b) (4)

2. ***Carton Label:***
   No carton included for the package.

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))	S	
Dosage strength	S	
Net contents	S	
"Rx only" displayed prominently on the main panel	S	
NDC number (21 CFR 207.35(b)(3)(i))	S	
Lot number and expiration date (21 CFR 201.17)	S	
Storage conditions	S	
Bar code (21CFR 201.25)	S	
Name of manufacturer/distributor	S	
And others, if space is available	-	

Reviewer's Assessment of Labels: Adequate with the comment below

- A secondary package is not used for this drug product since the tablets are well protected in the proposed HDPE bottles.

Delete : (b) (4) *located below storage statement on the container label*

List of Deficiencies:

Delete: (b) (4) *located below storage statement on the container label*

Overall Assessment and Recommendation: *Adequate with the proposed change in the package insert and container label*

Primary Labeling Reviewer Name and Date:

Shrikant Pagay, Ph.D. , May 8, 2017

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

Balajee Shanmugam, Ph. D. Date

APPEARS THIS WAY ON ORIGINAL

Balajee Shanmugam

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Date: 5/25/2017 12:47:00PM
GUID: 50758d5000003c1b1962e036ea11002c

Shrikant Pagay

Digitally signed by Shrikant Pagay
Date: 5/08/2017 03:28:10PM
GUID: 508da72000029ff475f33bf61de241b2

APPEARS THIS WAY ON ORIGINAL

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Reviewer's Assessment: Not Applicable

Post-Approval Commitments

Reviewer's Assessment: Not Applicable

Lifecycle Management Considerations

Pending

List of Deficiencies: Pending

Primary Facilities Reviewer Name and Date:

The review is currently **pending** completion of two inspections to support the Voxilaprevir drug substance manufacturing process.

Christina Capacci-Daniel, PhD – 26 April 2017
Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII

Secondary Reviewer Name and Date:

Christina Capacci-Daniel

Digitally signed by Christina Capacci-Daniel
Date: 4/26/2017 02:16:06PM
GUID: 51dc71a50000c6c3f0b616578caafab6

Derek Smith

Digitally signed by Derek Smith
Date: 4/26/2017 02:26:26PM
GUID: 508da7480002bfe5d5fe14a12da3599d

APPEARS THIS WAY ON ORIGINAL

BIOPHARMACEUTICS

NDA: 209195 Original 505(b)(1)

Applicant Name: Gilead Sciences, Inc.

Drug Product Name: Sofosbuvir, Velpatasvir and Voxilaprevir Tablets/ 400 mg / 100 mg / 100 mg (Fixed Dose Combination)

Dosage form: Immediate Release Tablets

Route of Administration: Oral

Indication: Treatment of chronic hepatitis C virus infection in adults

The proposed product, sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) tablets, is an immediate release fixed-dose combination (FDC) formulation containing 400 mg of SOF, 100 mg of VEL, and 100 mg of VOX. (b) (4)

(b) (4)

Single-agent product of SOF (Sovaldi®, NDA 204671, Gilead approved on 12/06/2013) and the FDC formulations of SOF with VEL (Epclusa®, NDA 208341, Gilead approved on 06/28/2016) or Ledipasvir (Harvoni®, NDA 205834, Gilead approved on 10/10/2014) are commercially available in the United States (US). VOX is a pangenotypic HCV NS3/4A protease inhibitor (PI) with potent antiviral activity across HCV genotypes and an improved resistance profile compared with other developed HCV NS3/4A PIs. The Applicant states that the SOF/VEL/VOX FDC product could offer a, single-tablet regimen for the treatment of HCV-infected patients (b) (4)

(b) (4)

Review Summary: ADEQUATE

The biopharmaceutics review focuses on the evaluation of the proposed dissolution method and acceptance criterion for the quality control of the proposed SOF/VEL/VOX Tablets.

The dissolution method was evaluated by determining the effect of varying dissolution parameters would have on the in vitro drug release (refer to table below). The following method parameters were evaluated: apparatus, rotation speed, buffer concetration in medium, medium pH, surfactant type and concentrationand found appropriate. The discriminating ability of the

dissolution method was demonstrated towards several critical material attributes (CMAs) (b) (4) (b) (4) (b) (4) The submitted information is sufficient to support the appropriateness and discriminating ability of the dissolution method.

Based on the dissolution results from clinical and developmental batches of SOF/VEL/VOX tablets, a dissolution acceptance criteria was proposed with the primary accetance criterion set as Q (b) (4)% at 30 minutes for all the APIs and a secondary acceptance criterion NLT (b) (4)% is included for mean VOX dissolved at (b) (4)minutes (b) (4) (b) (4). If the mean amount of VOX dissolved a (b) (4) minutes is less than (b) (4)%, an additional tier, level, of testing is proposed (b) (4) (b) (4) The provided in vitro dissolution data from clinical/stability batches supports the proposed acceptance criteria. As an added control stragegy, the proposed acceptance criterion of of NMT (b) (4)% (b) (4) is reasonable based on comparative dissolution data.

The adequacy of formulation bridging for different phases of clinical trials and the commercial formulation was also assessed. The Phase 1 (b) (4) formulation and Phase1/2 (b) (4) (b) (4) formulation, as well as, the final phase 3 SOF/VEL/VOX tablets were well bridged by relative bioavailability studies (reviewed by the Office of Clinical Pharmacology). The commercial batches have the same formulation and batch size as the Phase 3 clinical batch; therefore no bridging of formulations is necessary.

Based on the review, the submission is adequate and this NDA is recommended for APPROVAL from a biopharmaceutics perspective.

The dissolution method and acceptance criteria approved for SOF/VAL/VOX Tablets

USP Apparatus	Rotation Speed	Dissolution Medium	Volume	Sampling Time Point(s)	Acceptance Criteria
II	75 rpm	2.0 % polysorbate 80 and 0.001% BHT in 50 mM acetate buffer, pH 5.0	900 mL	10, 15, 20, 30, 45 and 60 minutes	NLT (b) (4)% (Q) of the label amount of SOF, VEL and VOX dissolved at 30 minutes NLT (b) (4)% of the label amount of VOX dissolved at 60 minutes (b) (4) (b) (4). When the mean amount of VOX dissolved at 60 minutes is less than (b) (4)% (b) (4) the (b) (4) content of VOX (b) (4) limit is NMT (b) (4)%[a]

[a] If required, (b) (4)

Initial Dissolution Risk Assessment (provided by ATL): medium (considering the BCS Class of VEL (Class IV) and VOX (Class II))

Updated Dissolution Risk/Mitigation Assessment (based on Biopharmaceutics Review): low

As VEL and VOX were incorporated in the formulation (b) (4) (b) (4), solubility property of both APIs can be improved by maximized solubility and enhanced surface area. The dissolution of all the APIs from the proposed formulation is rapid and a complete of dissolution (no less than (b) (4)%) can be achieved within 30 minutes. Additional control of VOX (b) (4) in the final product is also incorporated in the dissolution testing and it further reduces the risk of dissolution on in vivo performance due to dissolution property of VOX. Therefore, this reviewer recommend changing dissolution risk to "low".

List Submissions being reviewed (table):

Date	Submission details
12/08/2016	NDA 209195/Original submission
03/16/2017	eCTD-0009(11) Quality/Response to Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

BCS Designation

Solubility:

Sofosbuvir

The solubility of sofosbuvir (b) (4) is provided in **Table 1** (submission dated 03/16/2017 M 1.11.1). According to the BCS classification Guidance[1], SOF is highly soluble across the pH range from 2.0 to 6.8. (b) (4)

(b) (4)

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf

Table 1. Solubility of SOF, VEL and VOX at 37 °C Across the Physiologically Relevant pH Range

pH (Media)	Solubility (mg/mL)		
	Sofosbuvir	Velpatasvir (b) (4)	Voxilaprevir (b) (4)
1.2[a] (HCl)	1.3	35	$< 5.0 \times 10^{-4}$
2.0 (HCl)	2.0	2.1	$< 5.0 \times 10^{-4}$
4.5 (Acetate Buffer)	2.1	0.2	6.1×10^{-4}
5.0 (Acetate Buffer)	2.2	0.1	1.2×10^{-3}
6.8 (Phosphate Buffer)	1.9	0.1	2.5×10^{-2}

a (b) (4)

Velpatasvir

(b) (4) (b) (4) The solubility data of VEL (b) (4) is provided in **Table 1**. Based on the data, VEL shows low solubility in the aqueous media across physiological pH range, (b) (4) in the formulation. According to the BCS classification criteria, VEL's solubility is considered low for this product.

Voxilaprevir

(b) (4) (b) (4) VOX exhibits an aqueous solubility of < 1 µg/mL at pH ≤ 5. VOX solubility increases with increasing pH, with an aqueous solubility of 400 µg/mL at pH 8 where just meets the criterion of high solubility (the highest strength is soluble in less than 250 mL of aqueous media). Overall, VOX has low solubility across physiological pH range.

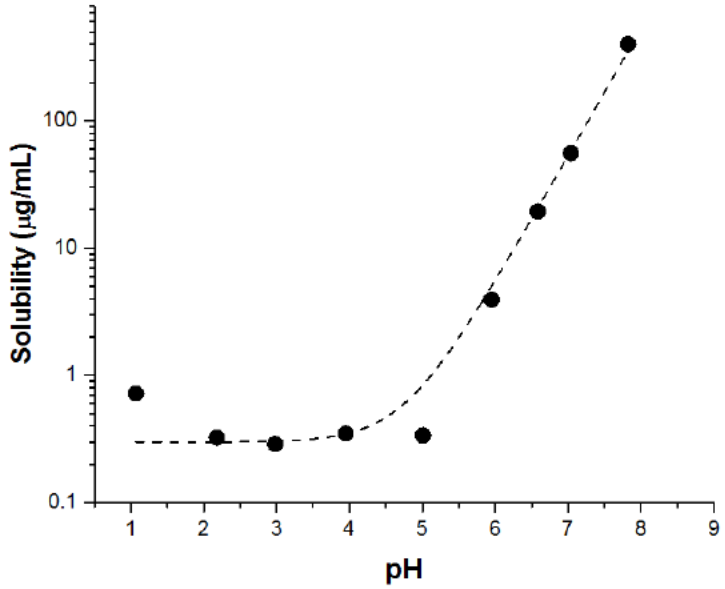

Figure 1. pH-solubility profile of (b) (4) VOX at room temperature

(b) (4)

VOX single-agent tablet development was initiated using (b) (4) drug substance. (b) (4) was manufactured through a non-scalable process, and was used in (b) (4) tablets, 10 mg and 50 mg. When equilibrium solubility and interconversion experiments were used to compare (b) (4) it was determined that (b) (4)

(b) (4)

designated commercial VOX drug substance (VOX DS) was made during Phase I development. This transition was driven by manufacturability of VOX DS at a commercial scale. VOX DS was subsequently formulated (b) (4) (b) (4) (b) (4) As shown in Figure 2, the kinetic solubility of VOX (b) (4) in FaSSIF (pH 6.5) at 90 minutes is 3- to 10-fold higher than (b) (4) VOX DS.

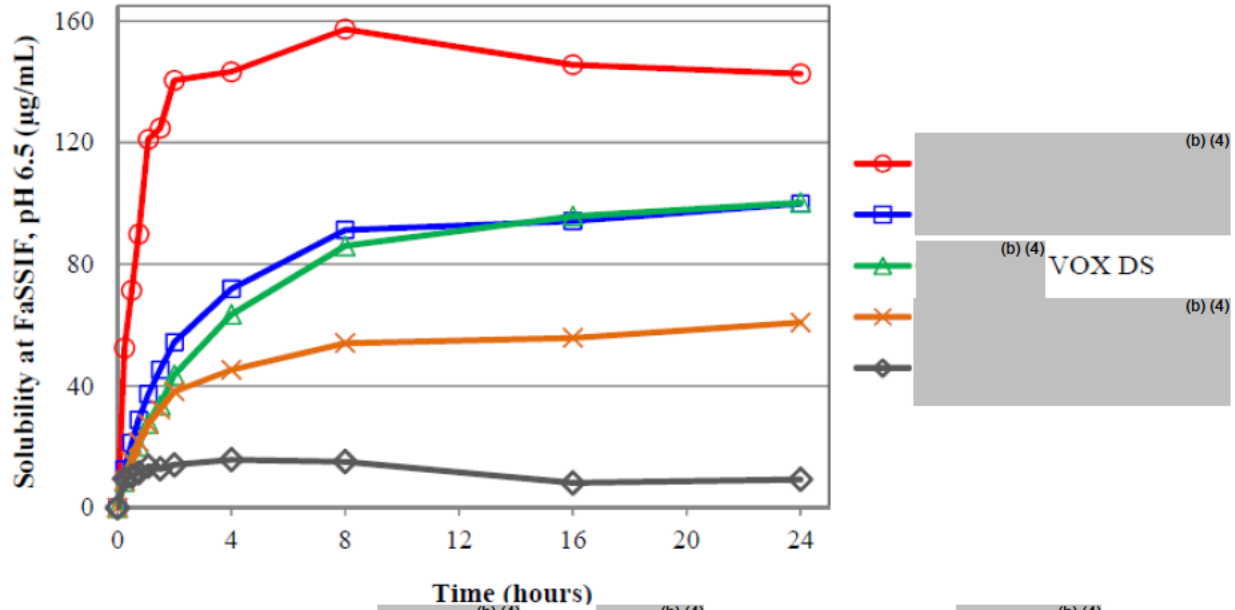

Figure 2. Kinetic solubility of (b) (4) VOX (b) (4) compared to VOX (b) (4) in FaSSIF, pH 6.5

Permeability:

Sofosbuvir

The permeability of SOF was determined using Caco-2 cell monolayers at a SOF concentration of 3 mM (1.6 mg/mL). The apparent $P_{A\rightarrow B}$ and $P_{B\rightarrow A}$ permeability coefficients for SOF were 0.71 $\times 10^{-6}$ cm/s and 4.11 $\times 10^{-6}$ cm/s, respectively, with an efflux ratio of 5.81. SOF is considered by the Applicant to have low apparent permeability with the potential for efflux. Detailed permeability study data are provided in **AD-334-2003**: Membrane Permeability of SOF (In Vitro) under Module 2. 6.5.

The single dose PK profile of SOF was determined in mice, rats, and dogs following oral administration. In dogs, it reported that SOF's absolute bioavailability is 38.7% (Module 2.4 Nonclinical Overview Page 20). Although the bioavailability data of SOF in humans was not found in this submission, the non-clinical studies indicate SOF has low permeability.

Velpatasvir

In vitro permeability study for VEL couldn't be located in this submission by this reviewer. The single-dose PK profile of VEL has been determined in mice, rats, rabbits, dogs, and monkeys following oral administration. The oral bioavailability of VEL is modest in nonclinical species, ranging from 25% to 30% in the rat, dog, and monkey.

Voxilaprevir

The permeability of VOX was assessed in Caco-2 cell monolayers at 37 °C. The apparent $P_{A\rightarrow B}$ and $P_{B\rightarrow A}$ permeability coefficients for VOX were 4.4×10^{-6} cm/s and 13.1×10^{-6} cm/s, respectively, with an efflux ratio of 3.0. VOX is considered to have high apparent permeability with the potential for some efflux.

Dissolution: *See **Dissolution Method and Acceptance criteria***

Reviewer's Assessment:

The Applicant classified SOF, VEL and VOX as BCS Class III, IV and II compounds, respectively. These classifications are reasonable based on the provided data and information. However, the conclusions of these classifications were not used in support of waiver of in vivo bioavailablity/bioequivalence studies and therefore not the subject of review by the FDA BCS Committee. The solubility and permeability information are used in consideration of *in vitro* dissolution acceptance critieria.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

1. Proposed dissolution method and acceptance criteria

Table 3. Proposed dissolution method and acceptance criteria for batch release and stability

USP Apparatus	Rotation Speed	Dissolution Medium	Volume	Sampling Time Point(s)	Proposed Acceptance Criteria
II	75 rpm	2.0 % polysorbate 80 and 0.001% BHT in 50 mM acetate buffer, pH 5.0	900 mL	10, 15, 20, 30, 45 and 60 minutes	NLT (b) (4)% (Q) of the label amount of SOF, VEL and VOX dissolved at 30 minutes NLT (b) (4)% of the label amount of VOX dissolved at 60 minutes (b) (4) (b) (4)

					When the mean amount of VOX dissolved at 60 minutes is less than (b) (4)% (b) (4) the (b) (4) content of VOX (b) (4) is NMT (b) (4) [a]

[a] If required (b) (4)

2. Dissolution method development information

(b) (4)

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(b) (4)

Dissolution (obtained from the QC method) was used as one the CQA for the evaluation of trial batches within a certain range of the above material and formulation variables. Based on the results, it found that SOF/VEL/VOX tablets manufactured within the evaluation range of water content, (b) (4) desicant level and packaging configuration, particle size of VOX (b) (4), VEL (b) (4) and SOF, exhibited acceptable dissolution properties. Product specifications of these variables were set accordingly based on these studies' results. (b) (4) (b) (4) VOX in the final product, the content (b) (4) (b) (4) could impact the dissolution the product, as described in the discriminating ability of the dissolution method. Based on the in vitro dissolution data, the specifications for (b) (4) (b) (4) VEL (b) (4) and VOX (b) (4) were set (b) (4). The control of VOX (b) (4) content was addressed in the dissolution testing as provided in dissolution acceptance criteria.

Overall, the application of dissolution testing for aiding in formulation development seems approapriate from a biopharmaceutics perspective.

Bridging of Formulations

Reviewer's Assessment:

Multiple formulations were developed for clinical trials duing the formulation development. In Phase I studies, a single-agent VOX formulation (b) (4) was explored initially. The in vitro dissolution of this formulation was obtained from a non-QC method using a medium of 1% w/v Polysorbate 20 in 50 mM Phosphate Buffer, pH 6.8; both tablet lots exhibited >(b) (4)% VOX dissolved within 15 minutes (note the medium used in this study is different from the QC method (b) (4) (b) (4) Food effect study was conducted in healthy subjects at a 100 mg single dose (Lot DY1401B); administration of voxilaprevir with food, either light meal or high-calorie/high-fat meal, increased the extent of voxilaprevir adsorption by approximately 2-fold with no effect on the terminal half-life.

In Phase 1 and 3 clinical trials, VOX (b) (4) was developed and hence used as a more suitable drug substance (b) (4)

(b) (4)

The VOX (b) (4) tablet formulation was modified to include 400 mg SOF and 100 mg VEL (b) (4) in order to evaluate a fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir in Phase 3 clinical trials. VEL (b) (4) has demonstrated excellent physical stability, chemical stability, and manufacturing process performance during development of Epclusa® (SOF/VEL) tablets). In relative bioavailability study GS-US-367-1176, the selected SOF/VEL/VOX FDC tablet formulation, 400/100/100 mg, demonstrated similar pharmacokinetic performance to co-administered Epclusa tablets, 400/100 mg, and VOX (b) (4) (b) (4) tablets, 100 mg and with no need for dose adjustment (the 90% confidence intervals

(CIs) of the geometric least squares mean (GLSM) ratios for all primary PK parameters remained within the PK equivalence bounds of 70% to 143%). SOF/VEL/VOX tablets, 400/100/100 mg, were subsequently used in all pivotal Phase 3 clinical trials and stability studies, and are the designated commercial formulation. SOF/VEL/VOX tablets, 400/100/100 mg, Lots 15GEI002UR, 15GEI003UR, and 15GEI004UR were manufactured to support Phase 3 clinical studies, with all aspects of the formulation and associated manufacturing process equivalent to those used to produce Lot 15GEI001UR.

Based on the comparison of formulation comparision between the clinical and designed commercial tablets, all the components and corresponding composition are exactly identical between the batched used for Phase 3 and relative BA study (AM-6382-128) or Phase 3 batch and proposed commercial batch. Same batch size (b) (4) as that of Phase 3 clinical batch (Batch #16GEI002UR) was proposed for the commercial batches; therefore no bridging of formulations is necessary.

Table 8. Clinical Development History of SOF/VEL/VOX Tablets, 400/100/100 mg

Attribute		Phase 1		Phase 1 Pharmacokinetic Study	Phase 1 / Phase 2	Relative Bioavailability	Phase 3 / Designated Commercial
Drug Substance Form	Sofosbuvir	—		—	—	(b) (4)	
	Velpatasvir	—		—	—		
	Voxilaprevir	(b) (4)		VOX DS	VOX DS	VOX DS	VOX DS
Drug Product Intermediates		—		—	—	VEL (b) (4)	VEL (b) (4)
		—		VOX (b) (4)	VOX (b) (4)	VOX	VOX
Drug Product		(b) (4)		VOX	VOX (b) (4)	SOF/VEL/VOX FDC Tablet	SOF/VEL/VOX FDC Tablet
Dosage Strength (mg)		10	50	100	100	400/100/100	400/100/100
(b) (4)	Sofosbuvir	—	—	—	—	(b) (4)	(b) (4)
	Velpatasvir	—	—	—	—		
	Voxilaprevir	(b) (4)					(b) (4)
Key Formulation Change from Previous Phase		(b) (4)			No Change	Initial SOF/VEL/VOX FDC tablet formulation	No Change

(b) (4)

R Regional Information

Comparability Protocols

Reviewer's Assessment:

N/A

Post-Approval Commitments

Reviewer's Assessment:

N/A

Lifecycle Management Considerations

N/A

List of Deficiencies (Dated Apr 26, 2017): None

Primary Biopharmaceutics Reviewer Name and Date:

Min Li, Ph.D. (Branch 3\DB\ONDP\OPQ), April 26, 2017

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

I concur with the biopharmaceutics assessment.

Date: April 27, 2017

Kimberly Raines, Ph.D., Acting Biopharmaceutics Lead (Branch 3\DB\ONDP\OPQ)

Kimberly Raines

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Min Li

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Sofosbuvir, Velpatasvir and Voxilaprevir 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**		Acc	
Physical stability (solid state)	Vox and Vel both (b) (4) (b) (4) low solubility	**M**	See bulleted overview in Exec Summary	Acc	
Content uniformity	Based on (b) (4) % drug load for Vel and Vox	**M**	Controls on process parameters and input materials; (b) (4) monitored in VOX specification	Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV		**M**	Method is discriminatory and AC are appropriate.	Acc	

Stephen Miller

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