CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214187Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 214187
Assessment # 1

Drug Product Name	Epclusa
Dosage Form	Oral pellets
Strength	150/37.5 mg and 200/50 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 001	12/15/2020	All (New NDA)
eCTD 002	1/8/2021	Quality
eCTD 003	1/22/2021	Quality
eCTD 004	1/28/2021	Quality
eCTD 006	2/23/2021	Quality
eCTD 008	3/26/2021	Quality
eCTD 011	4/20/2021	Quality
eCTD 0014	5/06/2021	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Rohit Tiwari	Paresma Patel
Drug Product	Hailin (Sheena) Wang	Thomas Oliver
Manufacturing	Brijeshkumar Vaghasia	Bo Jiang
Microbiology	NA	
Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	

Environmental	NA	

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Active	Refer to DP review for assessment of container closure system	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	204671	Sovaldi
NDA	208341	Epclusa
IND	118605	Epclusa

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology		Refer to pharm/tox review		
CDRH	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ). The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on 04/27/2021.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed product is the pediatric oral pellet formulation of Epclusa (sofosbuvir and velpatasvir tablets), which was approved under NDA 208341 in 2016. The proposed product is indicated for the treatment of Hepatitis C Virus (HCV) in pediatric patients 3 years of age and older, and will be available in two strengths: 200 mg/50 mg and 150 mg/37.5 mg (sofosbuvir/velpatasvir). The labeling describes that the oral pellets should not be chewed, and should be administered by sprinkling the pellets on one or more spoonfulls of non-acidic soft food at or below room temperature and taken within 15 minutes. The examples in the labeling include pudding, chocolate syrup and ice cream.

Proposed Indication(s) including Intended Patient Population	Treatment of (b) (4) in adult and pediatric patients
Duration of Treatment	12 weeks
Maximum Daily Dose	400 mg/100 mg sofosbuvir/velpatasvir
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance information for sofosbuvir and velpatasvir are referenced to Gilead's previously approved NDA 204671 and NDA 208341, respectively. For sofosbuvir, the retest period is (b) (4) months when stored at (b) (4)°C. For velpatasvir, the retest period is (b) (4) months when stored below (b) (4)°C.

This NDA is recommended for approval from a drug substance perspective. For additional details, refer to the review by Rohit Tiwari, Ph.D.

Drug Product: Adequate

Sofosbuvir/velpatasvir (SOF/VEL) oral pellets are an immediate-release, (b) (4) dosage form available as unit-dose packets containing either 150 mg of SOF and 37.5 mg of VEL (SOF/VEL, 150/37.5 mg) or 200 mg of SOF and 50 mg of VEL (SOF/VEL, 200/50 mg). Velpatasvir is amorphous and sofosbuvir drug substance is crystalline (b) (4)), (b) (4) (b) (4) (b) (4). XRPD data collected on SOF/VEL oral (b) (4)/pellets in the selected commercial formulation supports the physical stability of both APIs after manufacturing and upon storage under accelerated conditions.

The results from the in-use compatibility studies showed that the oral pellets are chemically stable after exposure to non-acidic soft foods for up to 30 mins in chocolate pudding and ice cream, and up to 60 min in chocolate syrup. This supports the proposed in-use time of 15 min at room temperature after exposure to non-acidic soft foods as described in current PI. Satisfactory results from 12 months of long term stability data (at 30°C/75% RH) and 6 months of accelerated stability data at 40 °C/75% RH for the three primary stability batches ((b) (4) scale) supports the proposed shelf-life of 24 months for both strengths.

The applicant has submitted a claim of categorical exclusion including a statement of no extraordinary circumstances. The categorical exclusion cited at 21 CFR 25.31(d) and 21 CFR 25.31(b) is appropriate for this application, and is acceptable.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by Hailin (Sheena) Wang, Ph.D.

Labeling: Adequate

Labeling recommendations have been communicated to the OND PM.

Manufacturing: Adequate

In the drug product manufacturing process, Velpatasvir (b) (4) is manufactured via the same route described for the approved Epclusa tablets. (b) (4) (b) (4) drug product. The drug product is packaged in unit dose sachets.

The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on 04/27/2021. There are no recommendations at this time for a post-approval inspection.

This NDA is recommended for approval from a Manufacturing perspective. For additional details, refer to the review by Brijeshkumar Vaghasia, Ph.D.

Biopharmaceutics: Adequate

The Biopharmaceutics Review focused on the evaluation of (1) the in vitro dissolution method and acceptance criteria as a quality control (QC) test for the proposed drug product, (2) the in vitro dissolution profiles of the proposed drug product mixed with various soft foods, (3) the need for bridging. The dissolution method and acceptance criteria (Q = (b) (4)% in 15 minutes for Sofosbuvir Q = (b) (4)% in 30 minutes for Velpatasvir) are acceptable as the QC test for the proposed drug product. The dissolution data are also supportive for the administration of the product in the labeled soft foods. The NDA included a PK bridge between the Epclusa pellets and Epclusa tablets. From a Biopharmaceutics perspective, no additional bridging is needed between the pivotal clinical trial product and the proposed commercial product (e.g. same formulation, manufacturing process, manufacturing site, and comparable dissolution profiles).

This NDA is recommended for approval from a Biopharmaceutics perspective. For additional details, refer to the review by Mei Ou, Ph.D.

Microbiology (if applicable): N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay		Low		Acceptable	

Physical State		Medium	(b) (4)	Acceptable	
Microbial Limits		Low		Acceptable	
Dissolution		Medium	The test method and acceptance criteria were found acceptable	Acceptable	
Palatability		Medium		Acceptable	
Content Uniformity		Medium		Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies *(Specify discipline, such as Environmental)*

Application Technical Lead Name and Date

Erika E. Englund, Ph.D. 5/21/2021

APPEARS THIS WAY ON ORIGINAL

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

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

NDA 214817

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION (as revised in SD10 on 04/14/21)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	Dosage form "oral pellets" is consistent with OPPQ's recommendation for the approved Harvoni (ledipasvir/sofosbuvir) oral pellets in NDA 212477 by Gilead.
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Soft-food compatibility data provided in 3.2.P.2. supports the proposed in-use time of 15 min after mixing with non-acid soft foods at or below room temperature.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	"Do not chew" statement is included to avoid bitter aftertaste due to sofosbuvir. Mixing with food is recommended and is supported by product quality data.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be	N/A	

applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Dosage form "oral pellets" is consistent with OPPQ's recommendation for the approved Harvoni (ledipasvir/sofosbuvir) oral pellets in NDA 212477 by Gilead.
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	The applicant accepted the recommended addition of "film-coated" to the description of the oral pellets.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Inactive ingredients used for (b) (4) core and film-coating of the oral pellets are separately listed which are consistent with information provided in 3.2.P.1.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	Remains the same as previously provided for the Epclusa tablet product
Chemical name, structural formula, molecular weight	Adequate	Remains the same as previously provided for the Epclusa tablet product
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Both tablets and oral pellets are listed
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	The applicant accepted the recommended addition of "film-coated" to the description of the oral pellets.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Consistent with storage statement proposed for the Epclusa tablets
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Consistent with information provided in Section 11: Description
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels (taken from SD9 on 04/07/2021)

Representative Epclusa OP 150/37.5 mg US Packet ((b) (4))

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

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence (21 CFR 201.10(g)(2))	Adequate	The font of the established name appears to be at least half as large as the letters comprising the proprietary name. The propriety name and established name appear to have the same prominence.
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents ((21 CFR 201.51(a) e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	Present on both container and carton labels
NDC	Adequate	Present on both container and carton labels
Lot number and expiration date	Adequate	Present on both container and carton labels
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Not present on container labels but present on carton labels
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Present on both container and carton labels
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *{Adequate}*

The container and carton labels for both 150mg/37.5mg and 200mg/50mg presentations are adequate.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:

Hailin (Sheena) Wang, Ph.D. 04/19/2021

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

Thomas F. Oliver, Ph.D. 5/21/2021

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 5/21/2021 11:42:27AM
GUID: 508da71f00029ed4697700cee3d31ca0

Sheena Hailin Wang

Digitally signed by Sheena Hailin Wang
Date: 5/21/2021 11:22:30AM
GUID: 5203a2110001f7235a14cac1b60d05c4

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

CHAPTER VI: BIOPHARMACEUTICS

NDA: 214187-ORIG-1 [505(b)(1)]
Drug Product Name/Strength: Epclusa® (Sofosbuvir/Velpatasvir) Oral Pellets, 150 mg/37.5 mg and 200 mg/50 mg
Route of Administration: Oral
Proposed Indication: For the treatment of hepatitis C virus (HCV) infection in pediatric patients 3 years of age and older
Applicant Name: Gilead Sciences, Inc.
Submission Date: 12/15/2020, 01/28/2021, 02/23/2021
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Elsbeth Chikhale, Ph.D.

EXECUTIVE SUMMARY

The proposed drug product, Epclusa® (Sofosbuvir/Velpatasvir, SOF/VEL) Oral Pellets, 150 mg/37.5 mg and 200 mg/50 mg, is an immediate-release dosage form. Each SOF/VEL pellet is approximately 2 mm in diameter. SOF/VEL pellets are packaged into (b) (4) packets. The 150 mg/37.5 mg strength contains (b) (4) counts and the 200 mg/50 mg strength contains (b) (4) counts of SOF/VEL oral pellets in each unit-dose packet. In the proposed labeling, the recommended dosage in pediatric patients 3 years (b) (4) of age is based on body weight, as 400 mg/100 mg SOF/VEL for children weighing ≥ 30 kg, 200 mg/50 mg SOF/VEL for children weighing < 30 kg and ≥ 17 kg, and 150 mg/37.5 mg SOF/VEL for children weighing < 17 kg, once daily with or without food for 12 weeks.

The Applicant submitted this NDA 214187, as a 505(b)(1) application, based on the pharmacokinetic (PK), efficacy, and safety data from Study GS-US-342-1143 entitled "*A Phase 2, Open-Label, Multicenter, Multi-cohort, Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir in Adolescents and Children with Chronic HCV Infection*" to support the proposed recommendation for the use of SOF/VEL oral pellets in pediatric patients aged 3 to < 18 years old. The Applicant also submitted a Phase 1 Study GS-US-342-1142, evaluating the relative bioavailability of the proposed pellets compared to the approved Epclusa® (sofosbuvir and velpatasvir, SOF/VEL) Tablets, 200 mg/50 mg, 400 mg/100 mg (NDA 208341) and food effect of SOF/VEL oral pellets in healthy adult subjects to support this NDA. Another Phase 1 Study GS-US-337-4565, a taste assessment study of SOF/VEL oral pellets in healthy adult subjects to address the palatability of the oral pellets is also submitted to support this NDA.

In the current NDA 214187, the Biopharmaceutics Review focuses on the evaluation of (1) the in vitro dissolution method and acceptance criteria as a quality control (QC) test for the proposed drug product, (2) the in vitro dissolution profiles of the proposed drug product mixed with various soft food, (3) the need for bridging.

In Vitro Dissolution Testing of the Finished Drug Product:
The following dissolution method and acceptance criteria are found acceptable as the QC test for the proposed drug product.

USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Medium and Volume	900 mL of 25 mM potassium phosphate buffer, containing 1.0% polysorbate 80 and 0.001% butylated hydroxytoluene (BHT), pH 6.8
Temperature	37 ± 0.5°C
Acceptance Criteria	Q = (b)(4)% in 15 minutes for Sofosbuvir (SOF) Q = (b)(4)% in 30 minutes for Velpatasvir (VEL)

In Vitro Drug Release Profiles in Soft Food:
The provided dissolution data are adequate to support the labeling recommendations regarding the administration of the proposed drug product with non-acidic soft food without chewing.

The Need for Bridging:
This NDA's reliance on the safety and efficacy of the approved Epclusa tablets is justified by the PK bridge between the proposed Epclusa pellets and the Epclusa tablets. Per the Office of Clinical Pharmacology (OCP) reviewer, the 90% confidence internal (C.I.) of C_{max} of SOF between the pivotal clinical formulation #2 (oral pellets) and the approved Epclusa tablets, 71.91%-89.8%, is acceptable, and the slightly lower bound of C_{max} of SOF will not affect the safety and efficacy of the proposed drug product (from OCP's scoping meeting dated 01/11/2021). The 90% C.I. of C_{max} of VEL, AUCs of SOF and VEL, between the formulation #2 (oral pellets) and the approved Epclusa tablets, are all within 80-125% range.

From the Biopharmaceutics perspective, no additional in vivo and in vitro bridging studies are needed between the pivotal clinical and commercial drug product, based on the following considerations:

(i) The quantitative composition of pivotal clinical formulation #2 is the same as the primary stability and commercial formulation;
(ii) The manufacturing process is the same for the clinical formulation #2 and commercial drug products;
(iii) The drug product manufacturing site (b) (4)), and the packaging site (b) (4)) are the same for all clinical, registration and commercial batches;
(iv) The pivotal clinical batch and registration/stability batches have comparable in vitro dissolution profiles.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 214187 for the proposed drug product, Epclusa® (Sofosbuvir/Velpatasvir, SOF/VEL) Oral Pellets, 150 mg/37.5 mg and 200 mg/50 mg, is recommended for **APPROVAL**.

BIOPHARMACEUTICS REVIEW

The quantitative composition of the proposed drug product is presented in Table 1 below.

Table 1: Quantitative Composition of the proposed SOF/VEL Oral Pellets

Component	Composition		Unit Formula (mg/unit)		Quality Standards	Function
	% w/w	(b) (4) mg (mg/granule) 1 count	150/37.5 mg (b) count	200/50 mg (b) count		
(b) (4)						
Sofosbuvir[a]		(b) (4)	150.00	200.00	In-house	Active Ingredient
Velpatasvir[b,c]			37.50	50.00	In-house	Active Ingredient
Copovidone[b,c]				(b) (4)	NF, Ph. Eur.	(b) (4)
(b) (4)					USP, Ph. Eur.	
Lactose Monohydrate[a,b]					NF, Ph. Eur.	
Microcrystalline Cellulose					NF, Ph. Eur.	
Croscarmellose Sodium					NF, Ph. Eur.	
Magnesium Stearate					NF, Ph. Eur.	
(b) (4)						
Colloidal Silicon Dioxide				(b) (4)	NF, Ph. Eur.	(b) (4)
Magnesium Stearate					NF, Ph. Eur.	
Total Oral Granule Core(s)						
(b) (4)		(b) (4)				
(b) (4)					In-house	(b) (4)
					USP, Ph. Eur.	
(b) (4) **Coat**						
Amino Methacrylate Copolymer (b) (4)				(b) (4)	NF, Ph. Eur.	(b) (4)
Talc					USP, Ph. Eur.	
Stearic Acid					NF, Ph. Eur.	
Colloidal Silicon Dioxide					NF, Ph. Eur.	
L-Tartaric Acid					NF, Ph. Eur.	
(b) (4)					USP, Ph. Eur.	
(b) (4)				(b) (4)	NF, Ph. Eur.	
Packaging						
Packets (b) (4)	—	—	1 packet	1 packet	In-house	Packaging

The quantitative composition of the velpatasvir (b) (4) (b) (4) is provided in Table 2 below.

(b) (4)

1. Solubility, Permeability and Chemical Stability of Drug Substances

The drug substances, Sofosbuvir (SOF) and Velpatasvir (VEL), have been used in the following approved drug products from the same Applicant:

- Harvoni® (ledipasvir/sofosbuvir, LDV/SOF) Oral Pellets, 33.75 mg/150 mg, 45 mg/200 mg, approved on 08/28/2019 under NDA 212477
- Sovaldi® (sofosbuvir, SOF) Oral Pellets, 150 mg and 200 mg, approved on 08/28/2019 under NDA 212480
- Sovaldi® (sofosbuvir, SOF) Tablets, 200 mg and 400 mg, approved on 12/06/2013 under NDA 204671
- Epclusa® (sofosbuvir and velpatasvir, SOF/VEL) Tablets, 200 mg/50 mg, 400 mg/100 mg, approved on 06/28/2016 under NDA 208341

The Applicant did not request official BCS designations for Sofosbuvir (SOF) or Velpatasvir (VEL), however, the Applicant stated that SOF is a BCS 3 compound and VEL is a BCS 4 compound.

(1) **Sofosbuvir (SOF)** has pH independent high solubility over the physiological pH range from pH 2 to pH 7.7 (Table 3 below).

Table 3: Solubility of Sofosbuvir in Aqueous Media at 37°C
(data from current NDA, M.3.2.S.1.3)

pH (Media)	Solubility (mg/mL)
2 (HCl)	2.0
4.5 (Acetate buffer)	2.1
6.8 (Phosphate buffer)	1.9
7.7 (Unbuffered)	2.2

Per the Applicant, the permeability coefficients of sofosbuvir solutions (1.6 mg/mL) across Caco-2 monolayers were 0.71×10^{-6} cm/s for apical to basolateral transport and

4.11 × 10^{-6} cm/s for basolateral to apical transport, with an efflux ratio of 5.81. However, per FDA BCS guidance (December 2017), this Reviewer cannot conclude the permeability category of SOF without the data of permeability marker drugs conducted in the same study[1, 2].

Per the Applicant, SOF has the maximum chemical stability under (b) (4)

(b) (4)

SOF (b) (4) is the (b) (4) (b) (4) and (b) (4) during the drug substance manufacturing process. However, the (b) (4) product may contain (b) (4) (b) (4). Per the Applicant, the (b) (4)

(b) (4)

(2) **Velpatasvir (VEL)** amorphous (b) (4) is designated commercial drug substance (b) (4) (b) (4) (b) (4)) (b) (4). VEL (b) (4) has a pH dependent solubility over the physiological pH range from pH 2 to pH 8 (Figure 2 and Table 4 below).

[1] NDA 212477 Biopharmaceutics review: https://panorama.fda.gov/internal/document/preview?versionID=5d3ef7e000044006f75c96191abb5bc7&ID=5d3cdce900024bc19af395509ce84a4d

[2] NDA 212480 Biopharmaceutics review: https://panorama.fda.gov/internal/document/preview?versionID=5d3ef85f00045a5c88667b6edef0b3de&ID=5d3cddc100024fa7e174d279c2f9692a

Figure 2: pH-Dependent Solubility Profile of Amorphous Velpatasvir at Room Temperature (data from NDA 208341, M.3.2.P.1)

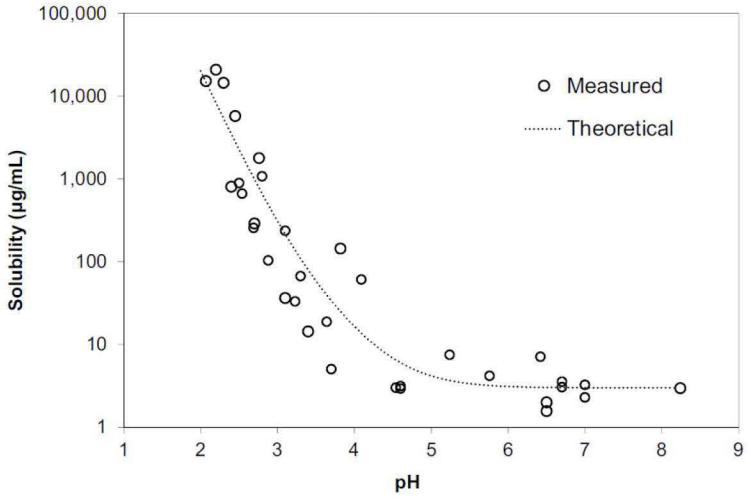


Table 4: Solubility of Velpatasvir in Aqueous Media at 25°C (data from current NDA, M.3.2.S.1.3)

Aqueous Media	Solubility (mg/mL)
Water, pH 1.2[a]	> 36
Water, pH 2.0[a]	3.6
Sodium acetate buffer, pH 5.0	< 0.1
Phosphate buffer, pH 6.8	< 0.1
FeSSIF, pH 5.0[b]	0.1
FaSSIF, pH 6.5[c]	< 0.1

Per the Applicant (from NDA 208341), VEL permeability could not be reliably determined in vitro by Caco-2 cell monolayers due to low recovery and poor reproducibility. However, absorption of VEL is considered low based on the oral bioavailability (25 to 30%) following oral administration of solution formulations in various nonclinical species (rats, dogs, and monkeys). Therefore, the Applicant stated VEL has low permeability.

(b) (4)

(b) (4)

[redacted]

2. In Vitro Dissolution Method and Acceptance Criteria

There is no dissolution method development report submitted in the current NDA. The originally proposed dissolution method and acceptance criteria for the proposed drug product, Epclusa® (Sofosbuvir/Velpatasvir, SOF/VEL) Oral Pellets, 150 mg/37.5 mg and 200 mg/50 mg, are listed below.

Originally Proposed Dissolution Method and Acceptance Criteria		
Current NDA 214187 Epclusa® (Sofosbuvir/Velpatasvir, SOF/VEL) Oral Pellets, 200 mg/50 mg and 150 mg/37.5 mg	USP Apparatus	II (Paddle)
	Rotation Speed	75 rpm
	Medium and Volume	900 mL of 25 mM potassium phosphate buffer, pH 6.8, containing (b) (4) % polysorbate 80 and 0.001% butylated hydroxytoluene (BHT) (b) (4) (b) (4)
	Temperature	37 ± 0.5°C
	Acceptance Criteria	Q = (b) (4) % in 30 minutes for both Sofosbuvir (SOF) and Velpatasvir (VEL)

The approved dissolution methods and acceptance criteria for other approved SOF (alone or in combination) drug products are listed below.

Acceptable Dissolution Methods and Acceptance Criteria		
NDA 212477[3] Harvoni® (ledipasvir/sofosbuvir, LDV/SOF) Oral Pellets, 33.75 mg/150 mg, 45 mg/200 mg	USP Apparatus	II (Paddle)
	Rotation Speed	75 rpm
	Medium and Volume	900 mL of 25 mM potassium phosphate buffer, pH 5.5, containing 1.0% polysorbate 80 and 0.005 mg/mL butylated hydroxytoluene (BHT)
	Temperature	37 ± (b) (4)°C
	Acceptance Criteria	Q = (b) (4)% in 30 minutes for both Ledipasvir (LDV) and Sofosbuvir (SOF)
NDA 212480[4] Sovaldi® (sofosbuvir, SOF) Oral Pellets, 150 mg and 200 mg	USP Apparatus	II (Paddle)
	Rotation Speed	75 rpm
	Medium and Volume	900 mL of 25 mM potassium phosphate buffer, pH 5.5
	Temperature	37 ± (b) (4)°C
	Acceptance Criteria	Q = (b) (4)% in 30 minutes for Sofosbuvir (SOF)
NDA 204671[5] Sovaldi® (sofosbuvir, SOF) Tablets, 200 mg and 400 mg	USP Apparatus	II (Paddle)
	Rotation Speed	75 rpm
	Medium and Volume	900 mL of 50 mM potassium phosphate buffer, pH (b) (4)
	Temperature	(b) (4) ±
	Acceptance Criteria	Q = (b) (4)% in (b) (4) for Sofosbuvir (SOF)
NDA 208341[6] Epclusa® (sofosbuvir and velpatasvir, SOF/VEL) Tablets, 200 mg/50 mg, 400 mg/100 mg	USP Apparatus	II (Paddle)
	Rotation Speed	75 rpm
	Medium and Volume	900 mL of 50 (b) (4) acetate buffer, pH 5.0 with 0.5% cetyltrimethyl ammonium bromide (CTAB)
	Temperature	(b) (4) ±
	Acceptance Criteria	Q = (b) (4)% in 20 minutes for both Sofosbuvir (SOF) and Velpatasvir (VEL)

[3] NDA 212477 Biopharmaceutics Reviews:
https://panorama.fda.gov/internal/document/preview?versionID=5d3ef7e000044006f75c96191abb5bc7&ID=5d3cdce900024bc19af395509ce84a4d
https://panorama.fda.gov/internal/document/preview?versionID=5d52e550002ac11876b3e1f2962d8b5c&ID=5d4c26de0015c1ac6c2129e0aeeb7431

[4] NDA 212480 Biopharmaceutics Reviews:
https://panorama.fda.gov/internal/document/preview?versionID=5d3ef85f00045a5c88667b6edef0b3de&ID=5d3cddc100024fa7e174d279c2f9692a
https://panorama.fda.gov/internal/document/preview?versionID=5d5465850005105236f43a2ee61316cb&ID=5d4c27830015db417039180087ea408d

[5] NDA 204671-S-14 Biopharmaceutics Review:
https://panorama.fda.gov/internal/document/preview?versionID=5ec590fc0029b84205d69f6e920baa2d&ID=5d0918ae002848aa2df0e5e41ddc873d

[6] NDA 208341-S-14 Biopharmaceutics Review:
https://panorama.fda.gov/internal/document/preview?versionID=5e27880e02cead64e0b837d1ca960e8a&ID=5e1f2ae40000acae5439963e7b3e2b3b

(b) (4)

foods. (b) (4) has been used as (b) (4) (b) (4) for SOF for the previously approved drug products, Harvoni® (ledipasvir/sofosbuvir, LDV/SOF) Oral Pellets (NDA 212477) and Sovaldi® (sofosbuvir, SOF) Oral Pellets (NDA 212480).

(b) (4)

(b) (4)

[redacted]

The Applicant provided the requested data on 01/28/2021, as presented in the Table 5, and Figures 6 to 11 below. *Note that the proposed shelf life of drug product is 24 months, and long-term stability condition is 30°C/75% RH.*

Table 5: Manufacturing History of SOF/VEL Oral Pellets Used in the requested Dissolution Study (information from 01/28/2021 submission)

Packaged Lot No.	Batch Size (kg)[a]	Date of Mfg[b]	Mfg Site[c]	Storage Condition	Age of Batch (months)	Dissolution Testing Date
Strength: 150/37.5 mg						
FH1901B1	(b) (4)	March 2019	(b) (4)	Warehouse (8 months) and 30 °C/75% RH (14 months)	22	18-Jan-2021, 19-Jan-2021, 07-Oct-2020[d]
FH1902B1		March 2019		Warehouse (8 months) and 30 °C/75% RH (14 months)	22	18-Jan-2021, 19-Jan-2021, 08-Oct-2020[d]
FH1903B3		March 2019		Warehouse (8 months) and 30 °C/75% RH (14 months)	22	18-Jan-2021, 19-Jan-2021, 09-Oct-2020[d]
Strength: 200/50 mg						
FH1901B2	(b) (4)	March 2019		Warehouse (8 months) and 30 °C/75% RH (14 months)	22	18-Jan-2021, 19-Jan-2021, 20-Jan-2021, 08-Oct-2020[d]
FH1902B2		March 2019		Warehouse (8 months) and 30 °C/75% RH (14 months)	22	19-Jan-2021, 20-Jan-2021, 22-Jan-2021, 08-Oct-2020[d]
FH1903B2		March 2019		Warehouse (8 months) and 30 °C/75% RH (14 months)	22	18-Jan-2021, 19-Jan-2021, 20-Jan-2021, 08-Oct-2020[d]

a (b) (4).
b Defined as date SOF and VEL (b) are combined with excipients.
c Refers to manufacturing site for core granules. Packaging was performed at (b) (4) (Section 3.2.P.3.1).
d Results per TM-381 (n = 6) acquired as part of scheduled stability study and are included for completeness. At time of analysis, the batch age was 19 months (7 months in warehouse and 12 months at 30 °C/75% RH).

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

(b) (4)

Based on the provided dissolution data in Figures 6-11, a dissolution medium of 25 mM potassium phosphate buffer containing 1.0% polysorbate 80 and 0.001% BHT, pH 6.8, is found appropriate for the proposed drug product.

Dissolution data profiles of the clinical batch (FH1701C1, in Phase 2 Study GS-US-342-1143) and six registration/stability batches (FH1901B1, FH1902B1, FH1903B3 for SOF/VEL oral pellets 150 mg/37.5 mg, and FH1901B2, FH1902B2, FH1903B2 for SOF/VEL oral pellets 200 mg/50 mg) using the originally proposed dissolution method (containing (b) (4) polysorbate 80) instead of by the recommended dissolution method (containing 1.0% polysorbate 80) are provided, as presented in the following Figure 12 and 13 (*detailed data of six registration batches are provided in M.3.2.P.5.4*). Clinical batches and registration/stability batches showed comparable dissolution profiles.

(b) (4)

The dissolution data of six registration batches showed that both SOF and VEL have (b) (4)% mean dissolution in 15 minutes under long-term stability condition (30°C/75%RH) for up to 12 months (sampling time at 10, 15, 20, 30, 45 and 60 minutes, n=6 or 12) with no trend observed.

Based on the overall data, the following dissolution method and acceptance criteria were recommended and agreed upon by the Applicant (*see Appendix 1, Biopharmaceutics Information Requests*):

Dissolution Method: USP Apparatus II (Paddle), 75 rpm, 900 mL of 25 mM potassium phosphate buffer containing 1.0% polysorbate 80 and 0.001% butylated hydroxytoluene (BHT), pH 6.8, 37°C.

Acceptance Criteria: Q = (b) (4)% in 15 minutes for Sofosbuvir (SOF), Q = (b) (4)% in 30 minutes for Velpatasvir (VEL)

3. Administration of Drug Product with Soft Food

One packet of SOF/VEL oral pellets ((b) (4) counts, lot FH1904B) were mixed into non-acidic soft foods, such as chocolate pudding, chocolate syrup, and vanilla ice cream, for one hour at room temperature to evaluate the chemical stability and dissolution.

Based on the assay data (Table 5 below), the Applicant claims that SOF and VEL are chemically stable in all tested soft foods for one hour with no significant degradation products detected.

Table 5: Chemical Stability of SOF/VEL Oral Pellets After Exposure to Various Soft Foods (Lot FH1904B) (data from current NDA, M.3.2.P.2.2)

		Sofosbuvir		Velpatasvir	
Type of Food[a]	Soft Food Exposure Time (minutes)	Assay (%)	Total Degradation Products (%)	Assay (%)	Total Degradation Products (%)
Control (no food)	Not applicable	100.7	0.0	99.8	0.5
Chocolate Syrup	15	99.8	0.0	97.9	0.5
	30	100.0	0.0	98.9	0.5
	60	99.8	0.0	98.8	0.5
Chocolate Pudding	15	99.7	0.0	98.8	0.5
	30	100.9	0.0	99.1	0.5
Ice Cream	15	99.4	0.0	98.6	0.5
	30	102.5	0.0	100.4	0.5

a SOF/VEL oral granules, 200/50 mg, mixed into each type of food.

The stability and assay data will be reviewed by the Drug Product CMC Reviewer.

Based on the dissolution data (Table 6 below), SOF and VEL had (b) (4)% dissolution in 30 minutes after being left in soft foods for up to one hour. *Note that these dissolution data were generated by the originally proposed dissolution method (containing (b) (4)% polysorbate 80).*

Table 6: Dissolution of SOF/VEL Oral Pellets After Exposure to Various Soft Foods (Lot FH1904B) (data from current NDA, M.3.2.P.2.2)

Type of Food[a]	Soft Food Exposure Time (min)	% Sofosbuvir Released at 30 min[b]	%Velpatasvir Released at 30 min[b]
Control (no food)	Not applicable	99	99
Chocolate Syrup	30	99	99
	60	99	100
Chocolate Pudding	15	96	93
	30	96	91
Ice Cream	15	98	99

a SOF/VEL oral granules, 200/50 mg, mixed into each type of food.
b Dissolution method: USP Type 2 (Paddle), 75 rpm, 900 mL of 25 mM potassium phosphate buffer, pH 6.8, with (b)% polysorbate 80 and 0.001% butylated hydroxytoluene (BHT), 37 °C.

The proposed labeling has the following statements: "if EPCLUSA pellets are administered with food, sprinkle the pellets on one or more spoonfuls of non-acidic soft food at or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, and ice cream. Take EPCLUSA pellets within 15 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste", "if EPCLUSA pellets are administered without food, pour the entire contents of the EPCLUSA oral pellets packet directly in the mouth and swallow without chewing to avoid a bitter taste. Water may be taken after swallowing the pellets, if needed. Make sure that no EPCLUSA oral pellets remain in the packet".

This Reviewer considers that the dissolution data are supportive for the labeling recommendations with regards to administration of the proposed drug product with non-acidic soft food without chewing.

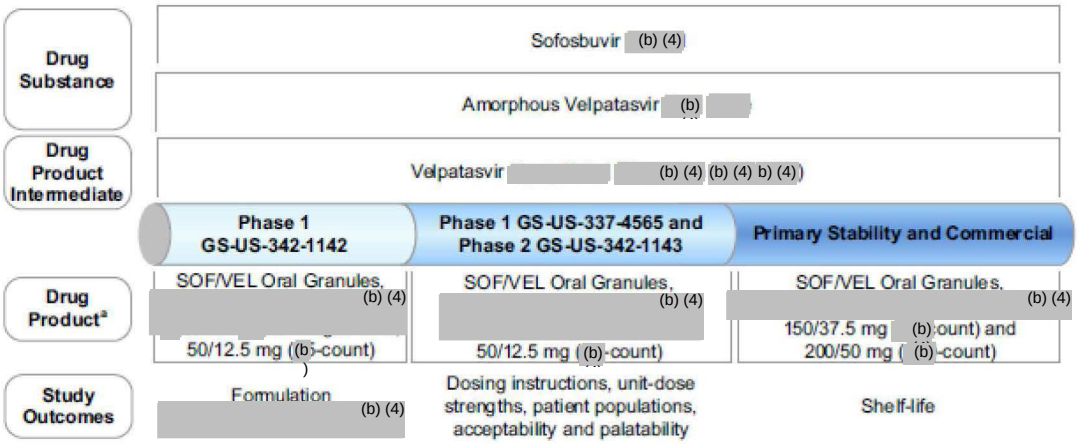
4. Bridging

Two SOF/VEL oral pellets formulations were tested during development. The SOF/VEL formulation #1 (FDC1) was initially developed for evaluation in the Phase 1 relative bioavailability (rBA) Study GS-US-342-1142. Formulation #1 (b) (4) (b) (4) (b) (4) The results of clinical Study GS-US-342-1142 demonstrated that the PK performance of formulation #1 was not equivalent to the adult-strength SOF/VEL 400 mg/100 mg tablet (b) (4) (b) (4) The SOF/VEL formulation #2 (FDC2) used the same formulation components as formulation #1 (b) (4) (b) (4) (b) (4) (b) (4) Formulation #2 was evaluated in a second cohort of rBA Study GS-US-342-1142, which demonstrated no clinically relevant difference in PK performance to that of the adult-strength SOF/VEL 400 mg/100 mg tablet when administered with and without food. Therefore, the SOF/VEL oral pellets formulation #2 was selected and subsequently used in the following Phase 1 Study GS-US-342-1143 and Phase 1 Study GS-US-337-4565, as well as designated as the final commercial formulation. Consequently, two packaging configurations were identified for the commercial formulation, (b) (4)-count pellets, equivalent to a 150 mg dose of SOF and a 37.5

mg dose of VEL, and (b) (4)-count pellets, equivalent to a 200 mg dose of SOF and a 50 mg dose of VEL.

An overview of the clinical development of SOF/VEL oral pellets is provided in Figure 14. The composition of development formulations and the relevant clinical lots and trials are provided in Table 7.

Figure 14: Summary of Drug Substances, (b) (4) and Drug Products Used in Clinical Development of SOF/VEL Oral Pellets
(data from current NDA, M.3.2.P.2.2)



a Composition of SOF/VEL Oral Granule, Cores, did not change throughout clinical development

Table 7: Clinical Development History of SOF/VEL Oral Pellets
(data from current NDA, M.3.2.P.2.2)

Development Stage		Phase 1 and 2			Primary Stability Batches and Designated Commercial	
Oral Granule Packaged Lot Number		FH1701B1	FH1701C1	FH1701C2	FH1901B1 FH1902B1 FH1903B3	FH1901B2 FH1902B2 FH1903B2
Key Clinical Studies		GS-US-342-1142	GS-US-342-1142 GS-US-342-1143	GS-US-342-1143 GS-US-337-4565	N/A	N/A
Oral Granule Core Weight (mg)		(b) (4)				
Amount Per Granule (mg)	Sofosbuvir					
	Velpatasvir					
Unit-Dose Strength (mg)	Sofosbuvir	50	50	50	150	200
	Velpatasvir	12.5	12.5	12.5	37.5	50
Granules Per Packet (count)		(b) (4)				
(b) (4)						
Drug Product Description		(b) (4) packet containing (b) white SOF/VEL oral granules, 50/12.5 mg of SOF/VEL			(b) (4) packet containing (b) or (b) white SOF/VEL oral granules for SOF/VEL unit-doses of 150/37.5 mg and 200/50 mg	
Key Formulation or Packaging Changes		Initial formulation	(b) (4)		Changed number of oral granules per packet to provide the commercial unit doses	

The pivotal clinical formulation (formulation #2) is the same as the registration and commercial formulation. Based on OCP's scoping meeting dated 01/11/2021, OCP considered that the 90% confidence internal (C.I.) of C_{max} of SOF between the pivotal clinical formulation #2 (oral pellets) and the approved Epclusa tablets, 71.91%-89.8%, is acceptable, and the slightly lower bound of C_{max} of SOF will not affect the safety and efficacy of the proposed drug product. The 90% C.I. of C_{max} of VEL, AUCs of SOF and VEL, between the formulation #2 (oral pellets) and the approved Epclusa tablets, are all within 80-125% range. The PK information of the pivotal clinical formulation #2 is acceptable per OCP. Therefore, this NDA's reliance on the safety and efficacy of the approved Epclusa tablets is justified by the PK bridge (relative BA study) between the proposed Epclusa pellets and the Epclusa tablets.

This Reviewer considers that no additional in vivo and in vitro bridging studies are needed between the clinical and commercial formulations, based on the following considerations:

(i) The qualitative and quantitative composition of clinical formulation #2 is same as that of the primary registration and commercial formulation;
(ii) The manufacturing process is same from clinical formulation #2 to commercial formulation;
(iii) The manufacturing site ((b) (4)), and the packaging site (b) (4)) are the same for all clinical and registration batches.
(iv) The pivotal clinical batch and registration batches have comparable in vitro dissolution profiles.

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

Mei Ou

Digitally signed by Mei Ou
Date: 3/25/2021 06:20:01PM
GUID: 54ca9d7000073c57d2eb7cc6e42c05bb

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 3/26/2021 09:11:38AM
GUID: 50743ccc000031928b54eba1769a5df9

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIKA E ENGLUND
05/21/2021 01:52:45 PM