

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212477Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 212477 Assessment # 2

Drug Product Name	ledipasvir and sofosbuvir, LDV and SOF, (GS-5885 and GS-7977)
Dosage Form	Oral Pellets
Strength	33.75 mg /150 mg; 45 mg/200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	Applicant's Responsible Official: Linda Lintao, RAC, Associate Director, Regulatory Affairs

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0007	6/25/2019	Quality
eCTD 0011	8/01/2019	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	George Lunn	Balajee Shanmugam
Manufacturing	Nathan Davis	Rapti Madurawe
Microbiology	N/A	N/A
Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	N/A	
Environmental	George Lunn	Balajee Shanmugam

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS, Other Documents and Consults

Refer to Review #1

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

*From the Product Quality perspective, NDA 212477 is recommended for **Approval**.* The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on August 22, 2019. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Refer to Review #1

Proposed Indication(s) including Intended Patient Population	Treatment of chronic hepatitis C in pediatric patients
Duration of Treatment	12-24 weeks
Maximum Daily Dose	The recommended doses are: 90mg/400 mg per day (adults and pediatric patients >35 kg); 45mg/200 mg per day (pediatric patients 17-35 kg) and 33.75mg/150 mg per day (pediatric patients at least 3 years of age and < 17 kg).
Alternative Methods of Administration	The oral pellets can be taken in the mouth without chewing, or with non-acidic food. The oral pellets can be administered with non-acidic food, such as pudding, chocolate syrup, mashed potato and ice cream.

B. Quality Assessment Overview

Drug Substance: Adequate

Refer to Review #1

Drug Product: Adequate

Refer to Review #1

Labeling: Adequate

Refer to Review #1

Manufacturing: Adequate

Refer to Review #1 for additional discussion.

In Review #1, there were outstanding concerns regarding the packaging process due to the OAI facility status and missing commercial manufacturing equipment. The outcome of the (b) (4) (primary packaging) was OAI due, in part, to missing commercial manufacturing equipment per the FDA-483.

An addendum to the original review (Review #2) was completed on 8/21/2019. The final outcome of the PAI review and EIR review can be found in CMS WA # 283608. The final outcome is adequate after review of FDA-483 responses and the firm response to an RAI. The inspection final classification is VAI and therefore the NDA is recommended for approval from an OPF perspective.

Biopharmaceutics: Adequate

Note, at the time that IQA #1 was finalized, the biopharmaceutics review #1 could not be archived in Panorama. This IQA includes both biopharmaceutics review #1, and the addendum to biopharmaceutics review #1, which recommended the NDA for approval.

Biopharmaceutics Review #1 described a pending IR regarding the controls in place to assure the integrity of the taste masking coat at batch release and during the shelf life of the product. The pending IR also requested a risk mitigation strategy to assure the integrity of the taste masking coat, which could include a two-phase dissolution test.

On 08/01/2019, the Applicant responded that the FDA's recommended two-stage dissolution method is not necessary because adequate formulation and manufacturing controls were developed, evaluated, and implemented to ensure the integrity of the taste-mask coating of the drug

product at the time of batch release and during its shelf life. The biopharmaceutics reviewer found that the provided information/data for the formulation design, manufacturing controls, and results of the taste assessment and coating integrity tests, fully support the integrity of the taste-mask coating of the SOF pellets, and the information also demonstrates that the coating remains intact during storage. Therefore, based on the satisfactory justification and the overall information provided, this Reviewer agrees with the Applicant's proposal of not using a two-stage dissolution method to control the quality of the proposed drug product. It is noted that the Applicant also proposes to continue testing the primary stability batches of the proposed drug product through their shelf life using the coating integrity test. The NDA is recommended for approval from a biopharmaceutics perspective.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

Refer to Review #1

D. List of Deficiencies for Complete Response

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

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

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

None

Application Technical Lead Name and Date:

Erika. E. Englund, Ph.D.

8/22/2019



Erika
Englund

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Date: 8/22/2019 08:46:21PM

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BIOPHARMACEUTICS**NDA: 212477 [505(b)(1)]****Drug Product Name/Strength:** Harvoni (ledipasvir/sofosbuvir, LDV/SOF) Oral Granules; 33.75 mg/150 mg, 45 mg/200 mg**Route of Administration:** Oral**Applicant Name:** Gilead Sciences, Inc.**Proposed Indication:** Treatment of chronic hepatitis C in Pediatric patients 3 years of age and older**Submission Dates:**

02/28/2019 (Original Submission)

06/25/2019 (Response to Biopharmaceutics Information Request)

Primary Reviewer: Mei Ou, Ph.D.**Secondary Reviewer:** Elsbeth Chikhale, Ph.D.**EXECUTIVE SUMMARY**

The proposed drug product, Harvoni (ledipasvir/sofosbuvir; LDV/SOF) Oral Granules, 33.75 mg/150 mg, 45 mg/200 mg, is an immediate-release dosage form. Each LDV/SOF oral granule unit has a diameter of approximately 2 mm and has a taste-masking^{(b) (4)} coating. LDV/SOF oral granules are packaged into ^{(b) (4)} packets. The 33.75 mg/150 mg strength contains 90 counts and the 45 mg/200 mg strength contains 120 counts of LDV/SOF oral granules in each unit-dose packet. In the proposed labeling, the recommended dosage in pediatric patients 3 years ^{(b) (4)} is 33.75/150 mg to 90/400 mg per day with or without food.

In the current NDA 212477 submissions, the Biopharmaceutics Review focuses on the evaluation of (1) the in vitro dissolution method as a quality control (QC) test and acceptance criteria of the proposed drug product, (2) the in vitro dissolution profiles of the proposed drug product mixed with various soft food, (3) the need for in vitro bridging between the clinical formulation and the to-be-marketed/commercial formulation.

In Vitro Dissolution Testing of the Finished Drug Product:

The Applicant proposed *USP Apparatus II (Paddle)*, 75 rpm, 900 mL of 25 mM potassium phosphate buffer, pH 5.5, containing 1.0% polysorbate 80 and 0.005 mg/mL butylated hydroxytoluene (BHT), 37±0.5°C as the dissolution method for quality control (QC) and stability testing. The proposed dissolution method resulted in rapid dissolution for LDV (i.e., more than ^{(b) (4)}% dissolution in 30 minutes) and very rapid dissolution for SOF (i.e., more than ^{(b) (4)}% dissolution in ^{(b) (4)} minutes) and has limited discriminating ability toward ^{(b) (4)}. The possibility of a 2 phase dissolution test that can ensure the integrity of the taste-masking coat is currently considered. The acceptability of the proposed dissolution method cannot be determined at this point due to an outstanding response to an information request (IR) regarding a control strategy to ensure the integrity of the taste-masking coat.

Dissolution Acceptance Criteria:

The originally proposed dissolution acceptance criterion for the proposed drug product is “Q= (b) (4) % in 30 minutes for both LDV and SOF”. The acceptability of the dissolution acceptance criterion cannot be determined at this point due to an outstanding response to an IR regarding the control strategy to ensure (b) (4).

In Vitro Drug Release Profiles in Soft Food:

The stability of the drug product, including the integrity of the taste-masking (b) (4) coating, cannot be determined at this point due to an outstanding response to an IR.

The Need for In Vitro Formulation Bridging:

The Phase 2/3 clinical formulation is the same as the proposed to-be-marketed formulation. The Phase 2/3 drug product batches and the to-be-marketed drug product batches have the same manufacturing process and manufacturing site. Therefore, studies to bridge clinical and to-be-marketed formulations are not needed.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 212477 for the proposed Harvoni (Ledipasvir/Sofosbuvir, LDV/SOF) Oral Granules, 33.75 mg/150 mg, 45 mg/200 mg, is **PENDING** at this point due to an outstanding response to and IR.

BIOPHARMACEUTICS REVIEW

1. Drug Substances Solubility and Permeability

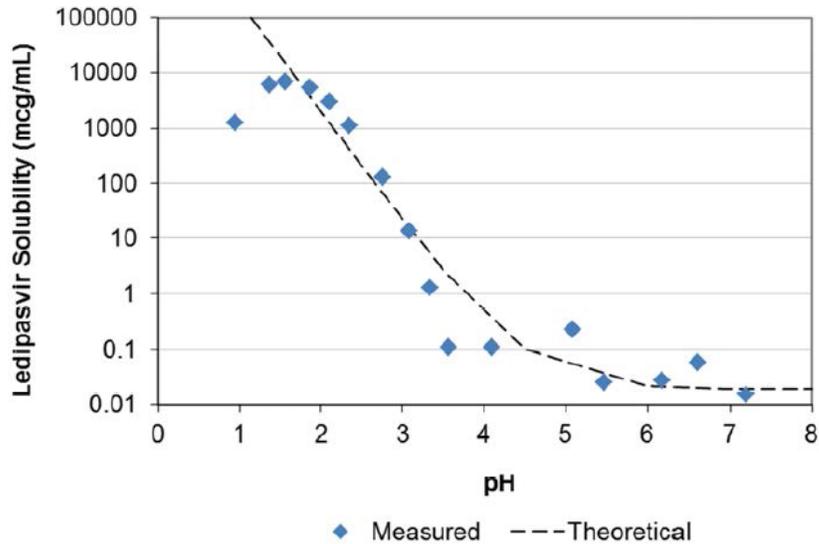
The Applicant did not request an official BCS designation for SOF or LDV.

(1) The Applicant stated that the drug substance ledipasvir (LDV) is a BCS class 2 compound (low solubility and high permeability). LDV has pH dependent solubility (Table 1 and Figure 1). (b) (4)

Table 1: Solubility of Ledipasvir (LDV) at 37°C across the Physiologically pH Range

pH (Media)	Ledipasvir Solubility (mg/mL)
1.6 (HCl)	6.8
2.3 (HCl)	1.1
4.1 (HCl)	0.0001
6.2 (unaltered)	0.0003
FaSSIF (pH 6.5)	0.025
FeSSIF (pH 5.0)	0.230

Figure 1: Solubility of Ledipasvir (LDV) as a function of pH at Room Temperature



The line is the nonlinear least-squares regression fit using equation $S = S_0 \left(1 + \frac{10^{pH - pK_{a1}}}{1 + 10^{pH - pK_{a2}}} \right)$ (b) (4) with an intrinsic solubility (S_0) of $(b) (4)$ $\mu\text{g/mL}$ and a weakly basic pK_{a1} and pK_{a2} values of $(b) (4)$ and $(b) (4)$ respectively.

The Applicant stated that the permeability of LDV was assessed in Caco-2 cell monolayers using 10 μ M LDV solutions. The apparent apical to basolateral ($P_{A \rightarrow B}$) and basolateral to apical ($P_{B \rightarrow A}$) permeability coefficients for LDV were 1.76×10^{-6} cm/s and 0.68×10^{-6} cm/s, respectively, with an efflux ratio of 0.38. The Applicant stated that LDV has high apparent permeability with no efflux potential. However, without the data of permeability marker drugs conducted in the same study, per FDA BCS guidance (December 2017), this Reviewer cannot conclude the permeability category of LDV.

(2) The Applicant stated that the drug substance sofosbuvir (SOF) is a BCS class 3 compound (high solubility and low permeability). SOF has pH-independent and high solubility over the physiological range from pH 2.0 to 6.8 (Table 2).

Table 2: Solubility of Sofosbuvir (SOF) at 37°C across the Physiologically pH Range

pH (Media)	Sofosbuvir Solubility (mg/mL) ^a
1.2 ^b (HCl)	1.3
2.0 (HCl)	2.0
4.5 (Acetate Buffer)	2.1
6.8 (Phosphate Buffer)	3.6
FaSSIF (pH 6.5)	2.1
FeSSIF (pH 5.0)	1.8

(b) (4)

The Applicant stated that the permeability of SOF was assessed in Caco-2 cell monolayers using 3 mM (1.6 mg/mL) SOF solutions. The apparent $P_{A \rightarrow B}$ and $P_{B \rightarrow A}$ permeability coefficients for SOF were 0.71×10^{-6} cm/s and 4.11×10^{-6} cm/s, respectively, with an efflux ratio of 5.81. SOF is considered to have low apparent permeability with the potential for efflux. However, without the data of permeability marker drugs conducted in the same study, per FDA BCS guidance (December 2017), this Reviewer cannot conclude the permeability category of SOF.

2. Chemical Stability of Drug Substances

(b) (4)



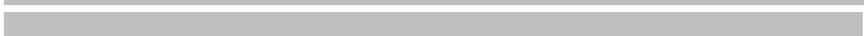
3. In Vitro Dissolution Method

The proposed dissolution method and acceptance criteria are summarized as below:

USP Apparatus	II (paddle)
Rotation Speed	75 rpm
Dissolution Media 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°C
Proposed Acceptance Criteria	$Q = \frac{(b)}{M}$ % in 30 min for both LDV and SOF

Because SOF is bitter tasting, the Applicant  (b) (4)



 therefore; the Applicant will be asked to provide dissolution data to show the stability of the coating at pH  (b) (4)

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The complete dissolution method development is submitted in report PDM-3099. The following dissolution parameters were evaluated during the dissolution method development:

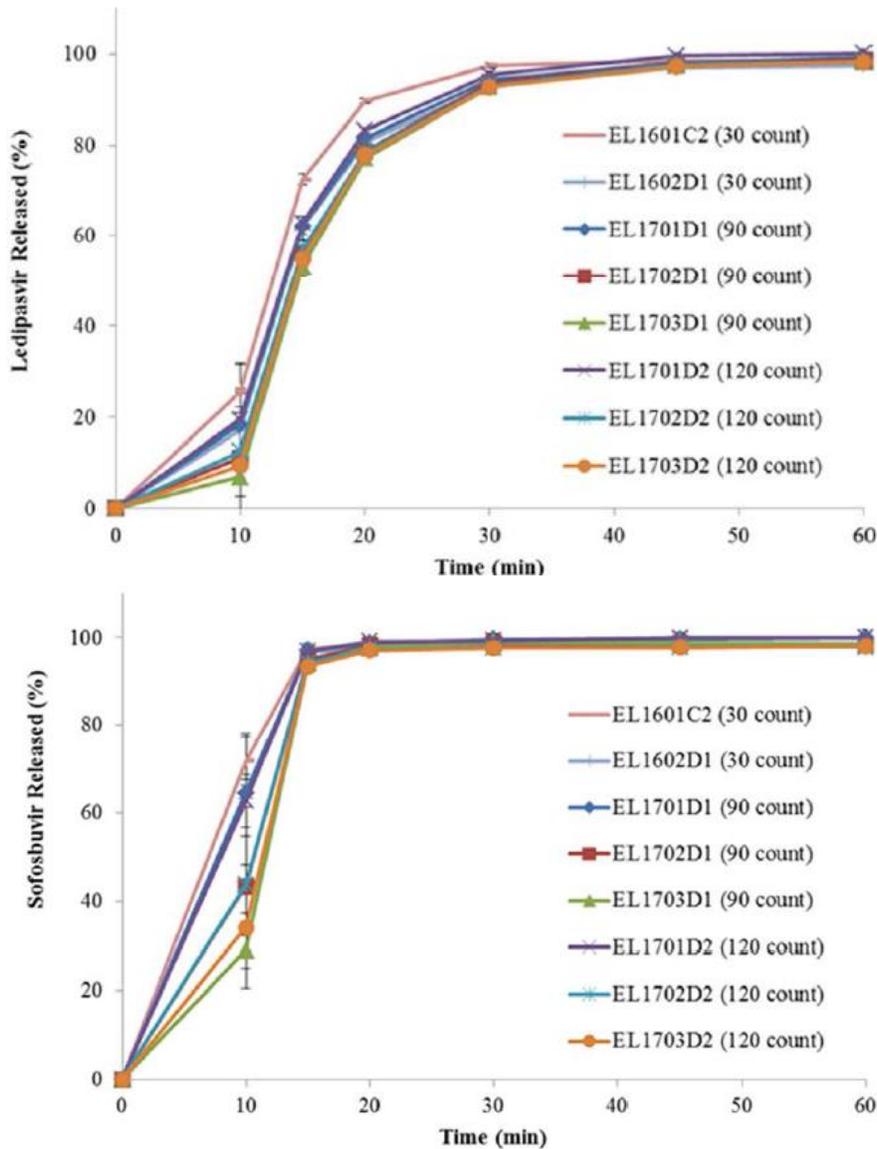
(b) (4)



4. Dissolution Data and Acceptance Criteria

Dissolution data profiles of the proposed drug product (the clinical and primary stability batches) are presented in the following Figure 15. Ledipasvir (LDV) showed more than (b) (4) % dissolution in 30 minutes, and Sofosbuvir (SOF) showed more than (b) (4) % dissolution in (b) (4) minutes. Note that this Reviewer considers that the small difference in amount of antioxidant BHT ((b) (4) mg/mL showed in Figure 16 below versus the proposed 0.005 mg/mL) will not affect the dissolution profiles of drug product.

Figure 15: Dissolution of Ledipasvir (top) and Sofosbuvir (bottom) from Clinical and Primary Stability Batches



Note:

(1) Batch EL1601C2 (11.25 mg/50 mg, 30 counts of LDV/SOF oral granules) has same formulation with to-be-marked formulation and was used in Phase 1 BA study GS-US-337-2091;

- (2) Batch EL1602D1 (11.25 mg/50 mg, 30 counts LDV/SOF oral granules) has same formulation with to-be-marked formulation and was used in Phase 2/3 safety and efficacy study GS-US-337-1116 and taste assessment study GS-US-337-4565;
- (3) Batches EL1701D1, EL1702D1, EL1703D1 (33.75 mg/150 mg, 90 counts LDV/SOF oral granules) are three registration batches;
- (4) Batches L1701D2, EL1702D2, EL1703D2 (45 mg/200 mg, 120 counts LDV/SOF oral granules) are three registration batches;
- (5) Dissolution test condition (the proposed dissolution method) is: USP Apparatus 2 (paddle), 75 rpm, 1.0% w/v polysorbate 80 with (b) (4) mg/mL BHT in 25 mM potassium phosphate, pH 5.5, 900 mL, at 37°C, for both LDV and SOF.

The dissolution data of six registration batches (33.75 mg/150 mg, batches EL1701D1, EL1702D1, EL1703D1 and 45 mg/200 mg, batches L1701D2, EL1702D2, EL1703D2) in various stability conditions (sampling time at 10, 15, 20, 30, 45 and 60 minutes, n=6) showed that LDV has a mean dissolution > 93% in 30 minutes, SOF has a mean dissolution > 93% in 15 minutes when stored up to 12 months at long-term stability condition (30°C/75%RH).

The proposed dissolution acceptance criterion is: $Q = \frac{(b)}{(4)}\%$ in 30 minutes for both LDV and SOF. Considering the BCS Class 2 for LDV, the proposed criterion of " $Q = \frac{(b)}{(4)}\%$ in 30 minutes for LDV" may be acceptable. However, because of the BCS Class 3 for SOF, this Reviewer recommended a data-driven acceptance criterion of " $Q = \frac{(b)}{(4)}\%$ in 15 minutes for SOF" to the Applicant conveyed on 06/13/2019 (see **Appendix 1 Biopharmaceutics Information Request**). In the response submitted on 06/25/2019, the Applicant wishes to retain the acceptance criterion of " $Q = \frac{(b)}{(4)}\%$ in 30 minutes for SOF".

Due to an outstanding response to an information request (see **Appendix 2 Biopharmaceutics Information Request**), the acceptability of the dissolution acceptance criteria cannot be determined at this point.

5. Administration of Drug Product with Soft Food

One packet of 45 mg/200 mg LDV/SOF (120 counts oral granules) were mixed into various soft foods to evaluate the chemical stability and dissolution. The soft foods included chocolate pudding, chocolate syrup, and vanilla ice cream.

Based on the data presented in Table 3 below, the LDV/SOF oral granules are chemically stable in all tested foods for (b) (4) with no significant degradation products detected.

**Table 3: Chemical Stability of LDV/SOF Oral Granules in Various Soft Foods
(Lot JB1789)**

Type of Food ^a	Sofosbuvir		Ledipasvir	
	Assay After (b) (4) in Soft Food (%)	Total Impurities and Degradation Products After (b) (4) in Soft Food (%)	Assay After (b) (4) in Soft Food (%)	Total Impurities and Degradation Products After (b) (4) in Soft Food (%)
Control (no food)	99.6	0	102.2	0.1
Chocolate Syrup	97.8	0	99.9	0.1
Chocolate Pudding	98.7	0	101.0	0.1
Ice Cream	97.5	0	100.4	0.1

a 120-count LDV/SOF oral granules, 45/200 mg mixed into each type of food.

As shown in Table 4 below, the LDV/SOF oral granules (b) (4) % dissolution at 30 minutes after being left in soft food for (b) (4)

**Table 4: Dissolution of LDV/SOF Oral Granules in Various Soft Foods
(Lot JB1789)**

Type of Food ^a	Soft Food Incubation Time (min)	%SOF Released at (b) (4)	%LDV Released at (b) (4)
Control (no food)	N/A	98	99
Chocolate Syrup	(b) (4)	98	99
Chocolate Pudding	(b) (4)	97	99
Ice Cream	(b) (4)	97	100

a 120 count LDV/SOF oral granules, 45/200 mg mixed into each type of food.

The acceptability of these data will be determined after the Applicant responds to the outstanding IR, because the integrity of the taste-masking coat needs to be assured while the drug product is in contact with food.

6. In Vitro Formulation Bridging:

Per the Applicant (Table 5), the formulation used in Phase 2/3 clinical studies (GS-US-337-1116 and GS-US-337-4565) are the same as the proposed to-be-marketed formulation. Also, the Phase 2/3 batches and the to-be-marketed batches have the same manufacturing process and manufacturing site. Therefore, studies to bridge the clinical and to-be-marketed formulations are not needed.

Table 5: Clinical Development History of the proposed LDV/SOF Oral Granules

		Relative Bioavailability 1	Relative Bioavailability 2	Phase 2 /Phase 3	Primary Stability Batches/ Designated Commercial	
(b) (4)						
Unit Dose	Configuration	(b) (4)	(b) (4) packets	(b) (4) packets	(b) (4) packets	
	Ledipasvir Strength (mg)	11.25	11.25	11.25	33.75	45.0
	Sofosbuvir Strength (mg)	50	50	50	150	200
(b) (4)						
Key Formulation Change from Previous Phase						
Oral Granules Lots		EL1502C	EL1601C2	EL1602D1	EL1701D1 EL1702D1 EL1703D1	EL1701D2 EL1702D2 EL1703D2
Key Clinical Studies		GS-US-337-1115 ^b	GS-US-337-2091 ^c	GS-US-337-1116 ^d GS-US-337-4565 ^e	NA	
(b) (4)						

b Relative BA study GS-US-337-1115 compared 240 x LDV/SOF oral granules with a single Harvoni tablet, 90 mg LDV/400 mg SOF (Lot DK1208B1R)
c Relative BA study GS-US-337-2091 compared 240 x LDV/SOF oral granules with a single Harvoni tablet, 90 mg LDV/400 mg SOF (Lot DK1303B1)
d Study GS-US-337-1116: A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination in Adolescents and Children with Chronic HCV-Infection
e Taste assessment study GS-US-337-4565 evaluated LDV/SOF oral granules in various foods

Since the only difference of the proposed 33.75 mg/150 mg and 45 mg/200 mg strengths are the granule counts (e.g., 90 counts and 120 counts of LDV/SOF oral granules in each unit-dose packet) (b) (4), in addition, the dissolution profile data are comparable across the proposed two strengths of LDV/SOF oral granules (Figure 16 above), bridging across the proposed strengths is considered established.

APPENDIX 1

BIOPHARMACEUTICS INFORMATION REQUESTS and RESPONSES

Biopharmaceutics 1st IR (conveyed on 6/13/2019):

Based on the provided dissolution data of all registration batches (EL1701D1, EL1702D1, EL1703D1, EL1701D2, EL1702D2, and EL1703D2), FDA recommends that you implement a sofosbuvir dissolution acceptance criterion of “ $Q = \frac{(9)}{(4)}\%$ in 15 minutes” for the proposed drug product, Harvoni (ledipasvir/sofosbuvir) Oral Granules 33.75 mg/150 mg and 45 mg/200 mg. Update the dissolution acceptance criterion in the drug product release and stability specifications and other relevant sections of your NDA accordingly.

Summary of Applicant’s Response to 1st IR (submitted on 06/25/2019):

[Application 212477 - Sequence 0007 - Response to the Question Number 1 of FDA Email Request for Information dated 2019-06-13](#)

The Applicant proposes to retain the acceptance criterion of “ $Q = \frac{(9)}{(4)}\%$ in 30 minutes” for sofosbuvir per FDA guidance for industry (August 2018): *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances*.

**APPENDIX 2
BIOPHARMACEUTICS INFORMATION REQUESTS**

Biopharmaceutics 2nd IR (conveyed on 07/19/2019):

We have a potential concern about the assurance of the integrity of the taste masking coat at drug product batch release and during the shelf life of your proposed drug product.

- a) Provide an overview of the controls that you have in place to assure the integrity of the taste masking coat at batch release and during the shelf life of your proposed drug product.
- b) Provide a risk mitigation strategy to assure the integrity of the taste masking coat at the batch release and during the shelf life of your proposed drug product. This strategy could include, for example, the following two-phase dissolution test at batch release, during stability studies, and/or to support post approval CMC changes:

USP Apparatus	(b) (4)
Rotation Speed	
Dissolution Media and Volume	
Temperature	
Acceptance Criteria	

- c) If available, provide data to show the integrity of the taste masking coat at pH (b) (4)

The response to this IR is currently pending.



Mei
Ou

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Elsbeth
Chikhale

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BIOPHARMACEUTICS REVIEW ADDENDUM**NDA: 212477 [505(b)(1)]****Drug Product Name/Strength:** Harvoni (ledipasvir/sofosbuvir, LDV/SOF) Oral Pellets; 33.75 mg/150 mg, 45 mg/200 mg**Route of Administration:** Oral**Applicant Name:** Gilead Sciences, Inc.**Proposed Indication:** Treatment of chronic hepatitis C in Pediatric patients 3 years of age and older**Submission Dates:**

02/28/2019 (Original Submission)

06/25/2019 (Applicant's Response to Biopharmaceutics Information Request)

08/01/2019 (Applicant's Response to Biopharmaceutics Information Request)

Primary Reviewer: Mei Ou, Ph.D.**Secondary Reviewers:** Elsbeth Chikhale, Ph.D. and Angelica Dorantes, Ph.D.**Addendum Summary:**

This review is an Addendum to the Original Biopharmaceutics review for NDA 212477 for Harvoni (ledipasvir/sofosbuvir; LDV/SOF) Oral Pellets, 33.75 mg/150 mg, 45 mg/200 mg. The Original Biopharmaceutics review was archived in Panorama on 07/29/2019¹; however, the Biopharmaceutics recommendation was pending at that time because of the outstanding response to the Biopharmaceutics Information Request (IR) dated 07/19/2019².

On 08/01/2019, the Applicant responded the above IR³. In the response, the Applicant states that the FDA's recommended two-stage dissolution method is not necessary because adequate formulation and manufacturing controls were developed, evaluated, and implemented to ensure the integrity of the taste-mask coating at the time of batch release and during the product's shelf life. The Applicant states that the implemented controls will prevent the release/dissolution of SOF in the oral cavity when the product is ingested without chewing (*SOF is the bitter tasting compound in the proposed LDV/SOF oral granules product*).

Additionally, to further prevent the release/dissolution of SOF during its administration, the product's labeling indicates the following; i) "Take HARVONI granules within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste", and (b) (4)

¹ Biopharmaceutics Review for NDA 212477:

<http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88334eae3>

² <\\cdsesub1\evsprod\nda212477\0011\m1\us\112-other-correspondence\comments-advice-req-nda.pdf>

³ <\\cdsesub1\evsprod\nda212477\0011\m1\us\111-information-amendment\quality.pdf>

Reviewer’s Assessment:

The provided information/data for the formulation design, manufacturing controls, and results of the taste assessment and coating integrity tests, fully support the integrity of the taste-mask coating of the SOF pellets, and the information also demonstrates that the coating remains intact during storage. It is noted that the Applicant also proposes to continue testing the primary stability batches of the proposed drug product through their shelf life using the coating integrity test.

Overall, this Reviewer considers that the implemented manufacturing controls and labeling recommendations are adequate to prevent the release/dissolution of SOF in the oral cavity when the product is ingested without chewing. Therefore, based on the satisfactory justification and the overall information provided, this Reviewer agrees with the Applicant’s proposal of no using a two-stage dissolution method to control the quality of the proposed drug product.

The following one-stage dissolution method and acceptance criteria are acceptable for the Quality Control of the proposed drug product at release and on stability:

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 ± 0.5°C
Acceptance Criteria	Q = ^(b) ₍₄₎ % in 30 minutes for both Ledipasvir (LDV) and Sofosbuvir (SOF)

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 212477 for the proposed Harvoni (Ledipasvir/ Sofosbuvir, LDV/SOF) Oral Pellets, 33.75 mg/150 mg, 45 mg/200 mg, is recommended for **APPROVAL**.



Mei
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Angelica
Dorantes

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Erika
Englund

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RECOMMENDATION

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<input checked="" type="checkbox"/> Complete Response

NDA 212477 Assessment # 1

Drug Product Name	ledipasvir and sofosbuvir, LDV and SOF, (GS-5885 and GS-7977)
Dosage Form	Oral Pellets
Strength	33.75 mg /150 mg; 45 mg/200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	Applicant's Responsible Official: Linda Lintao, RAC, Associate Director, Regulatory Affairs

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	2/28/2019	All
eCTD 0002	3/18/2019	Labeling
eCTD 0004	4/18/2019	Quality
eCTD 0005	4/19/2019	Quality
eCTD 0006	4/23/2019	Quality
eCTD 0007	6/25/2019	Quality
eCTD 0010	7/15/2019	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	George Lunn	Balajee Shanmugam
Manufacturing	Nathan Davis	Rapti Madurawe
Microbiology	N/A	N/A
Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	

Application Technical Lead	Erika Englund	
Laboratory (OTR)	N/A	
Environmental	George Lunn	Balajee Shanmugam

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
	II		Refer to referenced NDA 205834 and NDA 204671			
Variable	III (if applicable)		Refer to DP review			

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

Document	Application Number	Description
NDA	204671	Sovaldi (Sofosbuvir tablet)
NDA	205834	Harvoni (Ledipasvir and sofosbuvir tablet)
IND	106739	Sofosbuvir
IND	115268	Ledipasvir/sofosbuvir
IND	108214	Ledipasvir

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology		Refer to DP review		
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical				
Other	NA			

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

From the Product Quality perspective, **NDA 212477** is recommended for a **Complete Response**. The NDA, as amended, has not provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The manufacturing and testing facilities for this NDA are not deemed acceptable and an overall “**Withhold**” recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on July 26, 2019. Therefore, this NDA is recommended for a complete response by the Office of Pharmaceutical Quality (OPQ).

The response to the biopharmaceutics IR, and the evaluation of (b) (4) responses to the observations from the inspection are pending. An addendum to this review will be completed upon receipt and evaluation of these pending items.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed drug product in this NDA is orange oral pellets. Each pellet has a (b) (4) taste masking coat and weighs approximately (b) (4) mg, with 2 mm X 2 mm dimensions. Note that in this NDA and in the corresponding reviews, the product is referred to as mini-tablets, granules and oral pellets. All three of these terms were used to describe the same product. Per the 4/11/2019 e mail communication from Jibril Abdus-Samad in OPPQ, the dosage form name should be **oral pellets**.

The product will be available in two strengths of ledipasvir/sofosbuvir:

- 33.75 mg / 150 mg per packet (90 oral pellets per packet)
- 45 mg / 200 mg per packet (120 oral pellets per packet)

The oral pellets are supplied in unit-dose packets and the entire of contents are mixed with non-acidic food such as pudding, chocolate syrup, mashed potato and ice cream. The stability of the product in these non-acidic foods were evaluated.

A new strength of the conventional tablets is currently under review in NDA 205832 Supplement 29.

Proposed Indication(s) including Intended Patient Population	Treatment of chronic hepatitis C in pediatric patients
Duration of Treatment	12-24 weeks
Maximum Daily Dose	The recommended doses are: 90mg/400 mg per day (adults and pediatric patients >35 kg); 45mg/200 mg per day (pediatric patients 17-35 kg) and 33.75mg/150 mg per day (pediatric patients at least 3 years of age and < 17 kg).
Alternative Methods of Administration	The oral pellets can be taken in the mouth without chewing, or with non-acidic food. The oral pellets can be administered with non-acidic food, such as pudding, chocolate syrup, mashed potato and ice cream.

B. Quality Assessment Overview

Drug Substance: Adequate

This NDA referenced FDA approved NDA 204671 and NDA 205831 for all drug substance information. Some general information, sites of manufacture, specification, and stability data for the drug substance are provided in this NDA. Per an e mail from the drug substance branch chief, Su Tran, Ph.D., a separate drug substance review was not required for this NDA.

Drug Product: Adequate

The drug product consists of oral pellets that provide 33.75/150 mg or 45/200 mg ledipasvir/sofosbuvir in unit-dose heat-sealed pouches made of (b) (4). The pellets are about 2 mm in diameter and have a taste masking coating. The 33.75/150 mg presentation contains 90 pellets and the 45/200 mg presentation contains 120 pellets. Each pellet contains (b) (4) mg ledipasvir and (b) (4) mg sofosbuvir. The excipients are copovidone, (b) (4) lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, (b) (4), and (b) (4). Apart from (b) (4). The excipients are USP/NF compendial and (b) (4).

The drug product specification includes tests for appearance, identity, (b) (4) assay, impurities, content uniformity, dissolution, and microbial limits and is reasonable. The analytical methods are

described in detail and validation reports are provided. Satisfactory batch analyses are provided for 11 batches. The degradants have been identified and the degradants that are not metabolites have been toxicologically qualified.

Satisfactory stability data are provided for 3 batches of each dosage strength stored at 30°C/75% RH for 12 months and 40°C/75% RH for 6 months. One batch was tested in the light cabinet. The pellets are extremely stable and there were no out of specification results and no trends over 12 months at 30°C/75% RH or 6 months at 40°C/75% RH. The pellets should be (b) (4). An expiration dating period of 24 months with the storage statement “Store below 30°C” is reasonable.

The applicant has submitted a claim for a categorical exclusion from an environmental assessment (EA) for both substances in accordance with 21 CFR 25.31(b) and this is acceptable.

Labeling: Adequate

Per the 4/11/19 e-mail from Jibril Abdus-Samad, OPPQ communicated that the correct terminology for the dosage form is “oral pellets”

See labeling review. Recommendations have been conveyed to the OND review team.

Manufacturing: Inadequate

(b) (4)

[Redacted text block]

The applicant has adequately addressed the previously outstanding concerns. However, there are outstanding concerns regarding the packaging process due to the OAI facility status and missing commercial manufacturing equipment.

There are two manufacturing sites for Ledipasvir (b) (4) with demonstrated experience and prior approval for manufacturing (b) (4) so a PAI is not needed and will be sent for DFR. The principal DP site (b) (4) does not have an approved profile or inspectional history for mini-tablets (b) (4) so a PAI was requested. The primary packaging site ((b) (4)) had not been inspected by the FDA so a PAI was also requested.

DS sites and Testing labs are generally consistent with prior applications for similar responsibilities and therefore PAI requests do not appear to be necessary. The applicant has clarified manufacturing responsibilities for certain sites and updated the 356h to be consistent with manufacturer section.

Pre-Approval Inspections were completed at the DP site and the primary packaging site. The outcome of (b) (4) was NAI with an approve recommendation. The outcome of the (b) (4) (primary packaging) is OAI due, in part, to missing commercial manufacturing equipment per the FDA-483. A decision is made without the EIR or a firm response which are both unavailable. Therefore, the recommendation is to withhold and CR-Major, due to OAI at (b) (4) .

Biopharmaceutics: Inadequate

In this NDA, the Biopharmaceutics Review focused on the evaluation of (1) the in vitro dissolution method as a quality control (QC) test and acceptance criteria of the proposed drug product, (2) the in vitro dissolution profiles of the proposed drug product mixed with various soft food, (3) the need for in vitro bridging between the clinical formulation and the to-be-marketed/commercial formulation.

In Vitro Dissolution Testing of the Finished Drug Product:

The Applicant proposed USP Apparatus II (Paddle), 75 rpm, 900 mL of 25 mM potassium phosphate buffer, pH 5.5, containing 1.0% polysorbate 80 and 0.005 mg/mL butylated hydroxytoluene (BHT), 37±0.5°C as the dissolution method for quality control (QC) and stability testing. The proposed dissolution method resulted in rapid dissolution for LDV (i.e., more than (b) (4)% dissolution in 30 minutes) and very rapid dissolution for SOF (i.e., more than (b) (4)% dissolution in (b) (4) minutes) and has limited discriminating ability toward (b) (4) . The possibility of a 2-phase dissolution test that can ensure the integrity of the taste-masking coat is currently being considered. The acceptability of the proposed dissolution method cannot be determined at this point due to an outstanding response to an

information request (IR) regarding a control strategy to ensure the integrity of the taste-masking coat.

Dissolution Acceptance Criteria:

The originally proposed dissolution acceptance criterion for the proposed drug product is “Q=(b) (4) % in 30 minutes for both LDV and SOF”. The acceptability of the dissolution acceptance criterion cannot be determined at this point due to an outstanding response to an IR regarding the control strategy to ensure the integrity of the taste masking coat.

In Vitro Drug Release Profiles in Soft Food:

The stability of the drug product, including the integrity of the taste-masking (b) (4) coating, cannot be determined at this point due to an outstanding response to an IR.

The Need for In Vitro Formulation Bridging:

The Phase 2/3 clinical formulation is the same as the proposed to-be-marketed formulation. The Phase 2/3 drug product batches and the to-be-marketed drug product batches have the same manufacturing process and manufacturing site. Therefore, studies to bridge clinical and to-be-marketed formulations are not needed.

Pending IR:

An addendum will be written to this review once the response to the following information request is received:

We have a potential concern about the assurance of the integrity of the taste masking coat at drug product batch release and during the shelf life of your proposed drug product.

- a) Provide an overview of the controls that you have in place to assure the integrity of the taste masking coat at batch release and during the shelf life of your proposed drug product.
- b) Provide a risk mitigation strategy to assure the integrity of the taste masking coat at the batch release and during the shelf life of your proposed drug product. This strategy could include, for example, the following two-phase dissolution test at batch release, during stability studies, and/or to support post approval CMC changes:

USP Apparatus	(b) (4)
Rotation Speed	

Dissolution Media and Volume	(b) (4)
Temperature	
Acceptance Criteria	
<p>c) If available, provide data to show the integrity of the taste masking coat at pH (b) (4).</p> <p>Note: At this time, the biopharmaceutics review has been approved in Panorama by both the primary and secondary reviewer; however, the archiving function can not be completed. The archived biopharm review will be attached to the IQA as an addendum.</p>	

Microbiology (if applicable): Choose an item.

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	Formulation, raw materials, process parameter, scale/equipment site	L	(b) (4)	Acceptable	

Physical Stability	Formulation	M	(b) (4)	Acceptable	
Content Uniformity	Formulation, raw materials, process parameter	M		Acceptable	
Microbial Limits	Formulation, raw materials	L	The batch analyses show satisfactory microbial test results.	Acceptable	
Dissolution	Formulation, raw materials	M	The final conclusion from the biopharmaceutics review is pending the response to the IR.	Pending	
Patient Use considerations	Formulation	M	Pellets mixed with food showed no significant changes when mixed with food for up to 30 min	Acceptable	

D. List of Deficiencies for Complete Response

- Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

- Drug Substance Deficiencies

None

- Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

During a recent inspection of the [REDACTED] (b) (4) primary packaging facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

6. Biopharmaceutics Deficiencies

Refer to pending IR in biopharmaceutics section. An addendum will be written to this review after evaluation of the IR response.

7. Microbiology Deficiencies

None

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

None

Application Technical Lead Name and Date:

Erika. E. Englund, Ph.D.

7/28/2019



Erika
Englund

Digitally signed by Erika Englund

Date: 7/28/2019 08:46:13PM

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The terminology should be “oral pellets” throughout. The original terminology was “granules” and this was changed to “pellets” per an e-mail from OPPQ 4/11/19. See below for specific recommendations for the Package Insert and the container and carton labels. This review applies to the labeling supplied in the Amendment of 7/10/19.

2.0 PATIENT LABELING

1. Package Insert

The terminology should be oral pellets throughout. The original terminology was “granules” and this was changed to “pellets” per an e-mail from OPPQ 4/11/19.

(a) “Highlights” Section (21CFR 201.57(a))

-----DOSAGE FORMS AND STRENGTHS-----

HARVONI® (ledipasvir and sofosbuvir) oral granules

Oral Granules: 45 mg/200 mg and 33.75 mg/150 mg of ledipasvir and sofosbuvir, respectively

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	HARVONI® (ledipasvir and sofosbuvir)	Adequate
Dosage form, route of administration	oral granules	Should be oral pellets. The original terminology was "granules" and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.
Controlled drug substance symbol (if applicable)	NA	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths and salt equivalency statement	Oral Granules: 45 mg/200 mg and 33.75 mg/150 mg of ledipasvir and sofosbuvir, respectively	Should be oral pellets. The original terminology was "granules" and this was changed to "pellets" per an e-mail from OPPQ 4/11/19. Otherwise acceptable

(b) "Full Prescribing Information" Section

#2: Section 2 Dosage and Administration (21 CFR 201.57(c)(12))

Table 2 Dosing for Pediatric Patients 3 Years (b) (4)
Using HARVONI Tablets or Oral Granules

Body Weight (kg)	Dosing of HARVONI Tablets or Oral Granules	Ledipasvir/Sofosbuvir Daily Dose
at least 35	one 90/400 mg tablet once daily or two 45/200 mg tablets once daily or two 45/200 mg packets of granules once daily	90/400 mg/day
17 to less than 35	one 45/200 mg tablet once daily or	45/200 mg/day

	one 45/200 mg packet of granules once daily	
less than 17	one 33.75/150 mg packet of granules once daily	33.75/150 mg/day

(b) (4) Do not chew HARVONI granules. If HARVONI granules are administered with food, sprinkle the granules on one or more spoonfuls of non-acidic soft food (b) (4) at or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, mashed potato, and ice cream. Take HARVONI granules within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste.

Item	Information Provided in NDA	Reviewer's Assessment
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4) Do not chew HARVONI granules. If HARVONI granules are administered with food, sprinkle the granules on one or more spoonfuls of non-acidic soft food (b) (4) at or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, mashed potato, and ice cream. Take HARVONI granules within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste.	Chocolate pudding was the pudding tested in the NDA but the term "pudding" is reasonable.. Should be oral pellets. The original terminology was "granules" and this was changed to "pellets" per an e-mail from OPPQ 4/11/19. OPPQ recommended creating a separate section 2.x Preparation and Administration and that has been done in the most recent label.

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

- 45/200 mg Granules: orange granules in unit-dose packets. Each packet contains 45 mg ledipasvir and 200 mg sofosbuvir.
- 33.75/150 mg Granules: orange granules in unit-dose packets. Each packet contains 33.75 mg ledipasvir and 150 mg sofosbuvir.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Granules	Should be oral pellets. The original terminology was "granules" and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.
Strengths: in metric system and salt equivalency statement	33.75 mg ledipasvir and 150 mg sofosbuvir and 45 mg ledipasvir and 200 mg sofosbuvir	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. Include "functional score", if present.	orange granules in unit-dose packets	Adequate but should be pellets. The original terminology was "granules" and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.

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

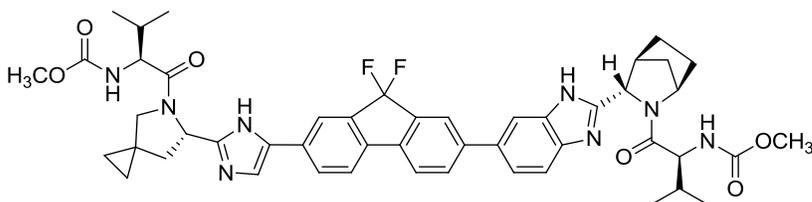
Granules

HARVONI granules are for oral administration, supplied as small, orange granules in unit-dose packets. Each unit-dose of HARVONI oral granule contain either 45 mg ledipasvir and 200 mg sofosbuvir or 33.75 mg ledipasvir and 150 mg sofosbuvir and the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hypromellose, talc, titanium dioxide, polyethylene glycol, iron oxide yellow, iron oxide red, amino-methacrylate copolymer.

Ledipasvir: The IUPAC name for ledipasvir is Methyl [(2S)-1-{{(6S)-6-[5-(9,9-difluoro-7-{2-[(1R,3S,4S)-2-{{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl]-

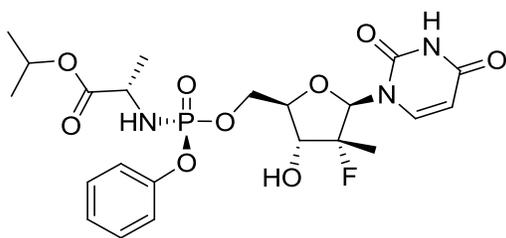
2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl]-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate.

It has a molecular formula of C₄₉H₅₄F₂N₈O₆ and a molecular weight of 889.00. It has the following structural formula:



Ledipasvir is practically insoluble (less than 0.1 mg/mL) across the pH range of 3.0–7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL).

Sofosbuvir: The IUPAC name for sofosbuvir is (S)-Isopropyl 2-((S)-(((2*R*,3*R*,4*R*,5*R*)-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 C₂₂H₂₉FN₃O₉P 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°C and is slightly soluble in water.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Harvoni granules	Should be HARVONI pellets
Dosage form and route of administration	granules are for oral administration	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each unit-dose of HARVONI oral granule contain either 45 mg ledipasvir and 200 mg sofosbuvir or 33.75 mg ledipasvir and 150 mg sofosbuvir	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	amino-methacrylate copolymer, colloidal silicon dioxide, copovidone, croscarmellose sodium, hypromellose, lactose monohydrate, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.	Adequate
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	Present	Adequate
Chemical name, structural formula, molecular weight	Present	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Ledipasvir is practically insoluble (less than 0.1 mg/mL) across the pH range of 3.0–7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL). 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°C and is slightly soluble in water.	Adequate

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

Tablets

HARVONI tablets 90 mg/400 mg are orange, diamond-shaped, film-coated, debossed with “GSI” on one side and “7985” on the other side of the tablet. Each bottle contains 28 tablets (NDC 61958-1801-1), a silica gel desiccant and polyester coil, and is closed with a child-resistant closure.

HARVONI tablets, 45 mg/200 mg, are white, capsule-shaped, film-coated, debossed with “GSI” on one side and “HRV” on the other side of the tablet. Each bottle contains 28 tablets (NDC 61958-1803-1), a silica gel desiccant and polyester coil, and is closed with a child-resistant closure.

- Store at room temperature below 30 °C (86 °F).
- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

Oral Granules

HARVONI granules, 45/200 mg, are orange granules supplied as unit-dose packets in cartons. Each carton contains 28 packets (NDC 61958-1804-1).

HARVONI granules, 33.75/150 mg, are orange granules supplied as unit-dose packets in cartons. Each carton contains 28 packets (NDC 61958-1805-1).

- Store (b) (4) below 30 °C (86 °F).
- Do not use if carton tamper-evident seal or packet seal is broken or damaged.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	HARVONI granules, 45/200 mg HARVONI granules, 33.75/150 mg	Adequate but should be pellets. The original terminology was "granules" and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.
Available units (e.g., bottles of 100 tablets). Include child-resistant closure, induction seal, coil, and desiccant as appropriate.	unit-dose packets in cartons. Each carton contains 28 packets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Include "functional score", if present.	orange granules	Should be orange pellets. The original terminology was "granules" and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.
Special handling (e.g., protect from light, do not freeze)	Do not use if carton tamper-evident seal or packet seal is broken or damaged	Adequate
Storage conditions	Store (b) (4) below 30 °C (86 °F).	Change to "Store below 30 °C (86 °F)" to conform to carton.

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

Manufactured and distributed by:

Gilead Sciences, Inc.

Foster City, CA 94404

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Gilead Sciences, Inc. Foster City, CA 94404	Adequate

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

The following recommendations will be made to the OND review team.

“Granules” should be changed to “pellets” throughout per an e-mail from OPPQ 4/11/19.

Section 16. Change to “Store below 30 °C (86 °F)” to conform to carton.

3.0 CARTON AND CONTAINER LABELING

1) Immediate Container Label



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Harvoni® (ledipasvir/sofosbuvir) oral granules	Adequate but should be oral pellets. The original terminology was “granules” and this was changed to “pellets” per an e-mail from OPPQ 4/11/19.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) and salt equivalency statement (space permitting)	33.75 mg/150 mg [or 45 mg/200 mg]	OPPQ recommends “33.75 mg/150 mg per packet” or “45 mg/200 mg per packet” (e-mail of 4/11/19)
Route of administration 21.CFR 201.100(b)(3))	oral	Adequate
Net contents* (21 CFR 201.51(a))	33.75 mg/150 mg [or 45 mg/200 mg]	OPPQ recommends “33.75 mg/150 mg per packet” or “45 mg/200 mg per packet” (e-mail of 4/11/19)
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not present	Acceptable for an oral product
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Not present	Should be added
Storage (not required)	Not present	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Not present	Should be added

Bar Code per 21 CFR 201.25(c)(2)***	Not present	Should be added
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured for: Gilead Sciences, Inc.	Adequate
Others	Fold at dotted line and tear at cut or use scissors where indicated	Defer to DMEPA

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

2) Carton Labeling



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Harvoni [®] (ledipasvir/sofosbuvir) oral granules	Adequate but should be oral pellets. The original terminology was “granules” and this was changed to “pellets” per an e-mail from OPPQ 4/11/19.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2)) and salt equivalency statement	33.75 mg/150 mg or 45mg/200 mg	OPPQ recommends “33.75 mg/150 mg per packet” or “45 mg/200 mg per packet” (e-mail of 4/11/19)
Net contents (21 CFR 201.51(a))	Contains: 28 packets of oral granules Each packet of oral granules contains 33.75 mg of ledipasvir and 150 mg of sofosbuvir.	Adequate but should be oral pellets. The original terminology was “granules” and this was changed to “pellets” per an e-mail from OPPQ 4/11/19.
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][201.10(a), 21CFR201.100(d)(2)]	Not present	Acceptable for an oral product
Sterility Information (if applicable)	NA	
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present	Adequate

Storage Conditions	Store below 30 °C (86 °F).	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 611958-1805-1	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Present	Adequate
Name of manufacturer/distributor	Manufactured for: Gilead Sciences, Inc. Foster City, CA 94404	Adequate
"See package insert for dosage information" (21 CFR 201.55)	See package insert for dosage and administration.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	KEEP OUT OF THE REACH OF CHILDREN	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Oral	Adequate

Recommendations for Harvoni pellets from the CMC point of view

The terminology should be oral pellets throughout. The original terminology was "granules" and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.

Package insert

Section 16. Change to "Store below 30 °C (86 °F)" to conform to carton.

Foil pouch

OPPQ recommends "33.75 mg/150 mg per packet" or "45 mg/200 mg per packet"
Rx Only, NDC number, and bar code should be added
Defer to DMEPA regarding the statement "Fold at dotted line and tear at cut or use
scissors where indicated" on the pouch

Carton

No changes recommended

Assessment of Carton and Container Labeling: The following recommendations will be made to the OND review team.

Package insert

Section 16. Change to “Store below 30 °C (86 °F)” to conform to carton.

Foil pouch

OPPQ recommends “33.75 mg/150 mg per packet” or “45 mg/200 mg per packet”

Rx Only, NDC number, and bar code should be added

Defer to DMEPA regarding the statement “Fold at dotted line and tear at cut or use scissors where indicated” on the pouch

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Generally the labeling is adequate. Some recommendations have been made to the OND review team.

Primary Labeling Assessor Name and Date: George Lunn, Ph.D., 7/12/19

Secondary Assessor Name and Date: Stephen Miller, Ph.D., 7/12/19



George
Lunn

Digitally signed by George Lunn
Date: 7/16/2019 08:41:44AM
GUID: 508da72000029f40833369b0a181e8b3



Stephen
Miller

Digitally signed by Stephen Miller
Date: 7/16/2019 12:20:46PM
GUID: 508da7210002a000609476bbebcd040f0



Erika
Englund

Digitally signed by Erika Englund

Date: 7/28/2019 09:04:25PM

GUID: 51389ea30003450414230afb8c3e8114