CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212480Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 212480
Assessment # 2

Drug Product Name	sofosbuvir (GS-7977)
Dosage Form	Oral Pellets
Strength	150 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 0010	7/9/2019	Quality
eCTD 0013	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

IQA NDA Assessment Guide Reference

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 212480*** *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 21, 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: 400 mg/day (adults and pediatric patients >35 kg); 200 mg/day (17-35 kg) and 150 mg/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: Inadequate

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 approve.

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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BIOPHARMACEUTICS

NDA: 212480 [505(b)(1)]
Drug Product Name/Strength: Sovaldi (sofosbuvir; SOF) Oral Granules, 150 mg and 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)
07/09/2019 (Response to Biopharmaceutics Information Request)
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Elsbeth Chikhale, Ph.D.

EXECUTIVE SUMMARY

The proposed drug product, Sovaldi (sofosbuvir; SOF) Oral Granules, 150 mg and 200 mg, under NDA 212480, is an immediate-release dosage form. Each SOF oral granule has a diameter of approximately 2 mm and has a taste-masking (b) (4) coating. SOF oral granules are packaged into (b) (4) heat-sealed packets. The 150 mg strength contains 60 counts and the 200 mg strength contains 80 counts of SOF oral granules in each unit-dose packet. In the proposed labeling, the recommended dosage in pediatric patients 3 years (b) (4) is 150 mg to 400 mg per day with or without food.

In the current NDA 212480 submissions, the Biopharmaceutics Review focuses on the evaluation of (1) the in vitro dissolution method as a quality control (QC) test and acceptance criterion 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 Product:
The Applicant proposed *USP Apparatus II (Paddle), 75 rpm, 900 mL of 25 mM potassium phosphate buffer, pH 5.5, 37±0.5°C* as the dissolution method for quality control (QC) and stability testing. The proposed dissolution method resulted in very rapid dissolution for SOF (i.e., more than (b) (4)% dissolution in (b) (4)minutes) and has limited discriminating ability toward (b) (4) of oral granules. 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 the control strategy to ensure the integrity of the taste masking coat.

Dissolution Acceptance Criterion:
The originally proposed dissolution acceptance criterion of "Q= (b) (4)% in 30 minutes for SOF" is permissive and not acceptable. The acceptability of the dissolution acceptance criterion cannot be determined at this point due to an outstanding response to an IR.

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 to-be-marked formulation has silicon dioxide while the Phase 1/2 clinical formulation has no silicon dioxide. Both the clinical formulations and to-be-marketed formulations have very rapid and similar dissolution profiles. Therefore, a bridge is established between the clinical Phase 1/2 formulation and the to-be marketed formulation.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 212480 for the proposed Sovaldi (Sofosbuvir; SOF) Oral Granules, 150 mg and 200 mg, is **PENDING** at this point due to an outstanding response to an IR.

BIOPHARMACEUTICS REVIEW

1. Drug Substance Solubility and Permeability

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

The Applicant stated that the drug substance sofosbuvir (SOF), a weak acid with a pK_a of 9.3, is a BCS class 3 compound (high solubility and low permeability). The sink conditions of SOF can be achieved across the pH range of 2 to 6.8 (Table 1).

Table 1: Solubility of Sofosbuvir (SOF) at 37ºC across in aqueous media

pH (Media)	Solubility (mg/mL)[1]	Sink Factor[2]	
		150 mg Dose	200 mg Dose
1.2 (HCl)	1.3[3]	7.9	5.9
2.0 (HCl)	2.0	12.0	9.0
4.5 (Acetate Buffer)	2.1	12.6	9.5
5.5 (Phosphate Buffer)	2.3	13.8	10.4
6.8 (Phosphate Buffer)	1.9	11.4	8.6
5.0 (FeSSIF)[4]	1.8	10.8	8.1
6.5 (FaSSIF)[5]	2.1	12.6	9.5

Note:
[2]Sink factor = Equilibrium Solubility / (Label Claim / 900 mL Dissolution Medium Volume).

(b) (4)

[redacted]

The Applicant provide permeability data of SOF in NDA 212477 and 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 $\times 10^{-6}$ cm/s and 4.11 $\times 10^{-6}$ 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 Substance

(b) (4)

[redacted]

(b) (4)

3. In Vitro Dissolution Method

The proposed dissolution method and acceptance criterion 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
Temperature	37ºC
Proposed Acceptance Criteria	Q= (b) (4)% in 30 min

Because SOF is bitter tasting and requires taste-masking and an age-appropriate formulation, a variety of dissolution methods (e.g., two-stage dissolution methods at various of dissolution media at pH (b) (4) were used to assess the potential of the coating systems for taste-masking in the oral cavity and sufficient SOF release in the stomach. (b) (4) is selected as taste-masking coating (b) (4)/agent. The Applicant claims (b) (4) . The target weight gain of (b) (4) is (b) (4) range). The Applicant will be asked to provide dissolution data to show the stability of the coating at pH (b) (4)

The complete dissolution method development is submitted in report PDM-3086. The following dissolution parameters were evaluated during the dissolution method development:

(b) (4)

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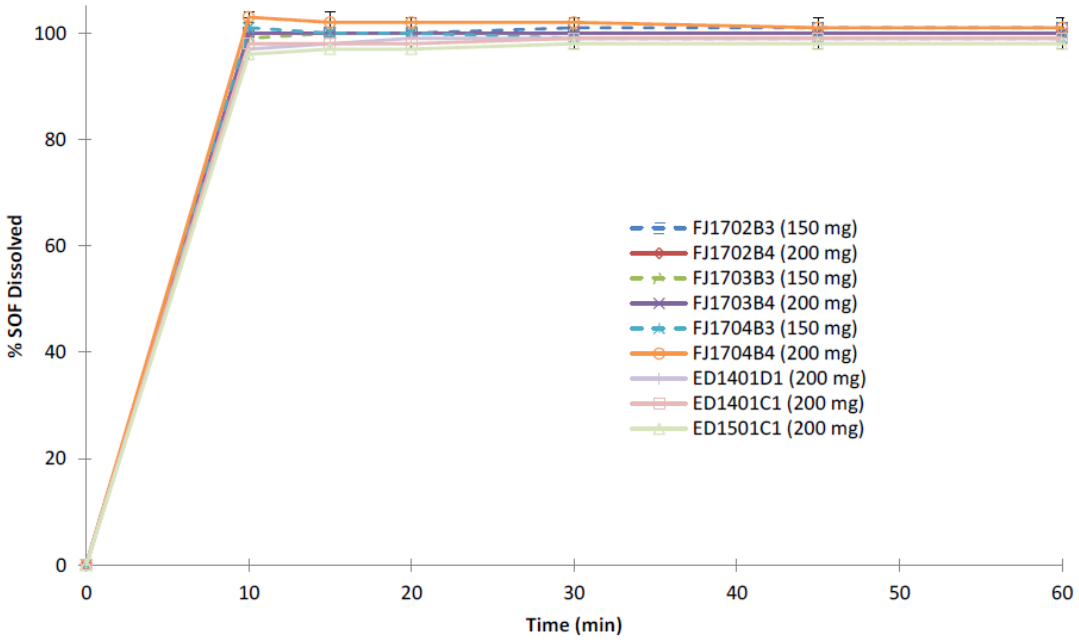
(b) (4)

4. Dissolution Data and Acceptance Criterion

Dissolution data profiles of clinical batches (200 mg, Lots ED1401D1, ED1501C1, ED1401C1) and primary registration batches (150 mg, Lots FJ1702B3, FJ1703B3, and FJ1704B3; 200 mg, FJ1702B4, FJ1703B4, and FJ1704B4) are presented in Figure 9 below. The proposed drug product show very rapid dissolution (> (b) (4) % in (b) (4) minutes).

Figure 9: Dissolution of Sofosbuvir from Clinical and Primary Stability Batches



Note: the dissolution condition is: USP Apparatus 2 Paddle, 75 rpm, 900 mL of 25 mM Potassium Phosphate buffer, pH 5.5 at 37°C. Mean profiles (n = 6 for ED1401D1, ED1501C1, ED1401C1; n = 12 all others).

The dissolution data of six registration batches (150 mg, Lots FJ1702B3, FJ1703B3, and FJ1704B3; 200 mg, FJ1702B4, FJ1703B4, and FJ1704B4) in various stability conditions (sampling time at 10, 15, 20, 30, 45 and 60 minutes, n=12 at initial and n=6 at 3, 6 and 12 months) showed that SOF has complete dissolution (100%) in (b) (4) minutes when stored up to 12 months at long-term stability condition (30ºC/75%RH).

The proposed dissolution acceptance criterion of "*Q=* (b) (4) *% in 30 minutes for SOF*" is permissive and not acceptable. The data-driven acceptance criterion of "*Q=* (b) (4) *% in 15 minutes for SOF*" was recommended on 06/13/2019. (*see* ***Appendix 1*** *Biopharmaceutics Information Request*). In the response submitted on 07/09/2019, the Applicant wishes to retain the acceptance criterion of "*Q=* (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 criterion cannot be determined at this point.

5. Administration of Drug Product with Soft Food:

One packet of 200 mg SOF oral granules was mixed into various soft foods to evaluate the chemical stability and dissolution. The soft foods included chocolate pudding, chocolate syrup, and ice cream and the dwell time prior to analysis was (b) (4).

Based on the data presented in Table 2 below, SOF oral granules are chemically stable in all tested foods for (b) (4) with no SOF-related degradation products detected.

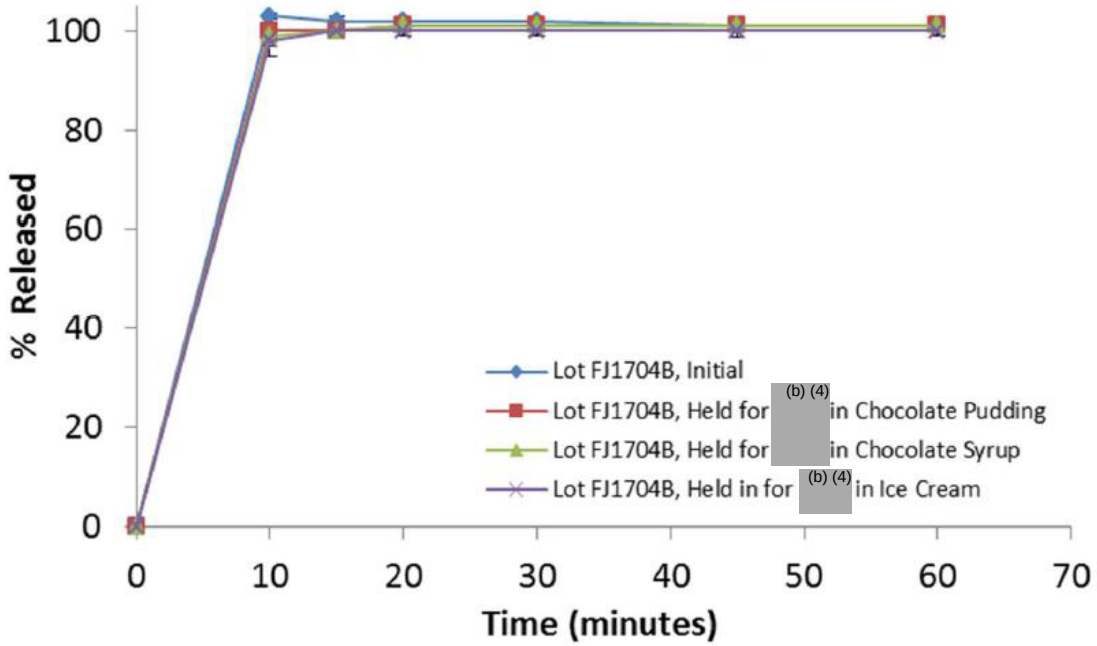
Table 3: Chemical Stability of SOF in SOF Oral Granules from Lot FJ1704B Stored in Non-Acidic Soft Foods at Room Temperature

Food Type	Hold Time (hours)	SOFAssay (%)	SOF Total Degradation Products (%)
Control	(b) (4)	100.8	0.0
Chocolate Pudding		100.8	0.0
Chocolate Syrup		100.5	0.0
Ice Cream		100.3	0.0

SOF oral granule dose was 200 mg (b) (4)

As shown in Figure 10 below, SOF dissolution was not impacted by the tested food vehicles (b) (4)% dissolution in 10 minutes).

Figure 10: Dissolution of SOF in SOF Oral Granules from Lot FJ1704B Stored in Non-Acidic Soft Foods at Room Temperature



Note: the dissolution condition is: USP Apparatus 2 Paddle, 75 rpm, 900 mL of 25 mM Potassium Phosphate buffer, pH 5.5 at 37°C. SOF oral granule dose tested during dissolution was 200 mg.

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:

Table 4 below shows that the to-be-marked formulation has silicon dioxide while the Phase 1/2 clinical formulation has no silicon dioxide. The dissolution data presented in

above Figure 9 show that the clinical batches (200 mg, Lots ED1401D1, ED1501C1, ED1401C1) and primary registration batches (150 mg, Lots FJ1702B3, FJ1703B3, and FJ1704B3; 200 mg, FJ1702B4, FJ1703B4, and FJ1704B4) have very rapid and similar dissolution profiles, establishing a bridge between the Phase 1/2 clinical formulation and the to-be-marketed formulation.

Table 4: Clinical Development History of the Sofosbuvir Oral Granule Formulation

Oral Granule Description	**Phase 1 and 2**			**Primary Stability Batches**
	White granules			**White to off-white granules**
	(b) (4)			(b) (4)
Unit-Dose Strength (mg)	50			150 and 200
Drug Product Description	(b) (4)			(b) (4) (b) (4) packet containing oral granules with unit-dose of 150 mg or 200 mg of SOF
Key Formulation or Packaging Changes from Previous Phase	Initial formulation			• Addition of silicon dioxide (b) (4) (b) (4) (b) (4)
Drug Product Lot Numbers	ED1401C1	ED1401D1	ED1501C1	150 mg: FJ1702B3, FJ1703B3, FJ1704B3 200 mg: FJ1702B4, FJ1703B4, FJ1704B4
Clinical Studies	GS-US-334-1111 GS-US334-1112	GS-US-334-1865	GS-US-334-1112 GS-US-337-4565	N/A
(b) (4)				

Since the only difference of the proposed 150 mg and 200 mg strengths are the granule counts (e.g., 60 counts and 80 counts of SOF oral granules in each unit-dose packet) (b) (4), in addition, the dissolution profile data are comparable across the proposed two strengths of SOF oral granules (Figure 9 above), bridging across the proposed strengths is considered established.

APPENDIX 1
BIOPHARMACEUTICS INFORMATION REQUESTS and RESPONSES

Biopharmaceutics 1st IR (conveyed on 06/13/2019):

Based on the provided dissolution data of all registration batches (FJ1702B3, FJ1703B3, FJ1704B3, FJ1702B4, FJ1703B4, and FJ1704B4), FDA recommends that you implement a dissolution acceptance criterion of "Q=(b) (4)% in 15 minutes" for the proposed Sovaldi (sofosbuvir) Oral Granules, 150 mg and 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 07/09/2019):

Application 212480 - Sequence 0010 - Response to FDA CMC Information Request dated 2019-06-13 received 2019-07-01

The Applicant proposes to retain the acceptance criterion of "Q (b) (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

Digitally signed by Elsbeth Chikhale
Date: 7/27/2019 09:03:47PM
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BIOPHARMACEUTICS REVIEW ADDENDUM

NDA: 212480 [505(b)(1)]
Drug Product Name/Strength: Sovaldi (sofosbuvir; SOF) Oral Pellets, 150 mg and 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)
07/09/2019 (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 212480 for Sovaldi (sofosbuvir; SOF) Oral Pellets, 150 mg and 200 mg. The Original Biopharmaceutics review was archived in Panorama on 07/29/2019[1]; however, the Biopharmaceutics recommendation was pending at that time because of the outstanding response to the Biopharmaceutics Information Request (IR) dated 07/19/2019[2].

On 08/01/2019, the Applicant responded to the above IR[3]. 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 of the drug product at the time of batch release and during its 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 a bitter tasting compound in the proposed oral granules product*).

Additionally, to further prevent the release/dissolution of SOF during its administration, the product's labeling indicates the following; i) "Take SOVALDI (b) (4) 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 212480:
http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88334eb17
[2] \\cdsesub1\evsprod\nda212480\0013\m1\us\112-other-correspondence\comments-advice-req-nda.pdf
[3] \\cdsesub1\evsprod\nda212480\0013\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 criterion 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
Temperature	37 ± 0.5°C
Acceptance Criterion	Q = (b) (4)% in 30 minutes

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 212480 for the proposed Sovaldi (sofosbuvir; SOF) Oral Pellets, 150 mg and 200 mg, is recommended for **APROVAL.**

Mei Ou

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Angelica Dorantes

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 212480
Assessment # 1

Drug Product Name	sofosbuvir (GS-7977)
Dosage Form	Oral Pellets
Strength	150 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 0003	4/01/2019	Quality
eCTD 0004	4/12/2019	Quality
eCTD 0005	4/18/2019	Quality
eCTD 0006	4/19/2019	Quality
eCTD 0007	4/23/2019	General Correspondence
eCTD 0010	7/9/2019	Quality
eCTD 0012	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

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
	II		Refer to referenced NDA 204671			
Variable	III		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

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 212480*** *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 white oral pellets. Each pellet has a taste masking coat and contains (b) (4) mg of sofosbuvir with 2mm X 2mm 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:

- 150 mg per packet (60 pellets per packet)
- 200 mg per packet (80 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.

Note that a new strength of the tablets is also currently under review as NDA 204671 Supplement 14.

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: 400 mg/day (adults and pediatric patients >35 kg); 200 mg/day (17-35 kg) and 150 mg/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 NDA 204671 for all drug substance information. Some general information, sites of manufacture, specification, and stability data for the drug substances 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 150 mg or 200 mg sofosbuvir in unit-dose heat-sealed packets. Each pellet contains (b) (4) mg sofosbuvir, is about 2 mm in diameter, and has a taste masking coating. The 150 mg presentation contains 60 pellets and the 200 mg presentation contains 80 pellets. The inactive ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, (b) (4), colloidal silicon dioxide, and sodium stearyl fumarate. In addition, there is (b) (4) taste-masking coat (b) (4) The excipients are USP/NF compendial or comprised of USP/NF compendial materials. Pellets are mixed with food (b) (4) pudding, chocolate syrup, ice cream, and mashed potato) for consumption and are reasonably stable in that matrix.

The specification includes tests for appearance, identity, (b) (4) assay, degradants, dose uniformity, dissolution, and microbial limits. Generally, the specification is conventional for this type of product and is similar to the specification for the adult 400 mg tablets. The assay limit of (b) (4) % through expiration is tighter than the more usual (b) (4) %. Tests for appearance, identity, uniformity, and microbial limits are reasonable. Degradants were observed for a batch made with an

elevated level of (b) (4)%). The applicant agreed to reduce the (b) (4) (b) (4) limit to (b) (4)%. The degradants are toxicologically qualified or are metabolites that do not require qualification. The limits for the specified degradants are higher than those specified for the original 400 mg tablets. A justification of these higher limits was provided by the applicant and accepted after some internal discussion. The analytical methods are comprehensively described, and full validation reports are provided. Satisfactory batch analyses are provided for 9 batches.

The container-closure system is a (b) (4) pouch made of (b) (4). The size is such that it can contain 60 or 80 pellets. The pouch material conforms to the relevant 21 CFR regulations.

Less than 12 months of long-term stability data were accepted in the initial submission because this product fulfills an unmet pediatric need. Eventually 12 months of long-term (30°C/75% RH) and 6 months of accelerated (40°C/75% RH) stability data were provided for 6 batches. A batch was tested in the light chamber. There are no out of specification results and no significant trends. No degradants are observed.

The applicant claims an expiration dating period of 24 months with the storage statement “Store below 30°C”. This is reasonable.

The applicant submitted a claim for a categorical exclusion from an environmental assessment in accordance with 21 CFR 25.31(b). 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. Labeling recommendations have been conveyed to the OND review team.

Manufacturing: Inadequate

The applicant plans to manufacture using (b) (4)

The applicant has addressed all of the previously outstanding concerns. However, the packaging process remains inadequate as equipment is missing from the packaging site.

Most of the facilities listed in the submission, including all DS sites and testing facilities, are approved for the adult sofosbuvir formulation, have prior experience with the proposed responsibilities and have a history of approvals based on DFR. Two Pre-Approval Inspections were requested for the primary DP manufacturing site and the primary DP packaging site. The outcome of the PAI at the DP manufacturing site was NAI and therefore acceptable. The outcome at the packaging site is initially OAI and an expedited review without access to EIR or firm response has been performed. The outcome of the expedited review is to concur with the initial recommendation of OAI. Therefore, the overall recommendation is withhold CR.

Biopharmaceutics: Inadequate

In the current NDA 212480 submissions, the Biopharmaceutics Review focuses on the evaluation of (1) the in vitro dissolution method as a quality control (QC) test and acceptance criterion 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 Product:
The Applicant proposed *USP Apparatus II (Paddle), 75 rpm, 900 mL of 25 mM potassium phosphate buffer, pH 5.5, 37±0.5°C* as the dissolution method for quality control (QC) and stability testing. The proposed dissolution method resulted in 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 the control strategy to ensure the integrity of the taste masking coat.

Dissolution Acceptance Criterion:
The originally proposed dissolution acceptance criterion of "Q= (b) (4)% in 30 minutes for SOF" is permissive. The acceptability of the dissolution acceptance criterion cannot be determined at this point due to an outstanding response to an IR.

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 to-be-marked formulation has silicon dioxide while the Phase 1/2 clinical formulation has no silicon dioxide. Both the clinical formulations and to-be-marketed formulations have very rapid and similar dissolution profiles. Therefore, a bridge is established between the clinical Phase 1/2 formulation and the to-be marketed formulation.

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	
Temperature	
Acceptance Criteria	

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

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.

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		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

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

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

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

(a) "Highlights" Section (21CFR 201.57(a))

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

SOVALDI® (sofosbuvir) tablets, for oral use
SOVALDI® (sofosbuvir) oral (b) (4)

- Tablets: 400 mg and 200 mg of sofosbuvir.
- Oral (b) (4) 200 mg and 150 mg of sofosbuvir.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	SOVALDI® (sofosbuvir) oral (b) (4)	Adequate But should be oral pellets. The original terminology was " (b) (4) and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.
Dosage form, route of administration	Oral (b) (4) 200 mg and 150 mg of sofosbuvir	Adequate But should be oral pellets. The original terminology was " (b) (4) and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths and salt equivalency statement	•Tablets: 400 mg and 200 mg of sofosbuvir. •Oral (b) (4) 200 mg and 150 mg of sofosbuvir.	Adequate But should be oral pellets. The original terminology was " (b) (4) and this was changed to "pellets" per an e-mail from OPPQ 4/11/19. Salt equivalency statement not required

(b) "Full Prescribing Information" Section

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

(b) (4)

(b) (4)

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

Body Weight (kg)	Dosing of SOVALDI Tablets or Oral (b) (4)	Sofosbuvir Daily Dose
at least 35	one 400 mg tablet once daily or two 200 mg tablets once daily or two 200 mg packets of (b) (4) once daily	400 mg/day
17 to less than 35	one 200 mg tablet once daily or one 200 mg packet of (b) (4) once daily	200 mg/day
less than 17	one 150 mg packet of (b) (4) once daily	150 mg/day

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Do not chew SOVALDI (b) (4) If SOVALDI (b) (4) are administered with food, sprinkle the (b) (4) 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 SOVALDI (b) (4) within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste.	Generally adequate. Data for mashed potato in the Amendment of 4/19/19. Data for other foods in the original NDA. (b) (4) pudding was the pudding tested in the NDA but it is reasonable to include other types of pudding in the examples. Should be oral pellets. The original terminology was "(b) (4) 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 this has been done.

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

SOVALDI is available as tablets or (b) (4) for oral use. Each dosage form is available
in two dose strengths.

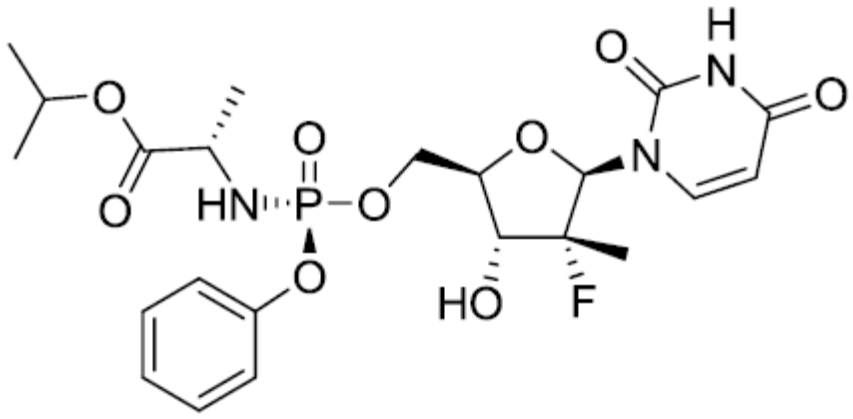
- 400 mg Tablets: 400 mg sofosbuvir: yellow, capsule-shaped, film-coated tablet debossed with "GSI" on one side and "7977" on the other side.
- 200 mg Tablets: 200 mg sofosbuvir: yellow, oval-shaped, film-coated tablet debossed with "GSI" on one side and "200" on the other side.
- 200 mg (b) (4) 200 mg sofosbuvir: white to off-white (b) (4) in unit-dose packets.

• 150 mg [redacted] 150 mg sofosbuvir: white to off-white [redacted] in unit-dose packets

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	200 mg and 400 mg tablets; 200 mg and 150 mg oral [redacted]	Adequate But should be oral pellets. The original terminology was "[redacted] and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.
Strengths: in metric system and salt equivalency statement	150 mg, 200 mg, 400 mg	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.	yellow, capsule-shaped, film-coated tablet; yellow, oval-shaped, film-coated tablet; white to off-white [redacted]	Adequate but should be oral pellets. The original terminology was "[redacted] and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.

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

SOVALDI (sofosbuvir) is a nucleotide analog inhibitor of HCV NS5B polymerase. 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$C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



Sofosbuvir is a white to off-white crystalline solid with a solubility of ≥ 2 mg/mL across

the pH range of 2-7.7 at 37◦C and is slightly soluble in water.
SOVALDI tablets, 200 mg or 400 mg, are for oral administration. Each tablet contains
200 mg or 400 mg of sofosbuvir. The tablets include the following inactive ingredients:
colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and
microcrystalline cellulose. The tablets are film-coated with a coating material containing
the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, titanium
dioxide, and yellow iron oxide.
SOVALDI (b) (4) 150 mg or 200 mg, are for oral administration, supplied as white to off-white (b) (4) in unit-dose packets. Each unit-dose packet contains 150 mg or 200 mg of sofosbuvir. The (b) (4) include the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, colloidal silicon dioxide, sodium stearyl fumarate, hypromellose, polyethylene glycol, amino methacrylate copolymer, talc, stearic acid, silicon dioxide, and sodium lauryl sulfate.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	SOVALDI (b) (4) 150 mg or 200 mg; sofosbuvir	SOVALDI (b) (4) should be SOVALDI (sofosbuvir) pellets
Dosage form and route of administration	(b) (4) oral	Adequate but should be oral pellets. The original terminology was " (b) (4) and this was changed to "pellets" per an e-mail from OPPQ 4/11/19.
Active moiety expression of strength with equivalence statement for salt (if applicable)	150 mg and 200 mg	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Present	In the most recent label the inactive ingredients have been placed in alphabetical order
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	nucleotide analog inhibitor of HCV NS5B polymerase	Adequate
Chemical name, structural formula, molecular weight	Present	Adequate. The (b) (4) from the sofosbuvir chemical name has been removed in the most recent label
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	white to off-white crystalline solid with a solubility of ≥ 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
SOVALDI tablets, 400 mg, are yellow, capsule-shaped, film-coated tablets containing
400 mg sofosbuvir debossed with "GSI" on one side and "7977" on the other side. Each

bottle contains 28 tablets (NDC 61958-1501-1), a silica gel desiccant and polyester coil
with a child-resistant closure.
SOVALDI tablets, 200 mg, are yellow, oval-shaped, film-coated tablets containing 200
mg sofosbuvir debossed with “GSI” on one side and “200” on the other side. Each bottle
contains 28 tablets (NDC 61958-1503-1) and a polyester coil with a child-resistant
closure.
Store (b) (4) below 30 °C (86 °F).
- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing

Oral (b) (4)
SOVALDI (b) (4) 150 mg, are white to off-white (b) (4) supplied as unit-dose packets in cartons. Each carton contains 28 packets (NDC 61958-1504-1).
SOVALDI (b) (4) 200 mg, are white to off-white (b) (4) supplied as unit-dose packets in cartons. Each carton contains 28 packets (NDC 61958-1505-1).
- Store (b) (4) below 30 °C (86 °F).
- Do not use if carton tamper-evident or packet seal is broken or damaged.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	SOVALDI (b) (4) 150 mg and 200 mg	Adequate but should be oral pellets. The original terminology was " (b) (4) 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	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Include "functional score", if present.	white to off-white (b) (4)	Adequate but should be oral pellets. The original terminology was " (b) (4) 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 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)."

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

2.0 PATIENT LABELING

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

Adequate. The following observations should be conveyed to the clinical review team. The original terminology was " (b) (4) and this was changed to "pellets" per an e-mail from OPPQ 4/11/19. Should be changed to "oral pellets" throughout.

Section 16: Storage conditions for the pellets should be “Store below 30 °C (86 °F)” to conform to carton.

3.0 CARTON AND CONTAINER LABELING

1) Immediate Container Label

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate. The recommendations above should be conveyed to the clinical review team.

Primary Labeling Assessor Name and Date: George Lunn, Ph.D., 5/30/19

Secondary Assessor Name and Date (and Secondary Summary, as needed): Stephen Miller, Ph.D., 6/29/19

George Lunn

Digitally signed by George Lunn
Date: 7/16/2019 08:46:58AM
GUID: 508da72000029f40833369b0a181e8b3

Stephen Miller

Digitally signed by Stephen Miller
Date: 7/28/2019 03:10:22PM
GUID: 508da7210002a000609476bbecd040f0

Erika Englund

Digitally signed by Erika Englund
Date: 7/28/2019 09:04:58PM
GUID: 51389ea30003450414230afb8c3e8114