

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205834Orig1s000

CHEMISTRY REVIEW(S)

NDA 205-834

Ledipasvir and Sofosbuvir Tablets, 90 mg and 400 mg

Gilead Sciences, Inc.

**George Lunn, Ph.D.
Division of Anti-Viral Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	12
C. CC Block	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	13
S DRUG SUBSTANCE [Ledipasvir, Gilead Sciences].....	13
S DRUG SUBSTANCE [Sofosbuvir, Gilead Sciences]	61
P DRUG PRODUCT [Ledipasvir (b) (4)].....	69
P DRUG PRODUCT [Ledipasvir and Sofosbuvir Tablets].....	88
A APPENDICES	132
R REGIONAL INFORMATION	133
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	134
A. Labeling & Package Insert	134
B. Environmental Assessment Or Claim Of Categorical Exclusion	136
III. List Of Deficiencies To Be Communicated.....	136



IV. EES137

Chemistry Review Data Sheet

1. NDA 205-834
2. REVIEW #: 1 - Addendum
3. REVIEW DATE: 26-Sep-2014
4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment

Document Date

10-Feb-2014
27-Feb-2014
04-Mar-2014
25-Mar-2014
25-Apr-2014
02-May-2014
30-Jun-2014
29-Jul-2014
04-Aug-2014

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Gilead Sciences, Inc.
Address: 333 Lakeside Drive
Representative: Foster City, CA 94404
Telephone: 650 574 3000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Ledipasvir and Sofosbuvir Tablets
c) Code Name/#: GS-5885 and GS-7977
d) Chem. Type/Submission Priority:
 • Chem. Type: 1,4
 • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Food Drug and Cosmetic Act 505 (b)(1)

10. PHARMACOL. CATEGORY: Anti-viral (Hepatitis C)

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: Ledipasvir 90 mg and sofosbuvir 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

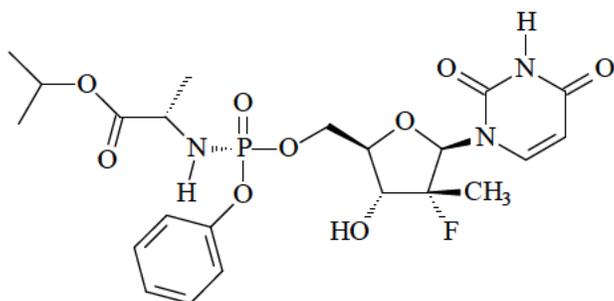
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(b) (4)



Sofosbuvir
 Molecular formula: $C_{22}H_{29}FN_3O_9P$
 Molecular weight: 529.45

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

Chemistry Review Data Sheet

(b) (4)		(b) (4)				
	III		4	Adequate		
	III		4	Adequate		
	III		4	Adequate		
	III		4	Adequate		
	III		4	Adequate		
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	III		4	Adequate		
	III		4	Adequate		
	III		4	Adequate		
	III		4	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

Chemistry Review Data Sheet

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	9/3/14	Rose Xu
Pharm/Tox	N A		
Biopharm	Acceptable	9/26/14	Sandra Suarez
LNC	NA		
Methods Validation	Pending (report not required before approval)		MV request submitted 2/26/14
OPDRA	NA		
EA	Categorical exclusion claimed. Claim is accepted.	2/25/14	G. Lunn
Microbiology	Acceptable	3/31/14	Steven P. Donald

The Chemistry Review for NDA 205-834

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. CMC information in the NDA (as amended July 29 and Aug 4, 2014) has been reviewed and found satisfactory, and the labeling has adequate CMC information which will be finalized during team review of labeling. The Quality Micro reviewer, Steven Donald, indicates that no product quality microbiology deficiencies were identified, and recommends approval. The Biopharm reviewer, Sandra Suarez, has also recommended approval. An Overall Recommendation of Acceptable was made in EES (Sept 3, 2014).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Complete sofosbuvir drug substance information is provided in approved NDA 204-671 and is incorporated in this NDA by reference. Sofosbuvir has a retest period of (b) (4) months at 25 °C/60% RH.

Ledipasvir drug substance is manufactured (b) (4)

The manufacturing process is described at a reasonable level of detail and the controls on the critical steps are acceptable. Laboratory studies have established PARs and the NORs are set within these limits. The proposed starting materials are acceptable. (b) (4)

A reasonable specification that includes tests for appearance, identity, (b) (4) assay, impurities, residual solvents, and elemental impurities is provided. The analytical methods are described at a satisfactory level of detail and have been validated. Satisfactory

Executive Summary Section

batch analyses are provided for 20 batches of the (b) (4) made at (b) (4) facilities on a (b) (4) scale. An acceptable justification of the specification is provided. Generally the specification is conventional and the acceptance criteria are reasonable. The specifications for appearance and (b) (4) are rather broad but acceptable justifications are provided. The impurities are toxicologically qualified and the residual solvents limits are in accord with ICH Q3C. Potential genotoxic impurities are controlled in an acceptable manner. Because the next step (b) (4)

Stability data of up to 24 months at 25°C/60% RH and 6 months at 40°C/75% RH are supplied. There are no out of specification results and no obvious trends although the material is light sensitive. A retest date of (b) (4) months when stored at 25°C is reasonable.

Ledipasvir (b) (4) drug substance is (b) (4)

Up to 12 months of satisfactory stability data obtained at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH are provided (b) (4). The shelf-life of 24 months at up to 25°C is reasonable.

The drug product consists of orange film-coated tablets that contain 400 mg sofosbuvir and 90 mg ledipasvir. The tablets are packaged 28 count in HDPE bottles containing 1 g silica gel desiccant and a polyester fiber coil. The bottles are closed with induction seals and child-resistant closures. An alternate trade dress for tablets for an access program is also described. These tablets are (b) (4)

Ledipasvir (b) (4)

The excipients are of compendial quality except for the film coats which are made of compendial components.

Executive Summary Section

The drug product specification contains tests for appearance, identity, water, assay, impurities, content uniformity, dissolution, and microbial limits (b) (4). A reasonable justification is provided. The analytical methods are described in detail and validation reports are provided. Satisfactory batch analysis data are provided for 15 batches of tablets.

For the acceptability of the dissolution method see the separate Biopharm review.

The presence of crystalline ledipasvir will be controlled using the dissolution test. Eventually an (b) (4) test will be added to the control strategy.

Up to 15 months of satisfactory stability data obtained at 30°C/75% RH are provided for 9 batches. Batches have been manufactured (b) (4). Their stability behavior is no different from other batches although the results of an end to end study are not yet available. An expiration dating period of 24 months when stored at or below 30°C is reasonable.

An Overall Recommendation of Acceptable has been made in EES.

B. Description of How the Drug Product is Intended to be Used

Ledipasvir and sofosbuvir tablets are indicated for the treatment of chronic hepatitis C genotype 1 infection in adults. The recommended dose is one tablet once daily with or without food. Each tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir. The tablets are supplied 28 count in 100 mL white HDPE bottles containing 1 g silica gel desiccant and a polyester coil and closed with white child-resistant (b) (4) screw caps and induction-sealed aluminum-faced liners. The expiration dating period is 24 months when stored in accordance with the recommended storage condition of "Store below 30°C".

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for ledipasvir and sofosbuvir drug substances have been reviewed and found to be satisfactory. The composition, manufacturing process, and specifications for the ledipasvir and sofosbuvir tablets are appropriate and the expiration dating period of 24 months when stored below 30°C is supported by adequate data. The container-closure system and labeling are appropriate. The data presented in the NDA are acceptable.

This NDA is recommended for approval from the CMC perspective. CMC information in the NDA has been reviewed and found satisfactory. The labeling has adequate CMC information.

III. Administrative**A. Reviewer's Signature**

Executive Summary Section

George Lunn, Ph.D.

Review Chemist

B. Endorsement Block

Stephen Miller, Ph.D. CMC-Lead and Acting Division Director

C. CC Block

142 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following
this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEORGE LUNN
09/26/2014

STEPHEN MILLER
09/26/2014

As Acting Division Director, I concur: this NDA is recommended for approval from the CMC perspective.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 205834/000	Sponsor:	GILEAD SCIENCES INC
Code:	530		333 LAKESIDE DR
Priority:	14		FOSTER CITY, CA 94404
Stamp Date:	10-FEB-2014	Brand Name:	LEDIPASVIR/SOFOSBUVIR FIXED DOSE COMBINA
PDUFA Date:	10-OCT-2014	Estab. Name:	
Action Goal:		Generic Name:	LEDIPASVIR/SOFOSBUVIR FIXED DOSE COMBINA
District Goal:	10-JUN-2014	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; SOFOSBUVIR; 400MG 001; TABLET; LEDIPASVIR; 90MG

FDA Contacts:	G. LUNN	Prod Qual Reviewer		3017961701
	S. DONALD	Micro Reviewer	(HFD-805)	4107795444
	A. CUFF	Product Quality PM	(HF-01)	3017964061
	L. ONAGA	Regulatory Project Mgr	(HFD-530)	3017960759
	S. MILLER	Team Leader		3017961418

Overall Recommendation:	ACCEPTABLE	on 03-SEP-2014	by R. XU	()	3017966187
	PENDING	on 03-SEP-2014	by EES_PROD		
	PENDING	on 02-MAY-2014	by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
	(b) (4)		
DMF No:		AADA:	N 204671
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-SEP-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
(b) (4)

DMF No: AADA: N 204671

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA: N 204671

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 2082946 FEI: 2082946
GILEAD SCIENCES, INC.

DMF No: SAN DIMAS, , UNITED STATES 917732957 AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-MAR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 2952384 FEI: 1000523075
GILEAD SCIENCES, INC.
FOSTER CITY, , UNITED STATES 944041147

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: DO RECOMMENDATION

Milestone Date: 03-SEP-2014

Decision: ACCEPTABLE

Reason: INSPECTION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Profile: OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-APR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Profile: OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-AUG-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA: N 204671

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-AUG-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

NDA 205-834

Ledipasvir and Sofosbuvir Tablets, 90 mg and 400 mg

Gilead Sciences, Inc.

**George Lunn, Ph.D.
Division of Anti-Viral Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	9
I. Recommendations	9
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III. List Of Deficiencies To Be Communicated.....	136

IV. EES	138
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Chemistry Review Data Sheet

1. NDA 205-834
2. REVIEW #: 1
3. REVIEW DATE: 04-Jun-2014
4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment

Document Date

10-Feb-2014
27-Feb-2014
04-Mar-2014
25-Mar-2014
25-Apr-2014
02-May-2014
30-Jun-2014

7. NAME & ADDRESS OF APPLICANT:

Name:

Gilead Sciences, Inc.

Chemistry Review Data Sheet

Address: 333 Lakeside Drive
Representative: Foster City, CA 94404
Telephone: 650 574 3000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Ledipasvir and Sofosbuvir Tablets
c) Code Name/#: GS-5885 and GS-7977
d) Chem. Type/Submission Priority:
 - Chem. Type: 1,4
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Food Drug and Cosmetic Act 505 (b)(1)

10. PHARMACOL. CATEGORY: Anti-viral (Hepatitis C)

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: Ledipasvir 90 mg and sofosbuvir 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

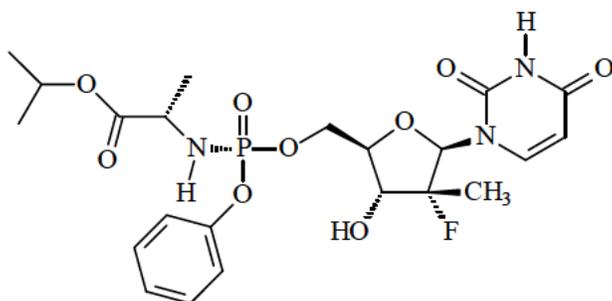
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(b) (4)



Sofosbuvir
Molecular formula: $C_{22}H_{29}FN_3O_9P$
Molecular weight: 529.45

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

Chemistry Review Data Sheet

(b) (4)	(b) (4)				
III		4	Adequate		
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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

Chemistry Review Data Sheet

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	N A		
Biopharm	Not acceptable	7/10/14	Sandra Suarez
LNC	NA		
Methods Validation	Pending		MV request submitted 2/26/14
OPDRA	NA		
EA	Categorical exclusion claimed. Claim is accepted.	2/25/14	G. Lunn
Microbiology	Acceptable	3/31/14	Steven P. Donald

The Chemistry Review for NDA 205-834

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is not recommended for approval from the CMC perspective. CMC information in the NDA has been reviewed and found satisfactory, and the labeling has adequate CMC information which will be finalized during team review of labeling. The Quality Micro reviewer, Steven Donald, indicates that no product quality microbiology deficiencies were identified. The Biopharm reviewer, Sanda Suarez, indicates that ONDQA-Biopharmaceutics cannot provide a recommendation because of the pending resolution on the Applicant's agreement to monitor for the (b) (4) content of the ledipasvir component.

However, this application is not recommended for approval for the following reasons:

- An overall recommendation of Acceptable has not been made in EES.
- The dissolution method and (b) (4) testing have not been agreed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Complete sofosbuvir drug substance information is provided in approved NDA 204-671 and is incorporated in this NDA by reference. Sofosbuvir has a retest period of (b) (4) months at 25 °C/60% RH.

Ledipasvir drug substance is manufactured (b) (4)

The manufacturing process is described at a reasonable level of detail and the controls on the critical steps are acceptable. Laboratory studies have established PARs and the NORs are set within these limits. The proposed starting materials are acceptable. (b) (4)

Executive Summary Section

A reasonable specification that includes tests for appearance, identity, (b) (4) assay, impurities, residual solvents, and elemental impurities is provided. The analytical methods are described at a satisfactory level of detail and have been validated. Satisfactory batch analyses are provided for 20 batches of the (b) (4) made at (b) (4) facilities on a (b) (4) (b) (4) scale. An acceptable justification of the specification is provided. Generally the specification is conventional and the acceptance criteria are reasonable. The specifications for appearance and (b) (4) are rather broad but acceptable justifications are provided. The impurities are toxicologically qualified and the residual solvents limits are in accord with ICH Q3C. Potential genotoxic impurities are controlled in an acceptable manner. Because the next step (b) (4)

Stability data of up to 24 months at 25°C/60% RH and 6 months at 40°C/75% RH are supplied. There are no out of specification results and no obvious trends although the material is light sensitive. A retest date of (b) (4) months when stored at 25°C is reasonable.

Ledipasvir (b) (4) drug substance is (b) (4)

(b) (4)

Up to 12 months of satisfactory stability data obtained at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH are provided (b) (4) The shelf-life of 24 months at up to 25°C is reasonable.

The drug product consists of orange film-coated tablets that contain 400 mg sofosbuvir and 90 mg ledipasvir. The tablets are packaged 28 count in HDPE bottles containing 1 g silica gel desiccant and a polyester fiber coil. The bottles are closed with induction seals and child-resistant closures. An alternate trade dress for tablets for an access program is also described. These tablets are (b) (4)

Ledipasvir (b) (4)

Executive Summary Section

The excipients are of compendial quality except for the film coats which are made of compendial components.

The drug product specification contains tests for appearance, identity, water, assay, impurities, content uniformity, dissolution, and microbial limits (b) (4). A reasonable justification is provided. The analytical methods are described in detail and validation reports are provided. Satisfactory batch analysis data are provided for 15 batches of tablets.

For the acceptability of the dissolution method see the separate Biopharm review. It is interesting to note that the dissolution method is (b) (4).

The (b) (4) is not determined. Large amounts of (b) (4) ledipasvir (b) (4) but the smallest amount that was tested was (b) (4)%. The applicant has developed a (b) (4) method which has a limit of detection (b) (4).

Up to 15 months of satisfactory stability data obtained at 30°C/75% RH are provided for 9 batches. Batches have been manufactured (b) (4). Their stability behavior is no different from other batches although the results of an end to end study are not yet available. An expiration dating period of 24 months when stored at or below 30°C is reasonable.

Currently the Overall Recommendation in EES is Pending.

B. Description of How the Drug Product is Intended to be Used

Ledipasvir and sofosbuvir tablets are indicated for the treatment of chronic hepatitis C genotype 1 infection in adults. The recommended dose is one tablet once daily with or without food. Each tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir. The tablets are supplied 28 count in 100 mL white HDPE bottles containing 1 g silica gel desiccant and a polyester coil and closed with white child-resistant (b) (4) screw caps and induction-sealed aluminum-faced liners. The expiration dating period is 24 months when stored in accordance with the recommended storage condition of "Store below 30°C".

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for ledipasvir and sofosbuvir drug substances have been reviewed and found to be satisfactory. The composition, manufacturing process, and specifications for the ledipasvir and sofosbuvir tablets are appropriate and the expiration dating period of 24 months when stored below 30°C is supported by adequate data. The container-closure system and labeling are appropriate. The data presented in the NDA are acceptable.

This NDA is not recommended for approval from the CMC perspective. CMC information in the NDA has been reviewed and found satisfactory, with the exception of the deficiencies noted

Executive Summary Section

below. The labeling has adequate CMC information which will be finalized during team review of labeling.

However, this application is not recommended for approval at this time for the following reasons:

- An overall recommendation of Acceptable has not been made in EES.
- The dissolution method and (b) (4) testing have not been agreed.

III. Administrative**A. Reviewer's Signature**

George Lunn, Ph.D.

Review Chemist

B. Endorsement Block

Rapti Madurawe, Ph.D.

Branch Chief

C. CC Block

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEORGE LUNN
07/10/2014

RAPTI D MADURAWA
07/11/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205-834**

2. DATES AND GOALS:

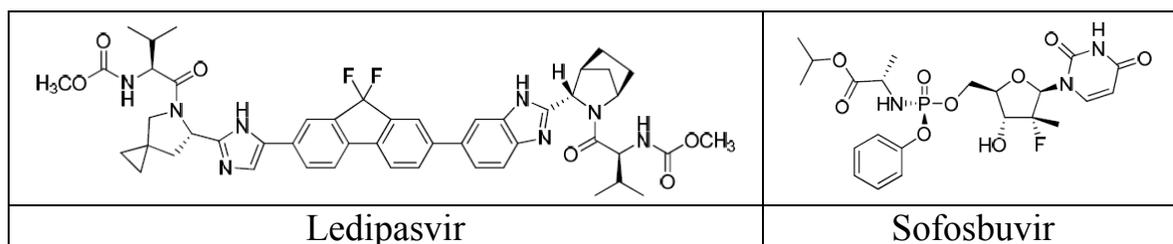
Letter Date:	Submission Received Date : Feb 10, 2014
PDUFA Goal Date: Oct 10, 2014	Primary Reviews Signed-Off in DARRTS: Approx. July 10, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Harvoni (conditionally acceptable)
Established or Non-Proprietary Name (USAN):	Ledipasvir and Sofosbuvir
Dosage Form:	Tablets
Route of Administration	Oral
Strength/Potency	90mg / 400mg
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of chronic genotype 1 hepatitis C virus (HCV) infection.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h):

Gilead Sciences, Inc.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

7. SUBMISSION PROPERTIES:

Review Priority:	Priority (PDUFA-V)
Submission Classification (Chemical Classification Code):	Type 1, 4 (New Molecular Entity; new combination – not previously approved in the US)
Application Type:	505(b)(1)
Breakthrough Therapy	Yes
Responsible Organization (Clinical Division):	DAVP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation	X		Consult in DARRTS (Feb 26, 2014)
Environmental Assessment		X	
CDRH		X	
Other		X	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes
CMC Filing Issues:
1. None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
Yes
CMC Comments for 74-Day Letter: NOTE: These comments were conveyed to the Applicant on March 21, 2014 by the ONDQA PM.
<ol style="list-style-type: none">1. Although the detailed CMC information for sofosbuvir drug substance is referenced to NDA 204-671, Module 3 should also include a drug substance section (i.e., 3.2.S) for sofosbuvir. Include in Module 3 of NDA 205-834 the current information on sofosbuvir drug substance (such as manufacturers, physico-chemical properties, specification, storage condition and retest date, etc.), as well as a discussion of attributes of sofosbuvir drug substance that are important for the manufacture and quality of the ledipasvir and sofosbuvir tablet.2. Provide a Letter of Authorization to allow FDA to reference all information in NDA 204-671.3. Provide one bottle each of the US (active) tablets, and the Access (active) tablets. We wish to examine the tablets and the bottles, so container labels or induction seals are not necessary. If supplies are tight a sample of 10 tablets of each type in an appropriate container is sufficient.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes
Biopharmaceutics Filing Issues:
1. None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
Yes
Biopharmaceutics Comments for 74-Day Letter: NOTE: These comments were conveyed to the Applicant on March 21, 2014 by the ONDQA PM.
<ol style="list-style-type: none">1. To support the approval of the proposed dissolution method provide the following:<ol style="list-style-type: none">a. Confirm whether the proposed dissolution medium, 900 mL of 10 mM potassium phosphate, pH 6.0 with 1.5% polysorbate 80 and 0.0075 mg/mL BHT, was used

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

to assess the dissolution profiles of the pivotal clinical batches, registration stability and commercial batches.

- b. A list of the Critical Material Attributes (CMA) and Critical Process Parameters (CPP) affecting dissolution with supporting data.
 - c. Dissolution profiles for both LDV and SOF as a function of drug substance particle size, (b)(4) particle size, bulk density, water content, hardness, weight gain, film coating, and other relevant attributes.
 - d. There is a potential for the (b)(4) to change during drug product processing and stability. However, data supporting the discriminating ability of the dissolution method for these potential changes were not included in your submission. Provide rationale with supporting data.
2. Provide an explanation for the outlier behavior on the SOF dissolution profile for Batch DK1206B manufactured at (b)(4). Please include in your explanation the drug substance particle size, bulk density (b)(4) and in process parameters operating ranges for this batch.
3. To support the use of dissolution as a tool to monitor for LDV (b)(4) content provide:
- a. (b)(4)
4. To support the approval of the alternate manufacturing site provide:
- a. Dissolution profiles comparisons in three different media for the batches (at least 3) manufactured at (b)(4) vs. those manufactured at Gilead in Ireland.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

Yes

Microbiology Filing Issues:

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

This NDA is fileable per Dr. Donald's Microbiology Filing Review in DARRTS (date Feb 27, 2014). There are no Information Requests in Dr. Donald's filing review, and his review of this application will continue.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?		Yes	No
Suggested expertise for team:			
George Lunn	(CMC: DS and DP)		
Sandra Suarez	(Biopharm)		
Steven Donald	(Prod Qual Micro)		
Angelica Dorantes	(Biopharm Secondary Review)		
Rapti Madurawe	(Secondary Review)		
Althea Cuff	(ONDQA PM)		
Krishna Ghosh	(Compliance)		
Linda Onaga	(DAVP PM)		

Summary of Critical Issues and Complexities

CMC Assessment

Overview

This fixed dose combination (FDC) tablet combines ledipasvir (NME), an inhibitor of the Hepatitis C NS5A protein (accessory protein for the RNA polymerase and viral release), with sofosbuvir (approved Dec 2013 under NDA 204-671), an inhibitor of the Hep-C RNA-dependent RNA polymerase (NS5B). The proposed indication is for treatment of chronic infection with Genotype 1 Hep-C, which is the most common genotype in the US. Phase 3 studies show cure rates well in excess of 90%, and this FDC has been granted Breakthrough status.

The proposed dosing is one tablet dail [REDACTED] (b) (4)
[REDACTED]

**ONDQA Initial Quality Assessment (IQA) and Filing Review
 CMC and Biopharmaceutics
 NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
 For Pre-Marking Applications**

Ledipasvir Drug Substance (b) (4)

Initial Risk Identification based on Properties & Process

Drug Substance Aspects	Initial Risk Identification	Comments
Characterization	Low	Low solubility / High permeability (BCS 2)
Manufacturing Process	Medium	Is justification for the (b) (4) starting materials acceptable?
Facilities	Low	(b) (4)
Stability		
Identification	Low	Any evidence of (b) (4) properties?
Assay	Low	
Impurities	Medium	Potential for (b) (4) degradant (b) (4) to influence photo-toxicity has been discussed with Pharm/Tox
Residual Solvents	Low	
Heavy Metals	Low	
Particle Size	Low	(b) (4)
Polymorphic Form	Low	(b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

Sofosbuvir Drug Substance

Initial Risk Identification based on Properties & Process

Drug Substance Aspects	Initial Risk Identification	Comments
Characterization	Low	High solubility / Low permeability (BCS 3)
Manufacturing Process	Low	Process approved under NDA 204-671 (sofosbuvir tablet)
Facilities	Low	(b) (4)
Stability	Low	
Identification	Low	Appropriate control strategy in place under approved NDA 204-671
Assay	Low	Appropriate control strategy in place under approved NDA 204-671
Impurities	Low	Appropriate control strategy in place under approved NDA 204-671
Residual Solvents	Low	Appropriate control strategy in place under approved NDA 204-671
Heavy Metals	Low	Appropriate control strategy in place under approved NDA 204-671
Particle Size	Medium	(b) (4)
Polymorphic Form	Low	(b) (4)

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**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	<p>Three docs from the late IND phase of development (IND 115268) were emailed to review team members:</p> <ul style="list-style-type: none"> • July 2013 backgrounder for Pre-NDA meeting (including CMC and BP topics) • Aug FDA preliminary comments/responses (meeting then cancelled) • Gilead's Sept 2013 responses/explanations to our preliminary comments <p>Topics in this PreNDA exchange include:</p> <ul style="list-style-type: none"> • stability data for the ledipasvir DS • justification of starting materials, (b) (4) <div style="background-color: gray; width: 100%; height: 20px; margin-top: 5px;"></div> • justification of the controls that assure that the (b) (4) <div style="background-color: gray; width: 100%; height: 20px; margin-top: 5px;"></div> • dissolution information including solubility data for each drug substance covering the pH range.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
 CMC and Biopharmaceutics
 NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
 For Pre-Marking Applications**

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

**ONDQA Initial Quality Assessment (IQA) and Filing Review
 CMC and Biopharmaceutics
 NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
 For Pre-Marking Applications**

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Upon request the sofosbuvir facilities were added to the 356h.
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		Upon request the 356h was updated to confirm sites all are ready for inspection

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		21 CFR 25.31(b) – less than 1 ppb for each drug substance

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		All information is complete for the ledipasvir drug substance. No information on the sofosbuvir drug substance was included, and all was cross-referenced to Gilead's NDA 204-671
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		Information requested for sofosbuvir.
15.	Does the section contain controls for the DS?	X		Information requested for sofosbuvir.
16.	Has stability data and analysis been provided for the drug substance?	X		Information requested for sofosbuvir.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		<p>Narrative descriptions are included.</p> <p>LDV (b) (4)</p> <p>LDV (b) (4)</p> <p>One executed batch record for (b) (4)</p> <p>SOF/LDV tablets are manufactured at a (b) (4)</p> <p>SOF/LDV tablets are manufactured at a (b) (4) scale (theoretical batch size) at Gilead Cork (Gilead Sciences Limited, Cork, Ireland).</p> <p>One executed batch record for tablets (pilot batch DK1206) manufactured at (b) (4) is provided.</p>
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		Attached below
21.	Is there a batch production record and a proposed master batch record?		X	See Point 19, above.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		Bottle labels attached below.
24.	Does the section contain controls of the final drug product?			Attached below
25.	Has stability data and analysis been provided to support the requested expiration date?	X		<p>Primary data: 12 mo on 3 batches from (b) (4) at 30°C/75%RH, 25°C/60%RH and 6-mo accelerated.</p> <p>Three (b) (4) pilot batches made at Gilead Cork out to 6 mo.</p> <p>Two (b) (4) batches from (b) (4) held at 6 mo studied out to 9 mo, including a 9-mo accel timepoint related to “invalidated dissol results at 6 mo”</p> <p>In-use in (b) (4) at 25/60%RH and 30/75%RH for 45 days.</p> <p>Stress at 5degC, 50°C and 25°C/85%RH for 45 days, and ICH photostability studies.</p> <p>Access Tablets: studies initiated on one (b) (4) batch.</p> <p>Proposed 24 mo expiry period for “Store below 30°C”</p>
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)

	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY

	Parameter	Yes	No	Comment
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**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA
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H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	II			Jan 13, 2014	
	II			Jan 11, 2013	

15 LOAs for packaging components also provided

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		Attached below

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?	x		<p>Proposed dissolution method for both components: USP 2, 75 rpm, 900 mL; of 10 mM KH₂PO₄ containing 1.5% w/v polysorbate 80 maintained at 37°C.</p> <p>Refer to PDM-1586, Development and Rationale for the SOF/LDV Tablet Dissolution Method.</p>
34.	Is the dissolution test part of the DP specifications?	x		<p>Proposed dissolution acceptance criteria: Q=(b)(4) at (b)(4) for both components</p> <p>Refer to: \\cdsesub1\evsprod\NDA205834\0000\m3\32-body-data\32p-drug-prod\ldv-sof-tablet\32p5-contr-drug-prod\32p56-justif-spec</p>
35.	Does the application contain the dissolution method development report including data supporting the discriminating ability?	x		<p>Discriminating ability was evaluated towards:</p> <ul style="list-style-type: none"> • Presence of (b)(4) ledipasvir (b)(4) • Inclusion of neat ledipasvir (b)(4) • Absence of (b)(4) <p>Refer to: \\cdsesub1\evsprod\NDA205834\0000\m3\32-body-data\32p-drug-prod\ldv-sof-tablet\32p5-contr-drug-prod\32p52-analyt-proc</p>
36.	Is there a validation package for the analytical method and dissolution methodology?	x		The analytical data will be reviewed by the CMC Reviewer.
37.	Does the application include a biowaiver request?		x	
38.	Is there information/data supporting the biowaiver request?		x	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

39.	Is there enough information to assess the extended release designation claim?		x	Not applicable
40.	Are there any manufacturing changes implemented to the biobatch/clinical trial formulation?	x		
41.	Are data supporting the manufacturing changes implemented to the clinical trial formulation?			A manufacturing site change was implemented: (b)(4) vs. Gilead, Ireland.
42.	Does the application include an IVIVC model?		x	
43.	Does the application include information/data on in vitro alcohol dose-dumping potential?		x	Not Applicable
44.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		<ul style="list-style-type: none"> • PK study, GS-US-334-0101, was conducted to evaluate the potential for a drug-drug interaction between SOF and LDV. • PK Study GS-US-337-0101 evaluated the performance of the SOF/LDV tablet formulation to the 2 coadministered single-agent tablets, LDV (b)(4) 90-mg strength and SOF tablet 400-mg strength administered under fed and fast conditions. <p>These studies along with BA studies US-256-0110 and (US-248-0102 conducted during early development will be reviewed by OCP.</p>
47.	Is there any design space proposed using in vitro release as a response variable?		x	
48.	Is the control strategy related to in vitro drug release?		x	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

K. filing conclusion				
	Parameter	Yes	No	Comment
49.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTION OF THE APPLICATION FILEABLE?	x		
50.	If the NDA is not fileable from the product quality perspective, state the reasons.			Not applicable.
51	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons.			Not applicable.
52	Are there any potential review issues identified?	x		Refer to pages 3-4.
53	Are there any comments to be sent to the Applicant?	x		Refer to pages 3-4.
54.	Are there any internal comments to other disciplines?		x	

ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marketing Applications

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
CMC-Lead
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

{See appended electronic signature page}

Sandra Suarez, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

{See appended electronic signature page}

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Office of New Drug Quality Assessment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 205-834, ledipasvir/sofosbuvir FDC Tablet
For Pre-Marking Applications**

Appendix 1. Composition of Ledipasvir and Sofosbuvir Tablet

Component	Composition (% w/w)	Unit Formula (mg/tablet)	Reference Quality Standards	Function
Intragranular				
Sofosbuvir ^a	40.0	400.0	In-house	Active Ingredient
Ledipasvir ^{b,c,d,e}	9.0	90.0	In-house	Active Ingredient
Copovidone ^{d,e}	(b) (4)	(b) (4)	USP, Ph. Eur.	(b) (4)
(b) (4)			USP, Ph. Eur.	
Lactose Monohydrate ^{a,d}			NF, Ph. Eur.	
Microcrystalline Cellulose			NF, Ph. Eur.	
Croscarmellose Sodium			NF, Ph. Eur.	
(b) (4)			NF, Ph. Eur.	
Magnesium Stearate			NF, Ph. Eur.	
(b) (4)				
			NF, Ph. Eur.	
			NF, Ph. Eur.	
			NF, Ph. Eur.	
			--	
			In-house	
			USP, Ph. Eur.	
				(b) (4)

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(b) (4)



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Appendix 2. DP Specification

Test Description	Methods	Acceptance Limit
Appearance	TM-004	<i>SOF/LDV Tablets</i> are orange, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7985" on the other side. Packaging is visually consistent with the description provided.
Identification		
A. Chromatographic retention time	TM-214 or TM-215	The retention times of the main peaks in <i>SOF/LDV Tablets</i> are consistent with the reference standard of each active ingredient.
B. UV Spectrum	TM-219	The ultraviolet absorption spectrum of <i>SOF/LDV Tablets</i> is consistent with that of sofosbuvir and ledipasvir reference standards.
(b) (4)		
Strength	TM-214	<p><i>At Release:</i></p> <p>The strength of sofosbuvir and ledipasvir in <i>SOF/LDV Tablets</i> is each not less than (NLT) (b) (4)% and NMT (b) (4)% of the label strength.</p> <p><i>During Shelf-life:</i></p> <p>The strength of sofosbuvir and ledipasvir in <i>SOF/LDV Tablets</i> is each NLT (b) (4)% and NMT (b) (4)% of the label strength.</p>
Degradation Product Content	TM-214	<p><i>At Release:</i></p> <p><i>For Sofosbuvir</i></p> <p>A total of NMT (b) (4)% of sofosbuvir-related degradation products with NMT (b) (4)% each of GS-606965, GS-331007, GS-566500, GS-607669, GS-607670, (b) (4), and NMT (b) (4)% each of any SOF-related unspecified degradation product.</p> <p><i>For Ledipasvir</i></p> <p>A total of NMT (b) (4)% of ledipasvir-related degradation products with NMT (b) (4)% of GS-459666, and NMT (b) (4)% each of any ledipasvir-related unspecified degradation product.</p> <p><i>During Shelf-life:</i></p> <p><i>For Sofosbuvir</i></p> <p>A total of NMT (b) (4)% sofosbuvir-related degradation products with NMT (b) (4)% each of GS-606965, GS-331007, GS-566500, GS-607669, GS-607670, (b) (4), and NMT (b) (4)% each of any sofosbuvir-related unspecified degradation products</p> <p><i>For Ledipasvir</i></p> <p>A total of NMT (b) (4)% ledipasvir-related degradation products with NMT (b) (4)% of GS-459666, and NMT (b) (4)% each of any ledipasvir-related unspecified degradation product</p>
Uniformity of Dosage Units	TM-215 (USP <905> or Ph. Eur. 2.9.40)	<i>SOF/LDV Tablets</i> meet the USP or Ph. Eur. requirements for content uniformity.
Dissolution	TM-213 (USP <711> or Ph. Eur. 2.9.3)	<i>SOF/LDV Tablets</i> meet the USP or Ph. Eur. Criteria for the amount of sofosbuvir and ledipasvir dissolved at (b) (4) minutes when Q is (b) (4)%.

Access Tablet Appearance: SOF/LDV Tablets

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Appendix 3. Container Labels

(b) (4)



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Appendix 4. Ledipasvir DS and (b) (4) Specifications

Specification of Ledipasvir Drug Substance

Test Description	Test Method	Acceptance Limit
Appearance	TM-225	(b) (4)
Identification of LDV		
A. UV Spectrum	USP <197> or Ph. Eur. 2.2.25	The UV spectra (b) (4) sample and standard solutions in (b) (4) v/v/v of (b) (4) the same wavelengths over the range of (b) (4)
B. Chromatographic Retention Time	TM-216	The retention time of the main peak in the HPLC chromatogram of the sample is consistent with that of the reference standard.
Identification of (b) (4)		
C. Chromatographic Retention Time	TM-217	The retention time of the (b) (4) peak in the GC chromatogram is consistent with that of the (b) (4) standard.
(b) (4) Content	TM-217	Not more than (NMT) (b) (4)%
Clarity of Solution	TM-007	A (b) (4) w/v solution in (b) (4) is clear and essentially free of visible particles.
Water Content	USP <921> Method Ic or Ph. Eur. 2.5.12	NMT (b) (4)%
Assay	TM-216	Not less than (NLT) (b) (4)% and NMT (b) (4)% when calculated (b) (4)
Impurity Content	TM-216	(b) (4)
Residual Solvents Content	TM-217	(b) (4)
Elemental Impurities	TM-218	(b) (4)

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(b) (4)



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/s/

STEPHEN MILLER

03/26/2014

This NDA is fileable from the Product Quality perspective.

SANDRA SUAREZ

03/26/2014

ANGELICA DORANTES

03/26/2014

RAPTI D MADURawe

03/27/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

- 1. DMPQ Reviewer: **Krishna Ghosh**
- 2. NDA/BLA Number: **NDA 205834**
Submission Date: **2/10 /2014**
21st C. Review Goal Date: **August 10, 2014**
PDUFA Goal Date: **10/10/2014**

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None
Established or Non-Proprietary Name (USAN) and strength:	Ledipasvir/Sofosbuvir fixed does combination tablet
Dosage Form:	Oral fixed dose combination (90/400mg)

4. SUBMISSION PROPERTIES:

Review Priority :	Breakthrough Therapy- Priority review
Applicant Name:	Gilead Sciences Inc.
Responsible Organization (OND Division):	DAVP

II. Application Detail

1. INDICATION: Treatment of Genotype 1 Hepatitis C Infection (HCV)
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 90/400mg
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			
2.	Breakthrough Therapy Designation	X			
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug				
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		x		
10.	Other (e.g., expedited for an unlisted reason)	X			Priority review granted . PDUFA October 10, 2014

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	X		

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	X		New Molecular Entity
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights				
1. Drug Substance				
	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	There are 15 sites for this product and 7 of them are international sites.
2. Drug Product				
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	There is a complex intermediate (LDV ^{(b)(4)}) process described in Fig 1. This is a ^{(b)(4)} Ledipasvir. The firm has also submitted a reprocessing process ^{(b)(4)} which needs to be evaluated in a careful manner.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
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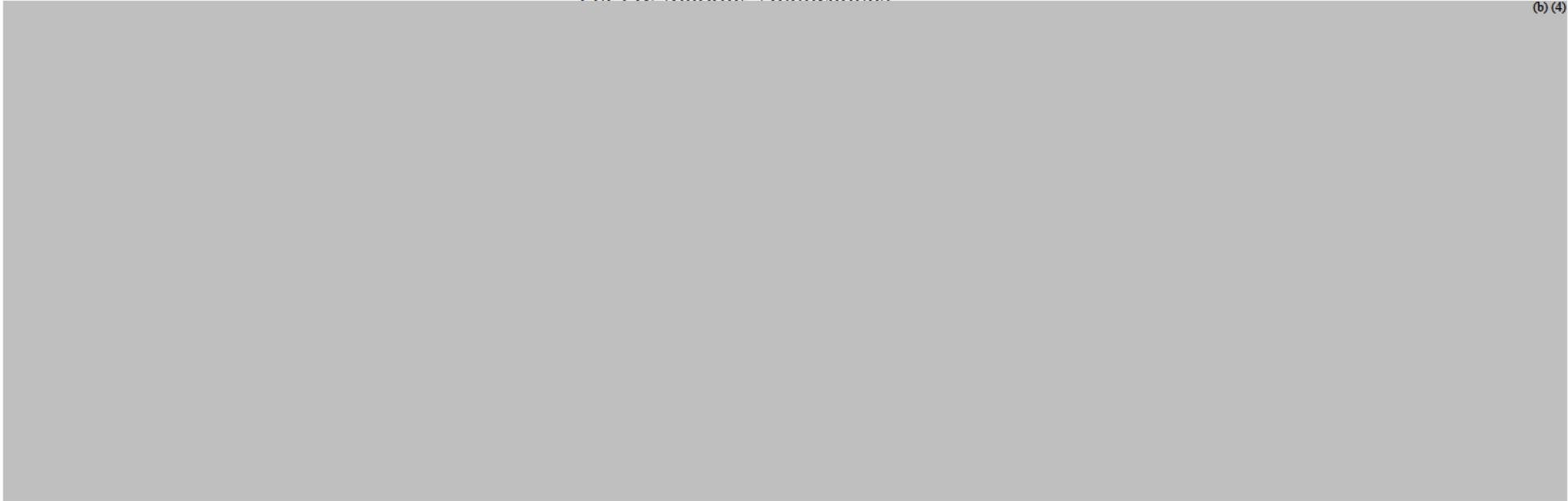
3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)

There are 15 manufacturing and testing sites are involved in this application with 7 foreign sites.

Additional information on Manufacturing issues or Complexities

(b) (4)

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V. Overall Conclusions and Recommendations

Is the application filable?
yes
At this time, is a (b) (4) warranted for any PAI? Yes
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? No
Comments for 74 Day Letter
1. N/A
2.
3.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
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REVIEW AND APPROVAL
(DARRTS)

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/s/

KRISHNA GHOSH
03/12/2014

MAHESH R RAMANADHAM
03/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: George Lunn, CMC Reviewer
Stephen P. Miller, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: george.lunn@fda.hhs.gov
Phone: (301)-796-1701
Fax.: (301)-796-9877

Through: Stephen P. Miller, CMC Lead
Phone: (301)-796-1418

and

Youbang Liu, ONDQA Methods Validation Coordinator
Phone: 301-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 205834

Name of Product: Ledipasvir and Sofosbuvir Tablets, 90 mg and 400 mg

Applicant: Gilead Sciences

Applicant's Contact Person: Michele Anderson

Address: 333 Lakeside Drive, Foster City, CA 94404

Telephone: 650-524-3858 Fax: 650-522-5489

Date NDA Received by CDER: **2/7/14**

Date of Amendment(s) containing the MVP: **2/7/14**

DATE of Request: **2/26/14**

Requested Completion Date **7/7/14**

PDUFA User Fee Goal Date: **8/7/14**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 204671
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
See lists in 3.2.R.3 Method Validation Package				
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.S.4.3 and 3.2.P.5.3
Other				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
TM-216.01	Identification, Assay, and Impurity Content of Ledipasvir (b) (4) Drug Substance by HPLC	3.2.S.4.2	0	Note that methods validation is not requested for the other drug substance, sofosbuvir.
TM-214	Identification, Strength, and Degradation Product Content of Ledipasvir and Sofosbuvir Tablets by UPLC	3.2.P.5.2	0	
Additional Comments:				

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

GEORGE LUNN
02/26/2014

STEPHEN MILLER
02/26/2014

YOUBANG LIU
02/26/2014