CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204671Orig1s000

<u>CHEMISTRY REVIEW(S)</u>

ONDQA Division Director's Memo
NDA 204-671, Sofosbivir Tablets, 400 mg
Date: 02-DEC-2013

Introduction

Sofosbuvir Tablets are formulated as yellow film-coated capsule-shaped tablets debossed with a "GSI" on one side and "7977" on the other. The tablets are to be marketed in a single dosage strength (400 mg). Inactive ingredients include mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

Sofosbuvir Tablets are indicated in combination with other agents for the treatment of chronic hepatitis C in adults. The recommended dose is one tablet daily with or without food.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation (EES) was issued by the Office of Compliance on 12-NOV-2013, and an approval recommendation from the Office of Compliance was issued in a final memo dated 20-NOV-2013.

All CMC review issues have been resolved, and I concur with the Chemistry, Manufacturing and Controls team's recommendation of "approval."

ONDQA recommends approval of this NDA.

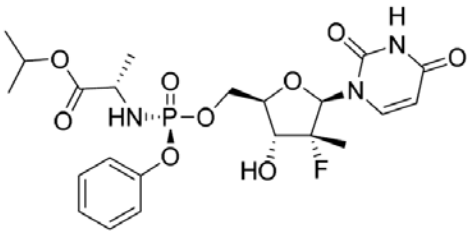
Administrative

The original submission of this 505(b)(1) NDA was received on 04-APR-2013. Several solicited CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (by Dr. G. Lunn and Dr. F. Liu, 05-SEP-2013), the final Chemistry Memo (19-NOV-2013 by Dr. G. Lunn and Dr. F. Liu), the final Compliance Memo (20-NOV-2013 by Ms. K. Ghosh), and the Biopharmaceutics Review (30-AUG-2013 by Dr. M. Hughes).

The NDA is supported by ten (10) drug master files (DMFs). All DMFs were assessed for adequacy as part of the chemistry review.

Drug Substance (sofosbuvir)

Chemical Name: (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate



Molecular Formula $C_{22}H_{29}FN_3O_9P$
Molecular Weight 529.45 g/mol

Sofosbuvir is a new molecular entity. The Applicant employs a [redacted] (b) (4)

Sofosbuvir is relatively stable; no extraordinary storage precautions are required. The proposed **re-test period of** (b) (4) **months** when stored in the recommended container closure system and under the proposed storage conditions is granted.

Drug Product – Sofosbuvir Tablets, 400 mg

Sofosbuvir Tablets are formulated as yellow film-coated capsule-shaped 400 mg tablets debossed with "GSI" on one side and "7977" on the other. They are packaged 28-count in 100-mL white HDPE bottles containing a 1-g silica gel desiccant and a polyester coil. Inactive ingredients are mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablets are coated with a yellow or white film coat containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow. The inactive ingredients are compendial except for the film coats which are composed of compendial materials.

The manufacturing process consists of [redacted] (b) (4) As stated in Chemistry Review #1 (05-SEP-2013), appropriate specifications are proposed for the drug product. However, an overall recommendation from the Office of Compliance had not yet been issued as of the date of the first Chemistry Review. This acceptable recommendation was ultimately issued on 12-NOV-2013 (please reference the final Compliance Memo and final Chemistry Memo for further information).

The Applicant proposed **a 24 month expiry** for this product when stored in the commercial packaging at the recommended storage condition of "Store below 30°C." Based on the stability data provided and in accordance with ICH Q1E, the Agency grants the proposed expiry.

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/s/

SARAH P MIKSINSKI
12/02/2013

NDA 204-671

Sofosbuvir Tablets, 400 mg

Gilead Sciences, Inc.

Fuqiang Liu, Ph.D.
George Lunn, Ph.D.
Office of New Drug Quality Assessment

CMC Review No. 1, Addendum No. 1

for the Division of Anti-Viral Drugs

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, is now 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. Office of Compliance has issued an overall recommendation of Acceptable for the manufacturing facilities.

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)

Drug Substance

Sofosbuvir is a new molecular entity (NME) filed under NDA 204671 by Gilead. This NDA describes the manufacture and processing of Sofosbuvir. The NDA contained relevant information regarding all aspects of the Sofosbuvir drug substance.

Drug substance is manufactured and tested by [redacted] (b) (4) Testing is also carried out by [redacted] (b) (4)
All drug substance manufacturing and testing sites have been found acceptable by the Office of Compliance. [redacted] (b) (4) was originally included in the NDA as a drug substance manufacturing site. [redacted] (b) (4) was withdrawn from the NDA due to CGMP deficiencies and the Applicant provided a statement that no launch product will utilize [redacted] (b) (4) drug substance.

Review of the NDA identified one potentially mutagenic impurity, [redacted] (b) (4). Gilead provided adequate information to demonstrate that [redacted] (b) (4) is purged to < (b) (4) ppm in the final drug substance when controlling this impurity at NMT [redacted] (b) (4)% in [redacted] (b) (4) [redacted] (b) (4). This is [redacted] (b) (4) the "negligible" level of [redacted] (b) (4) ppm using the most conservative TTC approach of (b) (4) µg/day for 400 mg daily dose. The above control strategy justified excluding this impurity from the drug substance specification.

Chemistry Assessment Section

Specifications for Sofosbuvir drug substance are adequate and include tests for appearance, identification, clarity of solution, assay, impurity content, organic volatile impurities/residual solvents, DSC, elemental impurities and particle size.

No degradation products have been observed over time in any of the batches of drug substance stored at long-term [redacted] (b) (4) and accelerated conditions [redacted] (b) (4) Based upon the real-time long-term and accelerated data, a retest period of [redacted] (b) (4) months is assigned for Sofosbuvir when stored at the recommended storage condition. Based on the stress studies, temperature excursions and shipping and handling of the DS at temperature of [redacted] (b) (4) may be permitted.

Drug Product

The drug product consists of yellow film-coated capsule-shaped 400 mg tablets debossed with "GSI" on one side and "7977" on the other. They are packaged 28 count in 100 mL white HDPE bottles containing 1 g silica gel desiccant and a polyester coil. The bottles are closed with white child-resistant [redacted] (b) (4) screw caps and induction-sealed aluminum-faced liners. Alternatively, [redacted] (b) (4) is used to provide [redacted] (b) (4) for tablets intended for Access countries. The inactive ingredients are mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablets are coated with a yellow [redacted] (b) (4) film coat containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow. The inactive ingredients are compendial except for the film coats which are composed of compendial materials.

Formulation development has not been extensive. The applicant states that this is not a QbD application and the applicant proposes to operate within the Normal Operating Ranges (NOR). Movement outside the NOR will require an investigation and possible regulatory filing. The major steps in the manufacturing process are [redacted] (b) (4) The critical process parameters for these operations have been identified and NORs defined. The proposed commercial NORs are relatively narrow and are supported by data from the development process. In general the manufacturing process is conventional and appears quite robust. Changes in the processing parameters had little effect on the finished product.

Drug product will be manufactured by [redacted] (b) (4) and Gilead Sciences, Ireland. The manufacturing processes employed by [redacted] (b) (4) Gilead are very similar and differ mostly in the scale employed [redacted] (b) (4) Drug product testing will be carried out by [redacted] (b) (4), and Gilead Sciences Ireland. All drug product manufacturing and testing facilities were found acceptable by the Office of Compliance.

Gilead Sciences, Foster City, CA was originally included as a drug substance and drug product testing site, but is now withdrawn from the NDA due to CGMP deficiencies. The applicant provided additional release data obtained at facilities other than Foster City to demonstrate that the drug substance and drug product conform to the specifications.

Reasonable drug product specifications with tests for appearance, identity, [redacted] (b) (4) assay, degradants, dose uniformity, and dissolution are proposed. The analytical methods are described

in reasonable detail and they have been validated. [redacted] (b) (4)

Satisfactory batch analyses are provided for 24 batches manufactured using the proposed commercial process from drug substance [redacted] (b) (4) No out of specification results are seen and no degradants are observed. The primary stability batches and the annual stability batches will also be tested for microbial limits.

The drug product is extremely stable. Satisfactory stability data covering 12 months at 25°C/60% RH and 30°C/75% RH and 6 months at 40°C/75% RH are provided for three [redacted] (b) (4) scale batches manufactured at [redacted] (b) (4) Satisfactory stability data covering 6 months at 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH are provided for three [redacted] (b) (4) scale batches manufactured at Cork. There are no out of specification results and no obvious trends. No degradants whatsoever are observed. In addition one batch was subjected to photostability testing and testing at 5°C, 50°C, and 25°C/80% RH and in open dishes at 25°C/60% RH and 30°C/75% RH for 45 days. There were no out of specification results and no obvious trends except that the [redacted] (b) (4) An expiration dating period of 24 months when stored in accordance with the recommended storage condition of "Store below 30°C" is acceptable.

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

Sofosbuvir tablets are indicated in combination with other agents for the treatment of chronic hepatitis C in adults. The recommended dose is one tablet once daily with or without food. Each tablet contains 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 [redacted] (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 the sofosbuvir drug substance have been reviewed and found to be satisfactory. The composition, manufacturing process, and specifications for the sofosbuvir tablets are appropriate and the expiration dating period of 24 months is supported by adequate data. The container-closure systems and labeling are appropriate. The data presented in the NDA are acceptable.

All manufacturing and testing sites have been found to be acceptable. Gilead Foster City and [redacted] (b) (4) which were on Withhold status at the time of CMC Review #1, are now withdrawn from the application. Although Gilead Foster City has been withdrawn it appears reasonable to accept data generated at this facility considering the concordance of the Foster City release data with the release data obtained by the cGMP compliant facilities [redacted] (b) (4) for drug

substance; Gilead Ireland and (b) (4) for drug product). This NDA is therefore now recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

Fuqiang Liu, Ph.D.
George Lunn, Ph.D.

B. Endorsement Block

Rapti D. Madurawe, Ph.D., Branch Chief

C. CC Block

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/s/

GEORGE LUNN
11/19/2013
All CMC issues have been addressed and this NDA is now recommended for approval.

FUQIANG P LIU
11/19/2013

RAPTI D MADURAWE
11/19/2013

NDA 204-671

Sofosbuvir Tablets, 400 mg

Gilead Sciences, Inc.

Fuqiang Liu, Ph.D.
George Lunn, Ph.D.
Division of Anti-Viral Drugs

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Chemistry Review Data Sheet

1. NDA 204-671

2. REVIEW #: 1

3. REVIEW DATE: 05-Sep-2013

4. REVIEW TEAM: Fuqiang Liu, Ph.D. (Drug Substance)
George Lunn, Ph.D. (Drug Product)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	04-Apr-2013
Amendment	21-May-2013
Amendment	26-Jun-2013
Amendment 008	03-Jul-2013
Amendment	23-Jul-2013
Amendment	13-Aug-2013
Amendment	20-Aug-2013

7. NAME & ADDRESS OF APPLICANT:

Executive Summary Section

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City CA 94404
Representative:	Shalini Gidwani Associate Director, Regulatory Affairs
Telephone:	650 522 2454

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Sofosbuvir
c) Code Name/# (ONDC only): GS-7977
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

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

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

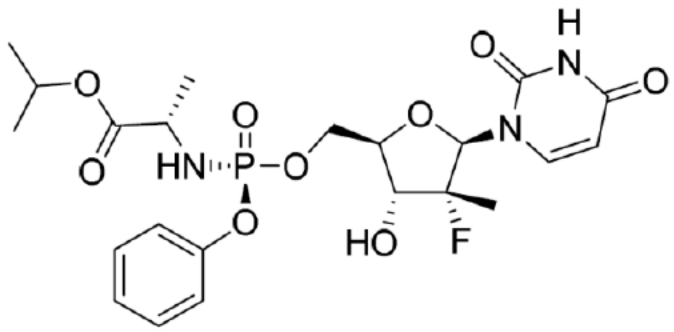
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

(S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate



$C_{22}H_{29}FN_3O_9P$

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)	4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

(b) (4)		(b) (4)				
	III		4	Adequate		
	IV		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
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:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	Acceptable, see separate review	30-Aug-2013	Minerva Hughes
LNC	NA		
Methods Validation	Pending		
OPDRA	NA		
EA	Request for categorical exclusion is granted	09-Apr-2013	George Lunn
Microbiology	See separate review		

The Chemistry Review for NDA 204-671

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 establishment status is pending as of the date of this review. There are reports of cGMP violations at [redacted] (b) (4) and Gilead Foster City and the Office of Compliance is recommending Withhold for these facilities. The impact of [redacted] (b) (4) and Gilead Foster cGMP issues, including the reliability of data from these sites, are currently under discussion. This NDA cannot be approved until these issues have been resolved and an overall recommendation of Acceptable is made for the establishments.

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)

Drug Substance

Sofosbuvir is a new molecular entity (NME) filed under NDA 204671 by Gilead. This NDA describes the manufacture and processing of Sofosbuvir. The NDA contained relevant information regarding all aspects of the Sofosbuvir drug substance.

Drug substance is manufactured and tested by [redacted] (b) (4) Testing is also carried out by Gilead Foster City-CA, [redacted] (b) (4) [redacted] An Overall Recommendation has not yet been made by the Office of Compliance and they are currently recommending Withhold for [redacted] (b) (4) and Gilead Foster City.

Review of the NDA identified one potentially mutagenic impurity, [redacted] (b) (4) Gilead provided adequate information to demonstrate that [redacted] (b) (4) is purged to < (b) (4) ppm in the final drug substance when controlling this impurity at NMT [redacted] (b) (4) % in [redacted] (b) (4) [redacted] (b) (4) This is [redacted] (b) (4) the "negligible" level of [redacted] (b) (4) ppm using the most conservative TTC approach of [redacted] (b) (4) µg/day for 400 mg daily dose. The above control strategy justified excluding this impurity from the drug substance specification.

Specifications for Sofosbuvir drug substance are adequate and include tests for appearance, identification, clarity of solution, assay, impurity content, organic volatile impurities/residual solvents, DSC, elemental impurities and particle size.

No degradation products have been observed over time in any of the batches of drug substance stored at long-term [redacted] (b) (4) and accelerated conditions [redacted] (b) (4) Based upon the real-time long-term and accelerated data, a retest period of [redacted] (b) (4) months is assigned for Sofosbuvir when stored at the recommended storage condition. Based on the stress studies, temperature excursions and shipping and handling of the DS at temperature of [redacted] (b) (4) may be permitted.

Drug Product

The drug product consists of yellow film-coated capsule-shaped 400 mg tablets debossed with "GSI" on one side and "7977" on the other. They are packaged 28 count in 100 mL white HDPE bottles containing 1 g silica gel desiccant and a polyester coil. The bottles are closed with white child-resistant [redacted] (b) (4) screw caps and induction-sealed aluminum-faced liners. Alternatively, a [redacted] (b) (4) is used to provide an [redacted] (b) (4) for tablets intended for Access countries. The inactive ingredients are mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablets are coated with a yellow [redacted] (b) (4) film coat containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow. The inactive ingredients are compendial except for the film coats which are composed of compendial materials.

Formulation development has not been extensive. The applicant states that this is not a QbD application and the applicant proposes to operate within the Normal Operating Ranges (NOR). Movement outside the NOR will require an investigation and possible regulatory filing. The major steps in the manufacturing process are [redacted] (b) (4) The critical process parameters for these operations have been identified and NORs defined. The proposed commercial NORs are relatively narrow and are supported by data from the development process. In general the manufacturing process is conventional and appears quite robust. Changes in the processing parameters had little effect on the finished product.

Drug product will be manufactured by [redacted] (b) (4) Gilead Sciences, Ireland and testing will be carried out by [redacted] (b) (4) and Gilead, Foster City CA. An Overall Recommendation has not yet been made by the Office of Compliance and they are currently recommending Withhold for Gilead, Foster City. The manufacturing processes employed by [redacted] (b) (4) and Gilead are very similar and differ mostly in the scale employed [redacted] (b) (4)

Reasonable drug product specifications with tests for appearance, identity, [redacted] (b) (4) assay, degradants, dose uniformity, and dissolution are proposed. The analytical methods are described

in reasonable detail and they have been validated. (b) (4) (b) (4)

Satisfactory batch analyses are provided for 16 batches manufactured using the proposed commercial process from drug substance (b) (4) No out of specification results are seen and no degradants are observed. The primary stability batches and the annual stability batches will also be tested for microbial limits.

The drug product is extremely stable. Satisfactory stability data covering 12 months at 25°C/60% RH and 30°C/75% RH and 6 months at 40°C/75% RH are provided for three (b) (4) scale batches manufactured at (b) (4). Satisfactory stability data covering 6 months at 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH are provided for three (b) (4) scale batches manufactured at Cork. There are no out of specification results and no obvious trends. No degradants whatsoever are observed. In addition one batch was subjected to photostability testing and testing at 5°C, 50°C, and 25°C/80% RH and in open dishes at 25°C/60% RH and 30°C/75% RH for 45 days. There were no out of specification results and no obvious trends except that the (b) (4) increased in the open dish experiments. An expiration dating period of 24 months when stored in accordance with the recommended storage condition of "Store below 30°C" is acceptable.

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

Sofosbuvir tablets are indicated in combination with other agents for the treatment of chronic hepatitis C in adults. The recommended dose is one tablet once daily with or without food. Each tablet contains 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 the sofosbuvir drug substance have been reviewed and found to be satisfactory. The composition, manufacturing process, and specifications for the sofosbuvir tablets are appropriate and the expiration dating period of 24 months is supported by adequate data. The container-closure systems and labeling are appropriate. The data presented in the NDA are acceptable.

The manufacturing sites have not all been found to be acceptable. The Office of Compliance is recommending Withhold for Gilead Foster City (key testing site) and (b) (4) (key drug substance manufacturer). Several Phase III clinical batches were made with (b) (4) drug substance. Testing conducted at Gilead Foster City show these batches are within specification. As both (b) (4) and Gilead Foster City are currently "Withhold," the acceptability of data

from these two sites is currently under discussion.. This NDA is therefore not recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

Fuqiang Liu, Ph.D.
George Lunn, Ph.D.

B. Endorsement Block

Rapti D. Madurawe, Ph.D., Branch Chief

C. CC Block

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/s/

GEORGE LUNN
09/05/2013

FUQIANG P LIU
09/05/2013

RAPTI D MADURAWE
09/05/2013

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

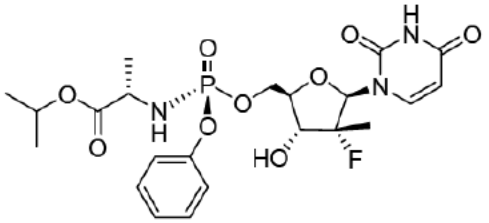
Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **204-671**

Submission Date:	Apr 8, 2013
Filing Meeting:	May 8
Mid-Cycle OND Mtg:	July 8
GRMP Goal Date:	Sept 6
Late-Cycle Mtg with Applicant:	Oct 10
PDUFA Goal Date:	Dec 8, 2013 (Sunday)

Review Team Assignments	
Drug Substance	Fuqiang Liu
Drug Product	George Lunn
Biopharmaceutics	Minerva Hughes
QbD	
Product Quality Microbiology	
ONDQA PM	Althea Cuff

2. PRODUCT PROPERTIES:

Structure:	
Trade or Proprietary Name:	
Established or Non-Proprietary Name (USAN) and strength:	Sofosbuvir; 400 mg
Dosage Form:	Tablet

Reference ID: 3306402

3. NAME OF APPLICANT:

Name:	Gilead

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Classification (Code):	Type 1 (New Molecular Entity)
Property (Legal Basis):	505 (b)(1)
Responsible Organization:	DAVP

Reference ID: 3306402

Review Information

1. INDICATION: Treatment of chronic Hepatitis C infection, in combination with other anti-HCV drugs.

2. ROUTE OF ADMINISTRATION: Oral

3. STRENGTH/POTENCY: 400 mg

4. Rx/OTC DISPENSED: ☒Rx ☐OTC

5. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

   Is this a SPOTS product? ☐Yes ☒No ☐ Not evaluated at time of IQA.

Reference ID: 3306402

6. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV		(b) (4)	Jan 11, 2013	
				March 15, 2013	
5 other LOAs are included for packaging components					

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clin Pharm		X	
EES	X		
Pharm/Tox		X	
Methods Validation	X		Because this is an NME
EA		X	
New Drug Micro	X		Consult recommended at ONDQA kick-off team meeting
CDRH		X	
Other ()		X	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
None			

d. Previous Communications with the Applicant to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND 106,739			

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X		1.

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Are there potential CMC review issues to be forward to the applicant with the 74 day letter?		
Yes	No	CMC Comments for 74 Day Letter
X		See below in "Summary or Highlights of the Application"

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	
X		See separate Biopharmaceutics Filing Review

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CMC Summary:
Critical Issues and Complexities

CMC Critical Issues or Complexities
Issues noted are listed in Summary below, but are not considered critical.

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
X		**Review Team Assignments are listed on Page 1**

Summary or Highlights of the Application ***(not already mentioned in other sections)***

Changes between Clinical DP and Proposed Commercial DP

Clinical Tablets	Commercial Tablets
Some Phase 3 studies were conducted with several formulations: [redacted] (b) (4) • 400 mg yellow [redacted] (b) (4) tablets	400 mg yellow [redacted] (b) (4) tablets
Human PK studies are said to bridge between the [redacted] (b) (4) and the [redacted] (b) (4) tablets, and between the [redacted] (b) (4) and the commercial 400 mg yellow [redacted] (b) (4) tablets. Efficacy in harder-to-treat patients with may also support the commercial [redacted] (b) (4) tablet.	

Sofosbuvir is an inhibitor of the Hepatitis C viral polymerase. It is proposed for treatment of chronic infection with Hepatitis C in conjunction with other drugs (e.g., PEG-interferon and ribavirin). The proposed dose is 400 mg/day for 12 to 16 weeks, depending on the genotype of the Hepatitis C virus.

It is a highly-soluble but low-permeability drug, so it is classified as BCS class 3.

Drug Substance

The proposed manufacturing process includes [redacted] (b) (4) [redacted] (b) (4) sofosbuvir are included in the NDA.

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Traditional experiements were used to demonstrate PARs for important process parameters. NORs are included in the process description in Section S.2.2. Each manufacturing facility will select setpoints within the NORs tailored to their individual process train. DOEs were used to "augment the understanding of the process and not to establish a design space." A decision was made at the ONDQA kick-off meeting that this would not be tracked as a QbD NDA, but that a Product Quality and Manufacturing Memo would be generated.

A few process parameters seem overly broad. These are mostly temperature parameters.

Three DS manufacturing facilities are listed: [redacted] (b) (4) Batches from each site are listed in the Batch Analysis table, although the scale at [redacted] (b) (4)

Studies are referenced to support the particle size controls for DS (limits on particles above [redacted] (b) (4) and to support the qualitative controls on solid state form [redacted] (b) (4)

Is the justification for [redacted] (b) (4) as a starting material been provided in the NDA or IND? Similarly, are there reasonable justifications for the [redacted] (b) (4) starting material [redacted] (b) (4)? See notes in Appendix 5.

[redacted] (b) (4) . Justification [redacted] (b) (4)) is provided to support the control on the one reported [redacted] (b) (4) compound [redacted] (b) (4) as an [redacted] (b) (4) impurity [redacted] (b) (4). Would it be better to list this as a specified impurity, with the same acceptance criterion?

Interesting approach to Unspecified Residual Solvents in DS Spec: "NMT [redacted] (b) (4)% or the PDE (per ICHQ3C)…"

All drug substance stability testing has been performed at Gilead Sciences Inc., Foster City (CA, USA).

Drug Product

Fairly large tablets (20 mm x 9 mm), similar to a multivitamin tablet. [redacted] (b) (4)

DOEs were included in process development studies of the [redacted] (b) (4) , to "establish process design spaces and PARs." Statement in P.2: "…although design spaces were established for a number of unit operations, Gilead is not filing a quality by design (QbD) application. Gilead intends to operate within the proposed normal operating ranges (NOR) and movement outside of the proposed normal

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operating ranges will be considered a change to the manufacturing process and would initiate a quality investigation and potentially regulatory post approval change process.

The process description in P.3.3 includes a table of [redacted] (b) (4) etc. Those "Proposed Commercial Targets / Ranges of Operating Parameters" seem to be moderately wide to me, and the identical values are shown for the two DP manufacturing sites.

The proposed storage statement is "Store below 30ºC (86ºF)."

Microbial testing is done annually as part of the stability protocol, at least for the NDA protocol and the first 3 commercial batch protocol. Is it part of the annual protocol?

All tablet stability testing was performed at Gilead Sciences, Inc. (Foster City, CA, USA).

Draft 74-Day Letter Comments:

Comment with input from CDER Compliance: In light of ORA observations that were communicated to Gilead, Foster City CA in the FDA form 483 dated April 26, 2013, clarify if different analytical procedures, or different versions of analytical procedures, than those submitted in this application were used for the NDA release and primary stability data. Please provide a detailed summary of the differences and include bridging data where appropriate.

Consider asking for microbial testing of tablets, at release and once per year, to be added to the Annual Commitment Stability Protocols for the US and Access tablets?

Consider asking for the available stability data on the one lot of Access tablets to be submitted by some appropriate time in the review cycle?

Description of Facility-Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.)

See EES for complete list of facilities related to this application.

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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?			See notes on acceptability of starting materials in Appendix 5.

B. FACILITIES*				
	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

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7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • 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		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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		

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10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		356h

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		21 CFR 25.31(b); with 5-yr estimate of (b) (4) (b) (4)

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

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E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	X		
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	X		
15.	Does the section contain information on impurities?	X		
16.	Does the section contain information regarding the characterization of the DS?	X		
17.	Does the section contain controls for the DS?	X		Attached below
18.	Has stability data and analysis been provided for the drug substance?	X		Data provided on the following batches: 2 from Gilead Alberta with data out to 12 mo 1 from (b) (4) with data out to 12 mo 1 from (b) (4) with release and 1-mo data 1 from (b) (4) with release and 1-mo data 3 other batches from Alberta and (b) (4) with data out to 3 months All pilot-scale batches (b) (4) with long-term data at 25ºC/60%RH and accelerated studies at 40ºC/75%RH Photostability and stress studies also included Summary indicates quite stable, except under forced degradation (b) (4) mo retest period proposed
19.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
21.	Does the section contain container and closure information?	X		

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F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	X		
23.	Does the section contain information on composition?	X		
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Narrative description is included, with operating ranges for parameters. The commercial scale is indicated in P.3.2 as (b) (4) [redacted] Executed batch records for one clinical and stability batch [redacted] (b) (4) [redacted] is provided in 3.2.R.1
25.	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		
26.	Is there a batch production record and a proposed master batch record?		X	No master batch record at commercial scale, but an executed pilot batch record is provided.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
28.	Have any Comparability Protocols been requested		X	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		HDPE bottle of 28 tablets with 1 g silica gel desiccant, induction seal and CR closure.
30.	Does the section contain controls of the final drug product?	X		Attached below

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31.	Has stability data and analysis been provided to support the requested expiration date?	X		Data provided on the following batches of the **US tablet:** 3 from [redacted] (b) (4) with data out to 12 mo 3 from Gilead-Ireland with data out to 6 mo All pilot-scale batches [redacted] (b) (4) with long-term data at 30ºC/75%RH and 25ºC/60%RH, and with accelerated studies at 40ºC/75%RH Photostability and stress studies also included, and in-use data on exposed tablets are provided, including 6-mo data on exposed tablets at 40ºC/75%RH. Summary indicates the tablets are very stable **Access Tablet:** One batch [redacted] (b) (4) made at [redacted] (b) (4) has been recently placed on stability, but no data are presented. 24 mo expiry period is proposed. [redacted] (b) (4) when stored below 30ºC.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Some use of DOE as part of routine development.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?		X	Data in Module 3 as usual in electronic NDAs

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?			Not sterile

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**

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36.	Has the draft package insert been provided?	X		
37.	Have the immediate container and carton labels been provided?	X		
38.	Does section contain tradename and established name?		X	Established name only at this time

FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
39.	**ARE THE PRODUCT SECTIONS OF THE APPLICATION FILEABLE?**	X		
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
41.	Are there any potential review issues identified?	X		Listed above in "Summary or Highlights of the Application"

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REVIEW AND APPROVAL

See appended electronic signature page}
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Office of New Drug Quality Assessment

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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/

STEPHEN MILLER
05/09/2013

RAPTI D MADURAWE
05/09/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204671
Submission Date	6 April 2013
Product name, generic name of the active	Sofosbuvir Tablets
Dosage form and strength	Oral Tablet/400 mg
Applicant	Gilead Sciences
Clinical Division	Division of Antviral Products
Type of Submission	NDA, Priority Review/New Molecular Entity
Biopharmaceutics Reviewer	Minerva Hughes, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Assignment Date	8 April 2013
Filing Date	7 June 2013
Filing Review Date	08 May 2013

I. SUBMISSION OVERVIEW

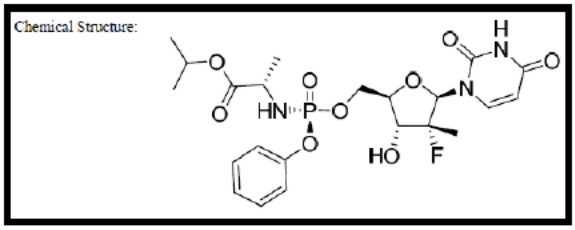
NDA 204671 was submitted in accordance with Section 505(b)(1) of the FDC Act for the use of sofosbuvir, 400 mg tablets, to treat chronic hepatitis C infection in adults with (b) (4) Sofosbuvir (SOF) is a novel nucleotide prodrug that potently inhibits genotype 1 to 6 HCV RNA replicons in vitro and has demonstrated sustained virologic response (SVR) rates when administered with ribavirin to subjects with chronic genotype 2 and 3 HCV infection and with pegylated interferon + ribavirin (PEG+RBV) to subjects with chronic genotype 1, 2, 3, 4, and 6 HCV infection.

The Phase 3 program for SOF includes 4 clinical studies: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), and GS-US-334-0110 (NEUTRINO), which evaluated the efficacy and safety of SOF +RBV or SOF+PEG+RBV for various durations and genotypes.

If approved, sofosbuvir will be the first nucleotide-analog HCV therapy.

II. BIOPHARMACEUTICS SUMMARY INFORMATION

The drug substance sofosbuvir is a small molecule nucleotide-analog with the following structure.



The Applicant notes (b) (4) that have been isolated in laboratory studies. (b) (4) The drug is slightly soluble in aqueous media (b) (4) However, based on the proposed dose, a BCS Class 3 designation is claimed.

The proposed drug product is a film-coated tablet containing 400 mg SOF and the excipients mannitol,

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microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate, polyvinylalcohol, titanium dioxide, (b) (4), talc, and yellow iron oxide. The formulation and dose of the proposed commercial SOF product were selected based on two bioavailability and food effects studies and 1 pharmacokinetics study evaluating (b) (4) Early formulations used in Phase 1 studies included a (b) (4)

Drug product manufacturing (b) (4) The process was optimized using quality by design principles. Although design spaces were established for various parameters, the Applicant intends to operate only at the normal operating range. Any changes outside the normal operating range, even if within the design space, will adhere to current post approval guidelines.

Dissolution is a critical quality attribute noted by the Applicant as critical for efficacy. A dissolution method (TM-195) was developed to assure the consistency of batch-to-batch dissolution performance.

Proposed dissolution method and acceptance criterion:

- USP II, 900 mL 50 mM potassium phosphate, 75 rpm
- Q = (b) (4)

This Biopharmaceutics review will evaluate the adequacy of the proposed dissolution method and acceptance criteria for its intended use. The review will also discuss the DOE studies that used dissolution as a response variable; however, the Applicant is not requesting regulatory flexibility for a design space. Therefore, the review will focus more on the data to support the proposed operating ranges for process parameters affecting dissolution performance.

III. POTENTIAL REVIEW ISSUES – DAY 74 LETTER COMMENTS

There are no review issues to be communicated to the Applicant in the Day 74 letter.

However, it is noted that the bioequivalence studies claim bioequivalence base on the active metabolite for all PK studies. Although this approach may be appropriate (defer to Clinical Pharmacology), the drug product is formulated with the prodrug and the rate and extent of the prodrug appears to differ between (b) (4) Whether this difference should be considered for setting clinically-relevant dissolution acceptance criteria is a review issue.

Additionally, the proposed dissolution method supports rapid dissolution and therefore the information/data supporting its discriminating ability will be closely evaluated .

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IV. FILING REVIEW CHECKLIST

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
1.	Does the application contain dissolution data?	x		Dissolution – Quality Control Dissolution – Response variable for process development DOE studies (3.2.P.2.3)
2.	Is the dissolution test part of the DP specifications?	x		Proposed Method: TM-195 USP II, 900 mL 50 mM potassium phosphate, 75 rpm Q = (b) (4)
3.	Does the application contain the dissolution method development report?	x		Development Report PDM1524 (in 3.2.P.5.2) Information also included in: Section 3.2.P.2.2 – Formulation (b) (4) Section 3.2.P.2.3 – DOE studies Section 3.2.P.5.6 – Selection of Q and time
4.	Is there a validation package for the analytical method and dissolution methodology?	x		QAVAL-0852R
5.	Does the application include a biowaiver request?		x	A BE study was completed between the 200 mg and 400 mg tablets. The 400 mg tablets were used for Phase 3 studies and the 200 mg for the initial clinical development.
6.	Does the application include a IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?	x		BCS Class 3 is proposed. Dissolution and Caco-2 cell permeability data provided in (2.3.P.2)
8.	Is information on mixing the product with foods or liquids included?		x	The product will not be mixed with food; however, it is intended to be taken without regard to food.
9.	Is there any in *vivo* BA or BE information in the submission?	x		▪ Study P7977-0111 – BA and food effect, (b) (4) vs. diastereoisomer ▪ Study P7977-1318 – BE and food effect, (b) (4) ▪ Comparative PK Study GS-US-334-0131 (400 mg Form I vs. Form II) Note: Phase 3 studies used the 400 mg to-be-marketed (b) (4) formulation.

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ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?		x	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}
Minerva Hughes
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

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

Reference ID: 3305765

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

/s/

MINERVA HUGHES
05/08/2013

ANGELICA DORANTES
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