

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203094Orig1s000

203094Orig2s000

CHEMISTRY REVIEW(S)

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

ation:	NDA 203094/000	Sponsor:	GILEAD SCIENCES INC
Org. Code:	530		333 LAKESIDE DR
Priority:	Y		FOSTER CITY, CA 94404
Stamp Date:	28-JUN-2012	Brand Name:	TYBOST (COBICISTAT)
PDUFA Date:	28-SEP-2014	Estab. Name:	
Action Goal:		Generic Name:	COBICISTAT
District Goal:	30-JUL-2014	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; COBICISTAT; (b) (4)

FDA Contacts:	K. GHOSH	Facility Reviewer	3017962644
	F. LIU	Prod Qual Reviewer	3017961469
	A. CUFF	Product Quality PM (HF-01)	3017964061
	K. WINESTOCK	Regulatory Project Mgr	3017960834
	S. MILLER	Team Leader	3017961418

Overall Recommendation:	ACCEPTABLE	on 10-JUN-2014	by EES_PROD
	PENDING	on 21-AUG-2013	by EES_PROD
	WITHHOLD	on 25-APR-2013	by EES_PROD
	PENDING	on 02-AUG-2012	by EES_PROD
	PENDING	on 02-AUG-2012	by EES_PROD
	PENDING	on 13-JUL-2012	by EES_PROD

Establishment:	CFN: (b) (4)	FEI: (b) (4)
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DMF No:	25188	AADA:	N 203093
			N 203100

Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-MAY-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

Establishment: CFN: 9615378 FEI: 3001027806

GILEAD ALBERTA ULC
(b) (4)

DMF No: 25188 AADA: N 203100
N 203093

Responsibilities: DRUG SUBSTANCE MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-MAY-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: FEI: 3006709727

GILEAD SCIENCES LIMITED
IDA BUSINESS & TECHNOLOGY PARK
CARRIGTOHILL, CO. CORK, IRELAND

DMF No: AADA: N 203093
N 203100

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

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-MAY-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

shment:

CFN:

(b) (4)

FEI:

(b) (4)

(b) (4)

DMF No:

AADA:

N 203100

N 203093

Responsibilities:

FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile:

TABLETS, PROMPT RELEASE

OAI Status:

NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

29-MAY-2014

Decision:

ACCEPTABLE

Reason:

DISTRICT RECOMMENDATION

Establishment:

CFN:

(b) (4)

FEI:

(b) (4)

(b) (4)

DMF No:

25188

AADA:

N 203100

N 203093

Responsibilities:

DRUG SUBSTANCE RELEASE TESTER

Profile:

CONTROL TESTING LABORATORY

OAI Status:

NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

10-JUN-2014

Decision:

ACCEPTABLE

Reason:

DISTRICT RECOMMENDATION

Establishment:

CFN:

FEI:

(b) (4)

(b) (4)

DMF No:

25188

AADA:

N 203093

N 203100

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

Profile:

NON-STERILE API BY CHEMICAL SYNTHESIS

OAI Status:

NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

28-MAY-2014

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE

NDA 203094

Tybost™ (cobicistat) Tablets, 150 mg

Gilead Sciences, Inc.

Fuqiang Liu, Ph.D.

**DPA II/Branch V
Office of New Drug Quality Assessment**

For Division of Anti-Viral Products

Review #2

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Chemistry Review Data Sheet

1. NDA 203094
2. REVIEW #: 02 (Resubmission)
3. REVIEW DATE: 4-Aug-2014
4. REVIEW TEAM:
Fuqiang Liu – Drug Substance and Drug Product
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 203094 CMC Review #1	19-Mar-2014
Addendum # 1 to CMC Review #1	25-Apr-2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SND 041: Resubmission	26-Mar-2014
SND 042: Resubmission/Class 2	28-Mar-2014
SND 045: Resubmission/Class 2	03-Apr-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404 USA
Representative:	Prena Menon, PhD, Manager, Regulatory Affairs Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Telephone:	650 522-4574

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tybost
 b) Non-Proprietary Name (USAN): Cobicistat Tablet
 c) Code Name/# (ONDC only): N/A
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Pharmacokinetic booster for HIV protease inhibitors Atazanavir and Darunavir

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150 mg

13. ROUTE OF ADMINISTRATION: Oral

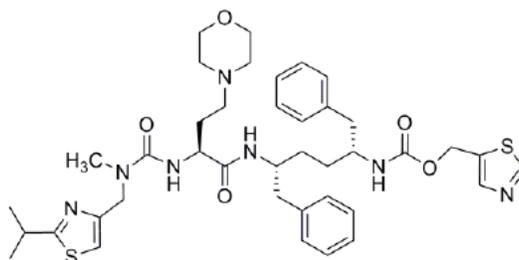
14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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



- **IUPAC:** 1,3-Thiazol-5-ylmethyl [(2*R*,5*R*)-5-{{(2*S*)-2-[(methyl{2-(propan-2-yl)-1,3-thiazol-4-yl}methyl)carbamoyl]amino}-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate

Chemistry Review Data Sheet

- **CAS:** 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (3*R*,6*R*,9*S*)-
- **Synonym (CAS):** Thiazol-5-ylmethyl [(1*R*,4*R*)-1-benzyl-4-({(2*S*)-2-[(methyl){2-(1-methylethyl)thiazol-4-yl]methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl} amino)-5-phenylpentyl]carbamate
- **USAN:** Cobicistat
- **Formula:** C₄₀H₅₃N₇O₅S₂
- **Formula Weight:** 776.0

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS (LOA Date)
25188	II	Gilead	Cobicistat DS	3	Adequate	22-Jul-2014 by Dr. G. Lunn for NDA 206353	28-Feb-2012
(b) (4)			(b) (4)	4	Adequate		9-Feb-2012
	III			4	Adequate		13-May-2011
	III			4	Adequate		22-Jul-2013
	III			4	Adequate		08-Oct- 2013
	III			4	Adequate		13-Jan-2014
	III			4	Adequate		11-Feb-2014
	III			4	Adequate		23-Jul-2013
	III			4	Adequate		10-May-2011
				4	Adequate		29-Jan-2014
	III			4	Adequate		02-Jan-2014

Chemistry Review Data Sheet

(b) (4)		(b) (4)			
	III		4	Adequate	02-Jan-2014
	III		4	Adequate	13-Jun-2012
	III		4	Adequate	19-Jul-2013
	III		4	Adequate	18-Feb-2014
	III		4	Adequate	23-Jul-2013
	III		4	Adequate	23-Jan-2014
	III		4	Adequate	22-Jul-2013
	III		4	Adequate	30-Jan-2014
	III		4	Adequate	28-Mar-2012
	III		4	Adequate	18-Nov-2013

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)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10-Jun-2014	Krishnakali Ghosh, Ph.D.
Pharm/Tox	Approval	21-Mar-2013	Laine Myers
Biopharm	Approval	18-Mar-2013	Deepika Lakhani, Ph.D.
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Microbiology	N/A		
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The Chemistry Review for NDA 203094

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203094 resubmission has provided adequate CMC information to assure the identity, strength, purity, and quality of the drug product. The Drug Master File (DMF 25188) for the cobicistat on silicon dioxide drug substance supporting this NDA is adequate. The labels and labeling are adequate from a CMC perspective, but are pending OND team review for finalization. The overall recommendation from the Office of Compliance is ACCEPTABLE as of June 10, 2014 for the establishment evaluation. Therefore, from the CMC perspective, this NDA is recommended for approval.

The recommendations in this review apply to (b) (4) the US-image and (b) (4)

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)

Please refer to NDA 203094 Review #1 dated March 19, 2013 and Review #1 Addendum #1 dated April 25, 2014 for a complete description of the drug product and drug substance. Review #1 concluded that the NDA had provided adequate information to support the identity, strength, purity and stability of the drug product. However, this conclusion was revised in Review #1-Addendum #1 and the NDA was NOT recommended for approval based on the evaluation by the Office of Compliance and the overall EES recommendation of WITHOLD for Gilead Foster City. The inspectional observation included deficiencies for changes to the analytical methods used for batch release and primary stability studies and lack of method validation justification and bridging. This review is an assessment of the resubmission and evaluation of the issues that were communicated in the Complete Response Letter from 26 April 2013.

Based on review of this NDA re-submission, the issues for preventing approval stated in the Complete Response Letter from 26 April 2013 have been adequately addressed as follows:

- Gilead Foster City has been removed as a facility for release and stability testing of Tybost drug product and Cobicistat drug substance.

Executive Summary Section

- Information on the analytical method changes, including a complete version history, and the bridging studies used to support the changes, have been included in the re-submission and are adequate. The methods are used in the batch analysis and primary stability evaluation, which are used to justify shelf life of the drug product.
- The updated primary stability data supports a new shelf life of 36 months when stored below 30 °C in the approved container closure system.

At this time, NDA 203094 can be concluded to contain adequate information to support the identity, strength, purity and stability of Tybost (Cobicistat) Tablet, 150 mg.

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

A single Tybost (cobicistat) 150 mg tablet is taken orally, once daily, with food. It must be administered with atazanavir or Darunavir in combination with other HIV-1 antiretroviral agents.

The tablets are packaged in (b) (4) high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and (b) (4) silica gel desiccant. Each bottle is capped with a (b) (4) (b) (4), child-resistant (b) (4) screw cap (b) (4) (b) (4). The bottle label states that the tablets are to be dispensed in the original container. The shelf life granted for Tybost 150 mg tablets in the approved container is 36 months when stored at 25 °C (excursions permitted 15 – 30 °C) (b) (4).

C. Basis for Approvability or Not-Approval Recommendation

Deficiencies cite in Review #1-Addendum #1 are now satisfactorily resolved. Information provided on drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is adequate to support the quality of the drug product through shelf-life. The DMF for the cobicistat drug substance is adequate. The labels and package insert are adequate from a CMC-perspective. This NDA was recommended for approval by Dr. Deepika Lakhani on March 23, 2013 from biopharm perspective.

The overall recommendation from the Office of Compliance is ACCEPTABLE as of June 10, 2014 for the establishment evaluation. Therefore, from the CMC perspective, this NDA is recommended for approval.

III. Administrative

A. Reviewer's Signature

Fuqiang Liu
On file

B. Endorsement Block

Executive Summary Section

Rapti Madurawe
On file

C. CC Block
On file

36 Pages have been Withheld in Full as B4(CCI/TS)
Immediately Following this Page

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/s/

FUQIANG P LIU
08/04/2014

RAPTI D MADURawe
08/06/2014



Memorandum

Regarding: NDA 203-094 TYBOST (Cobicistat) Tablets

Date: Apr 7, 2014

Subject: Resubmission Status Completeness Confirmed

This NDA was issued a CR letter in Apr 2013, with the following two deficiencies that relate to CMC issues:

CR Issue #2

During the current inspection of the Gilead Sciences, (Foster City, CA) facility for this application, FDA field investigators found significant deficiencies and discussed them with firm management. Firm management acknowledged these deficiencies in a letter dated April 23, 2013. Satisfactory resolution of significant deficiencies is required before this application may be approved.

Resubmission: All facilities are listed as ready for inspection on the 356h form in the March 26, 2014 resubmission.

CR Issue #3

During the Gilead Foster City inspection, FDA field investigators found significant concerns regarding the release and stability data presented in the NDA and in DMF 25188 because of lack of method validation of the test methods used to obtain this data. Before the application can be approved, the integrity of the drug substance and drug product release and stability data need to be assured by submission of a detailed explanation to reconcile the analytical methods submitted in the NDA and the DMF with those used at the Foster City site.

We recommend you submit a proposal outlining how you plan to resolve these deficiencies in a meeting package in preparation for NDA resubmission.

Resubmission: A 6-page summary of the new or updated information that is included in the resubmission is provided in Module 1, Section 1.11.1.

FDA Meeting Minutes from a Jan 22, 2014 (relevant extracts):

Gilead intends to include the method validation and bridging study reports for those analytical methods used during clinical development for release and stability testing of elvitegravir and cobicistat on silicon dioxide drug substances and Vitekta and Tybost drug products in DMF 25187, DMF 25188, NDA 203093 and NDA 203094, respectively.

Gilead stated that the most recent inspection was completed in October, 2013 and they plan to include data from the (b) (4) audit in the resubmission of the Vitakta and Tybost NDAs, along with updated stability data.

FDA inquired about development methods and final methods/commercial methods and asked if Gilead had conducted any bridging studies between methods. Gilead responded that they had conducted a bridging study and submitted the results in response to the 483 observations. FDA stated that Gilead should include a reference guide to the batch analysis data and the linkage to the different methods (development methods versus final methods/commercial methods) with supportive validation and bridging data.

Resubmission: The 6-page summary of the new or updated information that is included in the resubmission in 1.11.1 contains:

- Updated report in P.5.2 of development and method rationale for Dissolution method TM-165)
- Additional validation of the Identity/Assay/Degrad in tablets by UPLC (TM-163)
- Additional validation of the Dissolution by HPLC (TM-165) and by UPLC (TM-165)
- Additional validation of the tablet (b) (4)
- Table 3 in P.5.3 may have been updated with additional validation of the methods that use UV detection for Identification, Assay, Degradants and Dissolution (TM-164)
- Section P.5.4 includes clarification of method revision history and test sites for clinical product release (Table 7)
- Added method revision histories including method conditions, method validation, method comparability data and use period for analytical methods for testing of content uniformity, dissolution and identity/assay/degradation product content used during clinical development (STM-1157, STM-1155, STM-2395, STM-1388, STM-1828, and STM-1156)

Additional noteworthy elements listed in the 1.11.1 table include:

- Updated Microbiological Examination section in P.5.6 related to FDA recommendations in the Nov 9, 2012 IR letter
- Updated stability data to justify a 36 mo expiration dating period
- Updated stability data on the (b) (4) tablet
- Updated targets and normal operating ranges for some (b) (4) process parameters (3.2.P.3.3)
- Added (b) (4) hold time information in response to FDA recommendations in the Nov 9, 2012 IR letter (3.2.P.3.4)

Gilead plans to use alternative facilities (rather than Foster City) for commercial testing.

Resubmission: Changes have been made to facility responsibility to shift commercial responsibilities from Foster City to other sites. For example, (b) (4) will now add stability testing site for drug substance Cobicistat on Silicon Dioxide and for Cobicistat Tablets. Foster City now is only a batch release site (not testing site) for the drug product and drug substance.

Comprehensive third party audit reports are not required in the resubmission of these NDAs. Copies of the third party audit reports can be communicated to the district office, who will then communicate with CDER as needed. The certificates of the integrity of the analytical data generated at the Gilead Foster City site have been drafted and will be included in the resubmission of the Vitakta and Tybost NDAs.

Resubmission: A 3-page summary of the coverage and approach taken by (b) (4) as the third party auditor between Feb 3 and Mar 20, 2014 is included in 3.2.R.2. This report concludes: (b) (4) concluded that the raw data and databases including Empower and LIMS are well maintained and traceable to the stability data and method validation/bridging data generated at Foster City, CA and described in the NDA. The data integrity is verified following confirmation that all raw data is accurately recorded in Empower and/or LIMS. Therefore, it is concluded that 100% of the CMC data generated at Gilead, Foster City, CA, reviewed by (b) (4) and presented in the NDA 203094 is supported by the raw data.”

March 23, 2014 Advice from FDA to Gilead:

In NDA 205834 for Ledipasvir and Sofosbuvir tablets, where developmental methods were used in the batch analysis of ledipasvir drug substance, the specific methods were identified (Table 7 in S.4.4). Additionally, those methods and validation results were described in the NDA (S.7.3) together with bridging studies where appropriate. This approach could be very useful when the Cobicistat and Elvitegravir NDAs are resubmitted. It could also be useful to include in those resubmissions a summary of what was done as part of the supplemental validation listed for some methods in Gilead’s February 21, 2014 letter.

Resubmission: The revised Table 7 in Section P.5.4 includes clarification of method revision history and test sites for cobicistat tablet release, although there does not seem to be anything analogous for cobicistat drug substance.

Gilead’s Feb 21 letter includes these notes about Cobicistat Tablet Methods:

- “TN-163 Supplemental Validation Complete” – revised validation data included in 3.2.P.5.3
- “TN-165 Supplemental Validation Complete” – revised method and validation data included in 3.2.P.5.2 and P.5.3
- “TN-145 Supplemental Validation Underway” – not included in resubmission. During review discuss with CDER Compliance whether this should be requested

Conclusion: This amendment is a complete response to issues #2 and #3 in the Apr 23, 2013 CR action letter. It also includes CMC information as recommended by the FDA at the Jan 22, 2014 meeting and in the March 23, 2014 advice communication. It is therefore complete for filing from CMC perspective. Some additional notes for consideration during the review of the resubmission are included in the blue notes, above. The reviewers of the original NDA were:

- Fuqiang Liu (Drug Substance and Drug Product)
- Deepika Lakhani (Biopharmaceutics)

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/s/

STEPHEN MILLER

04/29/2014

From the CMC perspective, the resubmission is a complete response to the issues in both CR letters (Orig-1 and Orig-2), and can be accepted for review.

RAPTI D MADURAWA

05/01/2014

NDA 203094

Tybost™ (cobicistat) Tablets, 150 mg

Gilead Sciences, Inc.

**Addendum 1 to
Review #1**

Fuqiang Liu, Ph.D.

**DPA II/Branch V
Office of New Drug Quality Assessment**

For Division of Anti-Viral Products

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Chemistry Review Data Sheet

1. NDA 203094
2. REVIEW #: Addendum 1 to Review #1
3. REVIEW DATE: April 25, 2013
4. REVIEW TEAM:
Fuqiang Liu – Drug Substance and Drug Product
Deepika Lakhani - Biopharmaceutics
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 101283 Pre-NDA	01-May-2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SDN 026: Labeling/ Package Insert	22-March-2013
SDN 027: Labeling/ Package Insert	10-April-2013
SDN 029: Labeling/Package Insert	18-April-2013
SDN 030: Labeling/ Container/ Carton Draft	24-April-2013

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404 USA
Representative:	Christophe Beraud, PhD, Associate Director, Regulatory Affairs Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Telephone:	650 522-5093

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tybost™
b) Non-Proprietary Name (USAN): Cobicistat Tablet
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5, new formulation or manufacturer
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Pharmacokinetic booster for HIV protease inhibitors Atazanavir.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

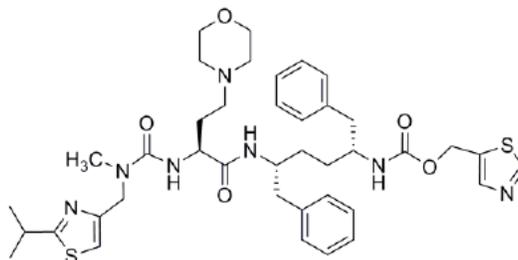
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



- **IUPAC:** 1,3-Thiazol-5-ylmethyl [(2*R*,5*R*)-5-{{(2*S*)-2-[(methyl{2-(propan-2-yl)-1,3-thiazol-4-yl)methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl}amino]-1,6-diphenylhexan-2-yl]carbamate
- **CAS:** 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (3*R*,6*R*,9*S*)-
- **Synonym (CAS):** Thiazol-5-ylmethyl [(1*R*,4*R*)-1-benzyl-4-({(2*S*)-2-[(methyl{2-(1-methylethyl)thiazol-4-yl)methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl}amino)-5-phenylpentyl]carbamate
- **USAN:** Cobicistat
- **Formula:** C₄₀H₅₃N₇O₅S₂
- **Formula Weight:** 776.0

17. RELATED/SUPPORTING DOCUMENTS:

CMC Product Quality Review #1 (19-Mar-2013)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Withhold	25-Apr-2013	Krishnakali Ghosh, Ph.D.
Pharm/Tox	N/A		
Biopharm	Approval	19-Mar-2013	Deepika Lakhani, Ph.D.
LNC	N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Methods Validation	N/A		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

The Chemistry Review for NDA 203094

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203094 is not recommended for approval from the CMC perspective. The Office of Compliance has issued an overall withhold recommendation for establishments due to significant deficiencies noted at the Gilead Sciences, Foster City, CA site. The Foster City site deficiencies bring into question the validity and conclusions of the batch analysis and primary stability data submitted in the NDA for the drug product and in DMF 25188 for the drug substance. Therefore the identity, strength, purity and the stability of the drug product and drug substance cannot be established at this time. The deficiencies cited in section II.C need to be resolved satisfactorily before this NDA can be recommended for approval.

Labeling review was not finalized by the OND review team.

The recommendations and conclusions from this review cover (b) (4) the US-image (b) (4) Tybost tablet information. (b) (4).

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)

Please refer to NDA 203094 Review #1 dated 19-Mar-2013 for a summary of the drug product and drug substance. Review #1 concluded that the NDA had provided adequate information to support the identity, strength, purity and stability of the drug product. This conclusion is now revised due to the following.

The Office of Compliance issued an overall recommendation of WITHHOLD for the establishments on April 25, 2013 due to significant deficiencies at the Gilead Sciences, Foster City, CA site. The Foster City site conducts batch release testing, stability testing and release of the drug product under the NDA as well as stability testing and release for cobicistat drug substance under DMF 25188. Inspection of Gilead Sciences, Foster City site identified significant deficiencies regarding analytical method validation reports, analytical methods used to test release and stability batches, and other CGMP concerns. Significant deficiencies were also identified regarding method validation results. These deficiencies bring into question the validity

Executive Summary Section

and conclusions from the batch analysis and primary stability data provided in the NDA for the drug product and therefore invalidate the conclusions of NDA 203094 Review #1. As DMF 25188 for the cobicistat drug substance also relies on the Foster City site for batch release and stability testing of the drug substance, DMF 25188 was determined to be inadequate in DMF review dated 25-April-2013. Additional information may need to be submitted to the NDA and DMF for re-evaluation of batch analysis and primary stability data for drug product and drug substance. Shelf-life conclusions in NDA 203094 Review #1 are also invalidated until additional information on the adequacy of method validations used at the testing site during primary stability studies can be confirmed.

At this time, the NDA 203094 cannot be concluded to contain adequate information to support the identity, strength, purity and stability of Tybost (cobicistat) Tablet, 150 mg.

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

A single Tybost (cobicistat) 150 mg tablet is taken orally, once daily, with food. It must be administered with atazanavir, darunavir (b) (4) and in combination with other HIV-1 antiretroviral agents.

The tablets are packaged in (b) (4) high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and (u) (u) silica gel desiccant. Each bottle is capped with a (b) (4) (b) (4), child-resistant (b) (4) screw cap (b) (4) (b) (4). The bottle label states that the tablets are to be dispensed in the original container.

At this time, a shelf-life is not assigned for Tybost for reasons discussed above.

C. Basis for Approvability or Not-Approval Recommendation

NDA 203094 is recommended not for approval based on the following:

(1) FACILITY INSPECTIONS

During the current inspection of the Gilead Sciences, (Foster City, CA) facility for this application, FDA field investigators found significant deficiencies and discussed them with firm management. Firm management acknowledged these deficiencies in a letter dated April 23, 2013. Satisfactory resolution of significant deficiencies is required before this application may be approved.

(2) STABILITY AND RELEASE TESTING

During the Gilead Foster City inspection, FDA field investigators found significant concerns regarding the release and stability data presented in the NDA and in DMF 25188 because of lack of method validation of the test methods used to obtain this data. Before the application can be approved, the integrity of the drug substance and drug product release and stability data need to

Executive Summary Section

be assured by submission of a detailed explanation to reconcile the analytical methods submitted in the NDA and the DMF with those used at the Foster City site.

Therefore, the Applicant has not provided sufficient information for assuring consistent identification, strength, purity and quality of the drug substance and the drug product.

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

Fuqiang Liu
On file

B. Endorsement Block

Rapti Madurawe
On file

C. CC Block

On file

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/s/

FUQIANG P LIU
04/25/2013

RAPTI D MADURawe
04/25/2013



Memorandum

Date: April 25, 2013

From: Krishna Ghosh, Compliance Officer
Generic Drug Manufacturing Assessment Branch (GDMAB)

Concurrence with District Office Withhold Recommendation
NDA 203094/000, TYBOST (Cobicistat) 150 mg Tablets

Through: Tara Goen, Acting Branch Chief
New Drug Assessment Branch (NDMAB)
Division of Good Manufacturing Practice Assessment (DGMPA)

To: NDA 203094

Applicant: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
United states

Control Testing Lab : Gilead Sciences Inc.
333 Lakeside Drive
Foster City, CA 94404
FEI 1000523075

The Office of Manufacturing and Product Quality (OMPQ) has conducted a review of mid-inspection deficiencies observed during an on-site inspection of Gilead Sciences Inc. Foster City, CA. This site is named as the testing lab for the API and finished dosage for NDA TYBOST (Cobicistat) NDA 203094. An inspection in support of listed operations per CPGM 7346.842 was initiated [REDACTED] (b) (4) by investigators Carl Lee and Kim Cruse. The profile class covered is CTL. Due to several product specific issues, a recommendation to withhold the application for TYBOST (Cobicistat) NDA 203094 was made [REDACTED] (b) (4) on April 19, 2013 to CDER/Office of Compliance. A review of these deficiencies, supportive documents along with the corrective action memo (dated April 23, 2013) provided by the firm was performed and the summary of conclusions are documented in this memo.

CDER/OC/OMPQ/DGMPA assessment:

On April 19th, 2013, I discussed the ongoing findings with the inspection team. The Office of Manufacturing and Product Quality (OMPQ) concurs with the [REDACTED] (b) (4) District Office [REDACTED] (b) (4) recommendation to withhold approval of NDA 203094. The following significant product specific deficiencies were identified:

1. The firm has failed to submit appropriate analytical test methods and validation reports for the clinical and primary stability studies reported in the application:
 - a. The firm has failed to validate the analytical test method for drug product assay and degradation STM-1155.04 which was used to test the samples up to 18 months. Some major changes were made in the next revision STM-2395 with regards to chromatographic conditions. No bridging studies were performed to establish equivalency of the previously used test method STM-1155.04. The method submitted to the agency was TM-163.
 - b. The firm has failed to validate STM-1828 (versions.01, 03, 04) for dissolution (using UV quantitation method) which was used during the stability studies up to 12 months and was not submitted for review to the agency. No bridging study has been performed due to major changes to the detection methodology from UV to HPLC/UPLC (1156 versions .04, .05) used to test the stability samples during 12 and 18 month time point.
 - c. Lack of assay validation and verifications were also observed in various analytical methods used in the primary stability studies of the drug substance including but not limited to (b) (4), ID, chiral purity, residual solvent.
 - d. Validation (b) (4) reported 24 executed runs but only 22 chromatograms were maintained and available. The weigh print outs were also missing for the missing chromatograms.

2. Analytical test method USP <921> has not been verified (b) (4) for the drug product.

In addition to the issues described above, I further noted the following significant issues from the corrective action plan provided to the investigators. The following are concerns associated with laboratory controls (21 CFR 211.160 and 211.194), the current findings and the current capability and readiness of the firm:

- i. Lack of formal analytical method validation process for clinical and prior to registration stability studies appears to be a systemic issue with the firm. Without additional evaluation, the validity of the assays used in the initial primary stability studies (stability data reported in the application) cannot be relied upon in the application. Informal studies have been conducted by the firm with no formal approved protocols, reviews or approvals.
- ii. The firm continually implemented changes to the analytical test methods during the course of stability studies of the drug substance and the product and test but did not conduct systemic bridging studies to compare and demonstrate the equivalency of the modified test methods, where appropriate. This appears to be a systemic issue with regards to firm's compliance program.
- iii. The firm demonstrated poor record controls, such as the complete lack of use log books for balances to establish sample traceability.

- iv. The firm failed to have appropriate equipment qualification for analytical equipment, [REDACTED] (b) (4).
- v. The firm failed to keep the records of lot numbers of excipients and documentation of weights for each component used in preparation of test samples for accuracy determination during assay validation studies (TM-163).

CDER/OC/OMPQ/DGMPA recommendation:

Due to these deficiencies, NDMAB concurs with [REDACTED] (b) (4) recommendation to withhold approval of NDA-203094 TYBOST (cobicistat) 150 mg tablets at this time.

If you have any questions, please contact me at 301-796-2644, or by email at Krishnakali.Ghosh@fda.hhs.gov.

Krishna Ghosh, Ph.D.
Compliance Officer
CDER/OC/OMPQ/DGMPA/GDMAB

CMS # 68605

HFD-320 Tara Goen, Acting BC, NDMAB

To: [REDACTED] (b) (4) Pre-Approval Manager, [REDACTED] (b) (4)
Fuqiang Liu, CDER/ONDQA
Rapti Madurawe, CDER/ONDQA
Stephen Miller, CDER/ONDQA

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/s/

KRISHNA GHOSH
04/25/2013

TARA R GOOEN
04/25/2013

NDA 203094

Tybost™ (cobicistat) Tablets, 150 mg

Gilead Sciences, Inc.

Fuqiang Liu, Ph.D.

**DPA II/Branch V
Office of New Drug Quality Assessment**

For Division of Anti-Viral Products

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Chemistry Review Data Sheet

1. NDA 203094
2. REVIEW #: 01
3. REVIEW DATE: 14-Mar-2013
4. REVIEW TEAM:
Fuqiang Liu – Drug Substance and Drug Product
Deepika Lakhani - Biopharmaceutics
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 101283 Pre-NDA	01-May-2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original: New NDA	27-Jun-2012
SDN 002: Quality/Quality Information Amendment	9-Jul-2012
SDN 004: Quality/Response to Information Request	21-Aug-2012
SDN 006: Quality/Response to Information Request	10-Sep-2012
SDN 009: Quality/Response to Information Request	05-Oct-2012
SDN 010: Labeling/Package Insert Draft	19-Oct-2012
SDN 012: Quality/Response to Information Request	27-Nov-2012
SDN 015: Quality/Response to Information Request	21-Dec-2012
SDN 020: Quality/Response to Information Request	11-Feb-2013
SDN 022: Labeling/Package Insert Draft	25-Feb-2013

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404 USA
Representative:	Christophe Beraud, PhD, Associate Director, Regulatory Affairs Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Telephone:	650 522-5093

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tybost
- b) Non-Proprietary Name (USAN): Cobicistat Tablet
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Pharmacokinetic booster for HIV protease inhibitors Atazanavir and Darunavir

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

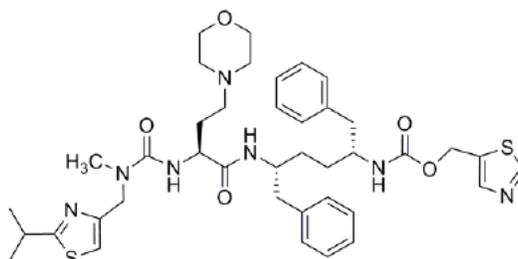
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



- **IUPAC:** 1,3-Thiazol-5-ylmethyl [(2*R*,5*R*)-5-{{(2*S*)-2-[(methyl{2-(propan-2-yl)-1,3-thiazol-4-yl)methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl}amino]-1,6-diphenylhexan-2-yl]carbamate
- **CAS:** 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (3*R*,6*R*,9*S*)-
- **Synonym (CAS):** Thiazol-5-ylmethyl [(1*R*,4*R*)-1-benzyl-4-({(2*S*)-2-[(methyl{2-(1-methylethyl)thiazol-4-yl)methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl} amino)-5-phenylpentyl]carbamate
- **USAN:** Cobicistat
- **Formula:** C₄₀H₅₃N₇O₅S₂
- **Formula Weight:** 776.0

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
25188	II	Gilead	Cobicistat DS	1	Adequate	March 2013	LOA 28-Feb-2012
(b) (4)			(b) (4)	4	N/A	N/A	9-Feb-2012
	III			4	N/A	N/A	LOA

Chemistry Review Data Sheet

(b) (4)	(b) (4)				13-May-2011 There is enough data in the application	
		III	4	N/A	N/A	LOA 13-Jun-2012 There is enough data in the application
		III	4	N/A	N/A	LOA 12-Apr-2012 There is enough data in the application
		III	4	N/A	N/A	LOA 28-Mar-2012 There is enough data in the application
		III	4	N/A	N/A	LOA 28-Mar-2012 There is enough data in the application
		III	4	N/A	N/A	LOA 05-Apr-2012 There is enough data in the application

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:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	IND 101283	Cobicistat IND
	NDA 203100	Stribild (COBI/EVG/FTC/TDF) NDA
	NDA 21976	Darunavir NDA
SDN 1239	IND 62477	Darunavir IND

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		Krishnakali Ghosh, Ph.D.
Pharm/Tox	N/A		
Biopharm	Approval	18-Mar-2013	Deepika Lakhani, Ph.D.
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

The Chemistry Review for NDA 203094

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203094 has provided adequate CMC information to assure the identity, strength, purity, and quality of the drug product. The Drug Master File (DMF 25188) for the cobicistat on silicon dioxide drug substance supporting this NDA is adequate. The labels and labeling are adequate from a CMC perspective, but are pending OND team review for finalization. The overall recommendation from the Office of Compliance is PENDING as of Mar. 14, 2012 for the establishment evaluation. Therefore, from the CMC perspective, this NDA is not recommended for approval at this time due to the pending establishment evaluation.

The recommendations in this review apply to (b) (4) the US-image (b) (4) Tybost tablets. (b) (4).

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)

Gilead Sciences' NDA 203094 provides for Tybost™ (cobicistat) Tablets, 150 mg. Cobicistat (COBI) was first approved in August 2012 as a new molecular entity in Gilead's NDA 203100 for Stribild, a four drug combination tablet.

Drug Substance

All drug substance information is referenced to Gilead's Drug Master File (DMF) 25188. The drug substance, as defined in DMF 25188, is Cobicistat on Silicon Dioxide. Cobicistat is isolated by adsorption onto silicon dioxide (b) (4). DMF 25188 was found adequate on May 2012. NDA 203094 only sources COBI drug substance manufactured at the (b) (4) and Gilead (b) (4) sites. (b) (4)

All other information submitted since May 2012 has not substantially altered the DMF and the DMF remains adequate (reviewed March 2013). Note that the same DS specification is used in NDA 203094, NDA 203100 and DMF 25188.

Executive Summary Section

Drug Product

The drug product is an immediate-release tablet containing 150 mg of cobicistat (b) (4). (b) (4)

(b) (4) The U.S. tablets are orange, round, biconvex, film-coated tablets, and debossed with "GSI" on one side and plain-faced on the other side. (b) (4)

(b) (4) . The film-coat is added for elegance and has no impact on drug release.

The cobicistat (COBI) tablet contains excipients commonly used in tablet dosage forms: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The film coat contains polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, sunset yellow FCF (FD&C yellow # 6 (b) (4)) aluminum lake and yellow iron oxide.

The commercial manufacturing scale range for the drug product is (b) (4). The tablets are manufactured (b) (4).

(b) (4) The DP manufacture process is described in sufficient detail and the process parameters and equipment used are identified. Critical process parameters (b) (4) are adequately justified.

Drug product specifications include tests for appearance, identification, (b) (4), assay, degradation product content, uniformity of dosage units, and dissolution. The degradation product specification includes the total, individually specified, individually unspecified and/or unidentified impurities. There are six specified degradation products, the same as in NDA 203100. The specification is adequately justified for the DP both at release and at shelf life.

Cobicistat tablets are stored in a HDPE bottle with silica gel desiccant, a (b) (4) child-resistant cap (b) (4).

Primary drug product stability data provided for three pilot scale (b) (4) US-image tablets in the primary container system included 18 months at 25 °C/60% RH and 30 °C/ 75% RH, and 6 months at 40 °C/75% RH. Additional stability data was provided for another US-image batch (b) (4) at 25 °C/60% RH and 30 °C/ 75% RH for 12 months, and 40 °C/ 75% RH for 6 months. (b) (4)

(b) (4) In addition, stress stability data and open dish study data were provided to support the drug product chemical and physical stability, adequacy of the container closure system, and in-use stability and moisture uptake of the tablets. Overall, the drug product shows limited degradation. The primary degradants observed, (b) (4) and their levels are well below the proposed specifications at shelf-life.

Executive Summary Section

Dissolution over shelf-life was found acceptable by the biopharmaceutics reviewer. Please refer to the biopharmaceutics review for details.

The submitted stability data supports a shelf life of (b) (4). The US image storage condition is “Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature). (b) (4)

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

A single Tybost (cobicistat) 150 mg tablet is taken orally, once daily, with food. It must be administered with atazanavir, darunavir, (b) (4) and in combination with other HIV-1 antiretroviral agents.

The tablets are packaged in (b) (4) high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and (b) (4) silica gel desiccant. Each bottle is capped with a (b) (4) (b) (4) child-resistant (b) (4) screw cap (b) (4). The bottle label states that the tablets are to be dispensed in the original container. The shelf life granted for Tybost 150 mg tablets in the approved container is (b) (4) when stored at 25 °C (excursions permitted 15 – 30 °C) (b) (4).

C. Basis for Approvability or Not-Approval Recommendation

Information provided on drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is adequate to support the quality of the drug product through shelf-life. The DMF for the cobicistat drug substance is adequate. The labels and package insert are adequate from a CMC-perspective although the labels and labeling are pending final OND team review.

At this time, this NDA is not recommended for approval due to the following: As of Mar. 14, 2013, the overall recommendation for the manufacturing and testing facilities is PENDING. Approval of this NDA is contingent upon an overall evaluation of “acceptable” in EES and the acceptability of the final labeling.

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

Fuqiang Liu
On file

B. Endorsement Block

Rapti Madurawe
On file

C. CC Block

On file

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/s/

FUQIANG P LIU
03/18/2013

RAPTI D MADURawe
03/19/2013

Office of New Drug Quality Assessment
Product Quality and Manufacturing Memo
(PQM Memo)

Memo Date: Sept. 25, 2012
From: Fuqiang Liu, Ph. D.
On behalf of the CMC Review Team

Through: Rapti Madurawe, Ph.D., Branch Chief Division V

NDA Number: 203094 GRMP Date: March 22, 2013
Applicant: Gilead Sciences Inc. PDUFA Date: April 28, 2013

Drug Product Name and Strength:

Cobicistat Tablets, 150 mg; also described as Tybost (trade name).

Drug Product Introduction:

The cobicistat (COBI) tablet is an immediate-release tablet containing 150 mg of cobicistat. This NDA provides (b) (4) for the US market (b) (4). The COBI tablets for the U.S. market are round, film-coated orange tablets debossed with "GSI" on one side and plain-faced on the other side. (b) (4)

The composition of the US to-be-marketed tablets is shown below (Table 1). The DP manufacture involves (b) (4). The manufacturing process for cobicistat (b) (4). (b) (4). (b) (4). The manufacturing process flow diagram is shown in Figure 1.

Table 1: Qualitative and Quantitative Composition of Cobicistat Tablets

Components	% w/w	Unit Formula (mg/unit)	Quality Standard	Function
Tablet Core				
Cobicistat on Silicon Dioxide	(b) (4)	(b) (4)	In-House	Active
Microcrystalline Cellulose			NF, Ph. Eur., JP	(b) (4)
Croscarmellose Sodium			NF, Ph. Eur., JP	
Magnesium Stearate			NF, Ph. Eur., JP	
Total				
Film Coat				
(b) (4)	(b) (4)	(b) (4)	In-House	(b) (4)
			USP, Ph. Eur.	

Figure 1: Process Flow Diagram for Cobicistat Tablets



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Drug Substance Introduction:

The ONDQA CMC Review team is conveying considerations for inspection for the manufacture of Cobicistat on silicon dioxide drug substance (DS). Even though this New Molecular Entity (NME) DS was recently approved under NDA 203100, many CMC review issues or concerns were observed throughout the review process of DMF 25188; therefore it is critical to confirm that the identified issues or concerns has been addressed properly.

(b) (4)

(b) (4) Information in regards to the manufacturing process of Cobicistat silicon dioxide is referenced to DMF 25188 and its corresponding CMC review in DARRTS, dated May 31, 2012.

Cobicistat on silicon dioxide DS is manufactured

(b) (4)

(b) (4)

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/s/

FUQIANG P LIU
09/25/2012

RAPTI D MADURawe
09/25/2012

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

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **203-094**

Submission Date: June 26, 2012

GRMP Goal Date: March 22, 2013

PDUFA Goal Date: Apr 28, 2013

2. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Tybost (proposed)
Established or Non-Proprietary Name (USAN) and strength:	Cobicistat Tablets, 150 mg
Dosage Form:	Film-coated Tablets

3. NAME OF APPLICANT:

Name:	Gilead Sciences
-------	-----------------

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Property (Legal Basis):	505 (b)(1)
Responsible Organization:	DAVP

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

Review Information

1. INDICATION: Pharmacokinetic booster for the HIV protease inhibitors atazanavir and darunavir

2. ROUTE OF ADMINISTRATION: Oral

3. STRENGTH/POTENCY: 150 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.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

6. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
25188	2	Gilead	Cobicistat DS	2/28/12	
(b) (4)			(b) (4)	2/9/12	
6 other LOAs for Type 3 DMFs are included for packaging components					

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Clin Pharm	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Clin-Pharm is part of the review team
EES	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Pharm/Tox	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Methods Validation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
EA	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
New Drug Micro	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
CDRH	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other ()	<input type="checkbox"/>	<input type="checkbox"/>	

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND 101,283			IND for Cobicistat Tablets

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
As listed in Section 1.6.3			

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Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
<input checked="" type="checkbox"/>	<input type="checkbox"/>	1.

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
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<ol style="list-style-type: none"> The information about specifications for the starting materials which are presented in Module 2 should either be revised to incorporate recent revisions under DMF 25188, or replaced with a reference to that DMF. Either revise the Description of the Manufacturing Process in 3.2.P.3.3 to make it comparably detailed to a batch record, or submit an unexecuted master batch record for the commercial drug product process. Because Cobicistat tablets may be used in all climatic zones world-wide, revise all post-approval stability protocols (b) (4) (b) (4) (b) (4) (b) (4) Tables and text in sections 3.2.P.8.3 and 2.3.P.8 should be revised. We note that you have presented Proven Acceptable Ranges (PAR) for process parameters in sec P2.3 that were determined on the basis of multivariate studies. However, your section P3.3 includes only Normal Operating Ranges (NOR) or set points for the parameters, where the NOR are a sub set of the PAR. Clarify, if you intend to handle movements within the PAR consistent with ICH Q8(R2). (Comment from S.Chatterjee and C.Cruz).

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Are there potential biopharmaceutics review issues to be forward to the applicant with the 74 day letter?		
Yes	No	Biopharmaceutics Comments for 74 Day Letter
<input type="checkbox"/>	<input checked="" type="checkbox"/>	1.

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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, only "Key."			
Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Is a team review recommended?		
Yes	No	Suggested expertise for team
<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Review Team Assignments (if known)		
Drug Substance	Fuqiang Liu	
Drug Product	Fuqiang Liu	
Biopharmaceutics	Deepika Arora Lakhani	
QbD		
Product Quality Microbiology		
ONDQA PM		

Summary or Highlights of the Application <i>(not already mentioned in other sections)</i>	
Changes between Clinical DP and Proposed Commercial DP	
Clinical Tablets	Commercial Tablets
Described under Drug Product, below	
Indication	
Two indications are proposed in this NDA: use of cobicistat to enhance the PK of the HIV protease inhibitors, atazanavir and darunavir. In present clinical practice both of these drugs are boosted with ritonavir for treatment of HIV infection. The proposed doses are:	
<ul style="list-style-type: none"> • 150 mg Cobicistat once daily with Atazanavir 300 mg once daily • 150 mg Cobicistat once daily with Darunavir 800 mg once daily 	
Drug Substance	
Detailed information including the quality control approaches are in DMF 25188, which was recently found to be adequate during the review of NDA 203-100 (Stribild tablet	

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which included cobicistat plus three other active ingredients).

The drug substance specification has been updated [REDACTED] (b) (4). Whether all changes to the DS specification which were recommended under review of 203-100 have been incorporated was not evaluated as part of this IQA.

The specifications for the starting materials (reported only in Module 2) do not incorporate recent changes made under the DMF.

Drug Product

The cobicistat tablets for US marketing are orange, round, film-coated tablets, supplied in one strength, 150 mg.

[REDACTED] (b) (4)

Stability data with 30°C/75%RH as a long-term condition is provided which may be able to justify storage of [REDACTED] (b) (4) at up to 30°C. [REDACTED] (b) (4)

The degradants that are observed in the tablet are:

[REDACTED] (b) (4)

These are the same degradants that were seen in the Stribild tablet (NDA 203-100). It does not appear that any new Pharm-Tox consults will be needed, since the qualification levels in the Stribild NDA review appear to be sufficiently high, but this should be verified early in the review.

After development [REDACTED] (b) (4)
[REDACTED] study, GS-US-216-0116, referred to as a “pivotal BE study” by Gilead, compared this formulation, BB0904B, to the Phase 1-2 formulation, BB0902A, in

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(b) (4)
This study evaluated the PK parameters for Cobi, and the PK of Elvitegravir boosted with Cobicistat versus Ritonavir boosting.

(b) (4)
The resulting Phase 3 formulation was studied in GS-US-216-0114, which compared safety and efficacy of atazanavir boosted with Cobicistat to atazanavir boosted with ritonavir.

The Clin-Pharm reviewer (Dr. Stanley Au) has raised some questions about whether the final Phase 3 / Commercial formulation has been linked adequately to the previous formulation (BB0904B) with regard to the ability to enhance the PK parameters of darunavir.

Process Development Including QbD Elements:

There are some QbD elements in this application:

- DOE during development (small scale) to understand (b) (4)

properties (b) (4)

- Studies on three batches (b) (4)

Process parameter ranges from these studies are summarized in Tables 7 and 8 in 3.2.P.2.3. It seems strange that “The ranges are specific to the equipment and scale utilized at this time,” but the equipment in Table 6 is only described in very general terms (b) (4). The parameter ranges are similar (but not always identical) to the Proven Acceptable Ranges listed in 3.2.P.3.3.

This statement is also included: “Values defined outside of the range will be assessed and validated as necessary.”

Surprisingly, (b) (4) step is not identified as critical, and only IPCs are identified as critical (b) (4)

The review team members have ample expertise to review these QbD elements. However, periodic informal communication with Dr. Sharmista Chatterjee and other members of the ONDQA QbD team may be valuable during the review, and has lead to one draft comment which may be included in the 74-day letter.

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Issues and Information Extracted from the CMC Review of NDA 203-100

(b) (4)

The above three comments, extracted from the CMC review of NDA, may have some relevance to review of the cobicistat tablet NDA.

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

A request from the Review perspective to inspect the drug substance manufacturing facilities, and to include a reviewer has been added to the EES Comments.

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

Biopharmaceutics Summary: Critical Issues, Complexities, and Consults

Summary

The Biopharmaceutics review will be focused on the evaluation and acceptability of the proposed dissolution method and acceptance criterion.

The dissolution of cobicistat tablets is assessed using the apparatus with paddles (USP Type 2) operated at 75 rpm. The dissolution medium is 900 mL of sodium acetate buffer (pH 4.5) maintained at 37 °C. The amount of cobicistat dissolved is determined by HPLC or UPLC reserved-phase chromatography, employing UV detection at (b) (4).

The dissolution method development is included in the NDA along with data to support the discriminating capability of the method (b) (4)

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(b) (4)

The proposed formulation for commercial release was not used throughout the product's development as Phase 1 and 2 studies used a concentrated solution of cobicistat in ethanol, and Phase 3 studies used cobicistat on silicon dioxide. The commercial formulation is identical to the one used in Phase 3 studies.

Dissolution data are provided from clinical batches and based upon that, the Applicant has proposed an acceptance criterion of NLT (b) (4) (Q) dissolved at 15 minutes.

From ONDQA Biopharmaceutics perspective, the NDA is fileable. There are no filing deficiencies for the 74 day letter.

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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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Dissolution report discussed in March 27, 2012 FDA Preliminary Comments and May 1, 2012 responses (see Mod 1.6)

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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.	<input type="checkbox"/>	<input type="checkbox"/>	NA

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7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <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) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <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) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
9.	<p>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:</p> <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) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Requested
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* 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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Under 21 CFR 25.31(b)

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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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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?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Information is in Drug Substance DMF
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Outlined in Module 2 Information is in Drug Substance DMF
15.	Does the section contain information on impurities?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	In Justification for Specification
16.	Does the section contain information regarding the characterization of the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Information is in Drug Substance DMF
17.	Does the section contain controls for the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Attached below
18.	Has stability data and analysis been provided for the drug substance?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Information is in Drug Substance DMF
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
21.	Does the section contain container and closure information?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Information is in Drug Substance DMF

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F. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
22.	Does the section contain quality controls of excipients?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Attached below
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Critical steps and process steps from 3.2.P.3.4:</p> <ul style="list-style-type: none"> • Uniformity of final blend, but will be tested "as needed" (b) (4) • (b) (4) • Appearance after film-coating <p>IPC for friability will be measured (b) (4)</p>
26.	Is there a batch production record and a proposed master batch record?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<p>Description of Manuf Process in .3.2.P.3.3 is not detailed to level of a batch record, and no master batch record is provided.</p> <p>Executed batch records are included in R.1 for a (b) (4) clinical batch (BB2003B1)</p>
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
28.	Have any Comparability Protocols been requested	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	HDPE bottle of 30 tablets with (b) (4) seal, desiccant and child-resistant cap

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30.	Does the section contain controls of the final drug product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>DP Specification is attached below</p> <p>The analytical procedures are included in the separate Corporate Specification document.</p> <p>For a number of attributes, testing will be performed by either USP or EP procedures.</p> <p>Are tablets physically acceptable [REDACTED] ^{(b) (4)} [REDACTED] ?</p> <p>Microbial limits is only tested in the stability protocol for the registration batches, and will not be part of the DP specification or post-approval stability protocols. Is justification suitable?</p>
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**ONDQA Initial Quality Assessment (IQA) and Filing Review
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31.	Has stability data and analysis been provided to support the requested expiration date?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>18 month data are reported for three pilot scale batches (BB1002B1, 1003B1 and 1004B1; (b) (4) and 12 mo data are included for an additional commercial-scale batch (BB1006B1; (b) (4)).</p> <p>These primary studies covered the 30°C/75%RH long-term condition recommended for products marketed in all climatic zones worldwide. Long-term data at 25°C/60%RH and accelerated data at 40°C/75%RH are also supplied.</p> <p>Additional 6-week studies on a commercial-scale batch (BB11002) covered the ICH Photostability test and these conditions:</p> <ul style="list-style-type: none"> • 25°C/80%RH • 50°C/ambRH • Exposed to 25°C/60%RH • Exposed to 30°C/75%RH <p>(b) (4)</p> <p>Some slowing of dissolution was reported for exposed tablets, but it is not clear if changes were seen under other conditions.</p> <p>Post-approval stability protocols list long-term studies (b) (4)</p> <p>A (b) (4) expiration dating period is proposed for product labeled as follows:</p> <ul style="list-style-type: none"> • US Product: Store at 25°C (77°F) (see insert) <p>(b) (4)</p>
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Small amount: Proven Acceptable Ranges are reported to be based partially on DOE studies.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

G. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
34.	Is there a methods validation package?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Suitable information is in Sections 3.2.P.5.2 and 3.2.P.5.3

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H. MICROBIOLOGY				
	Parameter	Yes	No	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>	NA

I. LABELING				
	Parameter	Yes	No	Comment
36.	Has the draft package insert been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Storage instructions from the Prescribing Information: Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature). • Keep container tightly closed • Dispense only in original container • Do not use if seal over bottle opening is broken or missing
37.	Have the immediate container and carton labels been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain tradename and established name?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
39.	Does the application contain dissolution data?	X		The proposed method uses USP Apparatus Type 2 at 75 rpm paddle speed. The dissolution medium is 900 mL of sodium acetate buffer (pH 4.5) maintained at 37 °C. The amount of cobicistat dissolved is determined by HPLC or UPLC reserved-phase chromatography, employing UV detection at (b) (4)
40.	Is the dissolution test part of the DP specifications?	X		The proposed dissolution acceptance criterion is Q= (b) (4) at 15 minute
41.	Does the application contain the dissolution method development report?	X		
42.	Is there a validation package for the analytical method and dissolution methodology?	X		
43.	Does the application include a biowaiver request?		X	
44.	Does the application include an IVIVC model?		X	

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45.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	
46.	Is there any in vivo BA or BE information in the submission?	X		To be reviewed by OCP
FILING CONCLUSION				
	Parameter	Yes	No	Comment
47.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
48.	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.
49.	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.
50.	Are there any potential review issues identified?	X		See comments above and attached draft information request.

REVIEW AND APPROVAL

{See appended electronic signature page}

Stephen Miller, Ph.D.
CMC-Lead
Office of New Drug Quality Assessment

{See appended electronic signature page}

Deepika Arora Lakhani, Ph.D.
Biopharmaceutics Reviewer
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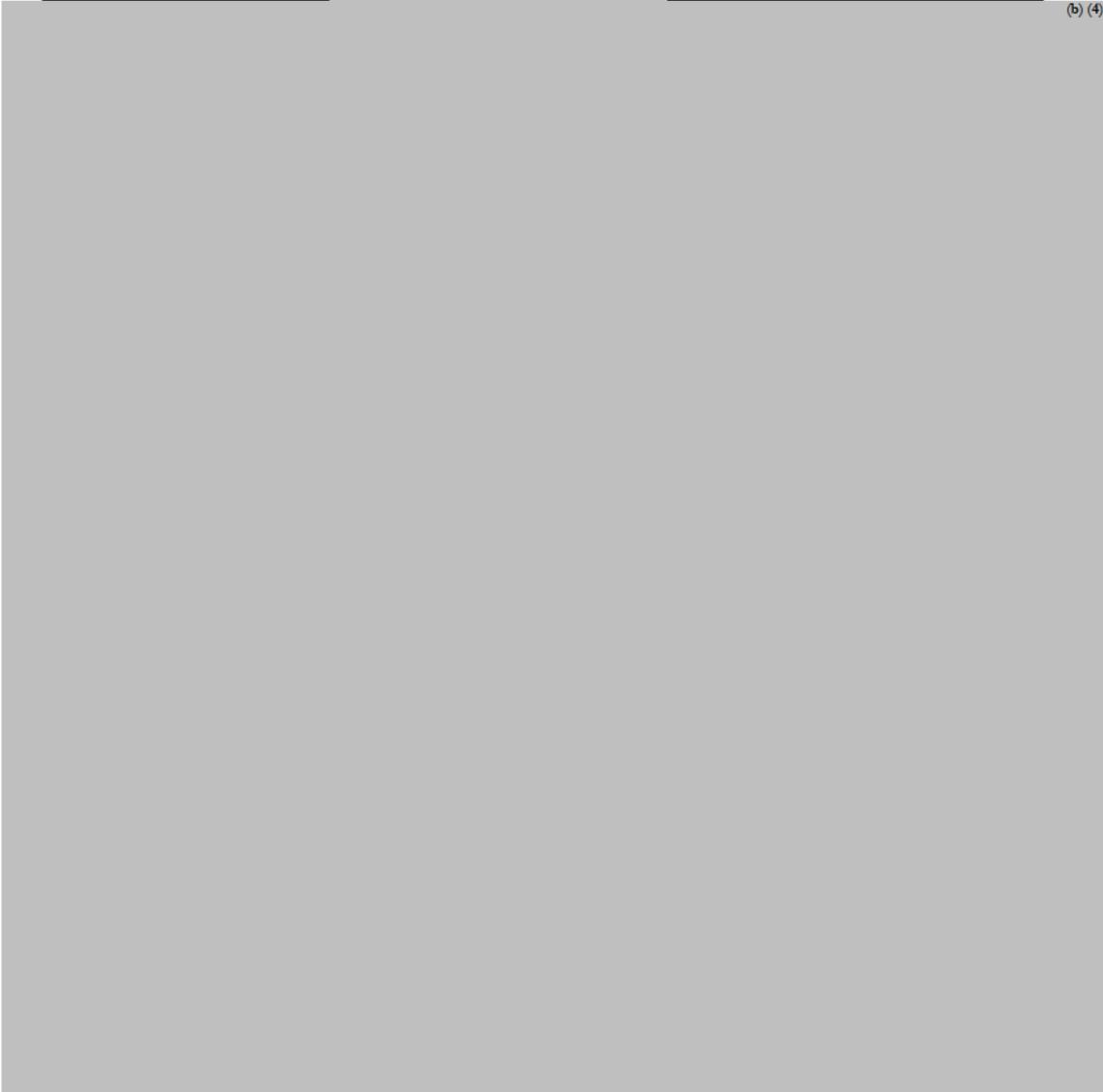
Rapti Madurawe, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

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Appendix 1. Composition of Drug Product

Components of the Tablet for US Marketing

Components	% w/w	Unit Formula (mg/unit)	Quality Standard	Function
Tablet Core				
Cobicistat on Silicon Dioxide	(b) (4)	(b) (4)	In-House	Active
Microcrystalline Cellulose			NF, Ph. Eur., JP	(b) (4)
Croscarmellose Sodium			NF, Ph. Eur., JP	
Magnesium Stearate			NF, Ph. Eur., JP	
Total				
Film Coat				
(b) (4)	(b) (4)	(b) (4)	In-House	(b) (4)
			USP, Ph. Eur.	



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Appendix 2. DP Specification for the US Cobicistat Tablet*

Test Description	Acceptance Limit
Description	<i>Cobicistat Tablets</i> are orange, round, biconvex, film-coated tablets, debossed with "GSP" on one side and plain-faced on the other side. The size and packaging are visually consistent with the description supplied.
Identification A: Chromatographic Retention Time B: UV Spectrum	The retention time of the main peak is consistent with that of the cobicistat reference standard. The UV spectrum of cobicistat tablets is consistent with that of a similarly measured cobicistat reference spectrum.
(b) (4)	(b) (4)
Assay	<i>At Release:</i> The strength of cobicistat is not less than (NLT) (b) (4) and NMT (b) (4) of the label claim. <i>During Shelf-life:</i> The strength of cobicistat is NLT (b) (4) and NMT (b) (4) of the label claim.
Degradation Product Content	<i>At Release:</i> NMT a total of (b) (4) degradation products, with NMT (b) (4) NMT (b) (4) each of any unspecified and/or unidentified degradation product. <i>During Shelf-life:</i> NMT a total of (b) (4) degradation products, with NMT (b) (4) NMT (b) (4) NMT (b) (4) each of any unspecified and/or unidentified degradation product.
Uniformity of Dosage Units	Meets the current USP or Ph. Eur. requirements for weight variation.
Dissolution	NLT (b) (4) (Q) of cobicistat dissolved at 15 minutes.

(b) (4)

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Appendix 3. DS Specification

Test Description	Acceptance Limit
Appearance	<i>Cobicistat on silicon dioxide</i> is a white to pale yellow powder.
Identification of Silicon Dioxide	<i>Cobicistat on silicon dioxide</i> meets the requirement for the identification of silicon dioxide in USP-NF: Silicon Dioxide.
Identification of Cobicistat	
A. UV Spectrum	The UV spectrum of cobicistat in <i>cobicistat on silicon dioxide</i> corresponds to that of the cobicistat reference standard.
B. HPLC Retention Time	The retention time of the main peak of cobicistat is consistent with that of the cobicistat reference standard.
C. IR Spectrum	The IR spectrum of cobicistat in <i>cobicistat on silicon dioxide</i> is consistent with that of the cobicistat reference standard.
(b) (4)	
Assay	The weight percent of cobicistat in <i>cobicistat on silicon dioxide</i> is not less than (NLT) (b) (4) and NMT (b) (4)
Impurity Content	<i>Cobicistat on silicon dioxide</i> contains: NMT a total of (b) (4) impurities, with NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) of any individual unspecified impurity.
Chiral Purity	<i>Cobicistat on silicon dioxide</i> contains: NMT (b) (4) NMT NMT
Residual Solvents	<i>Cobicistat on silicon dioxide</i> contains: NMT (b) (4) NMT NMT (b) (4) or the permitted daily exposure (PDE) as specified by ICH Q3C of any other solvent.
Heavy Metals	<i>Cobicistat on silicon dioxide</i> contains NMT (b) (4) total of heavy metals.
(b) (4) Density	The (b) (4) density of <i>cobicistat on silicon dioxide</i> is NLT (b) (4) and NMT (b) (4)

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

08/27/2012

This NDA is fileable from the CMC and BP perspectives

DEEPIKA LAKHANI

08/27/2012

NDA is fileable from Biopharmaceutics perspective.

ANGELICA DORANTES

08/27/2012

RAPTI D MADURAWAWE

08/28/2012