CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203093Orig1s000

CHEMISTRY REVIEW(S)

NDA 203903

Vitekta™ (Elvitegravir) Tablet, 85 and 150 mg

Gilead Sciences, Inc.

Drug Product Reviewer: Celia N. Cruz, Ph.D.*
Drug Substance Reviewer: Milton Sloan, Ph.D.**

***OPS/IO**
****ONDQA/DPA II/Branch V**

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-093

2. REVIEW #: Review # 2

3. REVIEW DATE: 04 Sept 2014

4. REVIEWERS:

Primary Review Team:

Reviewer	NDA Section
Milton Sloan, Ph.D.	Drug Substance: Elvitegravir DMF
Celia N. Cruz, Ph.D.	Drug Product
Kareen Riviere, Ph.D.	Biopharmaceutics Review

Secondary:

Reviewer	Section
Rapti Madurawe, Ph.D.	All, Overall Recommendation

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
COR-NDAACTION-07 (Complete Response)	26-April-2013
OCR-NDAIR-10 (General Advice Letter)	30-April-2013
COR-MEET-03 (Meeting Minutes)	11-Feb-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Received Date
Resubmission/Class 2	04-April-2014
Labeling/Container-Carton Draft	13-May-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404 USA
Representative:	Prerna Menon, Ph.D. 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: Vitekta
b) Non-Proprietary Name (USAN): Elvitegravir Tablets
c) Code Name: EVG
d) Chem. Type/Submission Priority:

- Chem. Type: 5, new formulation or manufacturer
- Submission Priority: Resubmission Class 2

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

10. PHARMACOL. CATEGORY: integrase inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 85 mg and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

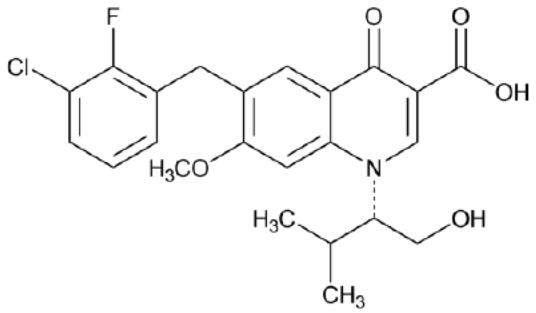
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:

Elvitegravir: (1) 3-Quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-; (2) 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.	 $C_{23}H_{23}ClFNO_5$, MW 447.88

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Adequate

The resubmission contained new DMFs for packaging materials not contained in the original NDA. The changes are shown below in **bold** and ~~strikethrough~~ font. Please refer to P.7 for discussion of container closure system.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
25187	II	Gilead	Elvitegravir	1	Adequate	M. Sloan 27-June-2012 M. Sloan 02-Jul-2012 M. Sloan 15-Mar-2013 M. Sloan 25-Apr-2013 M. Sloan 04 Sept 2014	LOA 21-OCT 2011
(b) (4)	IV	(b) (4)		4	N/A	N/A	LOA 09-Feb-2012: the quantitative composition, ingredient quality standards, and analytical methods submitted in the NDA.
	III			4	N/A	N/A	LOA

(b) (4)		(b) (4)				
						13-May-2011 There is enough data in the application
	III		4	N/A	N/A	LOA 13-June-2012 There is enough data in the application
	III		4	N/A	N/A	LOA **19 Jul 2013** 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 **13-Jan-2014** There is enough data in the application
	III		**4**	**N/A**	**N/A**	**22 July 2013**
	III		**4**	**N/A**	**N/A**	**11 Feb 2014**
	III		**4**	**N/A**	**N/A**	**08 Oct 2013**
	III		**4**	**N/A**	**N/A**	**10 May 2011**
	III		**4**	**N/A**	**N/A**	**29 Jan 2014**
	III		**4**	**N/A**	**N/A**	**18-Feb-2014**
	III		**4**	**N/A**	**N/A**	**30 Jan-2014**
	III		**4**	**N/A**	**N/A**	**23 July 2013**
	III		**4**	**N/A**	**N/A**	**23 July 2013**
	III		**4**	**N/A**	**N/A**	**23 Jan 2014**
	III		**4**	**N/A**	**N/A**	**22 July 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)

B. Other NDA Product Quality Reviews:

Review	Recommendation	DATE	REVIEWER
Biopharmaceutics Final	Recommendation of Q = (b)(4)% in 45 minutes; Dissolution method acceptable.	21-Mar-2013	Dr. Kareen Riviere
Product Quality Review #1	Not recommended for approval pending acceptable facilities recommendation.	21-March-2013	C. Cruz
GMP Establishment Review	WITHHOLD	25 April 2013	K. Ghosh
Product Quality Review #1 Addendum 1	Not recommended for approval due to overall WITHHOLD facilities recommendation and deficiencies found impacting analytical methods used for batch release and stability.	26-April-2013	C. Cruz

C. Consults or Outside CMC review team input:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Recommendation: ACCEPTABLE	04 Sept 2014	Krishnakali Ghosh
Pharm/Tox	N/A		
Methods Validation	N/A		
Environmental Analysis	N/A		

Quality Microbiology	N/A		
Biometrics	N/A		
Labeling	N/A		

D. Other Applications or Submissions Referenced:

The applications and submissions below were officially referenced in the NDA; they are all held by Gilead Sciences as the Sponsor/Applicant.

DOCUMENT Referenced	APPLICATION NUMBER	DESCRIPTION
Impurities (non-clinical studies)	NDA 203100	Stribild (EVG/COBI/TFC/TDF) NDA
General development	IND 72177	Elvitegravir IND

The Chemistry Review for NDA 203-093

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203093 has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Drug Master File for the elvitegravir drug substance supporting this NDA has been reviewed and found to be adequate. The overall recommendation from the Office of Compliance is ACCEPTABLE as of 04-Sept-2014. CMC labeling review was completed as part of Review #1 and all changes were adequately incorporated in the resubmission. Labeling for the resubmission is being completed by the OND review team. Therefore, from the CMC perspective, this NDA is recommended for approval at this time.

The recommendations and conclusions from this review cover both the US-image and Access-image Vitekta tablet information. The Access-image will not be marketed in the US.

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 203093 Review #1 dated March 21, 2013, 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, the conclusion was revised in Review #1 Addendum 1 dated April 26, 2014, based on the evaluation by the Office of Compliance and the overall 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 the 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 testing of Vitekta drug product and elvitegravir drug substance.
- 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 primary stability data supports a recommendation of 48 months when stored below 30 ºC in the approved container closure system.

At this time, the NDA 203093 can be concluded to contain adequate information to support the identity, strength, purity and stability of Vitekta (elvitegravir) Tablet, 85 mg and 100 mg.

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

A single Vitekta (elvitegravir) 150 mg or 85 mg tablet is taken orally, once daily, with food. Vitekta is co-administered with a ritonavir-boosted protease inhibitor.

Vitekta (elvitegravir) tablets are packaged in 60 ml, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and is capped with a white, continuous thread, child-resistan (b) (4) screw cap fitted with an induction sealed, aluminum-faced liner. The bottle label states that the tablets are to be dispensed in original container.

At this time, a shelf-life of 48 months when stored below 30 ºC in the original container is approved for Vitekta.

C. Basis for Approvability or Not-Approval Recommendation

NDA 203093 is recommended for approval from the CMC perspective. The Applicant has provided sufficient information for assuring consistent identification, strength, purity and quality of the drug product. The DMF for the drug substance is adequate and the overall site recommendation is ACCEPTABLE. The labeling is acceptable from CMC perspective. Please refer to NDA 203093 Review #1 and Review #1 Addendum 1 for a complete history.

III. Administrative

A. Reviewer's Signature
Celia N. Cruz, Milton Sloan
On file

B. Endorsement Block
Steve Miller on behalf of Rapti Madurawe
On file

C. CC Block
On file

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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/

CELIA CRUZ
09/04/2014

MILTON J SLOAN
09/05/2014

STEPHEN MILLER
09/05/2014

I concur: from the CMC perspective this application is recommended for approval. Please note that this review was originally filed in DARRTS on Sept 4, 2014, but needed to be resubmitted on Sept 5th to correct the filling classification within DARRTS.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Memorandum

Regarding: NDA 203-093 VITEKTA (Elvitegravir) Tablets

Date: Apr 17, 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 #1
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 April 4, 2014 resubmission.

CR Issue #2
During the inspection of the Gilead Sciences (Foster City, CA) manufacturing facility, FDA field investigators found significant concerns regarding the release and stability data presented in the NDA and in DMF 25187 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 manufacturing 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 9-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 (b) (4) 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 [redacted] audit in the resubmission of the Vitekta 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 9-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-168)
- Additional validation of the [redacted]
- Table 3 in P.5.3 may have been updated with additional validation of the method for Identification, Assay, and Degradants (TM-166)
- Tables 4 and 5 in P.5.3 may have been updated with additional validation of the methods that use HPLC or UPLC detection for Dissolution (TM-168)
-
- Section P.5.4 includes clarification of method revision history (Table 7).
- Added to P.8.3 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-0014, STM-0015, STM-0016)

Additional noteworthy elements listed in the 1.11.1 table include:

- Significant amount of revisions related to microbiological testing
- Updated stability data to justify a 48 mo expiration dating period
- Updated stability data on the Access variant of the tablet
- Transcriptional errors were corrected in the tables that summarize the developmental ranges of process parameters for [redacted] and film-coating (P.2.3 Tables 10-12)

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:

- Gilead Alberta site adds stability testing for drug substance
- [redacted] of elvitegravir is now listed as an additional responsibility of [redacted]
- [redacted] will now add stability testing site for elvitegravir tablets
- [redacted] adds release testing, mcrobiological testing and stability testing for tablets
- Gilead Ireland and Gilead San Dimas both add a role as batch release site for 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 Vitekta 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 27, 2014 is included in 3.2.R.2. (b) (4) concludes that: "the raw data and databases including Empower and LIMS are well maintained and traceable to the release data, 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 203093 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:** In Gilead's Feb 21 letter all elvitegravir methods that are listed say that the method validation status was determined to be "acceptable" with this one exception:
>
> - Heavy Metals by USP <231> Method II lists the method verification as "Complete" for elvitegravir drug substance
>
> The Apr 4 resubmission does not include any information about this compendial method, but it is not clear whether this method verification is important enough to request it be reported in the resubmission.

Conclusion: This amendment is a complete response to the two CMC-related issues in the Apr 23, 2013 CR action letter. It also includes CMC information as recommended by the FDA at the Jan 22, 2014 meeting. Very little of the March 23, 2014 advice communication applies to elvitegravir. The resubmission 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:

- Milton Sloan (Drug Substance)
- Celia Cruz (Drug Product)
- Kareen Riviere (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 the CR letter, and can be accepted for review.

RAPTI D MADURAWE

05/01/2014

NDA 203903

Vitekta™ (Elvitegravir) Tablet, 85 and 150 mg

Gilead Sciences, Inc.

Drug Product Reviewer: Celia N. Cruz, Ph.D.
Drug Substance Reviewer: Milton Sloan, Ph.D.

DPA II/Branch V

Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-093

2. REVIEW #: Review # 1, Addendum 1

3. REVIEW DATE: April 26, 2013

4. REVIEWERS:

Primary Review Team:

Reviewer	NDA Section
Milton Sloan, Ph.D.	Drug Substance: Elvitegravir DMF
Celia N. Cruz, Ph.D.	Drug Product
Kareen Riviere, Ph.D.	Biopharmaceutics Review

Secondary:

Reviewer	Section
Rapti Madurawe, Ph.D.	All, Overall Recommendation

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Preliminary comments on QUAD Pre-NDA meeting	08-Jul-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Received Date
SDN 026: Quality/Response to Information Request	27-March-2013
SDN 028: Labeling/Container/Carton Draft	03-April-2013
SDN 029: Labeling/Package Insert Draft	11-April-2013
SDN 030: Labeling/Package Insert Draft	19-April-2013
SDN 031: Labeling/Patient Package Insert	23-April-2013
SDN 032: Labeling/Package Insert Draft	24-April-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404 USA
Representative:	Prena Menon, Ph.D. 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: Vitekta
b) Non-Proprietary Name (USAN): Elvitegravir Tablets
c) Code Name: EVG
d) Chem. Type/Submission Priority:

- Chem. Type: 5, new formulation or manufacturer
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: integrase inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 85 mg and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

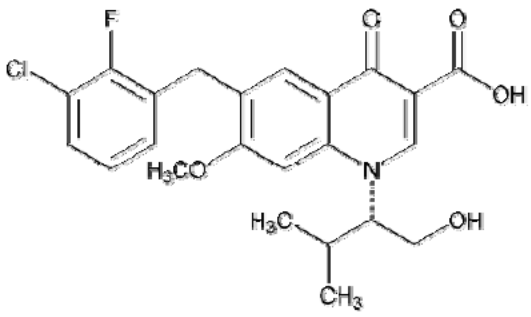
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:

Elvitegravir: (1) 3-Quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-; (2) 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.	 $C_{23}H_{23}ClFNO_5$, MW 447.88

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
25187	II	Gilead	Elvitegravir	1	Inadequate	M. Sloan 27-June-2012 M. Sloan 02-Jul-2012 M. Sloan 15-Mar-2013 M. Sloan 25-Apr-2013	LOA 21-OCT 2011
(b) (4)	IV	(b) (4)		4	N/A	N/A	LOA

		(b) (4)				09-Feb-2012: the quantitative composition, ingredient quality standards, and analytical methods submitted in the NDA.
(b) (4)	III		4	N/A	N/A	LOA 13-May-2011 There is enough data in the application
	III		4	N/A	N/A	LOA 13-June-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

[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 NDA Product Quality Reviews:

Review	Recommendation	DATE	REVIEWER
Biopharmaceutics Final	Recommendation of Q = (b)(4)% in 45 minutes; Dissolution method acceptable.	21-Mar-2013	Dr. Kareen Riviere

C. Consults or Outside CMC review team input:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Recommendation: WITHHOLD	25-Apr-2013 EES 25-Apr-2013 Final GMP Establishment Review	Krishnakali Ghosh
Pharm/Tox	N/A		
Methods Validation	N/A		
Environmental Analysis	N/A		
Quality Microbiology	N/A		
Biometrics	N/A		
Labeling	N/A		

D. Other Applications or Submissions Referenced:

The applications and submissions below were officially referenced in the NDA; they are all held by Gilead Sciences as the Sponsor/Applicant.

DOCUMENT Referenced	APPLICATION NUMBER	DESCRIPTION
Impurities (non-clinical studies)	NDA 203100	Stribild (EVG/COBI/TFC/TDF) NDA

General development	IND 72177	Elvitegravir IND

The Chemistry Review for NDA 203-093

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203093 is not recommended for approval from the CMC perspective. The Office of Compliance has issued an overall withhold recommendation for establishments as of April 25, 2013, 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 25187 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 below need to be resolved satisfactorily, before this NDA can be recommended for approval.

Labeling review was not finalized this review cycle by the OND review team.

The recommendations and conclusions from this review cover both the US-image and Access-image Vitekta tablet information. The Access-image will not be marketed in the US.

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 203093 Review #1 dated March 21, 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 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 and elvitegravir drug substance under DMF 25187. Inspection of Gilead 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

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 203093 review #1.

- As DMF 25187 for the elvitegravir drug substance also relies on the Foster City site for batch release and stability testing of the drug substance, DMF 25187 was determined to be inadequate in DMF review dated April 25, 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 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 203093 cannot be concluded to contain adequate information to support the identity, strength, purity and stability of Vitekta (elvitegravir) Tablet, 85 mg and 100 mg.

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

A single Vitekta (elvitegravir) 150 mg or 85 mg tablet is taken orally, once daily, with food. Vitekta is co-administered with a ritonavir-boosted protease inhibitor.

Vitekta (elvitegravir) tablets are packaged in 60 ml, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and is capped with a white, continuous thread, child-resistant (b) (4) screw cap fitted with an induction sealed, aluminum-faced liner. The bottle label states that the tablets are to be dispensed in original container.

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

C. Basis for Approvability or Not-Approval Recommendation

NDA 203093 is not recommended for approval from the CMC perspective due to 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, the FDA field investigator found significant concerns regarding the release and stability data presented in the NDA and in DMF 25187 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.

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
Celia N. Cruz, Milton Sloan
On file

B. Endorsement Block
Rapti Madurawe
On file

C. CC Block
On file

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/s/

CELIA CRUZ
04/25/2013

MILTON J SLOAN
04/25/2013

RAPTI D MADURAWE
04/26/2013

NDA 203903

Vitekta™ (Elvitegravir) Tablet, 85 and 150 mg

Gilead Sciences, Inc.

Celia N. Cruz, Ph.D.

DPA II/Branch V

Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-093

2. REVIEW #: Review 1.0

3. REVIEW DATE: March 21, 2013

4. REVIEWERS:

Primary Review Team:

Reviewer	NDA Section
Milton Sloan, Ph.D.	Drug Substance: Elvitegravir DMF
Celia N. Cruz, Ph.D.	Drug Product
Kareen Riviere, Ph.D.	Biopharmaceutics Review

Secondary:

Reviewer	Section
Rapti Madurawe, Ph.D.	All, Overall Recommendation

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Preliminary comments on QUAD Pre-NDA meeting	08-Jul-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Received Date

Original: New NDA	27-June-2011
SDN 001: Quality/Response to Information Request	05-Jul-2012
SDN 006: Quality/Response to Information Request	05-Oct-2012
SDN 015: Quality/Response to Information Request	15-Jan-2013
SDN 019: Quality/Response to Information Request	29-Jan-2013
SDN 022: Quality/Response to Information Request	04-Mar-2013
SDN 024: Quality/Response to Information Request	11-Mar-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404 USA
Representative:	Prena Menon, Ph.D. 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: Vitekta
b) Non-Proprietary Name (USAN): Elvitegravir Tablets
c) Code Name: EVG
d) Chem. Type/Submission Priority:

- Chem. Type: 5, new formulation or manufacturer
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: integrase inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 85 mg and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

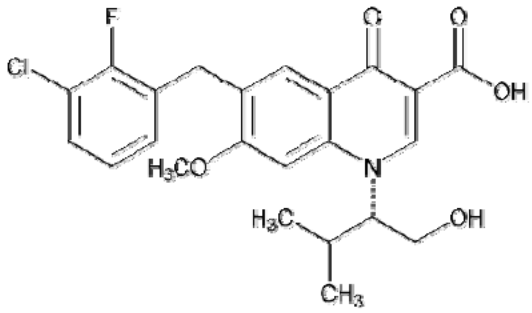
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:

Elvitegravir: (1) 3-Quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-; (2) 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.	 $C_{23}H_{23}ClFNO_5$, MW 447.88

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
25187	II	Gilead	Elvitegravir	1	Adequate	M. Sloan 27-June-2012 M. Sloan 02-Jul-2012 M. Sloan 15-Mar-2013	LOA 21-OCT 2011
(b) (4)	IV	(b) (4)		4	N/A	N/A	LOA 09-Feb-2012: the quantitative composition,

(b) (4)		(b) (4)				
						ingredient quality standards, and analytical methods submitted in the NDA.
	III		4	N/A	N/A	LOA 13-May-2011 There is enough data in the application
	III		4	N/A	N/A	LOA 13-June-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

[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 NDA Product Quality Reviews:

Review	Recommendation	DATE	REVIEWER
Biopharmaceutics Final	Recommendation of Q = (b)(4)% in 45 minutes; Dissolution method acceptable.	21-Mar-2013	Dr. Kareen Riviere

C. Consults or Outside CMC review team input:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	PENDING sites: Gilead Sciences Inc (WH) assigned inspection	21-Mar-2013 (see report attached)	Krishnakali Ghosh
Pharm/Tox	N/A		
Methods Validation	N/A		
Environmental Analysis	N/A		
Quality Microbiology	N/A		
Biometrics	N/A		
Labeling	N/A		

D. Other Applications or Submissions Referenced:

The applications and submissions below were officially referenced in the NDA; they are all held by Gilead Sciences as the Sponsor/Applicant.

DOCUMENT Referenced	APPLICATION NUMBER	DESCRIPTION
Impurities (non-clinical studies)	NDA 203100	Stribild (EVG/COBI/TFC/TDF) NDA
General development	IND 72177	Elvitegravir IND

The Chemistry Review for NDA 203-093

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203-093 has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Drug Master File for the elvitegravir drug substance supporting this NDA is adequate. Labeling review was completed with the OND review team and minor CMC-related revisions were communicated to the Applicant. The overall recommendation from the Office of Compliance is PENDING as of March 21, 2013, due to a pending inspection of a drug product testing site. Therefore, from the CMC perspective, this NDA is not recommended for approval at this time, pending an overall acceptable facilities recommendation.

The recommendations and conclusions from this review cover both the US-image and Access-image Vitekta tablet information. The Access-image will not be marketed in the US.

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 Product

Drug Product Description

Vitekta (elvitegravir) is an immediate-release tablet containing elvitegravir and is available in two strengths, 85 mg and 150 mg. Two tablet images were developed and reviewed for Vitekta under NDA 203903: the US image and the Access (export only) image. The US image for Vitekta for 85 mg and 150 mg tablet strength is described as follows:

- 85 mg tablets are green, pentagon-shaped, film-coated and debossed with "GSI" on one side and "85" on the other side.
- 150 mg tablets are green, triangle-shaped, film coated and debossed with "GSI" on one side and "150" on the other side.

The Access image has (b) (4)

- (b) (4)
-

The Vitekta (elvitegravir) tablets contain common excipients: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate. For the US image, the film coat contains polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, indigo carmine aluminum lake, and iron oxide yellow. For the Access image, the film coat contains (b) (4) In both cases, the film coat (b) (4) and has no impact on the drug release rate.

Vitekta (elvitegravir) 85 mg and 150 mg tablets are stored in 60-ml HDPE bottles with induction seal and child proof closure. The primary container was demonstrated to provide adequate control of quality upon storage. The bottle contains no desiccant.

Drug Product Manufacturing and Control Strategy

(b) (4)

(b) (4)

Drug product specifications include tests for: appearance, identification, assay, degradation product content, uniformity of dosage units, (b) (4), and dissolution. The degradation product specifications include limits on the total and on each of any degradation product. EVG has no specified individual degradation products, given that no degradation of this drug substance has been observed at any condition. Microbiological purity will be tested on annual stability.

The analytical methods were found to be adequately developed and validated, these include Identification by HPLC and UV, assay by HPLC, degradation product by HPLC, and dissolution by HPLC and UPLC. Content uniformity is performed by weight variation, which is acceptable for a (b) (4)% drug loading tablet with more than 200 mg total weight.

Drug Product Stability

For each tablet strength in the US-image, stability data in the primary container included three batches at 25 ºC/60% RH and 30 ºC/ 75% RH for 36 to 48 months and three batches at 40

ºC/75% RH for 6 months. The Access-image stability data in the primary container included one batch per strength at 25 ºC/60% RH and 30 ºC/ 75% RH for 9 months and at 40 ºC/75% RH for 6 months. The Access-image primary stability studies are on-going and will be included in the Annual Report.

Overall, the drug product shows no signs of EVG degradation over the 48 months of stability data generated, as EVG has been demonstrated to be a very stable drug substance. In addition, there are no changes noted on assay. Some minor changes in dissolution are noted at 30 ºC/ 75% RH for 48 months, but all batches are passing the final specification. (b) (4)

The complete set of stability data provided supports a shelf life of 48 months for Vitekta US-image tablets, when stored in the approved container at 25 ºC (with excursions permitted 15 to 30 ºC). The data is also supportive of a shelf life of 48 months, when stored in the approved container with recommendation of "Store below 30 ºC". The Access-image has (b) (4) The Access-image stability profile at 9 months also shows no changes to quality. Therefore, the approved shelf life for the Access-image tablet is 36 months, when stored in the approved container below 30 ºC.

Drug Substance

Elvitegravir (EVG)

Elvitegravir, drug substance information was referenced to Gilead's DMF 25187. The DMF was reviewed and found adequate on July 2, 2012. Elvitegravir drug substance is manufactured at three manufacturing sites, Gilead Alberta, (b) (4) . Elvitegravir drug substance is a white to pale yellow powder. (b) (4) polymorphs have been observed. (b) (4)

Elvitegravir is manufactured (b) (4) steps. The critical quality attributes for the elvitegravir manufacturing process were identified. Of the 31 compounds identified as potential impurities, 17 have limits specified and any other impurities will be limited as unspecified impurities.

The specifications for elvitegravir are: appearance, identification, water content, assay, impurity content, enantiomeric purity, residual solvents, residual (b) (4), heavy metals, residue on ignition, particle size distribution, and differential scanning calorimetry (melting point).

Most of the impurities in elvitegravir arise from the starting material or from the process. Elvitegravir stability studies show no degradation. There were no discernible trends up to 48 months for all stability test attributes at the 25 °C/60% RH long-term storage conditions. Accelerated stability studies at 40 °C/75% RH show only a trace (< (b) (4) %) for one impurity after 6 months. The data supports a retest period of (b) (4) months for the drug substance at the

recommended storage condition, "Store below (b) (4) °C". Stability data at the accelerated condition support temperature excursions of up to (b) (4)°C during shipping and handling for up to (b) (4) months.

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

A single Vitekta (elvitegravir) 150 mg or 85 mg tablet is taken orally, once daily, with food. Vitekta is co-administered with a ritonavir-boosted protease inhibitor.

Vitekta (elvitegravir) tablets are packaged in 60 ml, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and is capped with a white, continuous thread, child-resistant (b) (4) screw cap fitted with an induction sealed, aluminum-faced liner. The bottle label states that the tablets are to be dispensed in original container.

The shelf life granted for Vitekta (elvitegravir) US-image tablets in the approved container is 48 months when stored at 25 ºC (excursions permitted 15 – 30 ºC). The drug product stability profile also supports a labeled storage recommendation of "Store below 30 °C". The shelf life granted for Vitekta (elvitegravir) Access-image tablets in the approved container is 36 months when stored below 30 ºC.

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 to support expiry is adequate. The DMF for elvitegravir drug substance is adequate. The labeling has been reviewed by the OND team; CMC labeling edits have been communicated to the Applicant. The container/carton labels are adequate from a CMC-perspective. Therefore, the Applicant has provided sufficient information for assuring consistent product quality of the drug substance and the drug product.

At this time, this NDA is not recommended for approval due to the following: As of March 21, 2013, the overall recommendation for 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
Celia N. Cruz
On file

B. Endorsement Block
Rapti Madurawe
On file

C. CC Block
On file

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/s/

CELIA CRUZ
03/21/2013

RAPTI D MADURAWE
03/21/2013

NDA 203-093

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

Memo Date: September 28, 2012
From: Celia N. Cruz, Ph.D., Milton Sloan, Ph.D.

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

NDA Number: 203-093 GRMP Date: March 22, 2013
Applicant: Gilead Sciences Inc. PDUFA Date: April 26, 2013

Drug Product Name and Strength:

Tradename™ (elvitegravir) Tablets, 85 mg and150 mg, proposed proprietary or trade name is Vitekta tablets.

Drug Product Introduction:

The elvitegravir (EVG) tablet is an immediate-release tablet developed in two strengths, 85 mg and 150 mg. EVG tablets, 85 mg, are green, pentagon-shaped, film-coated and debossed with "GSI" on one side and "85" on the other side. EVG tablets, 150 mg, are green, triangle-shaped, film-coated and debossed with "GSI" on one side and "150" on the other side. The tablets are packaged in 60 mL, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and is capped with a white, continuous thread, child-resistant (b) (4) screw cap fitted with an induction sealed, aluminum-faced liner.

The drug product manufacturing process for the tablets is divided in (b) (4) major unit process steps: (b) (4) The process flow diagram captures the manufacture of EVG tablets shown in Figure 1.

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/s/

MILTON J SLOAN
09/25/2012

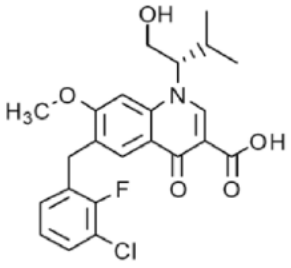
RAPTI D MADURAWE
09/25/2012

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

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **203-093**
   Submission Date: June 27, 2012
   GRMP Goal Date: March 22, 2013
   PDUFA Goal Date: Apr 26, 2013

2. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Vitekta (proposed)
Established or Non-Proprietary Name (USAN) and strength:	Elvitegravir Tablets, 85 mg and 150 mg
Dosage Form:	Film-Coated, Oral Tablet
Structure:	

3. NAME OF APPLICANT:

Name:	Gilead Sciences, Inc.

4. SUBMISSION PROPERTIES:

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

Review Information

1. INDICATION: Treatment of HIV Infection

2. ROUTE OF ADMINISTRATION: Oral

3. STRENGTH/POTENCY: 85 mg and 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.

6. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
25187	2	Gilead	Elvitegravir DS	2/28/12	
[redacted] (b) (4)				2/9/12	
5 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		X	
Clin Pharm		X	Clin-Pharm is part of the review team
EES	X		
Pharm/Tox		X	
Methods Validation		X	
EA		X	
New Drug Micro		X	
CDRH		X	
Other ( )			

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND 72,177			Elvitegravir IND

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
As listed in Section 1.6.3			

Overall Conclusions and Recommendations

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

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		1) 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). Other Comments are under discussion within the review team.

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

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
	X	

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
☐	☒	☐	

Is a team review recommended?		
Yes	No	Suggested expertise for team
X		

Review Team Assignments (if known)	
Drug Substance	Milton Sloan
Drug Product	Celia Cruz
Biopharmaceutics	Kareen Riviere
QbD	
Product Quality Microbiology	
ONDQA PM	

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

Changes between Clinical DP and Proposed Commercial DP

Clinical Tablets	**Commercial Tablets**
No differences in composition	

Indication

Elvitegravir is an integrase strand-transfer inhibitor (INSTI) that block integration of HIV-1 genetic material into the host-cell genome. The proposed indication is for use in combination with a protease inhibitor boosted with ritonavir, and other anti-HIV agents. The ritonavir will also boost the elvitegravir to give suitable plasma concentrations. Cobicistat may also be able to be used as a PK booster, but since Cobicistat is not yet

approved (pending NDA 203-100 and NDA 203-094) that approach is not included in the current indication. The proposed doses are:

- One 85 mg tablet once per day when coadministered with atazanavir or lopinavir and boosted with ritonavir
- One 150 mg tablet once per day when coadministered with darunavir, fosamprenavir or tipranavir and boosted with ritonavir

Drug Substance

Detailed information including the quality control approaches are in DMF 25187, which was recently found to be adequate during the review of NDA 203-100 (Stribild tablet which included elvitegravir, cobicistat, and two other active ingredients).

The drug substance specification has been updated to include the revised acceptance criteria for the impurities, (b) (4), which were tightened during the review of DMF 25187. However the column of test procedures that was added during review of the DMF, has been removed from the specification table that is presented in Sections 2.3.S.4 and 3.2.S.4.1. The test procedures are included in the separate Corporate Specification document in 3.2.S.4.1.

Drug Product

The elvitegravir tablets for US marketing are green, pentagonal (85 mg) or triangular (150 mg) film-coated tablets.

This application also includes data to support the "Access" version of this product, which would be marketed outside the US in low- and middle-income countries (e.g., the PEPFAR recipient nations). The only difference between the US tablets and the Access tablets is (b) (4)

Stability data with 30ºC/75%RH as a long-term condition is provided which may be able to justify storage of either tablet version at up to 30ºC. One topic for discussion during the review is whether this type of storage statement should be used for the US labeling as well as for the Access tablet. If so, a wider temperature range for the US Patient Prescribing Information might also be considered, e.g., Store at room temperature between 67ºF-86ºF (20ºC-30ºC). This would need to be discussed with the Office of Medical Policy (DMPP) reviewer.

(b) (4), so this is similar to the Stribild tablet. Some QbD elements are included. For example, process parameter ranges are referred to as a design space, and are based on DOE studies. The review team members have ample expertise to review these elements. However, periodic informal communication with Dr. Sharmista Chatterjee and other members of the ONDQA QbD team will be valuable, and has lead to one draft comment which may be included in the 74-day letter.

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 (especially (b) (4) and Gilead, Alberta; (b) (4) at OC's discretion), and to include a reviewer has been included in the EES Comments.

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

Biopharmaceutics Summary: Critical Issues and Complexities

Summary

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method as well as the proposed dissolution acceptance criterion. The Applicant conducted one pivotal Phase 3 efficacy and safety study with the 85mg and 150 mg strengths. Therefore, a biowaiver is not required for the approval of the lower strength.

The proposed dissolution method is shown below.

For 85 mg Tablet

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	75 rpm	700 mL	37°C	0.01N HCl w/ 2% polysorbate 80

For 150 mg Tablet

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	75 rpm	1000 mL	37°C	0.01N HCl w/ 2% polysorbate 80

The proposed acceptance criterion is shown below.

Acceptance Criterion
Q = (b) (4) % at 45 min

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion.

APPEARS THIS WAY ON ORIGINAL

CMC 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?			No specific requests found

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

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		Additional clarification provided July 27, 2012

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

* 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		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?	X		

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	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?		X	Information is in Drug Substance DMF
15.	Does the section contain information on impurities?	X		In Justification for Specification
16.	Does the section contain information regarding the characterization of the DS?		X	Information is in Drug Substance DMF
17.	Does the section contain controls for the DS?	X		DS Specification is attached below For a number of attributes, testing will be performed by either the USP, EP, or JP procedures.
18.	Has stability data and analysis been provided for the drug substance?		X	Information is in Drug Substance DMF
19.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not in this NDA
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
21.	Does the section contain container and closure information?		X	Information is in Drug Substance DMF

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		Attached below
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
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	Description of the (b) (4) step of Manuf Process in .3.2.P.3.3 seems about as detailed as the executed batch record. No master batch record is provided. Executed batch records are included in R.1 for a (b) (4) kg clinical batch (AJ0704)
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 30 tablets with induction seal and child-resistant cap
30.	Does the section contain controls of the final drug product?	X		DP Specification is attached below The analytical procedures are included in the separate Corporate Specification document. For a number of attributes, testing will be performed by either USP, EP or JP procedures.

31.	Has stability data and analysis been provided to support the requested expiration date?	X		36-48 month data are reported for three pilot scale batches of each strength. These primary studies covered the 30ºC/75%RH long-term condition recommended for products marketed in all climatic zones worldwide. Long-term data at 25ºC/60%RH and accelerated data at 40ºC/75%RH are also supplied.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		Moderate 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?			

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?		X	Suitable information is in Sections 3.2.P.5.2 and 3.2.P.5.3

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?			NA

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	X		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?	X		
38.	Does section contain tradename and established name?		X	Trademark to be submitted.

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

J. CMC FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
39.	**ARE THE PRODUCT QUALITY SECTIONS OF THE APPLICATION FILEABLE?**	X		
40.	If the NDA is not fileable from the CMC 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		See draft CMC comment above and attached draft information request.

BIOPHARMACEUTICS 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.	Is the dissolution test part of the DP specifications?	x		
2.	Does the application contain the dissolution method development report?	x		
3.	Is there a validation package for the analytical method and dissolution methodology?	x		
4.	Does the application include a biowaiver request?		x	Not Applicable.
5.	Is there information provided to support the biowaiver request?		x	Not Applicable.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?	x		
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any in *vivo* BA or BE information in the submission?	x		

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

REVIEW AND APPROVAL

See appended electronic signature page}
Stephen Miller, Ph.D.
CMC-Lead
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

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

Appendix 1. Composition of Drug Product

Note: The 85 mg and 150 mg strengths have identical composition in terms of weight %

Composition of the 85 mg US Tablet

Components	% w/w	Unit Formula (mg/tablet)	Quality Standard	Function
Tablet Core				
Elvitegravir	(b) (4)	85.00[a]	In-House	Active
Hydroxypropyl Cellulose		(b) (4)	NF, Ph. Eur.	(b) (4)
Sodium Lauryl Sulfate			NF, Ph. Eur., JP	
Lactose Monohydrate			NF, Ph. Eur., JP	
Microcrystalline Cellulose			NF, Ph. Eur., JP	
Croscarmellose Sodium			NF, Ph. Eur., JP	
Magnesium Stearate			NF, Ph. Eur., JP	
(b) (4)			USP, Ph. Eur.	
Total	100	(b) (4)		
Film-Coat				
(b) (4)				
(b) (4)				

Composition of the 85 mg Access Tablet

Components	% w/w	Unit Formula (mg/tablet)	Quality Standard	Function
Tablet Core				
Elvitegravir	(b) (4)	85.00[a]	In-House	Active
Hydroxypropyl Cellulose		(b) (4)	NF, Ph. Eur.	(b) (4)
Sodium Lauryl Sulfate			NF, Ph. Eur., JP	
Lactose Monohydrate			NF, Ph. Eur., JP	
Microcrystalline Cellulose			NF, Ph. Eur., JP	
Croscarmellose Sodium			NF, Ph. Eur., JP	
Magnesium Stearate			NF, Ph. Eur., JP	
(b) (4)			USP, Ph. Eur.	
Total	100	(b) (4)		
Film-Coat				
(b) (4)				
(b) (4)				

Appendix 2. DP Specification for the US Elvitegravir Tablet*

Test Description	Acceptance Limit
Appearance	*Elvitegravir Tablets, 85 mg*, are green, pentagon-shaped, film-coated tablets, debossed with "GSI" on one side and "85" on the other side. The size and packaging are visually consistent with the description supplied. *Elvitegravir Tablets, 150 mg*, are green, triangle-shaped, film-coated tablets, debossed with "GSI" on one side and "150" on the other side. The size and packaging are visually consistent with the description supplied.
Identification	
A: Chromatographic Retention Time	The retention time of the main peak is consistent with that of the elvitegravir reference standard.
B: UV Spectrum	The UV spectrum corresponds to that of the elvitegravir reference spectrum.
Assay	*At Release and During Shelf-life:* The strength of elvitegravir is not less than (NLT) (b) (4)% and not more than (NMT) (b) (4)% of the label claim.
Degradation Product Content	*At Release and During Shelf-life:* NMT a total of (b) (4)% degradation products, with NMT (b) (4)% each of any degradation product.
Uniformity of Dosage Units	Meets the current USP or Ph. Eur. requirements for weight variation.
Dissolution	NLT (b) (4)% (Q) at 45 minutes.

* The specification for the Access tablet is (b) (4)

Appendix 3. DS Specification from NDA 203-093 Section 3.2.S.4.1

Test Description	Acceptance Limit
Appearance	White to pale yellow powder
Identification	
A. HPLC	Retention time of the main peak is consistent with the reference standard, similarly measured
B. Infrared	IR spectrum is consistent with that of the reference standard, similarly measured
C. UV	UV spectrum is consistent with that of the reference standard
Water Content	Not more than (NMT) (b) (4) %
Assay	(b) (4) calculated on a dried basis
Impurity Content	NMT (b) (4) % of total impurities, with NMT (b) (4) % each of (b) (4), and (b) (4) NMT (b) (4) % each of (b) (4) and (b) (4) NMT (b) (4) % each of (b) (4) and (b) (4) NMT (b) (4) % of (b) (4) and NMT (b) (4) % each of any unspecified impurity
Enantiomeric Purity	NLT (b) (4) % (b) (4)
Residual Solvents	NMT (b) (4) % each of (b) (4) NMT (b) (4) % each of (b) (4) and NMT (b) (4) % or the PDE (per ICH Q3C) of any unspecified residual solvent
Residual (b) (4)	NMT (b) (4) ppm
Residue On Ignition	NMT (b) (4) %
Heavy Metals	NMT (b) (4) ppm, as (b) (4)
Particle Size	The d90 of the particle size distribution is NMT (b) (4) µm
Differential Scanning Calorimetry	The peak of the main melting endotherm is (b) (4) °C when measured at a scan rate of 1 °C/min

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/s/

STEPHEN MILLER
08/27/2012
NDA is fileable from the CMC and BP perspectives.

KAREEN RIVIERE
08/29/2012

ANGELICA DORANTES
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RAPTI D MADURAWE
08/29/2012