

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205551Orig1s000

CHEMISTRY REVIEW(S)



CMC Assessment Section

C. Establishment Evaluation Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 205551/000 Sponsor: VIIV HLHCARE
Org. Code: 530 5 MOORE DR
Priority: 4 RESEARCH TRIANGLE PARK, NC 27709
Stamp Date: 22-OCT-2013 Brand Name: GSK2619619 (ABACAVIR SULFATE, DOLUTEGRAV
PDUFA Date: 22-AUG-2014 Estab. Name: GSK2619619 (ABACAVIR SULFATE, DOLUTEGRAVIR, AND LAMIVUDINE)
Action Goal: Generic Name:
District Goal: 23-JUN-2014 Product Number; Dosage Form; Ingredient; Strengths

001; TABLET; ABACAVIR; 600MG
001; TABLET; LAMIVUDINE; 300MG
001; TABLET; DOLUTEGRAVIR; 50MG

FDA Contacts: M. ZHOU Prod Qual Reviewer 3017962163
E. PFEILER Micro Reviewer (HF-22) 3017960642
A. CUFF Product Quality PM (HF-01) 3017964061
S. MOSADDEGH Regulatory Project Mgr (HFD-530) 3017964876
S. MILLER Team Leader 3017961418

Overall Recommendation: ACCEPTABLE on 04-APR-2014 by R. XU () 3017966187
PENDING on 21-FEB-2014 by EES_PROD
ACCEPTABLE on 19-DEC-2013 by C. CAPACCI-DANIEL () 3017963532

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA: (b) (4)
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-DEC-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE



CMC Assessment Section

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

DMF No: AADA:

Responsibilities: INTERMEDIATE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

GLAXO (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

GLAXO (b) (4)

(b) (4)

DMF No: AADA: (b) (4)

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE



CMC Assessment Section

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

DMF No: (b) (4) **AADA:** (b) (4)

Responsibilities: DRUG SUBSTANCE STABILITY TESTER
 FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: (b) (4) **AADA:** (b) (4)

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-FEB-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: (b) (4) **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE



CMC Assessment Section

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

DMF No: AADA: (b) (4)

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: INTERMEDIATE MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA: (b) (4)

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE



CMC Assessment Section

Establishment: CFN: [REDACTED] FEI: (b) (4) (b) (4)
 [REDACTED]

DMF No: [REDACTED] AADA: [REDACTED]

Responsibilities: (b) (4) MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4) (b) (4)
 [REDACTED]

DMF No: [REDACTED] AADA: (b) (4)

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: [REDACTED] FEI: (b) (4) (b) (4)
 [REDACTED]

DMF No: [REDACTED] AADA: (b) (4)

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE



CMC Assessment Section

Establishment: **CFN:** [REDACTED] **FEI:** (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:** (b) (4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

/s/

MARY GRACE LUBAO
09/02/2014

NDA 205-551

**Abacavir, Dolutegravir, and Lamivudine Tablets
600 mg/50 mg/300 mg**

ViiV Healthcare Company

Maotang Zhou, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V**

**CMC REVIEW OF NDA 205-551
For the Division of Anti-Viral Products (DAVP)**

Table of Contents

Table of Contents	2
CMC Review Data Sheet	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of CMC Assessments	7
A. Description of the Drug Product and Drug Substance	7
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative	9
CMC Assessment.....	10
CMC Review #1 filed in DARRTS on July 14, 2014 contains a review of the Common Technical Document Quality Module 3.2. This addendum contains a review of the responses to Agency’s Information Request letters dated July 14, 2014 and the labeling review.	10
IR Letter Dated 7/14/2014.....	10
III. List Of Deficiencies communicated and to be resolved	16

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 205-551
2. REVIEW #: 1, Addendum #1
3. REVIEW DATE: 8/20/2014
4. REVIEWER: Maotang Zhou, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original IND 114820 submission
 Original IND 114820 CMC review by A. Yu
 End-of-phase-2 meeting (No CMC issues discussed)
 Pre-NDA meeting

Document Date

07-June-2012
 14-July-2012
 N/A
 27-Feb-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	10/22/2013	10/22/2013
Labeling package Insert	0009	03/14/2014	03/14/2014
Quality Amendment (Response to Agency Questions)	0010	03/14/2014	03/14/2014
Quality Amendment (Response to Agency Questions)	0012	04/18/2014	04/18/2014
Quality Amendment (Response to Information Request)	0015	06/02/2014	06/02/2014
Quality Amendment (Response to Information Request)	0018	07/18/2014	07/18/2014
Quality Amendment (Response to Information Request)			

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: ViiV Healthcare Company
Address: Five Moore Drive
Research Triangle Park, NC 27709
Representative: Anne Huffman, Sr. Director of QA/QC
Telephone: 877-844-8872

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Trimeq®
b) Non-Proprietary Name: Abacavir, Dolutegravir and Lamivudine
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: Type 4 (new combination – not previously approved in the US)
 - Submission Priority: Standard

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 50 mg/600 mg/300 mg

13. ROUTE OF ADMINISTRATION: Oral Tablet

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

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

CMC Review Data Sheet

Abacavir Sulfate	Dolutegravir Sodium	Lamivudine
(C ₁₄ H ₁₈ N ₆ O) ₂ H ₂ SO ₄	C ₂₀ H ₁₈ F ₂ N ₃ NaO ₅	C ₈ H ₁₁ N ₃ O ₃ S
670.76 g/mol (sulfate) (b) (4)	441.36 g/mol (sodium salt) 419.38 g/mol (free acid)	229 (b) (4) g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	N/A
NDA	N/A	N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	4/4/2014	R. Xu
Pharm/Tox	N/A		
Biopharm	Adequate	8/15/2014	E. Chikhale
LNC	N/A		
Methods Validation	N/A		
DMEPA*	Review in DARRTS	4/22/2014	R. Kapoor
EA	Categorical exclusion (see review)	4/23/2014	M. Zhou
Microbiology	Adequate	3/17/2014	E. Pfeiler

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 205-551

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

As revised, the NDA includes sufficient information on the drug substance and drug product to assure the strength, purity, and quality of the drug product through the expiration dating period. Labels and labeling contain adequate CMC information. An “Acceptable” site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

None

II. Summary of CMC Assessments

A. Description of the Drug Product and Drug Substance

The applicant intends to seek approval of the FDA for TRIUMEQ® (abacavir sulfate, dolutegravir, and lamivudine, or ABC/DTG/3TC) Tablets for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. The TRIUMEQ® tablet is a fixed dose combination product that contains three active ingredients: dolutegravir (DTG, GSK1349572), a 2- metal binding integrase inhibitor (INI), abacavir sulfate (ABC), a nucleoside reverse transcriptase inhibitor (NRTI), and lamivudine (3TC), also an NRTI.

All information regarding the chemistry, manufacturing and controls for the drug substances (abacavir sulfate, dolutegravir sodium, and lamivudine) were cross-referenced to the applicant’s approved NDA 20-977 for Ziagen® (abacavir sulfate) Tablets, approved NDA 204-790 for TIVICAY® (dolutegravir) Tablets, and approved NDA 20-564 for Epivir® (lamivudine) Tablets, respectively, and all amendments and supplements thereto.

The drug product, TRIUMEQ® (abacavir/dolutegravir/ lamivudine, or ABC/DTG/3TC) Tablet, is an immediate-release, purple, biconvex, film coated oval tablet, debossed with “572 Tri” on one face. Each Tablet contains (b) (4) of abacavir sulfate which is equivalent to 600 mg abacavir, 52.6 mg of dolutegravir sodium which is equivalent to 50 mg dolutegravir free acid, and 300 mg lamivudine. The formulation contains the inactive ingredients D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet film coating contains iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide. All excipients comply with USP/NF and are within levels used in other approved drug

Executive Summary Section

products. The TRIUMEQ® formulation was developed based on the formulations of TIVICAY® (dolutegravir) Tablets approved in NDA 204-790 and EPZICOM™ (abacavir sulfate and lamivudine) Tablets approved in NDA 21-652.

The drug product is manufactured at Glaxo (b) (4). The manufacturing process comprises of the process steps for the manufacture of (b) (4) and ABC/DTG/3TC Tablets ((b) (4) film coating). The (b) (4) process is identical to the process used in the manufacture of (b) (4). A risk management approach was applied during process development to identify and define the CPPs and important material attributes that are likely to have the greatest impact on product quality. Several ranges/targets of variables were investigated using pilot and production scale DoE or during production scale manufacture of clinical batches. (b) (4) and (b) (4) coating are identified as critical process parameters (CPP). The Control Strategy includes controls on the critical quality attributes (CQA) for the drug substances and in-process materials as well as CPPs related to the manufacturing process. The drug product will be tested for Description, Identification, (b) (4), Uniformity of Content, Drug-Related Impurities, assay, Dissolution, and Microbiological quality at release. The acceptance criteria are justified appropriately.

The drug product tablets are packaged in high density polyethylene (HDPE) bottles with desiccants, child-resistant closures and (b) (4). Stability data are provided for three primary stability batches of the drug product stored up to 12 months under the long term conditions (25 °C/60% RH and 30 °C/75% RH) and up to 6 months under the accelerated conditions (40 °C/75% RH). There are no significant changes in description, assay, drug-related impurity content, dissolution, and (b) (4) for any of the three active components. The potential for the formation of the (b) (4) is investigated in an in-use study for up to 1 month at 30 °C/75% RH, with and without the desiccant. Due to the observation of (b) (4) formation in the non-desiccant pack, precautionary statements will be used to prevent removal of desiccant from the pack. Overall, the available stability data support a shelf life of 24 months for the drug product when stored at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]. Precautionary statements are included to ensure that the product is stored in the original package with the bottle tightly closed to protect from moisture and the desiccant is not removed.

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

TRIUMEQ®, a combination of dolutegravir (a human immunodeficiency virus type 1 [HIV-1] integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue HIV-1 reverse transcriptase inhibitors) is indicated as a complete regimen for the treatment of HIV-1 infection. Tablets contain 50 mg of dolutegravir, 600 mg of abacavir, and 300 mg of lamivudine. The dosage for adult is one tablet daily. The tablet may be taken with or without food. TRIUMEQ® tablets are packaged in HDPE bottles with child-resistant closures, (b) (4).

Executive Summary Section

(b) (4), with the following precautionary statement: “Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove the desiccant.”

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, adequate specifications for assuring consistent product quality of the drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. Labels and labeling contain adequate CMC information. Minor labeling comments were conveyed to the review team. An “Acceptable” site recommendation from the Office of Compliance has been made for the manufacturing facilities.

In CMC Review #1 dated 7/14/2014, this NDA was recommended for approval by the CMC review team pending (1) an approval recommendation from the ONDQA Biopharmaceutics Reviewer and (2) the applicant’s satisfactory response to FDA’s IR letter dated 7/14/2014. The applicant responded the 7/14/2014 IR letter on 7/18/2014. The applicant’s responses were reviewed by the CMC review team and found adequate. On August 15, 2014, Dr. Elsbeth Chikhale, the ONDQA Biopharmaceutics Reviewer, has made an “approval” recommendation for the this NDA. As a result, the CMC information provided in the NDA is now considered adequate to assure identity, strength, purity, and quality of the drug product.

Therefore, from the CMC perspective, this NDA is recommended for approval.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

8 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MAOTANG ZHOU
08/20/2014

RAPTI D MADURawe
08/20/2014

NDA 205-551

**Abacavir, Dolutegravir, and Lamivudine Tablets
600 mg/50 mg/300 mg**

ViiV Healthcare Company

Maotang Zhou, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V**

**CMC REVIEW OF NDA 205-551
For the Division of Anti-Viral Products (DAVP)**

Table of Contents

Table of Contents	2
CMC Review Data Sheet	4
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	8
II. Summary of CMC Assessments	8
A. Description of the Drug Product and Drug Substance	8
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative	10
CMC Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	11
S. DRUG SUBSTANCE	11
S.2.1 Manufacturers	11
S.4.1 Specification	12
P. DRUG PRODUCT	17
P.1 Description and Composition of the Drug Product	17
P.2 Pharmaceutical Development	18
P.2.1 Components of the Drug Product	19
P.2.1.1 Drug Substance	19
P.2.1.2 Excipients	19
P.2.2 Drug Product	20
P.2.2.1 Formulation Development	20
P.2.2.2 Overages	21
P.2.2.3 Physicochemical and Biological Properties	21
P.2.3 Manufacturing Process Development	22
P.2.4 Container Closure System	32
P.2.5 Microbiological Attributes	32
P.2.6 Compatibility	32
P.3 Manufacture	32
P.3.1 Manufacturers	32
P.3.2 Batch Formula	33
P.3.3 Description of Manufacturing Process and Process Controls	35
P.3.4 Controls of Critical Steps and Intermediates	39
P.3.5 Process Validation and/or Evaluation	42
P.4 Control of Excipients	43
P.5 Control of Drug Product	43

- P.5.1 Specification 43
- P.5.2 Analytical Procedures 45
- P.5.3 Validation of Analytical Procedures 52
- P.5.4 Batch Analyses 59
- P.5.5 Characterization of Impurities..... 60
- P.5.6 Justification of Specification..... 60
- P.6 Reference Standards or Materials 67
- P.7 Container Closure System..... 67
- P.8 Stability 68
 - P.8.1 Stability Summary and Conclusion..... 68
 - P.8.2 Postapproval Stability Protocol and Stability Commitment..... 70
 - P.8.3 Stability Data 70
- A.1 Facilities and Equipment (biotech only) 73
- A.2 Adventitious Agents Safety Evaluation 73
- A.3 Novel Excipients 73
- R. REGIONAL INFORMATION 73
 - R1 Executed Batch Records 73
 - R2 Comparability Protocols 73
 - R3 Methods Validation Package 73
- II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 73
 - A. Labeling & Package Insert..... 73
 - B. Environmental Assessment Or Claim Of Categorical Exclusion 81
 - C. Establishment Evaluation Report..... 82
- III. List Of Deficiencies communicated and to be resolved 88

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 205-551
2. REVIEW #: 1
3. REVIEW DATE: 7/14/2014
4. REVIEWER: Maotang Zhou, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original IND 114820 submission
 Original IND 114820 CMC review by A. Yu
 End-of-phase-2 meeting (No CMC issues discussed)
 Pre-NDA meeting

Document Date

07-June-2012
 14-July-2012
 N/A
 27-Feb-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	10/22/2013	10/22/2013
Labeling package Insert	0009	03/14/2014	03/14/2014
Quality Amendment (Response to Agency Questions)	0010	03/14/2014	03/14/2014
Quality Amendment (Response to Agency Questions)	0012	04/18/2014	04/18/2014
Quality Amendment (Response to Information Request)	0015	06/02/2014	06/02/2014
Quality Amendment (Response to Information Request)			
Quality Amendment (Response to Information Request)			

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: ViiV Healthcare Company
Address: Five Moore Drive
Research Triangle Park, NC 27709
Representative: Anne Huffman, Sr. Director of QA/QC
Telephone: 877-844-8872

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Trimeq®
b) Non-Proprietary Name: Abacavir, Dolutegravir and Lamivudine
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: Type 4 (new combination – not previously approved in the US)
 - Submission Priority: Standard

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 50 mg/600 mg/300 mg

13. ROUTE OF ADMINISTRATION: Oral Tablet

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:

CMC Review Data Sheet

Abacavir Sulfate	Dolutegravir Sodium	Lamivudine
(C ₁₄ H ₁₈ N ₆ O) ₂ H ₂ SO ₄	C ₂₀ H ₁₈ F ₂ N ₃ NaO ₅	C ₈ H ₁₁ N ₃ O ₃ S
670.76 g/mol (sulfate) (b) (4)	441.36 g/mol (sodium salt) 419.38 g/mol (free acid)	229 (b) (4) g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	N/A
NDA	N/A	N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	4/4/2014	R. Xu
Pharm/Tox	N/A		
Biopharm	Adequate	7/7/2014	E. Chikhale
LNC	N/A		
Methods Validation	N/A		
DMEPA*	Review in DARRTS	4/22/2014	R. Kapoor
EA	Categorical exclusion (see review)	4/23/2014	M. Zhou
Microbiology	Adequate	3/17/2014	E. Pfeiler

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 205-551

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

As revised, the NDA includes sufficient information on the drug substance and drug product to assure the strength, purity, and quality of the drug product through the expiration dating period. However, an information request sent to the applicant concerning the manufacturing process description and the specification of an excipient is awaiting a response from the applicant. Labels and labeling contain adequate CMC information. Minor labeling comments have been conveyed to the review team. An “Acceptable” site recommendation from the Office of Compliance has been made. From the CMC perspective, this NDA may be recommended for approval pending satisfactory responses to the outstanding information request.

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

None

II. Summary of CMC Assessments

A. Description of the Drug Product and Drug Substance

The applicant intends to seek approval of the FDA for TRIUMEQ® (abacavir sulfate, dolutegravir, and lamivudine, or ABC/DTG/3TC) Tablets for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. The TRIUMEQ® tablet is a fixed dose combination product that contains three active ingredients: dolutegravir (DTG, GSK1349572), a 2-metal binding integrase inhibitor (INI), abacavir sulfate (ABC), a nucleoside reverse transcriptase inhibitor (NRTI), and lamivudine (3TC), also an NRTI.

All information regarding the chemistry, manufacturing and controls for the drug substances (abacavir sulfate, dolutegravir sodium, and lamivudine) were cross-referenced to the applicant’s approved NDA 20-977 for Ziagen® (abacavir sulfate) Tablets, approved NDA 204-790 for TIVICAY® (dolutegravir) Tablets, and approved NDA 20-564 for Epivir® (lamivudine) Tablets, respectively, and all amendments and supplements thereto.

The drug product, TRIUMEQ® (abacavir/dolutegravir/ lamivudine, or ABC/DTG/3TC) Tablet, is an immediate-release, purple, biconvex, film coated oval tablet, debossed with “572 Tri” on one face. Each Tablet contains (b) (4) of abacavir sulfate which is equivalent to 600 mg abacavir, 52.6 mg of dolutegravir sodium which is equivalent to 50 mg dolutegravir free acid, and 300 mg lamivudine. The formulation contains the inactive

Executive Summary Section

ingredients D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet film coating contains iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide. All excipients comply with USP/NF and are within levels used in other approved drug products. The TRIUMEQ[®] formulation was developed based on the formulations of TIVICAY[®] (dolutegravir) Tablets approved in NDA 204-790 and EPZICOM[™] (abacavir sulfate and lamivudine) Tablets approved in NDA 21-652.

The drug product is manufactured at Glaxo (b) (4). The manufacturing process comprises of the process steps for the manufacture of (b) (4) and ABC/DTG/3TC Tablets ((b) (4) film coating). The (b) (4) process is identical to the process used in the manufacture of (b) (4). A risk management approach was applied during process development to identify and define the CPPs and important material attributes that are likely to have the greatest impact on product quality. Several ranges/targets of variables were investigated using pilot and production scale DoE or during production scale manufacture of clinical batches. (b) (4) and (b) (4) and (b) (4) coating are identified as critical process parameters (CPP). The Control Strategy includes controls on the critical quality attributes (CQA) for the drug substances and in-process materials as well as CPPs related to the manufacturing process. The drug product will be tested for Description, Identification, (b) (4), Uniformity of Content, Drug-Related Impurities, assay, Dissolution, and Microbiological quality at release. The acceptance criteria are justified appropriately.

The drug product tablets are packaged in high density polyethylene (HDPE) bottles with desiccants, child-resistant closures and (b) (4). Stability data are provided for three primary stability batches of the drug product stored up to 12 months under the long term conditions (25 °C/60% RH and 30 °C/75% RH) and up to 6 months under the accelerated conditions (40 °C/75% RH). There are no significant changes in description, assay, drug-related impurity content, dissolution, and (b) (4) for any of the three active components. The potential for the formation of the (b) (4) is investigated in an in-use study for up to 1 month at 30 °C/75% RH, with and without the desiccant. Due to the observation of (b) (4) formation in the non-desiccant pack, precautionary statements will be used to prevent removal of desiccant from the pack. Overall, the available stability data support a shelf life of 24 months for the drug product when stored at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]. Precautionary statements are included to ensure that the product is stored in the original package with the bottle tightly closed to protect from moisture and the desiccant is not removed.

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

TRIUMEQ[®], a combination of dolutegravir (a human immunodeficiency virus type 1 [HIV-1] integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue HIV-1 reverse transcriptase inhibitors) is indicated as a complete

Executive Summary Section

regimen for the treatment of HIV-1 infection. Tablets contain 50 mg of dolutegravir, 600 mg of abacavir, and 300 mg of lamivudine. The dosage for adult is one tablet daily. The tablet may be taken with or without food. TRIUMEQ® tablets are packaged in HDPE bottles with child-resistant closures, (b) (4), with the following precautionary statement: “Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove the desiccant.”

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, adequate specifications for assuring consistent product quality of the drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. An information request (IR) has been sent to the applicant concerning the manufacturing process description and the specification of an excipient. Labels and labeling contain adequate CMC information.

Labels and labeling contain adequate CMC information. Minor labeling comments were conveyed to the review team. An “Acceptable” site recommendation from the Office of Compliance has been made for the manufacturing facilities. Therefore, from the CMC perspective, this NDA may be recommended for approval pending satisfactory responses to the outstanding information request.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

79 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MAOTANG ZHOU
07/14/2014

RAPTI D MADURawe
07/14/2014

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

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205-551**

2. DATES AND GOALS:

Letter Date:	Submission Received Date : Oct 22, 2013
PDUFA Goal Date: Aug 22, 2014	Reviews into DARRTS: June 22 (ODE signoff) or July14, 2014

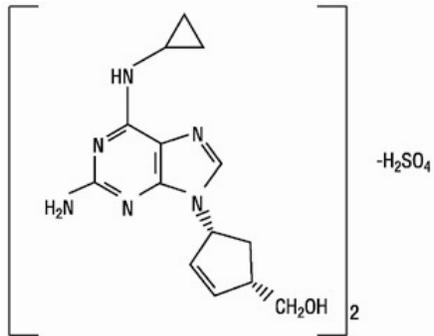
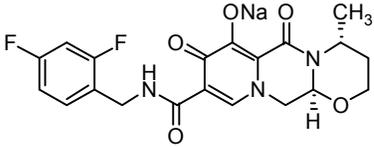
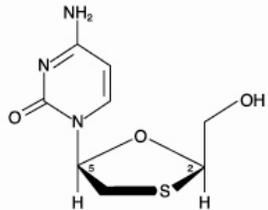
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Triumeq (proposed)
Established or Non-Proprietary Name (USAN):	Abacavir, Dolutegravir and Lamivudine
Dosage Form:	Tablet
Route of Administration	
Strength/Potency	600mg / 50mg / 300mg
Rx/OTC Dispensed:	Rx

4. INDICATION:

Treatment of HIV infection

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

		
Abacavir Sulfate	Dolutegravir Sodium	Lamivudine

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

ViiV Healthcare

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

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 4 (new combination – not previously approved in the US)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAVP

8. CONSULTS:

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

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

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes No
CMC Filing Issues:
1. None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes No
CMC Comments for 74-Day Letter:
1. Please provide the current specifications for the three drug substances. 2. The general recommendation for naming of antiviral products with multiple active ingredients is to list by alphabetical order. One exception is when one active ingredient is boosted by including a cytochrome P450 inhibitor; in that case the cytochrome inhibitor will be listed directly after the drug that is being boosted. We recommend that this product be named: <p style="text-align: center;">Trademark (abacavir, dolutegravir and lamivudine) Tablets 600mg / 50mg / 300mg</p> At an appropriate time, provided revised container labels and prescribing information.

Biopharmaceutics:

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

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes X No
Biopharmaceutics Comments (information requests) for 74-Day Letter:
1. Submit the following PK data from the BE Study (ING114580) in SAS Transport format in two separate files as described below: a. SUBJ SEQ PER TRT C _{max} AUC _t AUC _{inf} T _{max} T _{1/2} K _{el} b. SUBJ SEQ PER TRT C1 C2 C3 Cn
2. Provide a summary table for the bioanalytical method validation for each drug substance in the format provided below:

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

Matrix		
Sample Volume Required Storage Conditions Extraction Procedure		
Concentration Range		
HPLC Procedure		
Detection		
Regression Type		
Coefficient of Determination		
Between-Batch Accuracy	standards QCs	
Between-Batch CV	standards QCs	
Within-Batch	Accuracy CV	
Recovery	Drug Reference	
Stability in human plasma	Room temp Freeze/thaw Long term	
Solution Stability	at room temp at 4°C	
Reference Solution Stability	at room temp at 4°C	
LLOQ (Accuracy / CV)		
Processed Stability	at 4°C	
Dilution Integrity (v:v sample-blank)		

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?	
Yes	No
Microbiology Filing Issues:	
This NDA is fileable per Dr. Pfeiler's Microbiology Filing Review in DARRTS (Dec 11, 2013). The Information Request that is included in Dr. Pfeiler's review should be included in the filing or 74-day letter.	

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

Summary of Initial Quality Assessment

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

Is a team review recommended?		Yes	No
Suggested expertise for team:			
Maotang Zhou	(DS and DP)		
Elsbeth Chikhale	(BioPharm)		
Erika Pfeiler	(Prod Quality Micro)		
Rapti Madurawe	(Secondary Reviewer)		
Althea Cuff	(ONDQA PM)		
Sohail Mosaddegh	(DAVP PM)		

CMC Summary of Critical Issues and Complexities

Drug Substances

- Dolutegravir – all DS info is referenced to NDA 204790. A table showing submission dates and location of information is included in Module 3.
- Abacavir Sulfate – same approach cross-referencing to NDA 20-977.
- Lamivudine - same approach cross-referencing to NDA 20-564.

Note that all drug substance information is cross-referenced to these 3 applications. In the PreNDA meeting we recommended that some information be included directly in the application: “In addition, a cross-reference is not generally appropriate for the following information, which we recommend you included in the application:

- Physical or chemical attributes of the drug substance which are important for dosage form performance (e.g., characterization; justification of specification; etc.)
- The specification that is used for acceptance of the drug substance
- The analytical methods that will be used for acceptance of the drug substance
- Complete information on the manufacturing, release or stability testing, packaging, or labeling facilities for the drug substance

Particle size of (b) (4) dolutegravir sodium DS is said to be not critical, “based on results of a human in-vivo study (ING113068).” However, it is controlled by a one-sided X₉₀ of NMT (b) (4). The particle size distributions of the other two drug substances are not considered to be CQAs.

The preferred (b) (4) form of lamivudine (b) (4), abacavir sulfate (b) (4) and dolutegravir sodium (b) (4) are said to be controlled by the manufacturing processes. The specification for (b) (4) dolutegravir sodium is said to include a confirmatory test by (b) (4).

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

Drug Product

The product is a purple, biconvex, film coated oval tablet (approximately 22 x (b) (4)), debossed with "572 TRI" on one face. It is an immediate release tablet manufactured by a (b) (4) process from (b) (4) followed by film-coating.

Risk-assessment approaches and DoE studies were used to identify and define the CPPs and important material attributes, but this NDA does not need to be tracked as a QbD application.

Stability batches had different debossing from the commercial image. Stability batches had "572 TRI" and a breakline on the upper face and "TRI 572" and a breakline on the lower face.

One change seen in stressed stability studies was the generation of some (b) (4) which was observed in 1-week open-dish studies at 40°C/75% RH. The co-formulation with abacavir sulfate is believed to be responsible for this. It is not clear how high the (b) (4) content was in some open-dish studies, or whether this adversely affected any other attributes. An example spectrum shown in the stability method section appears by eye to be approximately (b) (4) % (b) (4).

A (b) (4) method can detect (b) (4) % (b) (4) and (b) (4) %. The (b) (4) form of the (b) (4) can be detected at (b) (4) % and quantitated at (b) (4) %.

To determine whether patient handling would generate any significant amount of (b) (4), an in-use study was conducted for 1 month at 30°C/75%RH. Levels of (b) (4) levels were not detectable (<(b) (4) %) for all samples except for one of the batches in a no-desiccant configuration. That sample was below the LOQ of (b) (4) %, and was also the sample that had the highest (b) (4) at the end of the study (b) (4). (b) (4) was undetectable (<(b) (4) %) for all samples.

Tablet (b) (4) drops from initial values of (b) (4) % down below (b) (4) % at initial time points. At the 25°C/60%RH condition, it appears to level off at (b) (4) % (b) (4). At 30°C/75%RH the (b) (4) reaches (b) (4) % and is still rising at the 12 mo timepoint. Solubility data are presented in the QOS which shows that the (b) (4) has approximately (b) (4) % of the kinetic solubility of the sodium salt at pH of simulated intestinal fluid. At gastric pH there is little difference, and the kinetic solubility of the (b) (4) is comparable to the sodium salt. Based on the dose-response profile, the applicant feels that the small amount of (b) (4) seen at present with the desiccant does not pose a risk of decreased efficacy. Are studies being continued to confirm low levels out to expiration, and perhaps to understand if this is linked to tablet (b) (4) levels?

Labeling

The PI and container labels contain this equivalence statement: "Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg of dolutegravir, abacavir sulfate equivalent to 600 mg of abacavir, and 300 mg of lamivudine."

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

The statements in the Medication Guide and the Patient Counseling Information suggest that the tablets are unusually sensitive to moisture: “Store in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.” This is to prevent the formation of [REDACTED] ^{(b) (4)}. A similar statement in the How Supplied section should possibly be modified to say: “Store **and dispense** in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.”

The applicant is adopting the USP recommendations to not show the counterion for abacavir. While many previous products used abacavir sulfate in the established name, switching to abacavir is consistent with the USP DP monograph for abacavir tablets, and also resolves the name/strength mismatch since strength has always been expressed on the basis of abacavir.

Alphabetical order should be used in the established name, based on the DAVP policy for antiviral drug combinations.

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

Biopharmaceutics Assessment

Biopharmaceutics Critical Issues or Complexities

This is a 505(b)(1) for a fixed dose combination (FDC) film coated oval tablet containing 50 mg (b) (4) dolutegravir (DTG), 600 mg abacavir and 300 mg lamivudine per tablet. The quantitative composition of the drug product is provided in Appendix 1 below.

The proposed once-daily FDC single tablet regimen (STR) that combines the integrase inhibitor (INI) DTG with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) is being developed for use in the treatment of human immunodeficiency virus (HIV) infection. The Applicant has performed numerous clinical safety and efficacy studies as well as a bioequivalence (BE) study (study ING114580) in healthy volunteers under fasted conditions to compare the bioavailability of the proposed FDC drug product to co-administration of the separate tablet formulations of DTG 50 mg and EPZICOM (ABC 600 mg/3TC 300 mg). A Biopharmaceutics Inspection Request for the clinical site as well as the bioanalytical site has to be submitted. Dissolution is considered a critical quality attribute for the proposed drug product and will be tested as part of the drug product release and stability testing.

The following dissolution methods and acceptance criteria are proposed:

Proposed dissolution method:

Apparatus 2, 900 mL 0.01 M phosphate buffer, pH 6.8 with 0.5% SDS at 85 rpm.

Proposed acceptance criterion:

Dolutegravir: $Q = \frac{(b)}{(4)} \% \text{ at } \frac{(b)}{(4)} \text{ minutes}$

Abacavir and lamivudine: $Q = \frac{(b)}{(4)} \% \text{ at } 30 \text{ minutes}$

The Biopharmaceutics review of this NDA will be focused on the evaluation of:

- The proposed dissolution method and acceptance criteria;
- The bioequivalence studies under fasted conditions;
- The bioequivalence study inspection report; and
- The bioanalytical method and method validation.

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

FILING REVIEW CHECKLIST

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

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	IND 114820 PreNDA mtg minutes Mar 8, 2013 – Yes, CMC recommendations were incorporated Pre-IND mtg min May 30, 2012 – No; see notes about drug substance information, above.

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

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

	Parameter	Yes	No	Comment
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) 	X		
8.	<p>Are drug product 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) 	X		

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

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

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		Below 1 ppb

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

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		X	All cross-referenced to the 3 approved NDAs
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	All cross-referenced to the 3 approved NDAs
14.	Does the section contain information regarding the characterization of the DS?		X	All cross-referenced to the 3 approved NDAs
15.	Does the section contain controls for the DS?		X	All cross-referenced to the 3 approved NDAs
16.	Has stability data and analysis been provided for the drug substance?		X	All cross-referenced to the 3 approved NDAs
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	No drug substance information in this NDA
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	No drug substance information in this NDA

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

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		<p>A narrative description is included</p> <p>Executed batch records for the 3 stability batches and the (b) (4) that they were (b) (4) are included in the Regional Information. Scale = (b) (4) The bioequivalence lot (R572216) was made from one of these (b) (4), with (b) (4) to different (b) (4) levels.</p> <p>An unexecuted batch record at (b) (4) kg batch is included in 3.2.R.</p> <p>Batch analyses are provided for (b) (4) production-scale batches from the commercial site.</p>
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		See Point 19, above
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		<p>HDPE bottles of (b) (4) or 30 tablets (monthly) with (b) (4) and desiccant.</p> <p>(b) (4) are not listed in the PI</p>
24.	Does the section contain controls of the final drug product?	X		

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

25.	Has stability data and analysis been provided to support the requested expiration date?	X	<p>12 months of long-term stability data are presented for (b) (4) production-scale batches made at the commercial manufacturing site ((b) (4)), in both presentations. A matrixed testing approach was used at both of the long-term conditions (25°C/60%RH and 30°C/75%RH) which were applied to the 30-count bottle. The (b) (4) was only studied at 25°C/60%RH, but also with a matrixed design.</p> <p>Additionally, photostability, freeze/thaw, 30-day in-use, and 50°C stress studies were performed.</p> <p>24 mo expiry proposed for storage at USP CRT.</p>
26.	Does the application contain Quality by Design (QbD) information regarding the DP?	X	Justification of process parameters with DoE studies
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	X	Automatic adjustment of (b) (4) is described in some depth.

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA

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

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
LOAs are provided for (b) (4) DMFs for (b) (4). Additionally, there is an LOA for an NIH pediatric clinical study.					

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

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

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
34.	Is the dissolution test part of the DP specifications?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<u>Proposed dissolution method:</u> Apparatus 2, 900 mL 0.01 M phosphate buffer, pH 6.8 with 0.5% SDS at 85 rpm. <u>Proposed acceptance criterion:</u> Dolutegravir: Q = $\frac{(b)}{(4)}$ % at $\frac{(b)}{(4)}$ minutes Abacavir and lamivudine: Q = $\frac{(b)}{(4)}$ % at 30 minutes
35.	Does the application contain the dissolution method development report?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	See P.5.3: Analytical Development report
36.	Is there a validation package for the analytical method and dissolution methodology?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
37.	Does the application include a biowaiver request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
38.	Does the application include data supporting the biowaiver?	<input type="checkbox"/>	<input type="checkbox"/>	N/A
39.	Does the application include an IVIVC model?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Is information such as BCS classification mentioned, and supportive data provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	BCS classification is mentioned in section 2.5. In particular, the Applicant states that DTG belongs to BCS class 2 and that ABC and 3TG belongs to BCS class 3
41.	Is information on mixing the product with foods or liquids included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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42.	Is there any <i>in vivo</i> BA or BE information in the submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The following bioequivalence study is included in the NDA: ING114580 - a single dose, 2-way crossover study conducted in healthy volunteers to evaluate the bioequivalence of a single combined formulated tablet (FDC) of DTG 50 mg, ABC 600 mg and 3TC 300 mg compared to co-administration of the separate tablet formulations of DTG 50 mg and EPZICOM (ABC 600 mg/3TC 300 mg) in the fasted state																																																																																	
43.	Did the Applicant provide raw data for the BA/BE study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The following information request should be send to the Applicant: Submit the following PK data from the BE Study (ING114580) in SAS Transport format in two separate files as described below: c.SUBJ SEQ PER TRT C _{max} AUC _t AUC _{inf} T _{max} T _{1/2} K _{el} d.SUBJ SEQ PER TRT C1 C2 C3 Cn																																																																																	
44.	Did the Applicant provide a summary table for the bioanalytical method validation?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The following information request should be send to the Applicant: Provide a summary table for the bioanalytical method validation for each drug substance in the format provided below: <table border="1" data-bbox="868 1270 1412 1774"> <tr><td>Matrix</td><td></td><td></td></tr> <tr><td>Sample Volume Required</td><td></td><td></td></tr> <tr><td>Storage Conditions</td><td></td><td></td></tr> <tr><td>Extraction Procedure</td><td></td><td></td></tr> <tr><td>Concentration Range</td><td></td><td></td></tr> <tr><td>HPLC Procedure</td><td></td><td></td></tr> <tr><td>Detection</td><td></td><td></td></tr> <tr><td>Regression Type</td><td></td><td></td></tr> <tr><td>Coefficient of Determination</td><td></td><td></td></tr> <tr><td>Between-Batch Accuracy</td><td>standards</td><td></td></tr> <tr><td></td><td>QC's</td><td></td></tr> <tr><td>Between-Batch CV</td><td>standards</td><td></td></tr> <tr><td></td><td>QC's</td><td></td></tr> <tr><td>Within-Batch</td><td>Accuracy</td><td></td></tr> <tr><td></td><td>CV</td><td></td></tr> <tr><td>Recovery</td><td>Drug</td><td></td></tr> <tr><td></td><td>Reference</td><td></td></tr> <tr><td>Stability in human plasma</td><td>Room temp</td><td></td></tr> <tr><td></td><td>Freeze/thaw</td><td></td></tr> <tr><td></td><td>Long term</td><td></td></tr> <tr><td>Solution Stability</td><td>at room temp</td><td></td></tr> <tr><td></td><td>at 4°C</td><td></td></tr> <tr><td>Reference Solution Stability</td><td>at room temp</td><td></td></tr> <tr><td></td><td>at 4°C</td><td></td></tr> <tr><td>LLOQ (Accuracy / CV)</td><td></td><td></td></tr> <tr><td>Processed Stability</td><td>at 4°C</td><td></td></tr> <tr><td>Dilution Integrity (v:v sample-blank)</td><td></td><td></td></tr> </table>	Matrix			Sample Volume Required			Storage Conditions			Extraction Procedure			Concentration Range			HPLC Procedure			Detection			Regression Type			Coefficient of Determination			Between-Batch Accuracy	standards			QC's		Between-Batch CV	standards			QC's		Within-Batch	Accuracy			CV		Recovery	Drug			Reference		Stability in human plasma	Room temp			Freeze/thaw			Long term		Solution Stability	at room temp			at 4°C		Reference Solution Stability	at room temp			at 4°C		LLOQ (Accuracy / CV)			Processed Stability	at 4°C		Dilution Integrity (v:v sample-blank)		
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**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A (fileable)
3.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A (fileable)
4.	Are there any potential review issues identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	See comment for the 74 day letter

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

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

See appended electronic signature page

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

Appendix 1. Composition of Drug Product

Component	Quantity (% w/w)	Function	Reference to Standard
(b) (4)			
Supplier USP and Ph. Eur. USNF and Ph. Eur. USP and Ph. Eur. USNF and Ph. Eur. USP and Ph. Eur.			
(b) (4) Tablet (b) (4)			
Component	Quantity (mg/tablet)	Function	Reference to Standard
Dolutegravir (b) (4) ³	(b) (4)	Active (b) (4)	-
Abacavir Sulfate ⁴	(b) (4)	Active	Supplier
Lamivudine ¹	300.0	Active	Supplier
Microcrystalline Cellulose	(b) (4)	(b) (4)	USNF and Ph. Eur.
Sodium Starch Glycolate	(b) (4)	(b) (4)	USNF and Ph. Eur.
Magnesium Stearate	(b) (4)	(b) (4)	USNF and Ph. Eur.
Film Coating			
Opadry II Purple 85F90057 ⁵	(b) (4)	Film coat	Supplier
(b) (4)	(b) (4)	(b) (4)	USP and Ph. Eur.
Total Coated Tablet Weight	(b) (4)	-	-

Note:

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

Appendix 2. DP Specification

Test	Acceptance criteria
Description	Purple, biconvex, film coated oval tablet, debossed with "572 Tri" on one face
Identification of dolutegravir, abacavir and lamivudine ¹ by HPLC by UV	(b) (4)
Uniformity of dosage units with respect to Dolutegravir by HPLC ¹	Complies with Pharmacopoeia (USP <905>)
Uniformity of dosage units with respect to abacavir by HPLC ¹	Complies with Pharmacopoeia (USP <905>)
Uniformity of dosage units with respect to lamivudine by HPLC ¹	Complies with Pharmacopoeia (USP <905>)
Dolutegravir content by HPLC (% label claim) ²	(b) (4)
Abacavir content by HPLC (% label claim) ²	(b) (4)
Lamivudine content by HPLC (% label claim) ²	(b) (4)
Dolutegravir drug-related impurities content by HPLC (% area) Any dolutegravir related unspecified impurity ³ Total dolutegravir related impurities ⁴	Not greater than (b) (4) Not greater than (b) (4)

Continued

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

DP Specification (continued)

Test	Acceptance criteria
Abacavir drug-related impurities content by HPLC (% area)⁵ Any abacavir related unspecified impurity ³ Total abacavir related impurities ⁴	Not greater than 0.2 Not greater than 1.0
Lamivudine drug-related impurities content by HPLC (% area)⁵ Any lamivudine related unspecified impurity ³ Total lamivudine related impurities ⁴	Not greater than (b) (4) Not greater than 0.6
Dolutegravir dissolution by HPLC (%released)	Complies with Pharmacopoeia (USP <711> where Q = (b) (4)% at (b) (4) minutes
Abacavir dissolution by HPLC (%released)	Complies with Pharmacopoeia (USP <711> where Q = (b) (4)% at 30 minutes
Lamivudine dissolution by HPLC (% released)	Complies with Pharmacopoeia (USP <711> where Q = (b) (4)% at 30 minutes
Microbiological Quality of Drug Product (b) (4)	Not greater than (b) (4)
Microbial Limits Test 6, 7 (b) (4)	Complies with Harmonised Pharmacopoeia *
Total Aerobic Microbial Count (TAMC) (CFU/g) Total combined yeasts / mould count (TYMC) (CFU/g)	Not greater than (b) (4) Not greater than (b) (4)
Specified micro-organisms: <i>Escherichia coli</i>	Absent in (b) (4)

Notes:

* Ph.Eur. / USP / JP

1. Performed at release only
2. For batch release the mean result from the uniformity of dosage unit test can be applied
3. Excludes any detected drug substance synthetic process impurity
4. Includes degradation products and drug substance synthetic process impurities that have been detected at a level of (b) (4)% or greater
5. Any unidentified impurities obtained on the abacavir and lamivudine drug-related impurities method are quantified as abacavir related impurities
6. (b) (4)
7. (b) (4) will be tested on 30 batches of tablets after which microbiological quality tests will not be performed routinely

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

Appendix 3. Container Labels

(b) (4)



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

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

/s/

ELSBETH G CHIKHALE
12/18/2013

STEPHEN MILLER
12/18/2013

RICHARD T LOSTRITTO
12/19/2013

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12/19/2013