CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022142Orig1s000

PRODUCT QUALITY REVIEW(S)

OPQ Memorandum for NDA 22242 Orig-1 Resub-65

Product: SYMFI (efavirenz, lamivudine and tenofovir DF) Tablets, 600mg/300mg/300mg
Applicant: Mylan Labs, Ltd.
Submitted: Sept 22, 2017

This NDA is recommended for Final Approval from the product quality perspective.

Summary:
This NDA received Tentative Approval for treatment of HIV infection on Sept 3, 2009 under the PEPFAR program. Matrix was the original applicant, and Mylan subsequently became the applicant. In the Sept 22, 2017 submission Mylan requested full approval, which would allow marketing in the US, once applicable patents have expired. The cover letter includes a summary of changes made since the 2009 TA action and includes copies of the PEPFAR permitted letters for post-TA changes.

Facilities:
There are three DP manufacturing facilities and the current view of the NDA in EDR shows three separate DP sections. In response to an Information Request sent by FDA on Oct 11, 2017, Mylan responded on Oct 24, 2017 with a summary table of all manufacturing facilities including a history of change in facilities since the original submission.

(b) (4) was withdrawn from the application for commercial manufacturing responsibilities in a late amendment during this final approval submission. However, the facility remains listed in the application as the manufacturer of the batches that support the clinical studies showing bioequivalence to the RLD in accordance with 314.50. Additional manufacturing facilities, supported by sufficient CMC data, are included as the final proposed commercial manufacturing sites. Given the recent Warning Letter noting potential data reliability concerns, an assessment was completed regarding the original batches manufactured at (b) (4) to support the original tentative approval and bioequivalence. The acceptable bioequivalence study was carried out in Sept-Oct 2008, using product made during April 2008 at the (b) (4) site (Batch (b) (4). The (b) (4) site was acceptable at that time and there is no indication that the current issues at the facility impact this batch and the data. Therefore, the facility recommendation is for full approval of this NDA without the (b) (4) facility proposed for commercial operations.

In the Mar 12, 2018 amendment, (b) (4)

An overall inspection recommendation of Approve was entered in Panorama by Derek Smith on Mar 16, 2018. For further details, see Derek Smith's comments under Inspection View in Panorama.

Drug Substance:
The three drug substances can be sourced from the following Drug Master File holders:

- DMF 18230 for Efavirenz USP; Holder is Mylan Laboratories; Adequate; See H. Sarker's Rev#14 (Feb 23, 2018).
- DMF (b) (4) for (b) (4); Holder is (b) (4); Adequate; See H. Sarker's Rev#4 (Mar 9, 2018).
- DMF (b) (4); Holder (b) (4); LOA Adequate; See M. Ethirajan's Rev#12 (Apr 21, 2017)
- DMF 17750 for Lamivudine USP; Holder is Mylan Laboratories; Adequate; See H. Sarker's Rev#23 (Feb 21, 2018)
- DMF 20108 for Tenofovir DF; Holder is Mylan Labs; Adequate; See H. Sarker's Rev#13 (Nov 5, 2017)
- DMF (b) (4) for (b) (4); Holder is (b) (4); Adequate; See Y. Lin's Rev#23 (Oct 13, 2016).

For additional details, see Haripada Sarker's drug substance review, below.

Drug Product:
SYMFI (efavirenz, lamivudine and tenofovir disoproxil fumarate) Tablets 600mg/300mg/300 mg are white, film-coated, capsule shaped, debossed with M 152 on one side of the tablet and plain on the other side. The product will be marketed in the US only in HDPE bottles of 30 tablets with desiccant, induction seal and child-resistant cap. (b) (4) An expiration dating period of (b) (4) months was granted for the 30-count bottle on July 30, 2016 (PEPFAR Permitted Letter). Based on the acceptable behavior on stability under 30°C/75%RH long-term condition (including 36-month data for (b) (4) tablets and 24-month data for (b) (4) tablets) a storage statement of "Store below 30°C (86°F)" and an expiration dating period of (b) (4) months were recommended for the current final approval action. Mylan agreed in the March 14, 2018 amendment, and updated the labels/labeling. An adequate assessment of the risk from elemental impurities in the drug product was supplied in the Feb 15, 2018 amendment.

The NDA is organized with three drug product section, one for each of the tablet manufacturing sites. In the Mar 12, 2018 amendment Mylan agreed that previous product quality agreements documented in the 3.2 (b) (4) section of the NDA will apply to product made at the (b) (4) facilities. As an example, in that Amendment the 30°C/75%RH long-term condition was added to the post-approval commitments in P.8.2 (b) (4) and P.8.2 (b) (4) For additional details, see Milton Sloan's drug product review, below.

Biopharmaceutics:
After evaluation of dissolution data from (b) (4) commercial batches (Mylan states in the Feb 15, 2018 amendment that (b) (4) commercial batches have been manufactured), and additional information submitted in the Feb 23, 2018 amendment, the acceptance criteria were tightened to:

- Efavirenz: Q (b) (4)% in 60 minutes
- Lamivudine: Q= (b) (4)% in 45 minutes
- Tenofovir DF: Q= (b) (4)% in 45 minutes

The dissolution method uses 2% sodium lauryl sulfate (b) (4) at 75 rpm (Apparatus-II/paddle). For additional details, see Zhuojun (Joan) Zhao's biopharmaceutics review, below.

Labeling:
Edits recommended from the product quality perspective for the prescribing information and the container labels have been conveyed to the OND review team, for consideration during labeling negotiations. Final bottle and carton labels were submitted in the Mar 14, 2018 amendment, and an image of the bottle label is inserted here:

Stephen P. Miller, Ph.D.
Application Technical Lead for NDA 22142 Resub-65

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BIOPHARMACEUTICS

Product Background:
NDA: 22142 (Resubmission of New Drug Application-505(b)(2)

Drug Product Name / Strength: Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 600/300/300 mg

Route of Administration: Oral

Applicant Name: Mylan Laboratories Limited

Review Summary:
Mylan Laboratory Limited's Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 600/300/300 mg was tentatively approved for use as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults on September 3, 2009[1]. The listed drugs for this 505(b)(2) application are Sustiva®, Viread® and Epivir®.

On September 22, 2017, the resubmission of NDA 22142 requests the final approval of the proposed Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 600/300/300 mg.

This Biopharmaceutics Review evaluates the currently approved dissolution method and acceptance criterion.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Resubmission	09/22/2017
IR Responses	2/15/2018, 2/23/2018 and 3/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Final acceptable dissolution method and acceptance criteria:

Apparatus	USP II (Paddle)
Medium	2% SLS
Rotation Speed	75 rpm
Volume	1000 mL
Dissolution acceptance criteria	Efavirenz: NLT (b)(4)% (Q) at 60 minutes Lamivudine and Tenofovir: NLT (b)(4)% (Q) in 45 minutes

Recommendation:
From the Biopharmaceutics perspective, NDA 22142 for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 600/300/300 mg is recommended for **APPROVAL**.

[1] DARRTS: COR-NDAACTION-06 (Tentative Approval), final date 09/3/2009

DISSOLUTION METHOD AND ACCEPTANCE CRITERION:
The following dissolution method and acceptance criterion were previously approved as shown below[2]:

Apparatus	USP II (Paddle)
Medium	2% SLS
Rotation Speed	75 rpm
Volume	1000 mL
Acceptance Criterion (for all components)	NLT (b) (4) % (Q) in (b) (4) minutes

DISSOLUTION DATA:
Based on previously submitted dissolution data for four (4) drug product batches (Appendix 1) all three components are released more than (b) (4) % in 15 minutes. Therefore, a tighter dissolution acceptance criterion of NLT (b) (4) % (Q) in (b) (4) minutes was suggested to the Applicant (IR dated 1/30/2018, Appendix 2).

In the Applicant's response dated 2/15/2018 to IR dated 1/30/2018 (Appendix 2), the Applicant provided dissolution data of (b) (4) commercial batches (Appendix 3) and evaluation results with respect to the recommended tighter acceptance criterion (showing S1, S2, S3 and OOS percentage). Based on the evaluation of the overall dissolution data as well as the PK behavior of the proposed drug product, the Applicant submitted the newly proposed revised dissolution acceptance criteria as shown below:

Component	Newly Proposed Revised Dissolution Acceptance Criteria
Efavirenz	NLT (b) (4) % (Q) in 60 minutes
Lamivudine Tenofovir Disoproxil Fumarate	NLT (b) (4) % (Q) in 45 minutes

The Applicant was requested to provide the age and storage conditions of batches at the time of dissolution testing for the (b) (4) batches in IR dated 2/21/2018 (Appendix 4).

In the response dated 2/23/2018 (Appendix 4), the Applicant provided storage and age information of the (b) (4) batches, which indicated that the batches were stored at NMT 25 °C and none of the batches were expired at the time of dissolution testing.

Reviewer's assessment of the overall provided dissolution data and justification:
Based on the overall submitted dissolution data (Appendix 3) and justification of the newly proposed revised dissolution acceptance criteria (Appendix 2) provided on February 15, 2018, the Applicant's newly proposed, revised dissolution acceptance criteria are acceptable.

[2] DARRTS: REV-QUALITY-03 (General Review), final date 05/19/2009 and 09/03/2009

The Applicant updated the drug product specification table accordingly in the IR Response dated 3/14/2018 (Appendix 5).

REVIEWER'S ASSESSMENT/RECOMMENDATION:
From the Biopharmaceutics perspective, NDA 22142 for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 600/300/300 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: *Zhuojun Zhao, Ph.D., 3/16/2018*

Secondary Reviewer Name and Date: *Elsbeth Chikhale, Ph.D., 3/16/2018*

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Appendix 4: Biopharmaceutics Information Request dated February 21, 2018 and the Applicant's Response dated February 23, 2018

Biopharmaceutics Request Comments:
Provide the storage condition and age at the time of dissolution testing for the (b) (4) batches that you included in your "Dissolution Data of Commercial Batches" Table that you submitted on 2/15/2018 as part of your Information Request response.

Applicant's Response to Biopharmaceutics-IR Comment:
The file shows that dissolution profiles for (b) (4) batches provided in the IR response dated February 15, 2018 are either initial release data or testing data at approximate age of 2 month (stored NMT 25°C).

Reviewer Note:
The Applicant's response is accepted. Based on the evaluation of (b) (4) commercial batches (Appendix 3) as well as the PK behavior of the proposed drug product, the Applicant's newly proposed revised dissolution acceptance criteria are accepted, as follows:

Component	Newly Proposed Dissolution Acceptance Criteria
Efavirenz	NLT (b) (4)% (Q) in 60 minutes
Lamivudine Tenofovir Disoproxil Fumarate	NLT (b) (4)% (Q) in 45 minutes

The Applicant only provided updated drug product specification for the (b) (4) site in the IR response dated 2/15/18. Thus, the Applicant was requested (Appendix 5) to provide updated drug product specification table with the revised dissolution acceptance criteria across all three drug product manufacturing sites.

Appendix 5: Biopharmaceutics Information Request dated March 9, 2018 and the Applicant's Response dated March 14, 2018

Biopharmaceutics Request Comments:

Based on the available information, including your responses in the amendments dated Feb 15 and Feb 23, 2018, we concur with the proposed acceptance criteria of NLT (b)(4)% (Q= (b)(4)%) in 45 minutes for lamivudine and tenofovir DF, and NLT (b)(4)% (Q (b)(4)%) in 60 min for efavirenz. Please update the appropriate documents throughout the application and across the three drug product manufacturing sites.

Applicant's Response to Biopharmaceutics-IR Comment:

Mylan acknowledges the Agency's concurrence on the proposed dissolution acceptance criteria of:

Specification of Dissolution (By HPLC) [2.0 % w/w SLS (b)(4), USP Apparatus II (Paddle), 1000 mL, 75 RPM]	
Components	***Cumulative % of drug release (label claim)***
Efavirenz, USP	Not less than (b)(4)**% (Q)** of the labeled amount of Efavirenz, $C_{14}H_9ClF_3NO_2$ should be dissolved in **60 minutes**.
Lamivudine, USP	Not less than (b)(4)**% (Q)** of the labeled amount of Lamivudine, $C_8H_{11}N_3O_3S$ should be dissolved in **45 minutes**.
Tenofovir Disoproxil Fumarate	Not less than (b)(4)**% (Q)** of the labeled amount of Tenofovir Disoproxil Fumarate, $C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$ should be dissolved in **45 minutes**.

In support of the revised dissolution limits, Mylan submitted the revised finished product specification, test procedure and shelf life specifications in the Information Request Response dated February 15, 2018 (Sequence No. 0056). Further, the revised finished product regulatory and shelf-life specifications, which includes the recommended dissolution limits, along with the newly updated storage conditions, are provided in Sections 3.2.P.5.1 and 3.2.P.8.1, respectively.

Mylan commits to adopt the same drug product specifications across all of the approved drug product manufacturing sites.

Reviewer Note:

The Applicant's response is satisfactory. Drug product specifications for drug products manufactured at all 3 sites have been updated with the revised dissolution acceptance criteria.

Zhuojun Zhao

Digitally signed by Zhuojun Zhao
Date: 3/16/2018 10:40:39PM
GUID: 508da6fd000284770cf4eecbae074722

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 3/17/2018 10:51:19PM
GUID: 50743ccc000031928b54eba1769a5df9

NDA 22-142

Efavirenz, Lamivudine, & Tenofovir Disoproxil Fumarate Tablets
600 mg/300 mg/300 mg

Applicant: Matrix Laboratories Ltd.

Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist
Branch IV
Division of Pre-Marketing Assessment II
ONDQA

CMC Review #1 for Division of Antiviral Products

Table of Contents

Chemistry Review Data Sheet

1. NDA **22-142**

2. REVIEW #: 1

3. REVIEW DATE: 8-28-2009

4. REVIEWER: **Rao V. Kambhampati, Ph.D.**

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date
Original	3-2-09
Amendment	5-29-09
Amendment	6-26-09
Amendment	8-25-09

7. NAME & ADDRESS OF APPLICANT:

Name:	Matrix Laboratories Limited
Address:	1-1-151/1, 4th Floor Sairam Towers Alexander Road Secunderabad-500 003 Andhra Pradesh (AP) India
Representative:	Ronald T. Groman Director, Regulatory Affairs Mylan Pharmaceuticals Inc. 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WA 26504-4310

Telephone: 304-554-5899
800-848-0461 Ext. 5899

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not applicable (PEPFAR drug)
b) Non-Proprietary Name: Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets.
c) Code Name/#: Not applicable
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 (new fixed dose combination)
- Submission Priority: P (fast-track)

9. LEGAL BASIS FOR SUBMISSION: Type 505 (b)(2); PEPFAR NDA for Tentative Approval (21 CFR 314. 105).

10. PHARMACOL. CATEGORY: Anti-viral (anti-HIV 1)

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 600 mg/300mg/300mg per tablet.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

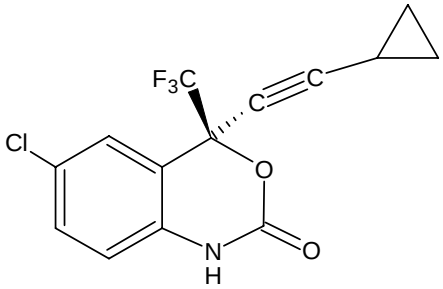
__X___Not a SPOTS product

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

Note: This drug product contains three active ingredients and they are as follows:

a) Efavirenz:

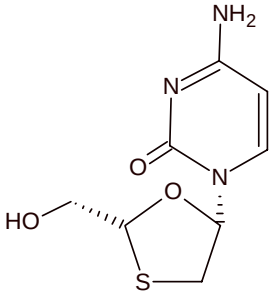
(*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.
CAS Number: 154598-52-4



$C_{14}H_9ClF_3NO_2$
315.67

b) Lamivudine:

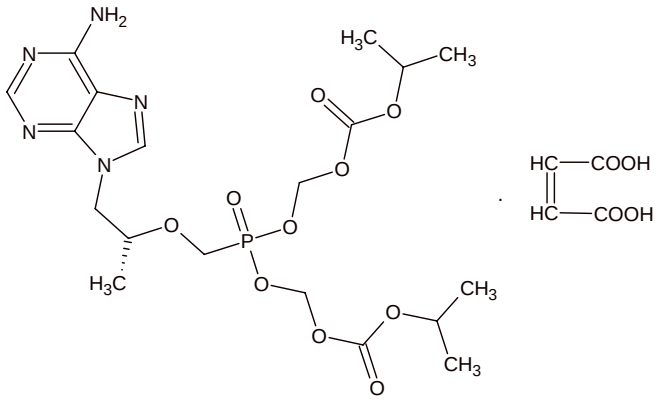
i) 2(1*H*)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-, (2*R*-*cis*)- or
ii) (–)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine
CAS Number: 134678-17-4



$C_8H_{11}N_3O_3S$
229.26

c) Tenofovir Disoproxil Fumarate:

i) (*R*)-5-[[2-(6-Amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]-2,4,6,8-tetraoxa-5-phosphanonanedioic acid, bis(1-methylethyl) ester, 5-oxide, (*E*)-2-butenedioate (1:1) or
ii) Bis(hydroxymethyl) [[(*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phosphonate, bis(isopropyl carbonate) (ester), fumarate (1:1); or
iii) 9-[(*R*)-2-[[Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1)
CAS Number: 202138-50-9



$C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$
635.51

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Component	Manufacturer	DMF #
Tenofovir Disoproxil Fumarate	Matrix Laboratories Limited	20108
Lamivudine		17750
Efavirenz		18230
(b) (4)		

Note: DMFs 20108; 17750; and 18230 were found to be adequate by the FDA review chemists. Other DMFs are either reviewed by the FDA chemists or the applicant provided adequate information in the NDA.

B. Other Documents:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Initial Quality Assessment (IQA)	22-142	Reviewed by PAL, Stephen Miller, Ph.D., see his review in DARRTS.

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Evaluation	Acceptable	8-26-09	E. Johnson (HFD-320, DMPQ)
Bioequivalence (Clinical Pharmacology)	Acceptable (Review in DARRTS)	6-25-09	Assadollah Noory, Ph. D. (DCP 4)
LNC	N/A because PEPFAR drug	8-28-09	Rao V. Kambhampati, Ph.D.
Methods Validation	Not submitted to FDA Lab per current ONDQA Policy	8-28-09	Rao V. Kambhampati, Ph.D.
EA	Categorical exclusion request acceptable	8-28-09	Rao V. Kambhampati, Ph.D.

The Chemistry Review for NDA 22-142

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC stand point the NDA# 22-142 is recommended for tentative approval under PEPFAR program for the following packaging configurations:

30-Tablet count HDPE Bottles (b) (4)

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Substances and Drug Product

Introduction: This is a fast track, 505 (b)(2) NDA that was submitted under PEPFAR program for the tentative approval of Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate, 600 mg/300 mg/300 mg Tablets. The drug product is indicated (b) (4) for the treatment of HIV-1 infection (b) (4) (b) (4)Even though the proposed drug product tablet contains previously approved active ingredients but it is unique because it is a new fixed dose combination product for the FDA. The reference drugs contain single active ingredients and they are Sustiva®, Epivir®, and Viread® tablets, which are marketed presently by Bristol Myers Squibb, GlaxoSmithKline , and Gilead Pharmaceuticals, respectively.

Drug Substances: The proposed fixed dose combination tablets contain three Active Pharmaceutical Ingredients (APIs; drug substances) i.e., efavirenz, lamivudine, and tenofovir disoproxil fumarate. All three APIs were previously approved by the FDA for their use in single, double, or triple API containing solid oral dosage forms. The CMC information for the APIs was cross-referenced to the corresponding DMFs (18230, 17750, and 20108) and the applicant is the Holder of all three DMFs. These three DMFs were reviewed recently by other FDA chemists when they were cross-referenced for the approval of other drug products, and all three DMFs were found to be adequate. In addition, the applicant provided some CMC information directly in the NDA. In the initial submission, the applicant did not include particle size distribution in the efavirenz drug substance specification, however, upon comment, the requested information was included, and revised specification was provided. In the past, the applicant (DMFs Holder) had used more than one facility for the manufacturing of these three APIs,

however, upon comment the applicant clarified that for the manufacturing of the proposed drug product tablets, the efavirenz drug substance manufactured at (b) (4) and the lamivudine and tenofovir disoproxil fumarate drug substances manufactured at (b) (4) (b) (4) will only be used. Upon FDA comment, the Applicant committed that the (b) (4) manufactured efavirenz drug substance will not be used for the manufacturing of the proposed drug product tablets.

Drug Product:

The proposed drug product is immediate release film-coated fixed dose combination tablet containing 600 mg of efavirenz, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir) as active ingredients and the following excipients: microcrystalline cellulose (b) (4), croscarmellose sodium (b) (4) hydroxyl propyl cellulose (b) (4), sodium lauryl sulfate (b) (4), sodium chloride (b) (4) magnesium sterarate (b) (4), lactose monohydrate (b) (4) All the excipients are of compendial grade (b) (4) . The levels of all the excipients present in the tablet are justified. The excipients used in the proposed tablet are same as those present in reference drugs (b) (4). The film coating contains ingredients that have been used in other approved film coatings. Therefore, there are no safety concerns from the excipients. The applicant performed many experiments as part of the product development in designing and optimizing the formulation and process.

The drug product is manufactured and packaged in the Applicant's facility at (b) (4) India. (b) (4) The drug product specification included description (appearance), identity (HPLC and TLC), dissolution (by HPLC), Uniformity of Dosage Units (USP, content uniformity method), related substances (impurities) by HPLC, assay (HPLC), and (b) (4) The dissolution method complies with USP <711> and the acceptance criterion is NLT (b) (4)% (Q) of each API should be dissolved in (b) (4) min. (b) (4) The revised specification including the acceptance criteria are acceptable. Upon comment, the applicant included a test for residual solvents per USP <467>. Batch analysis results were provided for three batches and the results met the proposed specification. The tablets are packaged in 30 count (b) (4)

(b) (4). It was demonstrated that the tablets remain stable for 12 months under long-term conditions and 6 months under accelerated conditions. Therefore, on the basis of these results, an expiration dating period of 24 months is acceptable when stored at (b) (4) °C.

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

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate, 600mg/300mg/300mg, tablets are white-colored, capsule shaped, film coated, debossed "M152" on one side and plain on other side. They are packaged as follows:

HDPE Bottles of 30 tablets NDC 65015-097–14

(b) (4)

The recommended dose is one tablet daily and should be taken orally on empty stomach, preferably at bedtime. A 30 count bottle will provide 30 days supply (b) (4). The tablet bottles are recommended to be stored (b) (4) (b) (4) 30ºC (b) (4) 86ºF) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

The applicant proposed to use currently used and approved APIs for the manufacturing of the drug product tablets. The drug substances are manufactured as according to the processes in the DMFs which were reviewed previously by the FDA chemists and they are adequate. The proposed chemistry, manufacturing, and controls (CMC) for the drug product are acceptable. It was demonstrated that the tablets can be manufactured and packaged with consistent quality and purity and they can be stored at the proposed conditions. Adequate in-process controls are in place during various stages of the manufacturing and packaging processes. The three drug substance manufacturing facilities and one drug product manufacturing and packaging facility were found to be acceptable and an Overall Acceptable Recommendation was given by the Office of Compliance. Since this is a PEPFAR product, no trademark/tradename review is needed. The proposed fixed-dose combination tablets were demonstrated to be bioequivalent to the reference drugs (Sustiva®, Epivir®, and Viread® Tablets) by conducting a bioequivalence study in humans and the study was found to be acceptable by the Clinical Pharmacology reviewer. Per current ONDQA policy, this drug product does not require analytical method validation by the FDA laboratory. The applicant satisfactorily addressed all the comments and recommendations in the 74-day letter and the CMC Information Request letter. The proposed revised package insert, patient medication guide, and container labels are acceptable from the CMC stand point. There are no pending CMC issues at this point. Therefore, the proposed NDA is recommended for tentative approval.

III. Administrative

Executive Summary Section

A. Primary Reviewer:

Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist
Branch IV, DPA II, ONDQA, OPS

B. Secondary Reviewer:

Norman N. Schmuff, Ph.D.
Branch Chief, Branch IV, DPA II, ONDQA, OPS

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22142	ORIG-1	MATRIX LABORATORIES LTD	EFV 600MG/LAMIV 300MG/TEN DF 300MG
NDA-22142	ORIG-1	MATRIX LABORATORIES LTD	EFV 600MG/LAMIV 300MG/TEN DF 300MG
NDA-22142	ORIG-1	MATRIX LABORATORIES LTD	EFV 600MG/LAMIV 300MG/TEN DF 300MG
NDA-22142	ORIG-1	MATRIX LABORATORIES LTD	EFV 600MG/LAMIV 300MG/TEN DF 300MG
NDA-22142	ORIG-1	MATRIX LABORATORIES LTD	EFV 600MG/LAMIV 300MG/TEN DF 300MG
NDA-22142	ORIG-1	MATRIX LABORATORIES LTD	EFV 600MG/LAMIV 300MG/TEN DF 300MG

/s/

RAO V KAMBHAMPATI
09/02/2009
Recommended for Approval.

NORMAN R SCHMUFF
09/03/2009