CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022141Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 22141-Orig-1-Resub-44
Review #3

Drug Name/Dosage Form	Lamivudine and Tenofovir Disoproxil Fumarate Tablets
Strength	300mg/300mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mylan
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Orig-1 Resubmission -44	Aug 31, 2017	Resubmission for Final Approval
Amendment	Oct 6, 2017	Quality
Amendment	Oct 18, 2017	Quality
Annual Update	Nov 6, 2017	Quality
Amendment	Dec 21, 2017	Quality
Amendment	Jan 4, 2018	Quality
Amendment	Feb 2, 2018	Quality
Amendment	Feb 7, 2018	Quality
Amendment	Feb 8, 2018	Quality
Amendment	Feb 20, 2018	Quality
Amendment	Feb 26, 2018	Quality

1. Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance & DMFs	Haripada Sarker	Charles Jewell
Drug Product & Labeling	Milton Sloan	Balajee Shanmugam
Process	NA	
Microbiology	NA	
Facility	Derek Smith	
Biopharmaceutics	Joan Zhao	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

2. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
17750	Type II	Mylan Laboratories Limited, India	Lamivudine DS	Adequate	2/15/2018 2/21/2018	Reviews under DMF
20108	Type II	Mylan Laboratories Limited, India	Tenofovir Disoproxyl Fumarate DS	Adequate	11/15/2017	Review under DMF
Various	Type III *(if applicable)*	See DP reviews				
	Type IV *(if applicable)*	See DP reviews				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDAs for similar products from other Applicants are listed in this public database:	http://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm	

3. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 22141 for Lamivudine and Tenofovir Disoproxil Fumarate Tablets (300mg/300mg) is recommended for final Approval from the Product Quality perspective.

II. Summary of Quality Assessments

A. Product Overview

This NDA received tentative approval for treatment of HIV infection on Sept 12, 2008 under the PEPFAR program. In the Aug 31, 2017 resubmission Mylan requests full approval, which would allow marketing in the US, once applicable patents have expired. The cover letter to that resubmission includes a cumulative list of changes that were implemented through Post-TA amendments since the 2008 tentative approval.

Proposed Indication(s) including Intended Patient Population	*In combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg.*
Duration of Treatment	*Chronic (limited by development of resistance)*
Maximum Daily Dose	*One tablet per day*
Alternative Methods of Administration	*None*

B. Quality Assessment Overview

Facilities:

(b) (4) . This recommendation for final approval relies on the CMC and bioequivalence data submitted in this review cycle on the tablets manufactured at the Aurangabad facility, supported by the manufacturing experience documented in previous FDA reviews of this product. In the Feb 20, 2018 amendment Mylan confirms that future manufacture of both PEPFAR product and US product will only use the Aurangabad facility upon final approval of NDA 22141 (b) (4) ssion. The Submission Overall Manufacturing Facility Status was "Approve" on Feb 26, 2018. See Derek Smith's evaluation of manufacturing facilities in Panorama (Inspection View) for additional details.

Drug Substance:
Tenofovir DF drug substance had been manufactured at two facilities under DMF 20108 (b) (4) The addition of Mylan Labs (b) (4) as alternative manufacturing site for Tenofovir DF under DMF 20108, which is supported by comparative testing results for three batches of TDF made at (b) (4) , is acceptable. The DS specification in the NDA is equivalent to the DS specification in this DMF (which applies to the three manufacturing sites). DMF 20108 remains adequate (see D. Skanchy's DMF Review #13, dated 11/15/2017).

The applicant was asked to explain why tablet batch 2008135 used TDF DS made under DMF (b) (4), rather than under DMF 20108, and to clarify if there are any differences between these two DMFs. The Oct 6, 2017 response stated that DMF (b) (4) (b) (4)

The lamivudine drug substance is manufactured under DMF 17750. The DS specification in the NDA is equivalent to the DS specification in this DMF. DMF 17750 remains adequate to support NDA 22141. For additional detail, see Haripada Sarkar's DMF reviews #22 and #23, dated 02/15/2018 and 2/21/2018, and his drug substance review (attached below).

Drug Product:
The 300 mg/300 mg tablets are white to off-white, film-coated, oval, unscored tablets debossed with M112 on one side of the tablet and plain on the other side. The August 31, 2017 resubmission proposed to add Mylan Laboratories Limited (FDF 2), Aurangabad as an alternate drug product manufacturing site. From the drug product perspective, manufacture of tablets at Aurangabad is adequately supported by the information from a demonstration batch (batch 2008135) at (b) (4) kg = (b) (4) tablets scale (commercial scales: (b) (4) kg). The input tenofovir DF drug substance was batch 50031278 (manufactured at Mylan (b) (4)). The following minor changes are also included in this resubmission:

(b) (4)

All tests and acceptance criteria in the drug product specification are unchanged with the exception of dissolution (see below).

The resubmission proposed addition of 90-count (b) (4) (white HDPE (b) (4)) and addition of (b) (4) version of the current 30-count bottle.

However, in the Feb 2, 2018 amendment the applicant indicated (b) (4)

(b) (4)

(b) (4)

Stability data out to 36 months at 25°C/60%RH, and 6 months accelerated data, support the 24 month expiration dating period when stored under USP CRT conditions. Upon request (December 22, 2018 cumulative IR), the 30°C/75%RH long-term condition was added to the stability protocols for the first three commercial batches and for the yearly batch. An in-use study on the 90-count bottle will be conducted to support the quality of the product during the 90-day period of use (Post-Approval Protocol in P.8.2). In the Feb 26, 2018 amendment, Mylan responded to FDA questions regarding why the 30°C/75%RH study on the Aurangabad batch 2008135 was not continued beyond 12 months. For further details, see Milton Sloan's drug product review, below.

Biopharmaceutics:
The August 31, 2017 resubmission proposes to change the acceptance criterion for dissolution from Q= (b) (4) to Q= (b) (4) Based on the dissolution data from the Aurangabad batch, FDA proposed an acceptance criterion of Q= (b) (4) % in 15 min for both actives, which was accepted by Mylan on Feb 26, 2018. The Aurangabad demonstration lot (batch 2008135) was debossed with (b) (4) . The "Comparability" table in 3.2.P.5.1 shows that the intended commercial image is debossing with M112 on one side and plain on the other side (matching previously manufactured batches of this product). Conformance of the commercial batches to the dissolution specification will be sufficient to bridge those minor differences in debossing. For further details, see Zhuojun (Joan) Zhao's Biopharmaceutics review, below.

C. Special Product Quality Labeling Recommendations (NDA only)

The recommendations in Milton Sloan's labeling review were conveyed to the OND PM for consideration as the labeling was finalized. Final labeling, including container labels, were submitted on Feb 27, 2018, and copies will be included in the action letter.

D. Final Risk Assessment (see Attachment)

Not applicable, because the 2008 product quality reviews did not include a formal risk assessment table.

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 22141 Resub-44

Stephen Miller

Digitally signed by Stephen Miller
Date: 2/27/2018 02:30:06PM
GUID: 508da7210002a000609476bbecd040f0

BIOPHARMACEUTICS

Product Background:

NDA: 22141 (Resubmission of New Drug Application-505(b)(2))

Drug Product Name / Strength: Lamivudine and Tenofovir Disoproxil Fumarate Tablet, 300 mg/300 mg

Route of Administration: Oral

Applicant Name: Mylan Laboratories Limited

Review Summary:

Mylan Laboratory Limited's Lamivudine and Tenofovir Disoproxil Fumarate Tablet, 300 mg/300 mg was tentatively approved for the treatment of HIV-1 infected patients under the President's Emergency Plan for AIDS Relief (PEPFAR) on September 12, 2008[1]. The listed drugs for this 505(b)(2) application are Viread® and Epivir®.

On August 31, 2017, the resubmission of NDA 22141 requests the final approval of the proposed Lamivudine and Tenofovir Disoproxil Fumarate Fixed Dose Combination (FDC) Tablets 300 mg/300 mg. The Applicant also submitted the following changes:

1. (b) (4) , as an alternate drug substance manufacturing site for Tenofovir Disoproxil Fumarate.
2. Mylan Laboratories Limited, Aurangabad as an alternate drug product manufacturing site.
3. Revision to the In-Process and Finished Product Specification and Analytical Procedure.
4. (b) (4)
5. Additional 90's (b) (4) HDPE bottle packs.
6. (b) (4)

This Biopharmaceutics Review assesses the dissolution data supporting the alternate drug product manufacturing site, (b) (4) (b) (4) between the Biobatch and the proposed commercial batch and change to the dissolution acceptance criterion.

Based on the provided dissolution data, the following dissolution method and revised acceptance criterion are acceptable and agreed upon:

[1] DARRTS: COR-NDAACTION-06 (Tentative Approval), final date 09/12/2008

Acceptable Dissolution Method and Revised Acceptance Criterion				
USP Apparatus	Speed (RPMs)	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
II (paddle)	50	0.1 N HCl	900 mL	Q= (b) (4)% at 15 minutes

From the Biopharmaceutics perspective, NDA 22141 for Lamivudine and Tenofovir Disoproxil Fumarate Tablet, 300 mg/300 mg is recommended for **APPROVAL**.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Resubmission	08/31/2017
IR Response	2/7/2018
IR Response	2/26/2018

Dissolution Method and Previous Dissolution Acceptance Criterion:

The Applicant's dissolution method and acceptance criterion found acceptable during the review of the original NDA are shown below[2]:

Apparatus	USP II (Paddle)
Medium	0.1 N HCl
Rotation Speed	50 rpm
Volume	900 mL
Acceptance Criterion	(b) (4) minutes

Dissolution Data:

The Applicant's proposed changes are classified as shown below:

Category	Changes	Level
		(b) (4)

Considering that both drug substance Lamivudine and Tenofovir Disoproxil Fumarate are classified as BCS III drug substance (high solubility)[2] and that the addition of an alternate drug product manufacturing site and (b) (4) (b) (4) (b) (4) dissolution data are required to support the proposed changes.

The Applicant manufactured one drug product batch at the proposed alternate drug product manufacturing site (Aurangabad) with changes in 1) (b) (4). In the approved formulation, (b) (4) (the tentatively approved drug product manufacturing site) uses (b) (4)

[2] DARRTS: REV-QUALITY-03 (General Review), final date 08/04/2008 and 09/04/2008

(b) (4) while the drug product batches manufactured at Mylan Laboratories Limited, Aurangabad contain (b) (4)

The registration batch 2008135 of the proposed drug product was used in the BE studies (Fasting 234-14 and Fed 235-14) comparing the proposed FDC drug product to the list drugs, Viread® and Epivir®. The Applicant provided the dissolution profile of Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300 mg/300 mg, manufactured at the proposed site MLL, Aurangabad (Appendix 2).

The Applicant proposes to tighten the dissolution limit from '*Not less than* (b) (4) *% (Q) of the labelled amount in* (b) (4) *minutes*' to '*Not less than* (b) (4) *% (Q) of the labeled amount in* (b) (4) *minutes*' for both Tenofovir Disoproxil Fumarate and Lamivudine as presented below:

Component	Current Approved dissolution acceptance criteria	Proposed dissolution acceptance criteria
Tenofovir Disoproxil Fumarate, 300 mg	(b) (4)	
Lamivudine USP, 300 mg		

Based on the provided dissolution data, the following revised acceptance criterion was recommended and agreed upon (Appendix 4):

Component	***Acceptance Criteria*** *Cumulative % of Drug Dissolved (Label Claim)*
Lamivudine	*Q=* (b) (4) *% at 15 minutes.*
Tenofovir Disoproxil Fumarate	

Bridging:

The Applicant proposes to use the approved description for products manufactured at (b) (4) for the commercial supplies manufactured at Aurangabad. The difference of the description (in debossing) between the biobatch and the commercial batch is shown in the table below:

Description	
Biobatch	**Proposed Commercial Batch**
A White to off white colored, oval, biconvex, film coated tablets debossed (b) (4) .	A White to off white colored, oval, shaped, biconvex, film coated tablets debossed "M112" on one side and plain on other side.

The difference in debossing is minor and conformance of the commercial batches to the dissolution specification will be sufficient to bridge those minor differences in debossing.

REVIEWER'S RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 22141 for Lamivudine and Tenofovir Disoproxil Fumarate Tablet, 300 mg/300 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: *Zhuojun Zhao, Ph.D. 02/26/2018*

Secondary Reviewer Name and Date: *Elsbeth Chikhale, Ph.D. 02/26/2018*

Appendix 1: Qualitative and Quantitative Composition of the Approved and Alternate Coating Material

Ingredients	300 mg / 300 mg		Quality Standards
	mg per tablet	% w/w	
(b) (4)			

NA- Not Applicable

(b) (4)

Appendix 2: Dissolution Data

Lamivudine

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N Hydrochloric acid
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	Complies with USP General Chapter <711> Not less than (b) (4) of the labeled amount of Lamivudine should be dissolved in (b) (4)	
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Laboratories Limited, Plot # H-12 & H-13, MIDC, Waluj, Aurangabad – 431136 Maharashtra, India Mylan Laboratories Ltd., R&D Center, Medak District-502325, Andhra Pradesh, India.	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 5	10	15	20	30	45	Study Report Location
N/A	07/11/2015	Lamivudine and Tenofovir Disoproxil Fumarate Tablets Batch # 2008135 Mfg. Date: December 2014	300 /300 mg Tablets	12	Mean	48	84	96	98	99	100	2.7 Clinical Summary
					Range	31-66	64-96	93-100	95-100	96-103	97-103	
					%CV	24.4	12.3	2.3	1.6	1.9	1.6	
	08/03/2015	Epivir® (Lamivudine) Tablets Batch # 3ZP8520 Exp. Date: July 2016	300 mg Tablets	12	Mean	70	81	84	85	87	89	
					Range	16-89	74-91	77-93	80-94	82-95	85-95	
					%CV	27.1	8.5	7.1	6.6	5.9	4.7	

Tenofovir Disoproxil Fumarate:

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N Hydrochloric acid
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	Complies with USP General Chapter <711> Not less than (b) (4) of the labeled amount of Tenofovir Disoproxil Fumarate should be dissolved in (b) (4) minutes.	
Dissolution Testing Site and Dissolution Method Validation Site (Name, Address)	Mylan Laboratories Limited, Plot # H-12 & H-13, MIDC, Waluj, Aurangabad – 431136 Maharashtra, India Mylan Laboratories Ltd., R&D Center, Medak District-502325, Telangana, India.	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	15	20	30	45	Study Report Location
N/A	07/11/2015	Lamivudine and Tenofovir Disoproxil Fumarate Tablets Batch # 2008135 Mfg. Date: December 2014	300 /300 mg Tablets	12	Mean	74	90	92	93	93	2.7 Clinical Summary
					Range	54-85	85-93	88-94	89-96	89-95	
					%CV	14.9	2.9	1.9	2.0	1.7	
	08/03/2015	Viread® (Tenofovir Disoproxil Fumarate) Tablets Batch # 002654 Exp. Date: May 2018	300 mg Tablets	12	Mean	90	91	91	92	93	
					Range	72-97	76-98	78-98	80-98	82-99	
					%CV	8.0	6.9	6.4	6.0	5.5	

APPENDIX 3: *Biopharmaceutics Information Requests dated January 30, 2018 and the Applicant's response dated February 7, 2018*

Biopharmaceutics Information Request Comment:
Based on the provided dissolution profile data, the following dissolution acceptance criteria are recommended for your proposed Lamivudine and Tenofovir Disoproxil Fumarate Tablet, 300 mg/300 mg.

Component	***Acceptance Criteria*** *Cumulative % of Drug Dissolved (Label Claim)*
Lamivudine	*Q= (b)(4)% at 15 minutes.*
Tenofovir Disoproxil Fumarate	*Q= % at15 minutes.*

Be aware that setting of the dissolution acceptance criterion is based on USP Stage 2 testing (n=12) and therefore sometimes Stage 2 testing and occasional Stage 3 testing maybe needed.

Revise the drug product specifications Table and the stability protocol to reflect agreement with the recommended dissolution acceptance criteria. Submit a copy of the updated drug product specifications Table and other pertinent documents.

Applicant's Response to Biopharmaceutics-IR Comment:
Mylan acknowledges the Agency's comment; however, we intend to keep the limits of the dissolution as NLT (b)(4)% (Q) in (b)(4) minutes, for both of the components of the drug product. This proposal is based on the following facts, that are related to the product behavior.

1) The Applicant submitted the original application in 2008, as a fixed dose combination for antiretroviral therapy. The Applicant conducted the bioequivalence study of the combination product, comparing it with individual reference products of Tenofovir Disoproxil Fumarate and Lamivudine Tablets. At the time of original submission, the bioequivalence study was conducted and the dissolution profile data of test and reference product was presented for the Agency's review.

   The physical attributes of the combination product, vary from those of the individual reference products in terms of size of the tablets (dimensions) and disintegration time of tablets, which have an impact on the release of drug substance in dissolution medium. The physical characterization data presented in the Original Submission, for the reference and test products is presented below:

Table 1: Physical Characterization:

Parameters	Viread® (Tenofovir Disoproxil Fumarate) Tablets, Exp: Dec 2008, Batch No. FDB023*	Epivir® (Lamivudine) Tablets, Exp: June 2009, Batch No. R245588*	Test Batch No. TLDA536001
Tablet weight	680 mg – 707 mg	599.7 mg – 619.2 mg	(b) (4)
Dimensions			
Length	17.00 mm	17.29 – 17.35 mm	
Breadth	10.45 mm	8.50 – 8.52 mm	
Thickness	5.13 – 5.22 mm	5.15 – 5.22 mm	
Disintegration time			(b) (4)

* Data for innovator is taken from Product Development Report (PDR-TLDT-001-00). Test product data extracted from the executed batch records submitted in original submission.

(b) (4)

Table 2: Release profile of Test vs. Innovator for Tenofovir Disoproxil Fumarate:

	Tenofovir Disoproxil Fumarate and Lamivudine Tablets 300/300mg							
Dissolution conditions	0.1N Hydrochloric acid, 900ml, USP II, 50 rpm							
	Test Batch No. TLDA536001				Viread® (Tenofovir Disoproxil Fumarate) Tablets, Exp: Dec 2008 Batch No. FDB023			
	% Drug release of Tenofovir Disoproxil Fumarate							
Time in minutes	Average	Min	Max	% RSD	Average	Min	Max	% RSD
5	35	9	76	**61.1**	96	91	99	**2.5**
10	61	21	86	**35.1**	99	95	103	**2.7**
15	78	39	92	**20.5**	99	97	102	**1.6**
30	90	84	96	**3.9**	98	97	100	**0.8**

Table 3: Release profile of Test vs. Innovator for Lamivudine:

	Tenofovir Disoproxil Fumarate and Lamivudine Tablets 300/300mg							
Dissolution conditions	0.1N Hydrochloric acid, 900ml, USP II, 50 rpm							
	Test Batch No. TLDA536001				Epivir® (Lamivudine) Tablets, Exp: June 2009, Batch No. R245588			
	% Drug release of Lamivudine							
Time in minutes	Average	Min	Max	% RSD	Average	Min	Max	% RSD
5	41	11	88	**58.3**	64	27	85	**26.4**
10	67	27	94	**33.2**	83	78	90	**3.9**
15	83	45	96	**19.4**	87	82	94	**3.9**
30	95	91	99	**3.2**	90	87	96	**2.8**

The dissolution data indicates that the test product shows slower release, than the individual reference products at early time points. However, it should also be noted that even with the difference in release profile of drug product at initial time points, the test product was found to be bioequivalent to the individual reference products. The summary of the bioequivalence study results of the test and innovator product are summarized below.

Table 4: Summary of Bioequivalence study results – Fasting (06-VIN-170)

Parameters	Tenofovir		Lamivudine	
	Mean ± SD		Mean ± SD	
	Reference product (Viread®) FDB023	Test Product (TLDA536001)	Reference product (Epivir®) R245588	Test Product (TLDA536001)
C_{max} (ng/mL)	285.395 ± 69.6909	267.946 ± 76.1327	2789.873 ± 638.2746	2750.937 ± 692.5088
T_{max} (h)	0.667 (0.5 – 1.75)	0.833 (0.50 -2.00)	1.250 (0.67 – 3.00)	1.250 (0.67 – 4.00)
AUC $_{0-t}$ (ng.h/mL)	1917.096 ± 421.1054	1916.888 ± 500.0709	11876.427 ± 2719.8134	11811.317 ± 2694.3780
AUC $_{0-\infty}$ (ng.h/mL)	2129.627 ± 449.5124	2120.071 ±498.1364	12145.938 ± 2720.5250	12087.933 ± 2654.5325
T1/2 (h)	16.934 ± 3.8764	16.572 ± 3.9534	5.143 ± 1.6930	5.014 ± 1.9004
In-transformed Conventional 90% Confidence Interval				
C_{max} (ng/mL)	86.77 % – 99.70 %		91.20 % – 104.92 %	
AUC_{0-t} (ng.h/mL)	93.52 % – 105.14 %		93.25 % – 106.01 %	
$AUC_{0-\infty}$ (ng.h/mL)	94.06 % – 104.42 %		93.70 % – 105.83 %	

Table 5: Summary of Bioequivalence study results – Fed (06-VIN-171)

Parameters	Tenofovir		Lamivudine	
	Mean ± SD		Mean ± SD	
	Reference product (Viread®) FDB023	Test Product (TLDA536001)	Reference product (Epivir®) R245588	Test Product (TLDA536001)
C_{max} (ng/mL)	321.297 ± 72.2569	312.058 ± 67.5515	2181.288 ± 734.3228	2242.671 ± 694.0967
T_{max} (h)	1.75 (0.75 – 4.00)	2.00 (1.00 – 3.00)	2.00 (0.75 – 4.00)	2.00 (1.00 – 4.00)
AUC_{0-t} (ng.h/mL)	2707.369 ± 679.8103	2753.876 ± 586.2355	10171.596 ± 2946.9866	10539.408 ± 2943.4974
$AUC_{0-\infty}$ (ng.h/mL)	2939.755 ± 681.2427	2970.328 ± 565.1436	10459.649 ± 2947.8932	10834.995 ± 2935.5849
T1/2 (h)	16.627 ± 3.2071	16.456 ± 2.1169	5.330 ± 1.3189	5.014 ± 1.3574
In-transformed Conventional 90% Confidence Interval				
C_{max} (ng/mL)	92.10 % - 102.10 %		98.33 % - 109.45 %	
AUC_{0-t} (ng.h/mL)	99.58 % - 105.87 %		100.90 % - 107.88 %	
$AUC_{0-\infty}$ (ng.h/mL)	98.97 % - 105.08 %		101.02 % - 107.71 %	

During the Final Approval Request submitted on August 31, 2017 (Sequence No. 0026), the Applicant has submitted the drug product batch (2008135) manufactured at MLL, Aurangabad, supported with bio-equivalency study. The physical characterization and release pattern of the test product and reference product is presented below:

Table 6: Physical Characterization:

Parameters	Viread® (Tenofovir Disoproxil Fumarate) Tablets, Exp: Dec 2008, Batch No. 002654	Epivir® (Lamivudine) Tablets, Exp: June 2009, Batch No. 3ZP8520	Test Batch No. 2008135
Tablet weight	703.98 mg	614.22 mg	1127.50 mg
Dimensions			
Length	16.99 – 17.07 mm	17.38 – 17.44 mm	19.1 mm
Breadth	10.46 -10.63 mm	8.58 – 8.62 mm	9.3 mm
Thickness	1'40" – 2'20"	5.44 – 5.49 mm	7.00 – 8.00 mm
Disintegration time			(b) (4)

Table 7: Release profile of Test vs. Innovator for Tenofovir Disoproxil Fumarate:

	Tenofovir Disoproxil Fumarate and Lamivudine Tablets 300/300mg							
Dissolution conditions	0.1N Hydrochloric acid, 900ml, USP II, 50 rpm							
	Test Batch No. 2008135				Viread® (Tenofovir Disoproxil Fumarate) Tablets, Exp: May 2018, Batch No. 002654			
	% Drug release of Tenofovir Disoproxil Fumarate							
Time in minutes	Average	Min	Max	% RSD	Average	Min	Max	% RSD
10	74	54	85	**14.9**	90	72	97	**8.0**
15	90	85	93	**2.9**	91	76	98	**6.9**
30	93	89	96	**2.0**	92	80	98	**6.0**
45	93	89	95	**1.7**	93	82	99	**5.5**

Table 8: Release profile of Test vs. Innovator for Lamivudine:

	Tenofovir Disoproxil Fumarate and Lamivudine Tablets 300/300mg							
Dissolution conditions	0.1N Hydrochloric acid, 900ml, USP II, 50 rpm							
	Test Batch No. 2008135				Epivir® (Lamivudine) Tablets, Exp: July 2016, Batch No. 3ZP8520			
	% Drug release of Lamivudine							
Time in minutes	Average	Min	Max	% RSD	Average	Min	Max	% RSD
5	48	21	66	**24.4**	70	16	89	**27.1**
10	84	64	96	**12.3**	81	74	91	**8.5**
15	96	93	100	**2.3**	84	77	93	**7.1**
30	99	96	103	**1.9**	87	82	95	**5.9**
45	100	97	103	**1.6**	89	85	95	**4.7**

It is observed that the dissolution data of batch manufactured at MLL, Aurangabad shows faster release than the drug product manufactured at (b) (4)

It is to be noted that (b) (4)% dissolution in (b) (4)minutes was not achieved, even in the case of the Reference Listed drug product namely Epivir® (Lamivudine) Tablets. The minimum value obtained for dissolution, at the (b) (4)minute time point was (b) (4)

The summary of the bioequivalence study results of the test and innovator product are summarized below.

Table 9: Summary of Bioequivalence study results – Fasting (234-14)

Parameters	Tenofovir Disoproxil Fumarate Mean ± SD		Lamivudine Mean ± SD	
	Reference product (Viread®) 002654	Test Product (2008135)	Reference product (Epivir®) 3ZP8520	Test Product (2008135)
C_{max} (ng/mL)	310.552± 72.9113	304.576± 94.5360	2698.804± 750.8342	2394.517± 699.4094
T_{max} (h)	0.830 (0.330-2.000)	1.000 (0.500-2.500)	1.500 (0.670-3.000)	1.500 (0.830-4.000)
AUC_{0-t} (ng.h/mL)	2214.269± 641.6588	2257.670± 589.0066	13607.653± 3375.6818	13144.374± 3334.2746
$AUC_{0-\infty}$ (ng.h/mL)	2487.586± 618.4678	2499.199± 595.0257	13927.196± 3360.2718	13468.167± 3311.4809
T1/2 (h)	19.060 ± 3.0294	18.975 ± 2.7599	5.878 ± 1.3989	5.992 ± 1.4037
In-transformed Conventional 90% Confidence Interval				
C_{max} (ng/mL)	88.16 % - 103.31 %		82.61 % - 94.19 %	
AUC_{0-t} (ng.h/mL)	93.96 % - 106.98 %		91.87 % - 101.01 %	
$AUC_{0-\infty}$ (ng.h/mL)	94.02 % - 106.15 %		92.19 % - 100.99 %	

Table 10: Summary of Bio study results – Fed (235-14)

Parameters	Tenofovir Disoproxil Fumarate Mean ± SD		Lamivudine Mean ± SD	
	Reference product (Viread®) 002654	Test Product (2008135)	Reference product (Epivir®) 3ZP8520	Test Product (2008135)
C_{max} (ng/mL)	312.367± 88.3428	314.272± 95.0715	2339.997± 543.1474	1997.460± 419.5444
T_{max} (h)	1.750 (0.500-6.000)	2.000 (1.000-6.000)	1.780 (0.750-4.000)	2.000 (0.750-6.000)
AUC $_{0-t}$ (ng.h/mL)	3212.671± 789.3495	3221.820± 737.9729	12684.633± 2359.4241	12130.138± 2705.3935
AUC $_{0-\infty}$ (ng.h/mL)	3474.886± 822.8186	3492.967± 796.3594	12984.137± 2360.1447	12487.640± 2740.7108
T1/2 (h)	18.822±2.5303	18.539±2.9663	5.867 ±1.1495	6.671 ± 3.2206
In-transformed Conventional 90% Confidence Interval				
C_{max} (ng/mL)	93.12 % - 109.29 %		81.05 % - 91.04 %	
AUC $_{0-t}$ (ng.h/mL)	97.50 % -103.96 %		91.60 % - 98.62 %	
AUC $_{0-\infty}$ (ng.h/mL)	97.52 % - 103.03 %		92.24 % - 99.04 %	

The data indicates that the test product and the reference products were found to be bioequivalent.

2) The Applicant would like to bring to the notice of the Agency that when tentative approval was granted for this product, the Agency approved the following dissolution specification in 2008.

Component	Approved dissolution acceptance criteria (For PEPFAR Application)
Tenofovir Disoproxil Fumarate, 300 mg	**Not less than** (b) (4) **% (Q)** of the labeled amount of Tenofovir Disoproxil Fumarate, $C_{19}H_{30}N_5O10P.C_4H_4O_4$ should be dissolved in (b) (4) **minutes.**
Lamivudine USP, 300 mg	**Not less than** (b) (4) **% (Q)** of the labeled amount of Lamivudine, $C_8H_{11}N_3O_3S$ should be dissolved in (b) (4) **minutes.**

During submission of the Final Approval Request, the Applicant has proactively tightened the dissolution specification, based on the dissolution results available on commercial batches manufactured at (b) (4) and exhibit batches of MLL, Aurangabad. The dissolution limit, proposed during the Final Approval Request (Sequence No. 0026) is presented as below. The Applicant has presented the specifications table with proposed dissolution limits in Sequence No. 0026.

Component	Approved dissolution acceptance criteria (For PEPFAR Application)
Tenofovir Disoproxil Fumarate, 300 mg	**Not less than** (b) (4) **% (Q)** of the labeled amount of Tenofovir Disoproxil Fumarate, $C_{19}H_{30}N_5O10P.C_4H_4O_4$ should be dissolved in (b) (4) **minutes.**
Lamivudine USP, 300 mg	**Not less than** (b) (4) **% (Q)** of the labeled amount of Lamivudine, $C_8H_{11}N_3O_3S$ should be dissolved in (b) (4) **minutes.**

3) From both of the Bioequivalence studies, it is evident that the T_{max} of both the innovator and test product, during fasting and fed conditions are similar (Please refer to tables 4, 5, 9 and 10). This confirms that the maximum plasma concentration (C_{max}) is achieved between 1 – 2hrs after dosing. Though the dissolution results of Tenofovir and Lamivudine in Batch No. 2008135 is more than (b) (4) % at (b) (4) minutes, the time taken for the drug substance to reach maximum concentration (C_{max}) is almost the same as that of Batch

No. TLDA536001 (manufactured at (b) (4), which showed relatively high variability in the dissolution results of initial time points. This data indicates that variability at initial time points is not indicative of in vivo performance of the drug product. Further, as evident from the bioequivalence results, T_{max} results are observed beyond (b) (4) min for each of the component in both the bioequivalence studies. Therefore, the Applicant is of the opinion that (b) (4) minutes time point is more indicative of product performance.

In addition, the prescribing information of Viread® tablets *(tenofovir disoproxil fumarate tablet, coated; tenofovir disoproxil fumarate powder, of Gilead Sciences, Inc., revised 04/2017)* and Epivir® tablets and Solution *(lamivudine tablet, film coated; lamivudine solution; of ViiV Healthcare Company, revised: 9/2017)* shows the T_{max} of approximately an hour after oral administration. Similar findings were observed during the Applicant's bioequivalence studies. Therefore, the proposed time point of (b) (4) minutes for the dissolution test (rather than (b) (4) minutes) is very unlikely to impact the bioavailability of Tenofovir and Lamivudine, and therefore the proposed dissolution limit is justified.

4) The drug product was tentatively approved for PEPFAR market and the Applicant has been supplying the drug product in PEPFAR listed countries since 2008. Mylan has supplied more than (b) (4) batches through PEPFAR approval and has not received any complaint to this point of time about the safety/efficacy of the drug product. This demonstrates the consistent quality of the drug product.

Based on the above facts and the Applicant's experience with the drug product, Mylan would like to retain the current proposed specification for dissolution as presented below:

Component	Approved dissolution acceptance criteria (For PEPFAR Application)
Tenofovir Disoproxil Fumarate, 300 mg	**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 (b) (4) **minutes.**
Lamivudine USP, 300 mg	**Not less than** (b) (4) **% (Q)** of the labeled amount of Lamivudine, $C_8H_{11}N_3O_3S$ should be dissolved in (b) (4) **minutes.**

Reviewer Note:

The Applicant's response is not acceptable. The Applicant was informed that the dissolution acceptance criterion is drug product specific and should be supported by the data of the Biobatch used in the BE studies.

APPENDIX 4: Biopharmaceutics Information Requests dated February 22, 2018 and the Applicant's responses dated February 26, 2018[3]

Biopharmaceutics Request Comments:
We received your response dated February 7, 2018, regarding the dissolution acceptance criteria. However, note that the dissolution profile data of your Biobatch No. 2008135 manufactured at MLL, Aurangabad, not the data of your product manufactured at the withdrawn site (b) (4) or the list drug products, are used to set the drug product dissolution acceptance criteria.

Based on the provided dissolution profile data of Biobatch No. 2008135, the following dissolution acceptance criteria are recommended for your proposed Lamivudine and Tenofovir Disoproxil Fumarate Tablet, 300 mg/300 mg.

Component	**Dissolution Acceptance Criteria** Cumulative % of Drug Dissolved (Label Claim)
Lamivudine	Q= (b) (4)% at 15 minutes.
Tenofovir Disoproxil Fumarate	Q %at15 minutes.

Be aware that setting of the dissolution acceptance criterion is based on USP Stage 2 testing (n=12) and therefore sometimes Stage 2 testing and occasional Stage 3 testing maybe needed.

Revise the drug product specifications Table and the stability protocol to reflect agreement with the recommended dissolution acceptance criteria. Submit a copy of the updated drug product specifications Table and other pertinent documents.

Applicant's Response to Biopharmaceutics-IR Comment 1:
The Applicant acknowledges the Agency's comment. The Applicant accepts the dissolution acceptance criteria as per Agency's recommendation and the details are presented below:

Component	**Dissolution Acceptance Criteria (Cumulative % of Drug Dissolved (Label Claim)**
Lamivudine	NLT (b) (4)% (Q= (b) (4)%) of the labeled amount of Lamivudine, C8H11N3O3S should be dissolved in 15 minutes.
Tenofovir Disoproxil Fumarate	NLT (b) (4)% (Q= (b) (4)%) of the labeled amount of Tenofovir Disoproxil Fumarate, C19H30N5O10P.C4H4O4 should be dissolved in15 minutes.

Reviewer Note:
The Applicant's response is satisfactory.

[3] In the unofficial IR response dated February 23, 2018, the Applicant proposed to use (b) (4) vessels in place of (b) (4) vessels for the dissolution test, which was not supported by any dissolution data and thus not acceptable. In an email from the Agency dated February 23, 2018, the Applicant was informed that they may submit a post-approval supplement for such a change with appropriate data.

Applicant's Response to Biopharmaceutics-IR Comment 2:
The updated regulatory and shelf-life specifications are provided in Sections 3.2.P.5.1 and 3.2.P.8.1, respectively.

Reviewer Note:
The Applicant's response is satisfactory.

Zhuojun Zhao

Digitally signed by Zhuojun Zhao
Date: 2/27/2018 10:48:28AM
GUID: 508da6fd000284770cf4eecbae074722

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 2/27/2018 10:52:46AM
GUID: 50743ccc000031928b54eba1769a5df9

NDA 22-141

Tenofovir Disoproxil Fumarate/Lamivudine Tablets

Matrix Laboratories, Ltd.

Brian Rogers

CMC Reviewer

Office of New Drug Quality Assessment
Division of Premarketing Assessment III & Manufacturing Science
Branch VI

CMC REVIEW OF NDA 22-141
For the Division of Anti-Viral Products (HFD-530)

CMC Review Data Sheet

1. NDA 22-141

2. REVIEW # 2

3. REVIEW DATE: 03-SEP-2008

4. REVIEWER: Brian Rogers

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	12-MAR-2008
Amendment (BC)	02-MAY-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (AC)	13-AUG-2008
Amendment (BL)	26-AUG-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Matrix Laboratories, Ltd.
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, WV 26504-4310
Telephone:	304-554-5899 or 800-848-0461, ext. 5899
FAX:	304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tenofovir Disoproxil Fumarate/Lamivudine Tablets

CMC Review Data Sheet

b) Non-Proprietary Name: Tenofovir Disoproxil Fumarate/Lamivudine Tablets
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 4
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Anti-viral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 300 mg/300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

***S.1.1 Nomenclature* - Lamivudine**

Chemical name 2(1*H*)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-, (2*R*-cis)- (–)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

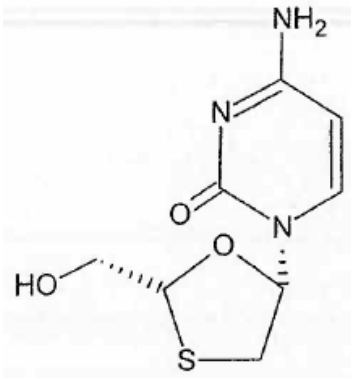
CAS Registry No [134678-17-4]

Molecular formula $C_8H_{11}N_3O_3S$

Molecular weight 229.26

CMC Review Data Sheet

S.1.2 Structure



***S.1.1 Nomenclature* - Tenofovir disoproxil fumarate**

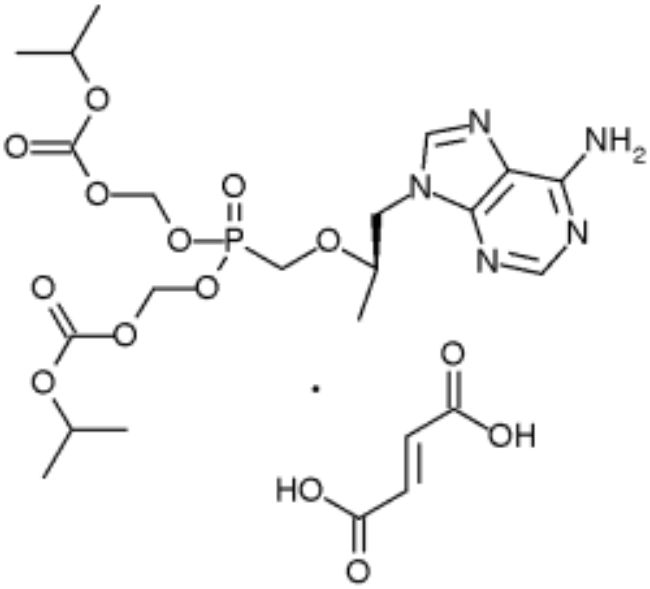
Chemical name (*R*)-5-{[2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl}-2,4,6,8- tetraoxa-5-phosphanonanedioic acid, bis(1-methylethyl) ester, 5-oxide, (*E*)-2-butenedioate (1:1)

CAS Registry No [202138-50-9]

Molecular formula $C_{19}H_{30}N_5O_{10}PC_4H_4O_4$

Molecular weight 635.51

S.1.2 Structure



CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
20108	2	Matrix Laboratories Limited	Tenofovir disoproxil fumarate	3	Adequate	12/5/07 by S. Rosencrance	LOA 3/24/07
17750	2	Matrix Laboratories Limited	Lamivudine USP	3	Adequate	10/26/06 by D. Roselle	LOA 1/11/07
(b) (4)	4	(b) (4)		N/A			LOA 10/9/06
	3			N/A			**LOA 6/23/08**
	3			N/A			LOA 4/18/07
	3			N/A			LOA 2/13/06
	3			N/A			LOA 7/19/07
	3			N/A			LOA 9/29/06
	3			N/A			LOAs 6/27/06, 6/22/07
	3			N/A			LOA 1/12/05
	3			N/A			LOA 6/28/06
	3			N/A			LOA 5/4/06
	3			N/A			LOA 9/21/06
	3			N/A			LOA 1/5/06

[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 NO.	DESCRIPTION
ANDA	79-071	Matrix Tenofovir DF Tablets
ANDA	78-545	Matrix Lamivudine Tablets
ANDA	79-079	Matrix Lamivudine/Zidovudine Tablets
NDA	22-085	Matrix/Astrix Lamivudine/Stavudine
NDA	22-061	Matrix Lamivudine/Zidovudine/Nevirapine
NDA	21-356	Tenofovir Disoproxil Fumarate 300 mg, (VIREAD®) brand of Gilead,
NDA	20-564	Lamivudine Tablets 300 mg, (EPIVIR®) brand of GlaxoSmithKline

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	5/27/08	N/A
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Reviewed according to the current ONDQA policy	6/20/08	B. Rogers
DMETS	N/A	N/A	N/A
EA	Categorical exclusion (see review)		
Microbiology	N/A	N/A	N/A

Executive Summary Section

The CMC Review for NDA 22-141

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC standpoint, the NDA# 22-141 is recommended for tentative approval. Deficiencies have been resolved pertaining to drug substance and drug product specifications, manufacturing controls, and labeling. There remains an outstanding request for a modification to the package insert. This request would not be an approvability issue.

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(s) and Drug Substance(s)

(1) Drug Substance

Tenofovir Disoproxil Fumarate (a pro-drug of tenofovir) is fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of Tenofovir. Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. It is a high solubility drug according to BCS. It has a single chiral center at the C-2 position of the propyl side-chain and it is manufactured as the *R*-enantiomer. It exists in (b) (4) and it was chosen as the drug substance. According to the USP definition, it is sparingly soluble in water (pH 7.2, 12.1 mg/mL. It is non-hygroscopic.

Tenofovir disoproxil fumarate is manufactured at Matrix Laboratories Ltd. Unit 8, G. Chodavaram Village, Pusapatirega (M) Vizianagaram District, Andhra Pradesh, India. The CMC information is referenced to DMF 20108 to which an a LOA is provided. This DMF was reviewed previously by S. Rosencrance and it was determined to be adequate (12/5/07). In the NDA, batch analysis results were provided for 3 primary batches. A retest period of (b) (4) months was proposed for tenofovir disoproxil fumarate which is acceptable.

Lamivudine Drug Substance: It is a white to off-white solid. It is soluble in water and has a melting point of 175±3°C and partition coefficient of -1.44 (n-octanol/water). Lamivudine has (b) (4) It is manufactured in India at Matrix Laboratories Limited (Unit-I), Survey No.10, Gaddapotharam, Kazipally, Medak district - 502319, Andhra Pradesh. The CMC information was cross referenced to the applicant's DMF#17750 and a LOA was provided. This DMF was reviewed

previously by Dominick Roselle, Ph.D. (OGD) and it was determined to be adequate (10/26/06). In the NDA, batch analysis results were provided for 3 primary batches. Lamivudine has a monograph in the USP and the same specifications are followed by Matrix. A retest period of (b) (4) months was proposed for lamivudine which is acceptable.

Both, drug substances (Tenofovir Disoproxil Fumarate and Lamivudine) and the drug product, Tenofovir Disoproxil Fumarate/Lamivudine tablets, are manufactured by Matrix Laboratories Limited, India

(2) Drug Product

The drug product is a fixed dose combination of two individually approved single entity reference drug products (RLD), mentioned below. This NDA is submitted under section 505(b)(2) of the Food Drug & Cosmetics Act.

The referenced drugs are:
Tenofovir Disoproxil Fumarate Tablets 300 mg (VIREAD®) of Gilead (NDA # 21-356) and Lamivudine Tablets 300 mg, (EPIVIR®) brand of GlaxoSmithKline (NDA # 20-564)

The drug product, Tenofovir Disoproxil Fumarate/Lamivudine tablets, are manufactured by Matrix Laboratories Limited, India.

The drug product is a white to off white colored, oval shaped, biconvex, film coated tablets debossed "M112" on one side and plain on other side. The tablets contain 300 mg of tenofovir disoproxil fumarate and 300 mg of lamivudine and have a total weight of 1122 mg. The tablets are packaged in bottle packs and may be stored for up to (b) (4) months in bulk packaging. Matrix employs a (b) (4) process for manufacturing of the tablets.

Manufacturing, release and stability testing of the drug product will be conducted at (b) (4) .

Other drug product testing will be provided at the following sites: Matrix Laboratories Ltd. Unit I, Survey No. 10, Gaddapotharam, Kazipally, Medak District, Andhra Pradesh, INDIA; (b) (4) Matrix Laboratories Ltd., Unit II, Survey No. 10 & 42, Gaddapotharam Kazipally, Medak District, Andhra Pradesh, INDIA; Matrix Laboratories Ltd., Plot Nos 38 to 40, 49 to 51 Unit III, Phase IV IDA Jeedimetla, Hyderabad, Andhra Pradesh, India; and Matrix Laboratories Limited Unit VII, Plot Nos. 14, 99 & 100, Pashamylaram Phase-II, Patancheru, Medak District, Andhra Pradesh, INDIA

The excipients are of USP/NF quality and they included microcrystalline cellulose, magnesium stearate, croscarmellose sodium and (b) (4) All excipients are well within limits specified in the FDA electronic inactive ingredient database or 21 CFR. The fundamental process is same for the exhibit (NDA; scale (b) (4) tablets) and intended commercial scale batches ((b) (4) tablets). Equipments used for exhibit and proposed commercial batches have the same principle of operation as per SUPAC.

The tablets are packaged in two configurations for marketing: HDPE bottles of 30- and (b) (4) count. In addition, (b) (4) of (b) (4) tablet count were also proposed by providing stability data for simulated (b) (4) Long-term (30°C/75%RH) and accelerated stability data (40°C/75%RH) were provided for 3 exhibit batches of each packaging configuration and with (b) (4). The stability specifications are same as release specifications. All batches met the proposed specifications. The proposed expiration dating period of 24 months is acceptable for the bottle packs on the basis of the 18 months long-term and 6 months accelerated stability data, Similarly, the proposed holding time period of (b) (4) months is acceptable for the bulk (b) (4).

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

Tenofovir disoproxil fumarate/Lamivudine tablets are available 300 mg/300 mg strength. The tablets are orally administered and no unusual preparation of dose prior to administration is required. The interval between doses should be 24 hrs and the tablets may be taken with or without food. The tablets are not recommended for (b) (4) The tablets are recommended to be stored at (b) (4) excursions permitted to 15° to 30°C (59° to 86°F). The stability data support a 24-month expiration dating period for the tablets when stored under recommended conditions.

C. Basis for Approvability or Not-Approval Recommendation

The application is currently tentatively approved from a CMC standpoint. All communicated deficiencies have been satisfactorily addressed.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Brian Rogers

B. Endorsement Block:

(See appended electronic signature page)

Norman Schmuff, Branch Chief, Branch IV, ONDQA

C. CC Block: entered electronically in DFS

CMC Assessment

This review is of the 8/13/08 amendment submitted in response to our 8/5/08 IR letter. The Agency's IR comment in BOLD font is followed by the applicant's response and then the reviewer's evaluation and any noted deficiencies in the response.

The applicant has also provided updated labeling in their 8/26/08 amendment. The labeling in this submission has been reviewed and found to be acceptable. The applicant should insert the name and location of the manufacturer in the HOW SUPPLIED section of the package insert.

The following comments pertain to the drug substance.

FDA Comment

1. **Provide updated drug substance specifications for both lamivudine and tenofovir disoproxil fumarate to comply with the ICH Q6A/B definition of specifications. The specifications should include the tested parameters, the acceptance criteria, and a definitive test method number or compendial reference for the analytical test method.**

Applicant's Response

The applicant has provided copies of the current specifications and test procedures in Attachments 1-2.

Evaluation

Satisfactory. Although the provided specification sheets do not include individual method numbers as requested, the specifications have a reference to the combined analytical methods document, including the revision number.

All of the related approved and tentatively approved applications have the same format as proposed in this application for the raw materials specifications.

FDA Comment

2. **Submit all analytical procedures from Raw Material Standard Test Procedures No. RMPTDF009R-04 for tenofovir disoproxil fumarate and RMPLMD006R-03 for Lamivudine USP with individual and unique method numbers, and a revision number which identifies the current version of each method. This is necessary to distinguish versions of the individual methods when changes are made pre- and post-approval. References to compendial methods are acceptable.**

Applicant's Response

Matrix states that their document control system capture all the individual methods for tests described in a specification in a single "consolidated" test procedure which is identified by a unique number and version number. Any change to anyone or more of the test procedures results into a revision for the "consolidated" test procedure and the change is captured in the "reason for revision" section included at the end of the test procedure.

CMC Assessment Section

The current analytical procedures for all the tests for Lamivudine and Tenofovir disoproxi1 fumarate are included in Attachment # 1 and # 2, respectively. The applicant notes that the specification and test method number for Lamivudine have been changed from RMPLMD006R to RMPLMD021 R because of change in the internal material code.

Evaluation

Satisfactory. The presence of the methods with some form of change documentation is acceptable. Matrix does not have separate analytical methods with individual version numbers in any of their approved or tentatively approved related applications.

The following comments pertain to the drug product.

FDA Comment

3. **The procedures for compaction (Steps 4.2 and 7.2) in your Master Batch Record note that the** (b) (4)

Applicant's Response

The applicant has submitted a copy of the revised batch records in Attachment 3. The intended batch records have been modified to include (b) (4) in the batch record.

In addition, they have revised the batch document to (b) (4) will be supported by appropriate process validation studies.

Evaluation

Satisfactory. The applicant has inserted the underlined guidance for the operator into the following paragraphs of the batch record:

(b) (4)

The above statement is adequate to assure (b) (4)

FDA Comment

4. **The in-process control for step 8.3 requires that** [redacted] (b) (4) **Modify the Master Batch Record to instruct the operator on the consequences of this result.**

Applicant's Response

The applicant states that their manufacturing control systems and procedures SOPs requires prior approval including intimation or approval from the Regulatory Agency, as appropriate, with any change from the stated manufacturing process/variables. They state that they do not establish these procedures in the batch record since the procedures to follow as a result of such failures are defined in their SOPs.

Evaluation

Satisfactory. This is acceptable as long as the situation is addressed in their manufacturing control documents.

FDA Comment

5. **The drug product specification does not include analytical method numbers. Provide an updated drug product specification sheet which includes the tested parameters, the acceptance criteria, and a definitive test method number or compendial reference for the analytical test method to comply with the ICH Q6A/B definition of specifications. Combine the Release Testing and Shelf-life specifications and methods into one specification sheet for ease of future reference. Testing only accomplished at release can be designated as such.**

Applicant's Response

The applicant has submitted a copy of the current drug product release and shelf-life specifications and test procedure in Attachment 4, reproduced at the end of this review.

Evaluation

Satisfactory. Although the provided specification sheets do not include individual method numbers as requested, the specifications have a reference to the combined analytical methods document, including the revision number.

All of the related approved and tentatively approved applications have the same format as proposed in this application for the drug product specifications.

FDA Comment

6. **Submit all analytical procedures from Finished Product (Regulatory and Shelf Life) Standard Test Procedure No. FPPTLD005R-01 for tenofovir disoproxil fumarate and lamivudine tablets 300 mg/300 mg with individual and unique method numbers, and a revision number which identifies the current version of each method. This is necessary**

to distinguish versions of the individual methods when changes are made pre- and post-approval. References to compendial methods are acceptable.

Applicant's Response
The applicant has provided the current version of the standard test procedure FPPTLD005R in Attachment 4. The document contains all test methods without individual method numbers.

Evaluation
Satisfactory. The presence of the methods with some form of change documentation is acceptable, even though the methods do not have individual method numbers as requested.

Matrix does not have separate analytical methods with individual version numbers in any of their approved or tentatively approved related applications.

FDA Comment
7. **The acceptance criteria for Dissolution (by HPLC) are not reflective of your data from your stability studies. Modify the acceptance criteria to read:**

   i. **Tenofovir Disoproxil Fumarate: Not less than (b) (4)% (Q) of the labeled amount of Tenofovir Disoproxil Fumarate, $C_{19}H_{30}N_5O_{10}P\cdot C_4H_4O_4$ should be dissolved in (b) (4) minutes.**

   ii. **Lamivudine: Not less than (b) (4)% (Q) of the labeled amount of Lamivudine, $C_8H_{11}O_3S$ should be dissolved in (b) (4) minutes.**

Applicant's Response
The applicant has provided updated specifications in Attachment 4 with the requested changes inserted.

Evaluation
Satisfactory. The changes were made as requested. The updated drug product specifications are reproduced at the end of this review.

FDA Comment
8. **The submitted stability data do not support the proposed (b) (4) acceptance criterion of NMT (b) (4) Considering the demonstrated instability of the tenofovir disoproxil fumarate dru(b) (4)e to (b) (4) modify the acceptance criterion for (b) (4) to NMT (b) (4)**

Applicant's Response
The applicant has provided updated specifications in Attachment 4 with the requested changes inserted.

CMC Assessment Section

Evaluation

Satisfactory. The changes were made as requested. The updated drug product specifications are reproduced at the end of this review.

FDA Comment

9. **The proposed (b) (4) month holding time for the bulk pack tablet storage container and 24-month expiry for the 30- and (b) (4) count presentations are premature prior to obtaining satisfactory full-term stability data. Provide an update of your stability data for the bulk pack, and 30- and (b) (4) count container/closure systems. We note that data from batch TLDA536002 using (b) (4) desiccant was missing from the original application. There were (b) (4) data from batch TLDA536003 submitted in the original application in the section where TLDA536002 data should have been. Data from batch TLDA536002 using (b) (4) desiccant should be submitted with the requested update.**

Applicant's Response

Matrix has submitted updated 18-months long-term stability data in Attachment 5, along with a data summary in Attachment 6.

They note that the (b) (4) month holding time data for the bulk pack has already been submitted in the original submission. They have provided complete stability data for all the batches in all the packaging configurations.

Evaluation

Satisfactory. All batches met the proposed specifications. The proposed expiration dating period of 24 months is tentatively acceptable for both bottle packs and desiccants on the basis of the 18 months long-term and 6 months accelerated stability data. Similarly, the proposed holding time period of (b) (4) months is acceptable for the bulk (b) (4).

The following results were seen in the 18-month 30°C/75% RH storage stability data:

Assay **- Small losses in potency of both APIs were measured, amounting to between (b) (4) (b) (4). There was no apparent correlation between the amount of potency lost and the identity of the desiccant or the bottle size. The batch-to-batch variability was greater than the effect of other variables.**

Dissolution **- Amounts of both APIs dissolved at (b) (4) min were (b) (4) and averaged a loss of (b) (4) of lamivudine and (b) (4) of tenofovir disoproxil fumarate. The changes were apparently independent of the desiccant and bottle size. Very little batch-to-batch variability.**

(b) (4) **The changes were apparently independent of the desiccant and bottle size. Very little batch-to-batch variability.**

Related Substances **- The only substantial change in individual related substances was in the increase of the (b) (4) well within the acceptance criteria of NMT (b) (4). The detectable change happened within the (b) (4) (b) (4) There was little or no change in (b) (4) impurity content after the (b) (4) (b) (4) time point. Degradation rates were apparently independent of the desiccant and bottle size. Very little batch-to-batch variability.**

FDA Comment

10. **Provide an updated stability protocol and commitments containing a (b) (4) month test point for the bulk holding container.**

Applicant's Response

The applicant has provided a revised post-approval stability protocol and commitments in Attachment 7, reproduced at the end of this review.

Evaluation

Satisfactory. The submitted post-approval stability protocol is acceptable.

FDA Comment

11. The following are preliminary CMC labeling comments and may not be comprehensive and complete at this time.

a. Insert the name and place of business of the manufacturer, packer or distributor into the HOW SUPPLIED section of the Physician Package Insert.

b. **Submit carton labeling for review.**

Applicant's Response

Matrix is not proposing a "carton" for packaging of this product. Accordingly, a carton labeling was not provided for review.

Matrix has provided updated labeling in their 8/26/08 amendment.

Evaluation

Satisfactory. The applicant has not inserted the name and place of business of the manufacturer, packer or distributor into the HOW SUPPLIED section of the Physician Package Insert as requested. The following comment was sent to the applicant in a letter dated 8/29/08.

> ***As requested in our communication dated August 5, 2008, insert the name and place of business of the manufacturer, packer or distributor into the HOW SUPPLIED section of the Physician Package Insert.***

Compliance with the above request is not necessary for tentative approval of this application.

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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/

Brian Rogers
9/3/2008 12:17:50 PM
CHEMIST

Norman Schmuff
9/4/2008 09:01:10 AM
CHEMIST