CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208255Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208255
Review 2

Drug Name/Dosage Form	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate
Strength	400mg/300mg/300mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mylan
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Orig-1 Amendment-23	July 25, 2017	Original Resubmission for final approval
Amendment	Nov 21, 2017	Quality
Amendment	Dec 7, 2017	Quality
Amendment	Dec 11, 2017	Labeling
Amendment	Jan 18, 2018	Labeling

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance & DMFs	Haripada Sarker	Ben Stevens
Drug Product & Labeling	Milton Sloan	Balajee Shanmugam
Process	NA	
Microbiology	NA	
Facility	Frank Wackes	Christina Capacci-Daniel
Biopharmaceutics	NA	
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
18230	Type II	Mylan	Efavirenz drug substance	Adequate	See DS review in Rev-2	DMF review in Panorama (under NDA)
17750	Type II	Mylan	Lamivudine drug substance	Adequate	See DS review in Rev-2	No DMF review needed
20108	Type II	Mylan	Tenofovir DF drug substance	Adequate	See DS review in Rev-2	DMF review in Panorama (under DMF)
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	See DP review in Rev-1	
	Type III *(if applicable)*			Adequate	See DP reviews in Rev-1 and Rev-2	

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	

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 208255 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 March 10, 2017 under the PEPFAR program. In the July 7, 2017 submission Mylan requests full approval, which would allow marketing in the US, once applicable patents have expired. To better match the dates of patent expiration, the July 7 submission was withdrawn on July 24 and resubmitted on July 25, 2017.

This product incorporates the new lower dose of efavirenz (400 mg/day), whereas previous products were based on a dose of 600 mg/day. Published results from the ENCORE1 clinical study demonstrated that the lower daily dose has comparable efficacy, with an equivalent or better safety profile.

Proposed Indication(s) including Intended Patient Population	***Adult Patients and Pediatric Patients 12 Years of Age and Older*** [(b) (4)] ***or more)***
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

Information on the three drug substances is cross-referenced to DMF 18230 (Efavirenz; HSarker; adequate 11/3/17), DMF 17750 (Lamivudine; KWindsor; adequate 6/20/17), and DMF 20108 (Tenofovir Disoproxil Fumarate; amendment SD-46 contains updates to drug substance manufacturing controls and stability; HSarker; adequate Nov 03, 2017). Mylan is the applicant for NDA 208255 as well as the holder of the DMFs for the three drug substances. These three DMFs were evaluated by Hari Sarker and were found to be Adequate as of Nov 3, 2017.

An alternate equivalent [(b) (4)] can be used for particle size testing of Tenofovir DF drug substance. The equivalence report (PR/QCD/GEN/005/14)

comparing the [redacted] was submitted in the Information Request Response dated January 11, 2017 (Sequence No. 0012). A copy of the revised drug substance specification, test procedure and Certificate of Analysis is provided in the Sections 3.2.S.4.1, 3.2.S.4.2 and 3.2.S.4.4, respectively. This alternative analytical method is acceptable. There are no other changes in the controls for the three drug substances relative to the specifications which were tentatively approved in March 10, 2017. For additional information, see Dr. Sarker's Drug Substance review in this document.

The drug product is a white to off-white, film-coated [redacted] tablet, oval, unscored tablet debossed with M on one side and TLE on the other side (21mm x 11mm x 8mm thick; 1600mg weight). It is closely related to 600mg/300mg/300mg tablet that was tentatively approved under Mylan's NDA 22142. Batch release and stability data were provided on four pilot scale batches of [redacted] tablets each. The March 10, 2017 tentative approval letter set an expiration dating period of 24 months when stored below 30°C, [redacted] In the Nov 21, 2017 amendment, 24 month stability data was provided on three batches and 18 mo data on a fourth, in [redacted] white [redacted] HDPE bottles. These data support the 24 month expiration dating period, [redacted] be distributed in the United States in the white bottle of 30 tablets with a child-resistant closure. See Dr. Milton Sloan's Drug Product and Labeling evaluation within this review for additional information.

All tests and acceptance criteria in the drug product specification are unchanged from the March 10, 2017 tentative approval. For additional information, see Dr. Milton Sloan's Drug Product evaluation and Dr. Gerlie Gieser's Biopharmaceutics evaluation in Product Quality Rev-1.

[redacted]

The only modification proposed for facilities is the addition of particle size testing to existing testing facility (Mylan Laboratories Limited (Unit 3) | FEI: 3003937580) that was previously evaluated in the IQA for the original application

and was recommended for Tentative Approval. Therefore, this amendment was documented using the OMIR since an update to the IQA is not required. An Overall Manufacturing Facility Recommendation of Approve was entered in Panorama on Nov 2, 2017. For additional information, see notes from Frank Wackes under Inspection View in Panorama.

C. Special Product Quality Labeling Recommendations (NDA only)

Language recommended for inclusion in the Action Letter:

A 24-month expiration dating period is granted for this product when stored below 30degC (86degF) and packaged in white HDPE bottles of 30 with desiccant, induction seals, and child-resistant closures.

Edits recommended from the product quality perspective for the labeling:

Recommendations for the labels and labeling have already been conveyed to OND and incorporated during labeling negotiations.

D. Final Risk Assessment (see Attachment)

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LABELING

{For NDA only}

R Regional Information

1.14 Labeling

Highlights of Prescribing Information

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 400 mg efavirenz, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate. (3)

FULL PRESCRIBING INFORMATION: CONTENTS

3 DOSAGE FORMS AND STRENGTHS

(b) (4) Tablets 400 mg of efavirenz, , 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

- .

Reviewer's Assessment:

Mylan has proposed the proprietary name of Symfi Lo (SIM-fee LOW). The proposed proprietary name has been found acceptable by DMEPA.

(b) (4)

Recommended revision for 3 Dosage Form and Strengths:

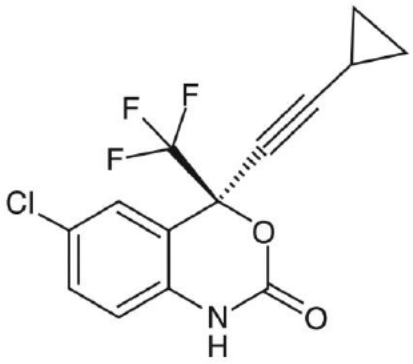
Tablets: 400 mg of efavirenz, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

11 DESCRIPTION

SYMFI LO (efavirenz, lamivudine and tenofovir disoproxil fumarate) is a fixed dosed combination tablet for oral administration. Each (b) (4) tablet contains 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate, which is

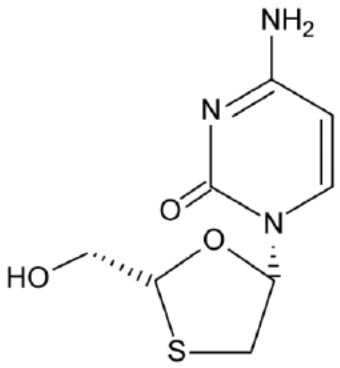
equivalent to 245 mg of tenofovir disoproxil. Each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, talc, titanium dioxide and yellow iron oxide.

Efavirenz: Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Efavirenz is chemically described as (*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one. Its molecular formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:



Efavirenz, is a white to slightly pink crystalline powder with a molecular mass of 315.67. It is soluble in methanol and practically insoluble in water (< 10 microgram/mL).

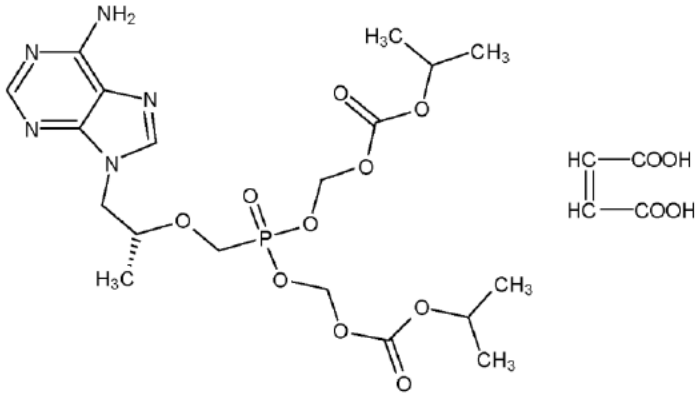
Lamivudine: Lamivudine (also known as 3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (-)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26 g per mol. It has the following structural formula:



Lamivudine, is a white to off-white solid with a solubility of approximately 70 mg per mL in water at 20°C.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.51. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white powder that is freely soluble in dimethylformamide and soluble in methanol. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25 °C.

Reviewer's Assessment:

Recommended revision for 11 Description:

SYMFI LO (efavirenz, lamivudine and tenofovir disoproxil fumarate) is a fixed dosed combination tablet for oral administration.

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMFI LO [redacted] (b) (4) tablets are supplied as fixed dosed combination tablets containing 400 mg of efavirenz,, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

SYMFI LO tablets are white to off-white, film-coated, oval, tablets debossed with "**M**" on one side and "**TLE**" on the other side. They are supplied as NDC (b) (4) unit of use cartons containing bottles of 30 tablets with desiccant, induction seal and child resistant caps.

Store below 30° C (86° F).

Dispense in original container.

Manufacturer/distributor name listed at the end of PI, following Section #17

Rx only

(b) (4)

Mylan®

Manufactured for:

(b) (4)

Manufactured by:
Mylan Laboratories Limited
Hyderabad — 500 034, India

(b) (4)

Patient Information

TRADENAME™ (phonetic spelling)
(efavirenz, lamivudine and tenofovir disoproxil fumarate) Tablets

(b) (4)

Reviewer's Assessment:

Minor changes/revisions are made above with tracked changes.

Recommended revision for 16 How Supplied/Storage and Handling:

- **In Section 16 of the PI: "…bottles of 30 tablets with desiccant, induction seal, and child-resistant cap"**

Immediate Container Label

Proposed Bottle Label for NDA 208255 (July 25, 2017 submission) with Edits Recommended by FDA

400 MG/300 MG/300 MG – BOTTLES OF 30 TABLETS

(b) (4)

[redacted]

Reviewer's Assessment:

The product quality review team recommends sending the following comment to Mylan as soon as practical, if concurred by DMEPA and others in the review team:

We note that a draft guidance on (b) (4) **was issued in** (b) (4)

(b) (4)

[redacted]

Based on this draft guidance, we ask you to consider whether the following text might be added to the prescribing information (PI) and the container labels:

- **In Section 16 of the PI: "…bottles of 30 tablets with desiccant, induction seal, and child-resistant cap"**
- (b) (4)

If you choose to follow this approach, please submit written verification that this child-resistant package meets the Consumer Product Safety Commission's standards under 16 CFR 1700. See lines 219-223 in the draft guidance which recommends that a verification statement such as this be located in Module 3, Section 3.2.P.7.

Proposed Carton Label for NDA 208255 (July 25, 2017 submission) with Edits Recommended by FDA

Back | Left | Front (Principal Display) | Right

(b) (4)

Top Panel | Bottom Panel

Product Quality review team recommends the same edits to the carton label.

Mylan's specific responses to the comments in the Agency's November 13, 2017, November 20, 2017 and November 28, 2017 email correspondences are as follows:

FDA COMMENT (November 13, 2017 Email Correspondence in Response to Mylan's Email Inquiry Dated November 13, 2017)
[Yes,] please incorporate the innovator label updates accordingly into your proposed labels. Please note the EPIVIR label was also updated on September 25, 2017.

MYLAN RESPONSE
As requested by the Agency, Mylan's proposed draft insert/Patient Information Leaflet has been revised in accordance with the most recently approved labeling for the RLDs, EPIVIR® (lamivudine) Tablets, approved on September 25, 2017 (NDA 020564/S-037) and SUSTIVA® (efavirenz) Tablets approved on October 10, 2017 (NDA 021360/S-044). Please refer to Mylan's proposed draft insert/Patient Information Leaflet in Section 1.14.1.3.

FDA COMMENTS (November 20, 2017 Email Correspondence)
Proposed Bottle Label for NDA 208255 (July 25, 2017 submission) with Edits Recommended by FDA

(b) (4)

(b) (4)

Based on this draft guidance, we ask you to consider whether the following text might be added to the prescribing information (PI) and the container labels:

- In Section 16 of the PI: "…bottles of 30 tablets with desiccant, induction seal, and child- resistant cap"
- (b) (4)

If you choose to follow this approach, please submit written verification that this child-resistant package meets the Consumer Product Safety Commission's standards under 16 CFR 1700. See lines 219-223 in the draft guidance which recommends that a verification statement such as this be located in Module 3, Section 3.2.P.7.

The Product Quality review team recommends the same edits to the carton label:

Back | Left | Front (Principal Display) | Right

FDA COMMENT (November 28, 2017 Email Correspondence)
Reference is made to your NDA 208255 and my previous email sent November 20, 2017. I am resending our label comments in an attachment.

MYLAN RESPONSE
We acknowledge the Agency's comments; (b) (4) Please note, however, that Mylan has revised the product name on the principal display panel to include the proprietary name, SYMFI LO™, in accordance with the Agency's Proprietary Name Request Conditionally Acceptable correspondence dated October 20, 2017.

As requested by the Agency, Mylan has revised our dispensing statement on the right panel of our proposed final printed bottle label to include reference to our child-resistant bottle to read as

"**This package is child-resistant. Keep this and all medication out of the reach of children.**". Please note that "**the**" was included in our dispensing statement in accordance with Mylan's current standard format. Mylan is also hereby submitting an updated Container Closure System description along with a declaration and study report in Section 3.2.P.7 with respect to Mylan's child-resistant bottle closure in accordance with the Agency's August 2017 draft Guidance, '*Child-Resistant Packaging Statements in Drug Product Labeling*' and as per the Consumer Product Safety Commission's standards under 16 CFR 1700. Further, as requested by the Agency, Mylan's proposed draft insert/Patient Information Leaflet was revised to reflect the description of the container closure in Section 16, HOW SUPPLIED/STORAGE AND HANDLING, as "cartons container bottles of 30 tablets with desiccant, induction seal, and child- resistant cap" accordingly.

Mylan acknowledges the Agency's comment requesting the same edits described above for Mylan's proposed final printed bottle label to be applied to Mylan's proposed final printed carton. (b) (4) . Please note that Mylan has also revised the product name on the principal display panels of our proposed final printed carton to include the proprietary name, SYMFI LO™, in accordance with the Agency's Proprietary Name Request Conditionally Acceptable correspondence dated October 20, 2017 and for alignment with our proposed final printed bottle label. In addition, Mylan has retained our dispensing statement as "**Keep this and all medication out of the reach of children.**" since our proposed final printed carton does not include a child-resistant feature and therefore cannot comply with the Agency's August 2017 draft Guidance, '*Child-Resistant Packaging Statements in Drug Product Labeling*' or Consumer Product Safety Commission's standards under 16 CFR 1700.

Please refer to Mylan's proposed draft insert/Patient Information Leaflet in Section 1.14.1.3 and Mylan's proposed final printed container labels in Section 1.14.2.1.

In accordance with the Agency's Guidance, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005), Structured Product Labeling (SPL) for SYMFI LO™ (efavirenz, lamivudine and tenofovir disoproxil fumarate) Tablets, 400 mg/300 mg/300 mg is provided in Section 1.14.1.3. As a review aid, Microsoft word versions have also been provided for the proposed labeling components.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval.

Reviewer's Assessment of Response to IR:

Recommended revision for 16 How Supplied/Storage and Handling:

Mylan agree to include the child-resistant statement on the CC and have included in the P.7 of the NDA that indicate compliance.

Recommended revision for Container Closure labeling:

Mylan has not accepted the recommended Container closure (CC) labeling nomenclature and are proposing to keep it as follows:

(b) (4)

Rather than the recommended:

SYMFI LO (efavirenz, lamivudine, and tenofovir disoproxil fumarate), Tablets, 400mg / 300mg / 300 mg*

(b) (4)

This response is unacceptable. The applicant will be asked to conform to the labeling practices for fully approved drug products that are fixed dosed combinations. Please see revisions as recommended and made with tracked changes in the container label below.

400 MG/300 MG/300 MG – BOTTLES OF 30 TABLETS

(b) (4)

400 MG/300MG/300 MG – CARTON OF ONE BOTTLE OF 30 TABLETS (ALL PANELS)

Back | Left | Front (Principal Display) | Right

(b) (4)

400 MG/300MG/300 MG – CARTON OF ONE BOTTLE OF 30 TABLETS (ALL PANELS)

Top Panel | Bottom Panel

(b) (4)

Primary Labeling Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
12/11/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Balajee Shanmugam, PhD
(Acting) Branch Chief
OPQ/ONDP/Div1/Branch III

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 12/12/2017 01:17:57PM
GUID: 50758d5000003c1b1962e036ea11002c

Milton Sloan

Digitally signed by Milton Sloan
Date: 12/12/2017 01:10:06PM
GUID: 508da72000029fa0e17abc24c6841f0a

ATTACHMENT I: Final Risk Assessments

Final Risk Table for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets (NDA 208255)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability	Tenofovir DF is moderately stable to hydrolysis	**L**		**L**	
Physical stability (solid state)	Based on efavirenz	**M**	(b) (4)	**L**	
Content uniformity	(b) (4)	**L**		**L**	
Microbial limits		**L**		**L**	
Dissolution – BCS Class II/IV (efavirenz) & I/III (lamivudine and tenofovir DF)	(b) (4)	**M**	Evaluation supports the proposed dissolution method for this product. The acceptance criteria were tightened to Q= (b) (4) in 20 minutes for each active.	**L**	
(b) (4)	(b) (4)	**M**	(b) (4)	**L**	
Drug Product Impurity Control	AC for total impurities (NMT (b) (4) (b) (4)	**M**	Acceptance criterion determined to be acceptable Same AC as for 600/300/300 tablet (NDA 22142)	**L**	

ATTACHMENT II: List of Deficiencies for Complete Response

Responses have been received to all Information Requests, and there are no remaining deficiencies from the Product Quality perspective.

OVERALL ASSESSMENT AND SIGNATURES:

From the Product Quality perspective NDA 208255 is recommended for final approval.

Stephen Miller, Ph.D.; CMC-Lead and ATL for NDA 208255

Stephen
Miller

Digitally signed by Stephen Miller
Date: 1/20/2018 09:52:56AM
GUID: 508da7210002a000609476bbecd040f0

Recommendation: Tentative Approval

NDA 208255
Review 1

Drug Name/Dosage Form	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate
Strength	400mg/300mg/300mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mylan
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
13-SEP-2016		Original (Resubmission)
18-MAY-2016		Quality Amendment
28-OCT-2016		Quality Amendment
21-NOV-2016		Quality Amendment
14-DEC-2016		Quality Amendment
22-DEC-2016		Quality Amendment
11-JAN-2017		Quality Amendment
31-JAN-2017		Quality Amendment

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Ali Al Hakim
Drug Product	Milton Sloan	Balajee Shanmugam
Process	Jiao Yang	Steven Frisbee
Microbiology	Jiao Yang	Steven Frisbee
Facility	Frank Wackes	Christina Capacci-Daniel
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	Mylan	Efavirenz drug substance	Adequate	08/15/2016	Review by Wei Song
	Type II	Mylan	Lamivudine drug substance	Adequate	12/28/2016	Review by Hari Sarker
	Type II	Mylan	Tenofovir DF drug substance	Adequate	12/28/2016	Review by Hari Sarker
	Type II	(b) (4)		Adequate	This review	Milton Sloan (DP reviewer)
	Type III *(if applicable)*			Adequate	This review	Milton Sloan (DP reviewer)

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	

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 208255 is recommended for Tentative Approval from the Product Quality perspective.

II. Summary of Quality Assessments

A. Product Overview

This product incorporates the new lower dose of efavirenz (400 mg/day), whereas previous products were based on a dose of 600 mg/day. Published results from the ENCORE1 clinical study demonstrated that the lower daily dose has comparable efficacy, with an equivalent or better safety profile.

Proposed Indication(s) including Intended Patient Population	***Adult Patients and Pediatric Patients 12 Years of Age and Older*** (b) (4) ***or more)***
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

Information on the three drug substances is cross-referenced to DMF 18230 (Efavirenz), DMF 17750 (Lamivudine), and DMF 20108 (Tenofovir Disoproxil Fumarate). Mylan is the applicant for NDA 208255 as well as the holder of the DMFs for the three drug substances. DMF 17750 and DMF 20108 are reviewed by Hari Sarker (Dec 28, 2016) and were found to be Adequate. DMF 18230 was previously reviewed (Review 13) by Wei Song dated 08/15/2016, and was found to be Adequate. For additional information, see Dr. Sarker's Drug Substance review chapter.

The drug product is a film-coated (b) (4) tablet (21mm x 11mm x 8mm thick; 1600mg weight). It is closely related to 600mg/300mg/300mg tablet that was tentatively approved under Mylan's NDA 22142. Batch release and stability data were provided on four pilot scale batches of (b) (4) tablets each. The drug product specification tests and methods are the same as approved under NDA 022-142, and acceptance criteria are equivalent. The commercial presentations are white (b) (4) HDPE bottles of 30 with desiccant and induction seal. (b) (4)

(b) (4) An expiration dating period of 24 months when stored below 30°C is supported by the stability data, which includes 9 months at 30°C/75%RH. See Dr. Milton Sloan's Drug Product review chapter for additional information.

(b) (4) For additional information, see Jiao Yang's Process review chapter.

All manufacturing facilities have been determined to be acceptable, and an Overall Manufacturing Facility Recommendation of Approve was entered in Panorama on Feb 14, 2017. See the Frank Wackes' Facility review chapter for further information.

The proposed dissolution method with revised acceptance criteria (Q=(b) (4) at 20 minutes for each active) is acceptable. Bridging data were not needed because the to-be-marketed drug product has the same formulation/manufacturer/process/ controls as the bio-batch and the other primary stability batches. For additional information, see Dr. Gerlie Gieser's Biopharmaceutics review chapter.

C. Special Product Quality Labeling Recommendations (NDA only)

Language recommended for inclusion in the Action Letter:

A 24-month expiration dating period is granted for this product when stored below 30degC (86degF) and packaged in white (b) (4) HDPE bottles of 30 with desiccant and induction seals. (b) (4)

Edits recommended from the product quality perspective for the labeling:

1. Given the stability of your product under the long-term condition of (b) (4) we recommend that the storage statement be revised to "Store below 30degC (86degF)." Please revised the storage statements in the prescribing information and the container label, and submit revised versions.

2. We recommend that you revise the container label to include the statement "Rx Only".

3. We recommend that the order of information in the Description Section be revised to start with the two paragraphs about the tablets, and then present the information on the drug substances.

4. Please revise the statement in the How Supplied section to read: "bottles of 30 tablets with desiccant and induction seal."

D. Final Risk Assessment (see Attachment)

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

BIOPHARMACEUTICS

Product Background:
NDA: 208255 (Resubmission)
Drug Product Name/Strength: Efavirenz, Lamivudine, Tenofovir Disoproxil Fumarate [ELT] Fixed Dose Combination [FDC] Tablets (400mg /300mg /300 mg)
Route of Administration: Immediate-Release Oral Tablets
Applicant Name: Mylan Pharmaceuticals, Inc.

Review Summary:
For the routine QC testing of the Efavirenz/Lamivudine/Tenofovir DF Fixed Dose Combination (ELT; 400mg/300mg/300mg) Tablets at batch release and during shelf-life, the following dissolution method and revised acceptance criterion, shown in the table below, are found acceptable.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
2 (paddles)	75 rpm	Purified Water with 2% SLS (degassed), 37 ± 0.5°C	1000 mL	Q = (b) (4)% at 20 min (for efavirenz, lamivudine and tenofovir DF)

Bridging data were not needed because the to-be-marketed drug product has the same formulation/manufacturer/process/controls as the bio-batch and the other primary stability batches.

From the Biopharmaceutics perspective, NDA 208255 for the Efavirenz/Lamivudine/ Tenofovir DF (400mg/300mg/300mg) Tablet is recommended for **APPROVAL**.

List Submissions being reviewed (table):
SDN-3, 3/31/2016 (Original NDA Submission)
SDN-6, 5/18/2016 (Applicant's Response to Quality Information Request)
SDN-7, 9/13/2016 (NDA Resubmission)
SDN-9, 11/21/2016 (Applicant's Response to Quality Information Request)
SDN-11, 12/22/2016/2016 (Applicant's Response to Quality Information Request)
SDN-13, 1/11/2017 (Applicant's Response to Quality Information Request)

Highlight Key Outstanding Issues from Last Cycle:

Adequacy of Proposed Dissolution Method and Acceptance Criteria

Concise Description Outstanding Issues Remaining:
None

Biopharmaceutics Classification Scheme (BCS) Classification

Reviewer's Assessment:
The Applicant did not request BCS designation for the proposed drug product which is a fixed-dose combination (FDC) tablet consisting of three APIs. As individual drug substances, efavirenz (EFV), lamivudine (3TC), and tenofovir DF (TDF) are known to exhibit solubility/permeability characteristics consistent with drug substances categorized into the (b) (4)

Solubility: Per BCS criteria, Efavirenz is Low Solubility; Lamivudine and Tenofovir DF are High Solubility.

Permeability: Efavirenz (Low Permeability – In 30-day human radiolabelled mass balance study, up to 61% of the administered dose (400 mg QD for 8 days) appeared as unchanged drug in the feces); Lamivudine (Low to High Permeability – reported mean absolute BA is 82 to 86%); Tenofovir DF (Low Permeability – oral BA of TDF is 25% in fasted subjects)

Dissolution: rapid to very rapid dissolution (at least 85% dissolved in 15 min) from the proposed ELT FDC Tablet, using the proposed QC dissolution method. Of note, the proposed QC dissolution medium contains 2% SLS, (b) (4)

Dissolution Method and Acceptance Criteria
The proposed QC dissolution method for ELT Tablets uses USP Apparatus 2 (paddle) at 75 rpm, 1000 mL of Purified water with 2% Sodium Lauryl Sulfate (SLS or SDS; degassed) maintained at 37 ± 0.5°C, and Reversed-Phase HPLC with gradient elution and UV-Vis detection at 265 nm and 295 nm. For routine QC testing at batch release and during shelf-life, the originally proposed dissolution acceptance criterion is 'Q = (b) (4)% of labeled amount at (b) (4) min' for all three component APIs.

Reviewer's Assessment: *ADEQUATE*

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During the course of the NDA review, several Biopharmaceutics Information Requests (IRs) were sent to the Applicant. To provide additional context to the Reviewer's conclusions, these IRs and the corresponding Reviewer's interpretation and evaluation of the Applicant responses are summarized below.

On 5/5/2016, the following information requests (IRs) was sent to the Applicant:

1. Provide an update of the stability data once the 9-month time points are available. We anticipate this should be available now. When you submit the 9-month stability data summary tables, provide the number of units tested (n) and the %RSD, in addition to the mean, min, and max at each dissolution sampling time point.
2. On page 87 of 3.2.P.2. Pharmaceutical Development Report, it appears that a [redacted] (b) (4) in the proposed QC dissolution medium (i.e., water with 2% SLS) after the 15 minute sampling time point. We note that your proposed dissolution acceptance criteria for batch release and stability testing of the ELT tablet is Q = [redacted] (b) (4) for all three APIs. Moreover, the tables on pages 31 to 36 of the report show that [redacted] (b) (4) (a highly soluble drug substance) in different pH media from the FDC tablet. At the current long-term stability time point, provide the dissolution data for ELT at all sampling time points (5, 10, 15, 30, 45, 60, 90 min) for the BE batch (Lot 2009057) and the three other registration batches using deaerated water with varying SLS concentrations (e.g., 1%, 1.5%, 2%) as the dissolution media. If the full dissolution profile was not acquired at the 9-month time point, we request that you obtain full profile data as soon as practical and not wait until the 12-month time point. In this case, report the storage history of the samples prior to the dissolution testing. The dissolution profiles to be provided should be obtained from 1 dosage unit (tablet) per vessel.

➢ *Based on the 5/18/2016 Sponsor Responses to the above IRs, there was no clear indication that* [redacted] (b) (4) *in the dissolution medium (purified water) would mitigate the apparent decrease in TDF dissolution. However, the updated dissolution on stability data submitted by the Applicant confirmed that using* [redacted] (b) (4) *as the specification time point would be feasible for all three APIs. Of note, the high variability in the dissolution data of TDF (a highly soluble drug substance) as shown in the tables on pages 33 to 36 of the Pharmaceutical Development Report remained a concern because such could increase unnecessary failures when using TDF dissolution data at* [redacted] (b) (4) *for routine QC testing.*

On 11/07/2016, the following second set of Biopharmaceutics information requests were conveyed to the Applicant.

1. We acknowledge receipt of the *in vitro* dissolution profile data for BE batch 2009057 (as well as the three other registration batches) collected at 11 months of long-term storage (25°C/55%RH). Based on the dissolution profile data generated using the proposed QC dissolution method for these drug product batches at batch release and during stability testing, FDA recommends a dissolution acceptance criteria of 'Q = [redacted] (b) (4) for all three APIs during routine QC of the ELT Tablets at batch

release and during stability testing. Revise the Finished Product Specification, the stability protocol, and all other pertinent NDA documents.

(b) (4)

- *The 11/21/2016 Applicant's Responses to the second set of Biopharmaceutics IRs are summarized below.*
- *For batch release and stability testing, a dissolution specification time point of 20 minutes for Q =* (b) (4) *was counterproposed for the following reasons:* (b) (4)

(b) (4)

-

(b) (4)

- *To demonstrate successful dissolution method transfer, the Applicant showed that both originating and receiving laboratories reported that the three API components of the 5 ANDA exhibit batches were all 'very rapidly dissolving' (at least 85% dissolved in 15 min) at the current intermediate stability time point.*
- *At a UV detection wavelength of (b) (4), the three APIs show major peaks in the HPLC chromatogram.*
- *Both Development Drug Product Lots 1686-052 and 1877-046 with efavirenz particle size distribution of (b) (4) (b) (4) respectively, exhibited proposed QC dissolution method. The dissolution profiles of the batches used in LOD optimization studies were not obtained because (b) (4) was not considered a critical determinant of dissolution in the Applicant's initial risk assessment.*

The below follow-up Biopharmaceutics information requests were sent to the Applicant on 12/08/2016:

1. We acknowledge your counter-proposed dissolution specification time point (20 minutes instead of the FDA recommended (b) (4)) for all three APIs in the Efavirenz/Lamivudine/Tenofovir DF (ELT) Tablet (b) (4)

2. If the three APIs are represented as major peaks of HPLC chromatograms when using a UV wavelength of (b) (4) consider using this one UV wavelength instead of (b) (4) for quantification of the three analytes in the dissolution samples.

➢ *On 12/14/2016, the Applicant's Response indicated that based on linear interpolation, the cumulative dissolution of efavirenz at 20 min from Batch #1877-*

052 is predicted to be significantly lower than (b) (4)% and thus, this aberrant batch would be anticipated to fail their counter-proposed dissolution acceptance criteria (Q (b) (6)% at 20 min for all three APIs). Additionally, the Applicant prefers to keep the two UV wavelengths because the UV absorbance of efavirenz is not maximal at (b) (4) and analytical method validation was accomplished using both (b) (4) (for TDF) and (b) (4) (for EFV and 3TC).

On 12/22/2016, the Applicant provided the individual unit dissolution profile data of Batch #1877-052, in response to the 12/19/2016 Follow-up Biopharmaceutics Information Request. Based on the Reviewer's own analysis, the mean predicted cumulative dissolution at 20 min for this intentionally manufactured aberrant batch would be (b) (4)%, i.e., if graphically interpolating between the (b) (4) data points. Furthermore, based on the Reviewer's simulations using the beta-version of the Division of Biopharmaceutics (DB) Web Tool [Q= (b) (4)%; mean (CV range) of batch with (b) (4) units = (b) (4) simulated number of batches = (b) (4); assuming normal distribution], this Reviewer concludes that this aberrant formulation is expected to have (b) (4)% batch passing rates at USP Stages (b) (4) dissolution testing when the dissolution acceptance criterion is 'Q = (b) (4)% at 20 min' for efavirenz (as well as tenofovir DF and lamivudine).

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Dissolution Method *– ADEQUATE*

The optimal method parameters were identified based on dissolution method development studies, as summarized in the Pharmaceutical Development Report (PDR). The Applicant's method development efforts focused mainly on the dissolution of efavirenz (a low-solubility drug substance).

The proposed QC method was shown to distinguish a developmental drug product batch that was manufactured (b) (4) (see Section 2.2.1.6.1.3 of the PDR) based on dissolution data at the (b) (4) time point (but not at (b) (4) and later sampling time points); the Reviewer-calculated f_2 value was 20.5 between Batch 1877-052 and 1686-052 containing (b) (4) (b) (4) respectively. The Reviewer's simulation showed that the predicted efavirenz dissolution at 20 min of this aberrant batch would also be significantly lower than (b) (4)%.

In dissolution method development studies, (b) (4)

(b) (4)

Based on the pH-solubility data (in the presence and absence of 2% SLS) provided by the Applicant for the individual drug substances, sink conditions are expected to be achieved and maintained in the proposed QC dissolution medium (1000 mL of water with 2% SLS), at 37 °C. In purified water with 2% SLS, the amounts of TDF, lamivudine, and efavirenz dissolved are (b) (4) respectively.

Based on the data provided by the Applicant in response to this Reviewer's information request, it appears that unlike lamivudine and efavirenz, tenofovir DF solubility in water decreases with the addition of (b) (4)

[Note that (b) (4) will be part of the drug substance specification of all three APIs. (b) (4) will also be part of the in-process specifications of the (b) (4). Efavirenz has (b) (4)

During analytical method validation, the pre-specified acceptance criteria for system suitability, specificity, linearity, precision, accuracy, robustness (with respect to HPLC conditions), solution stability (24 hours under bench-top conditions), and filter compatibility were met. To support the dissolution method transfer from the originating laboratory (ADS Mylan Lab, Hyderabad) to the receiving laboratory (QC Mylan Lab, Indore), system suitability (using standard solution), and dissolution data of 12 units at the 60 min time point were provided. To further support the successful method transfer and in light of the Reviewer's recommendation to use an earlier dissolution specification time point, the Applicant was asked to provide a comparison of dissolution profiles generated by the two laboratories for a single drug product batch. The provided comparative dissolution profile data confirmed the successful method transfer between the source and receiving laboratories.

Refer to the Drug Product Review for the evaluation of the overall acceptability of the HPLC method proposed for quantifying the three APIs in the dissolution samples.

Dissolution Acceptance Criteria – *ACCEPTABLE*

The originally proposed dissolution acceptance criterion (Q = (b) (4) for all three APIs) was not found acceptable. Based on the *in vitro* ELT dissolution profile data of Drug Product Batch #2009057 (generated using the proposed QC dissolution method; Figure 1) which was shown to be bioequivalent to the reference drug products in Pivotal Fasted BE Study (C15275), this Reviewer initially recommended 'Q = (b) (4)' as the dissolution acceptance criterion for all three APIs in the FDC tablet. Additionally, this Reviewer recommended (b) (4) as the specification time point because all later dissolution time points (b) (4)) would allow for batches with unacceptably low (b) (4) (e.g., Batch # #1877-052; see Figure 1A below, and Section 2.2.1.6.1.3, page 87 of the PDR) to pass Q = (b) (4)% or Q = (b) (4)% dissolution testing for efavirenz. The Applicant provided justification for a less stringent dissolution acceptance criterion (i.e., Q = (b) (4)% at 20 min) in order to accommodate the variability attributed to tenofovir DF dissolution, and based on the prediction that by (b) (4)

Based on the results of the Reviewer's simulation, the aberrant lot was predicted to have USP Stages 1, 2, and 3 passing rates of (b) (4)% when 20 min is set as the specification time point to achieve Q = (b) (4)% dissolution of efavirenz (as well as the two other API components). Thus, this Reviewer deems acceptable the Applicant's counter-proposed dissolution acceptance criterion (Q = (b) (4)% at 20 min for all three API's).

Figure 1

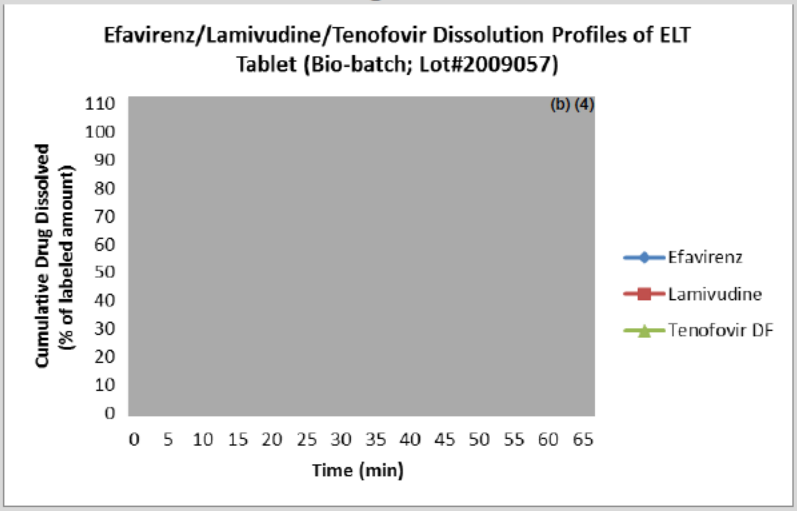
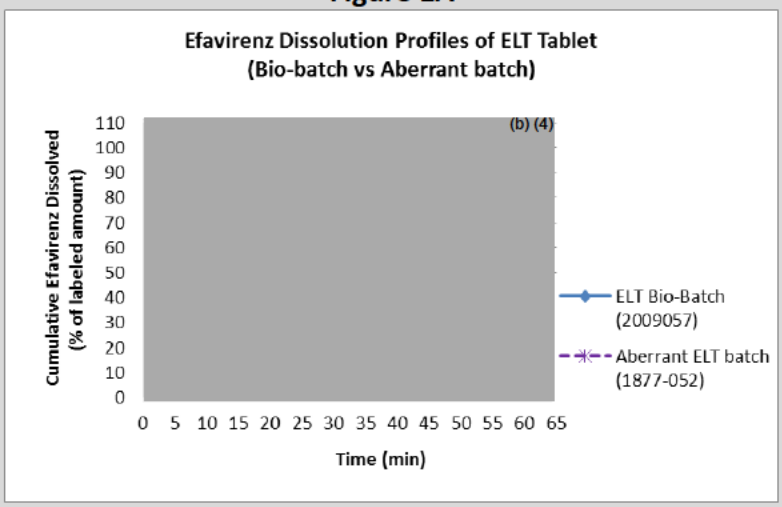


Figure 1A



Dissolution on Stability

Over 9 months of accelerated and intermediate stability testing (40°C and 30°C/75%RH), the bio-batch and the other registration batches (n= (b) (4) per lot) conformed to the Applicant's proposed dissolution acceptance criterion ('Q (b) (4)' for all three APIs).

Based on the updated 11-month dissolution profile data (n= (b) (4) per lot) of the bio-batch and the three other registration batches under long-term storage (25°C/55%RH), the Reviewer had initially recommended a dissolution acceptance criteria of 'Q = (b) (4) for all three APIs). The recently updated dissolution profile data at the (b) (4) stability time point for the bio-batch and three other ANDA exhibit batches show that all stability batches will comply with a dissolution acceptance criterion of 'Q = (b) (4)' at USP Stage 2 testing (n=12). This Reviewer notes that per agreement between the FDA and the Applicant, future stability testing (and batch release) will use 'Q = (b) (4) at 20 min for all three APIs' as the dissolution acceptance criterion; see the preceding section for the scientific justification.

Dissolution and other Quality Attributes

Efavirenz Particle Size Distribution

The clinical and the registration batches were produced from two drug substance batches with (b) (4) The Applicant proposed higher upper limits (i.e., (b) (4) for efavirenz drug substance d_{90} and d_{50} based on the similarity of the efavirenz dissolution (profiles) of drug product batches manufactured using efavirenz with d_{90} values of (b) (4) Based on the additional efavirenz particle size distribution (PSD) data (d_{50} values) provided for the drug substance batches used in pharmaceutical development studies ((b) (4) a

d_{90} of 'NMT (b) (4) µm' and a d_{50} of 'NMT (b) (4) µm' appear reasonable. This Reviewer defers to the Drug Product/Drug Subs viewer the final recommendation regarding the Efavirenz Drug Substance 3-tier PSD specification.

(b) (4)

Bridging of Formulations

Reviewer's Assessment: *NOT APPLICABLE*

Bridging data are not needed. The BE-batch is one of 4 pilot scale stability batches of the to-be-marketed formulation produced by the proposed commercial manufacturer (Mylan/Indore, India) using the proposed commercial manufacturing steps and controls.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Gerlie Gieser, PhD (1/13/2017)

Secondary Reviewer Elsbeth Chikhale, PhD (1/21/2017) I concur with Dr. Gieser' assessment and recommendation.

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 1/24/2017 08:07:05PM
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Gerlie Gieser

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ATTACHMENT I: Final Risk Assessments

Final Risk Table for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets (NDA 208255)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability	Tenofovir DF is moderately stable to hydrolysis	**L**		**L**	
Physical stability (solid state)	Based on efavirenz	**M**	(b) (4)	**L**	
Content uniformity	(b) (4)	**L**		**L**	
Microbial limits		**L**		**L**	
Dissolution – BCS Class II/IV (efavirenz) & I/III (lamivudine and tenofovir DF)	(b) (4)	**M**	Evaluation supports the proposed dissolution method for this product. The acceptance criteria were tightened to Q=(b) (4) in 20 minutes for each active.	**L**	
(b) (4)	(b) (4)	**M**	(b) (4)	**L**	
Drug Product Impurity Control	AC for total impurities (b) (4)	**M**	Acceptance criterion determined to be acceptable Same AC as for 600/300/300 tablet (NDA 22142)	**L**	

ATTACHMENT II: List of Deficiencies for Complete Response

Responses have been received to all Information Requests, and there are no remaining deficiencies from the Product Quality perspective.

OVERALL ASSESSMENT AND SIGNATURES:

From the Product Quality perspective NDA 208255 is recommended for Tentative Approval.

Stephen Miller, Ph.D.; CMC-Lead and ATL for NDA 208255

Stephen Miller

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