CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022344Orig1s000

PRODUCT QUALITY REVIEW(S)

OPQ Memorandum for NDA 22344 Orig-1 Resub-31

Product: Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300mg/300mg
Applicant: Aurobindo
Submitted: August 21, 2017
PDUFA Date: May 21, 2018

This NDA is recommended for final APPROVAL from the product quality perspective.

Summary:
This NDA received Tentative Approval for treatment of HIV infection on Jan 7, 2011 under the PEPFAR program. The indication is treatment of HIV infection in combination with other antiretroviral drugs, in adults and pediatric patients (b) (4) ≥35 kg (one tablet daily).

The cover letter for the Aug 21, 2017 submission stated that "there are no further changes in CMC (chemistry, manufacturing and controls data) after our last amendment i.e., February 14, 2017." Based on the August 21, 2017 resubmission, and the amendments of Dec 26, 2017 (clarification about one testing facility) and Jan 12, 2018 (cumulative list of all post-TA changes), Resub-31 was reviewed from the following product quality aspects: Facilities, Drug Substance, Drug Product.

The review cycle for Resub-31 was extended until May 21, 2018 to allow sufficient time to evaluate the manufacturing facilities that were listed in secondary DMFs contained within DMF (b) (4) Those additional facilities had not been listed on the 356h for Resub-31. The 356h submitted on Feb 28, 2018 did include those two facilities (b) (4)

Facilities:
The recommendation in Panorama for the (b) (4) pharmaceuticals facility (FEI: (b) (4) is Approve based on profile. An inspection was conducted in early (b) (4) for the (b) (4) facility (FEI: (b) (4)). As of May 8, the Submission Overall Manufacturing Facility Status for this application is "Approve". See Inspectional notes in Panorama for additional information.

Drug Substance:
The lamivudine drug substance is produced under DMF (b) (4) which is held by (b) (4) (b) (4) This DMF includes two cross-referenced (b) (4) that are referenced (b) (4) (b) (4) DMF (b) (4) is adequate to support to support NDA 22344 (see Review-14 by H. Sarker dated May 8, 2018).

The tenofovir DF drug substance is produced under DMF (b) (4) which is held by (b) (4) (b) (4) This DMF is Adequate (see Review-13 by Kande Amarasinghe dated Jan 27, 2017). Subsequently, no further review is need since no significant amendment is noted.

See Haripada Sarker's drug substance review, below, for additional information.

Drug Product:
The drug product is a blue colored, oval shaped, beveled edge, biconvex, film-coated tablet, debossed with 'J' on one side and '27' on the other side.

The packaging proposed for US marketing is a bottle of 30 tablets with induction seal, desiccant and child-resistant cap. The cover letter for the Aug 21, 2017 submission included the certification that the drug product complies as per 21 CFR 206; child-resistant packaging as per 16 CFR 1700.

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(b) (4)
(b) (4)

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See Milton Sloan's drug product review, below, for additional information.

Labeling:
The following edits, recommended from the product quality perspective for the prescribing information and the container labels, have been conveyed to the OND review team for consideration during labeling negotiations.

1) Revise Section 16 as follows:

Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg are blue colored, oval shaped, beveled edge, biconvex, film-coated tablets (b) (4)
(b) (4) are debossed with 'J' on one side and '27' on the other side.

Bottles of 30 tablets with desiccant, induction seal and child-resistant cap NDC 65862-543-30

(b) (4)

Store below 30°C (86°F)
After input from OPDP/DMPP regarding desiccant, we recommend this language, with edits to focus on the bottle since there is a carton that does not provide any protections:
Store in the original bottle. Do not remove desiccant, and keep the bottle tightly closed.

3) Revise Section 17 to use phrase "bottle" instead of [redacted] Perhaps include "Do not remove desiccant, and keep the bottle tightly closed" if OPDP/DMPP concurs.

4) Revise the Patient Information Section as follows:

- Store lamivudine and tenofovir disoproxil fumarate tablets below 30°C (86°F). [redacted]
- Keep lamivudine and tenofovir disoproxil fumarate tablets in the original [redacted] bottle. Do not remove desiccant, and keep the bottle tightly closed.

5) Revise the bottle and carton labels with this storage statement: Store below 30°C (86°F).

6) Add this statement to the bottle and carton labels:
Store in the original bottle. Do not remove desiccant, and keep the bottle tightly closed.

7) Add to the bottle label: This bottle is child-resistant.

8) Add to the carton label: The enclosed bottle is child-resistant.

[redacted]

Stephen Miller

Digitally signed by Stephen Miller
Date: 5/14/2018 10:33:21AM
GUID: 508da7210002a000609476bbecd040f0
Comments: ATL for NDA 22344 Resub-31

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NDA 022344

Lamivudine Tablets and Tenofovir Disoproxil Fumarate Tablets

Aurobindo Pharma Limited

Brian Rogers

CMC Reviewer

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II/Branch VI

CMC REVIEW OF NDA 022344
For the Division of Anti-Viral Products (HFD-530)

Table of Contents

CMC Review Data Sheet

1. NDA 22344

2. REVIEW # 1

3. REVIEW DATE: 07-JAN-2011

4. REVIEWER: Brian Rogers

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	01/11/2010
Original Submission	03/09/2010
Amendment	03/11/2010
Amendment	06/02/2010
Amendment	08/19/2010
Amendment	08/25/2010
Amendment	11/22/2010
Amendment	01/04/2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Aurobindo Pharma Limited
Address:	Unit- VII (SEZ). Survey No. 411/P, 425/P. 434/P, 435/P & 458/P Plot No. S1 (Part) Special Economic Zone (Pharma) APIIC. Green Industrial Park, Polepally Village Jedcheria Mandal, Mahaboob Nagar (DT) Andhra Pradesh - 509 302, INDIA
Representative:	Ms. Blessy Johns Office: Aurobindo Pharma USA, Inc. 2400 Route 130 North, Dayton, NJ 08810
Telephone:	732-839-4380;
Cell:	908-240-1822
FAX:	732-355-9940

8. DRUG PRODUCT NAME/CODE/TYPE:

CMC Review Data Sheet

a) Proprietary Name: Lamivudine and Tenofovir Disoproxil Fumarate Tablets
b) Non-Proprietary Name: Lamivudine and Tenofovir Disoproxil Fumarate Tablets
c) Code Name/#: N/A
d) Chem. Type/Submission Priority:
- Chem. Type: 4
- Submission Priority: S

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

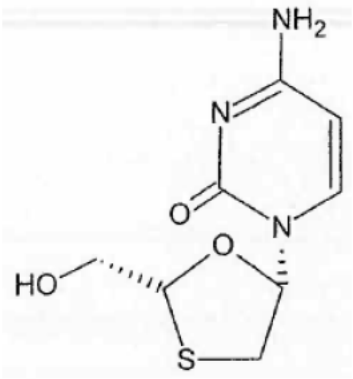
CAS Registry No [134678-17-4]

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**

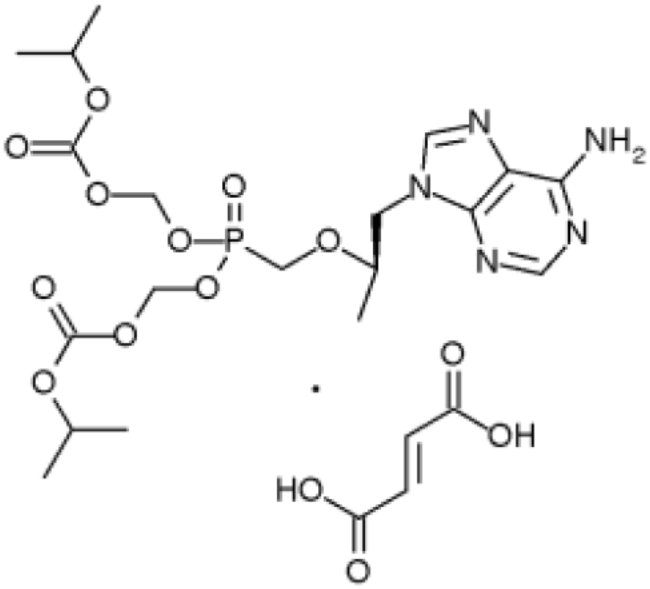
Chemical name (*R*)-5-{[2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl}-2,4,6,8- tetraoxa-5-phosphanonanedioic acid, bis(1-methylethyl) ester, 5-oxide, (*E*)-2-butenedioate (1:1)

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
(b) (4)	2	(b) (4)		1	Adequate	1/6/11 B. Rogers	LoA dated 11/18/2009
	2			3	Adequate		Reviewed 3/8/2010 by S. Bain
	4			N/A			
	4			N/A			
	4			N/A			
	3			N/A			
	3			N/A			
	3			N/A			
	3			N/A			
	3			N/A			
	3			N/A			
	3			N/A			
	3			N/A			
	3			N/A			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NO.	DESCRIPTION
NDA	21-356	Gilead VIREAD (Tenofovir DF, 300 mg) tablets
NDA	20-564	GSK EPIVIR (Lamivudine, 300 mg) tablets
NDA	22-141	Matrix Lamivudine/Tenofovir DF 300 mg/300 mg Tablets
NDA	22-459	Hetero Lamivudine/Tenofovir DF 300 mg/300 mg Tablets
NDA	200623	Cipla Lamivudine/Tenofovir DF 300 mg/300 mg Tablets

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	4/18/10	N/A
Pharm/Tox	N/A	N/A	N/A
Biopharm	Acceptable	8/25/10	J. Duan
LNC	N/A	N/A	N/A
Methods Validation	N/A, according to the current ONDQA policy	6/3/10	B. Rogers
DMETS	N/A	N/A	N/A
EA	Categorical exclusion (see review)		
Microbiology	N/A	N/A	N/A

The CMC Review for NDA 022344

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC standpoint, the NDA# 022344 is recommended for tentative approval. Deficiencies have been resolved pertaining to drug substance and drug product specifications, stability protocol, and quality of stability data. Manufacturing facilities have been determined to be acceptable.

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 Substances

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. (b) (4) 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 (b) (4) The CMC information is referenced to DMF (b) (4) to which an a LOA is provided. This DMF was reviewed previously by S. Bain and it was determined to be adequate (3/8/10). 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). It is manufactured at (b) (4) The CMC information was cross referenced to the applicant's DMF# (b) (4) and a LOA was provided. This DMF was reviewed on 1/5/11 and was determined to be adequate. 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 (b) (4) A retest period of (b) (4) months was proposed for lamivudine which is acceptable.

(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)

Manufacturing, release and stability testing of the drug product, Tenofovir Disoproxil Fumarate/Lamivudine tablets, will be conducted at Aurobindo Pharma Limited (b) (4)

The drug product is a blue colored, oval shaped, beveled edge, biconvex, film-coated tablet, debossed with "J" on one side and "27" on the other side. The tablets contain 300 mg of tenofovir disoproxil fumarate and 300 mg of lamivudine and have a total weight of 1066 mg. The tablets are packaged in a 30-count bottle with a CR closure (b) (4) hich may be stored for up to 24 months. Aurobindo employs a (b) (4) process for manufacturing of the tablets (b) (4) (b) (4)

The excipients are of USP/NF quality (b) (4) All excipients are well within limits specified in the FDA electronic inactive ingredient database or 21 CFR. (b) (4)

The tablets are packaged in one configuration for marketing: 30-count HDPE bottle with a CR closure (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. Although the applicant proposed the same stability specifications as release specifications, they have adopted separate specifications through our recommendation. All batches met the proposed specifications. The proposed expiration dating period of 24 months is acceptable (b) (4) (b) (4) on the basis of the 12 months long-term and 6 months accelerated stability data.

Final approved specifications and stability protocol/commitments are reproduced at the end of this review.

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 pediatric patients. The tablets are recommended to be stored at (b) (4)
The tablets have a proposed expiration dating period of 24 months 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, CMC Reviewer, Branch VI, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Stephen Miller, Acting Branch Chief, Branch V, ONDQA

C. CC Block: entered electronically in DFS

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/s/

BRIAN D ROGERS
01/07/2011

STEPHEN P MILLER
01/07/2011
I concur - this NDA is recommended for Tentative Approval from the CMC perspective

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**22-344**
Submission Date:	1/11/2010, 3/9/2010, 8/25/2010
Drug Name:	Lamivudine and Tenofovir DF Tablets, 300 mg/300 mg
Formulation:	Tablets
Strength:	300 mg/300 mg
Sponsor:	Aurobindo Pharma
Reviewer:	John Duan, Ph.D.
Submission Type:	Initial NDA

The current submission is for a fixed combination of lamivudine and tenofovir disoproxil fumarate 300mg/300mg tablets. Bioequivalence studies between the proposed product and the reference products (EPIVIR® Tablets (lamivudine tablets) 300 mg and VIREAD® (tenofovir disoproxil fumarate) Tablets 300 mg) were conducted, which will be reviewed by OCP. This review will focus on the in vitro release characteristics.

RECOMMENDATION

The proposed acceptance criteria should be revised. The following dissolution method and acceptance criteria are recommended. In a response dated 8/25/2010, the sponsor accepted the recommendation. Please have the sponsor amend the relevant part of the NDA.

Parameter	Value
Apparatus	Paddle (USP type II).
Rotating Speed	75 RPM
Medium	0.1 N Hydrochloric Acid.
Volume	900 mL
Temperature	37.0°± 0.5°C.
Specification	
Lamivudine	Not less than (b) (4)% (Q) of the labeled amount of Lamivudine is dissolved in 15 minutes.
Tenofovir Disoproxil Fumarate	Not less than % (Q) of the labeled amount of Tenofovir Disoproxil Fumarate is dissolved in 15 minutes.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 22344, Patrick Marroum, Angelica Dorantes, John Duan

COMMENTS

1. The current dissolution method and specification for Epivar 300 mg is as follows.

Parameter	Value
Apparatus	Paddle (USP type II).
Rotating Speed	75 RPM
Medium	0.1 N Hydrochloric Acid.
Volume	900 mL
Temperature	37.0°± 0.5°C.
Specification	Not less than (b) (4)% (Q) of the labeled amount of Lamivudine is dissolved in 15 minutes.

2. The current dissolution method and specification for Viread 300 mg is as follows.

Parameter	Value
Apparatus	Paddle (USP type II).
Rotating Speed	50 RPM
Medium	0.1 N Hydrochloric Acid.
Volume	900 mL
Temperature	37.0°± 0.5°C.
Specification	Not less than (b) (4)% (Q) of the labeled amount of Tenofovir Disoproxil Fumarate is dissolved in 30 minutes.

3. Based on the data provided (see Appendix), the following dissolution method and acceptance criteria are recommended.

Parameter	Value
Apparatus	Paddle (USP type II).
Rotating Speed	75 RPM
Medium	0.1 N Hydrochloric Acid.
Volume	900 mL
Temperature	37.0°± 0.5°C.
Specification	
Lamivudine	Not less than (b) (4)% (Q) of the labeled amount of Lamivudine is dissolved in 15 minutes.
Tenofovir Disoproxil Fumarate	Not less than (Q) of the labeled amount of Tenofovir Disoproxil Fumarate is dissolved in 15 minutes.

APPENDIX. Submission Summary

The drug product Lamivudine and Tenofovir Disoproxil Fumarate (DF) Tablets 300 mg/300 mg have been developed and will be manufactured, tested, and packaged by Aurobindo Pharma Limited. Both drug substances used to produce the NDA batches of drug product for Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg are manufactured (b) (4)

1. Drug product compositions

Formula Ingredients	Function	Qty in mg / tablet	Qty in % (w/w)
(b) (4)			

2. Solubility

Both lamivudine and tenofovir DF are water soluble (70 mg/mL in water at 20°C for lamivudine; 13.4 mg/ml in water at 25°C for tenofovir DF).

3. In-vitro dissolution

The dissolution method for Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg was referenced to similar products. The acceptance criterion for Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg was proposed as shown in the following table.

Parameter	Value
Medium	0.1 N Hydrochloric Acid.
Volume	900 mL
Temperature	37.0°± 0.5°C.
Apparatus	Paddle (USP type II).
Rotating Speed	75 RPM
Specification	
Lamivudine	Not less than (b) (4)% (Q) of the labeled amount of Lamivudine is dissolved in (b) (4) minutes.
Tenofovir Disoproxil Fumarate	Not less than (Q) of the labeled amount of Tenofovir Disoproxil Fumarate is dissolved in minutes.

4. Dissolution comparisons with mono entity

The following products were used for comparisons.

Product	Test	Reference
Product Name	Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg	EPIVIR® Tablets (lamivudine tablets) 300 mg and VIREAD® (tenofovir disoproxil fumarate) Tablets 300 mg
Manufacturer	Aurobindo Pharma Limited, India	GlaxoSmithKline and Gilead
Batch/Lot No.	LTSA09001	EPIVIR: 6H001; VIREAD: A171141D
Manufacture Date	May 2009	NA
Expiration Date	NA	EPIVIR: 8/2009;VIREAD: 2/2010
Strength	300mg/300mg	300mg/300mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b) (4)	
Production Batch Size		
Potency		
Content Uniformity (Mean, %CV)		
Administration Route	Oral	Oral

The in-vitro dissolution profiles for Lamivudine and Tenofovir Disoproxil Fumarate Tablets 300 mg/300 mg of sponsor's product are compared with those of EPIVIR® Tablets (lamivudine tablets) 300 mg of GlaxoSmithKline and VlREAD® Tablets (tenofovir disoproxil fumarate tablets) 300 mg of Gilead.

Dissolution conditions for the comparison are listed below

Medium: 1) 0.1N Hydrochloric acid
2) (b) (4)
3) (b) (4)
Volume: 900 mL
Apparatus: Apparatus II (Paddle)

Rotation: 75 rpm
Temperature: 37.0° ± 0.5°C
Sampling: (b) (4) 15 (b) (4) minutes

The comparison showed rapid dissolution in all three media. The following tables show the results of Lamivudine and Tenofovir in 0.1 N HCl for three lots.

(b) (4)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22344	ORIG-1	AUROBINDO PHARMA LTD	Lamivudine/Tenofovir Dixoproxil Fumarate FDC Tablets (300 mg/300)

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

/s/

JOHN Z DUAN
08/25/2010

PATRICK J MARROUM
08/25/2010