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DIVISION OF BIOEQUIVALENCE REVIEW OF PHARMACOKINETIC AND DISSOLUTION DATA

Drug Product Name	Bupropion Hydrochloride Extended Release Tablets (ANDA 077415)
Strength	300 mg
Applicant Name	Impax Laboratories, Inc.
Address	30831 Huntwood Avenue, Hayward, CA 94544
Submission Date of Submission Under Review	September 24, 2012
Reviewer	Division of Bioequivalence II
Study Number	A10-3574
Study Type	Fasting
Strength	300 mg
Clinical Site	Texas Tech University Health Science Center's (TTUHSC)
Clinical Site Address	Not reported
Analytical Site	Food & Drug Administration Center for Drug Evaluation and Research Office of Pharmaceutical Science Division of Product Quality Research, HFD-940
Analytical Site Address	White Oak Life Sciences Laboratory Bldg. 64 10903 New Hampshire Ave. Silver Spring, MD 20993-0002
OUTCOME DECISION	**UNACCEPTABLE**

1. Pharmacokinetic Results

Table 1. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table and Figure 1

Fasting Bioequivalence Study, Study No. A10-3574, N=24

Bupropion

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	1180.23	31.16	434.27	2043.88	1400.87	38.35	611.83	2633.15	0.84
AUCI	ng hr/mL	1501.35	27.71	824.68	2516.73	1743.46	32.39	974.59	2947.68	0.86
CMAX	ng/mL	86.61	32.28	47.20	148.12	120.51	47.65	53.69	278.39	0.72
TMAX	hr	4.00	.	1.00	6.00	5.00	.	3.00	8.00	0.80
KE	hr-1	0.02	56.05	0.00	0.05	0.02	65.73	0.00	0.05	1.10
THALF	hr	32.66	81.85	14.79	133.88	28.42	28.49	15.16	42.40	1.15

Hydroxy bupropion

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	18861.83	39.91	4475.54	30843.07	20636.35	31.68	5288.79	33786.42	0.91
AUCI	ng hr/mL	24397.18	42.98	4771.64	41207.05	27172.78	46.50	5586.78	72063.14	0.90
CMAX	ng/mL	432.24	37.24	114.80	722.63	505.02	29.84	181.40	792.62	0.86
TMAX	hr	16.00	.	6.00	24.00	12.00	.	5.00	24.00	1.33
KE	hr-1	0.03	31.35	0.01	0.05	0.03	34.61	0.01	0.05	0.95
THALF	hr	29.02	54.03	15.01	95.21	30.52	82.93	14.85	133.86	0.95

Erythro Bupropion

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	1192.10	35.63	547.37	2194.12	1239.50	32.90	604.05	2379.60	0.96
AUCI	ng hr/mL	1737.79	41.66	664.37	3697.84	1747.52	44.87	780.00	3668.76	0.99
CMAX	ng/mL	25.45	28.50	12.59	42.63	28.25	32.56	12.24	54.01	0.90
TMAX	hr	16.00	.	5.00	48.00	12.00	.	5.00	36.00	1.33
KE	hr-1	0.02	43.81	0.00	0.05	0.02	35.51	0.01	0.04	0.97
THALF	hr	38.21	66.31	12.74	140.73	33.91	39.90	15.82	72.36	1.13

Threo Bupropion

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	5624.61	42.93	2456.21	12318.90	5757.97	39.82	2514.91	12470.63	0.98
AUCI	ng hr/mL	9440.56	48.22	3982.88	21617.16	9608.45	54.44	3005.54	23812.58	0.98
CMAX	ng/mL	127.51	36.11	60.76	219.39	156.37	39.97	80.53	305.34	0.82
TMAX	hr	8.00	.	5.00	24.00	6.00	.	5.00	12.00	1.33
KE	hr-1	0.02	36.56	0.01	0.03	0.02	46.98	0.00	0.04	0.92
THALF	hr	53.54	42.36	26.49	107.76	52.09	49.93	19.39	139.40	1.03

Table 2. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Bupropion

Bupropion, 300 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. A10-3574, N=24					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1118.03	1304.10	0.86	76.71	95.82
AUC∞ (hr *ng/ml)	1395.75	1592.89	0.88	76.70	100.10
Cmax (ng/ml)	82.21	109.24	0.75	65.24	86.81

Hydroxy bupropion

Bupropion, 300 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. A10-3574, N=24					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	17122.04	19405.08	0.88	81.04	96.07
AUC∞ (hr *ng/ml)	21655.00	24618.93	0.88	78.18	98.97
Cmax (ng/ml)	398.35	480.90	0.83	76.46	89.73

Erythro Bupropion

Bupropion, 300 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. A10-3574, N=24					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1116.70	1177.31	0.95	85.84	104.81
AUC∞ (hr *ng/ml)	1589.87	1597.20	1.00	88.13	112.43
Cmax (ng/ml)	24.47	26.85	0.91	83.23	99.76

Threo Bupropion

Bupropion, 300 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. A10-3574, N=24					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	5186.32	5386.23	0.96	87.71	105.70
AUC∞ (hr *ng/ml)	8522.65	8466.23	1.01	90.77	111.64
Cmax (ng/ml)	120.10	146.18	0.82	73.82	91.43

Table 3. Additional Study Information, Fasting Study

Bupropion

Root mean square error, AUC0-t	0.2244	
Root mean square error, AUC∞	0.2022	
Root mean square error, Cmax	0.2882	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	17	17
Do you agree or disagree with this decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	17	0.88	0.56	0.95
Reference	17	0.89	0.81	0.97

Hydroxy bupropion

Root mean square error, AUC0-t	0.1716			
Root mean square error, AUC∞	0.2378			
Root mean square error, Cmax	0.1614			
	Test	**Reference**		
Kel and AUC∞ determined for how many subjects?	24	24		
Do you agree or disagree with this decision?	Agree	Agree		
Indicate the number of subjects with the following:				
measurable drug concentrations at 0 hr	0	0		
first measurable drug concentration as Cmax	0	0		
Were the subjects dosed as more than one group?	No	No		
Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	24	0.80	0.46	0.94
Reference	24	0.81	0.29	0.95

Erythro Bupropion

Root mean square error, AUC0-t	0.2013			
Root mean square error, AUC∞	0.2456			
Root mean square error, Cmax	0.1827			
	Test	**Reference**		
Kel and AUC∞ determined for how many subjects?	24	24		
Do you agree or disagree with this decision?	Agree	Agree		
Indicate the number of subjects with the following:				
measurable drug concentrations at 0 hr	0	0		
first measurable drug concentration as Cmax	0	0		
Were the subjects dosed as more than one group?	No	No		
Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	24	0.72	0.30	0.92
Reference	24	0.75	0.50	0.92

Threo bupropion

Root mean square error, AUC0-t	0.1882			
Root mean square error, AUC∞	0.2088			
Root mean square error, Cmax	0.2157			
	Test	**Reference**		
Kel and AUC∞ determined for how many subjects?	24	24		
Do you agree or disagree with this decision?	Agree	Agree		
Indicate the number of subjects with the following:				
measurable drug concentrations at 0 hr	0	0		
first measurable drug concentration as Cmax	0	0		
Were the subjects dosed as more than one group?	No	No		
Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	24	0.62	0.39	0.85
Reference	24	0.65	0.32	0.87

Comments on Pharmacokinetic and Statistical Analysis:

The 90% confidence intervals for bupropion of ln-transformed AUC_t, AUC_i, and C_{max} ratios are not within the acceptable limits of 80-125%.

Although the 90% confidence intervals for hydroxy-bupropion of ln-transformed AUC_t and AUC_i ratios are within the acceptable limits of 80-125%, the 90% confidence interval of ln-transformed C_{max} ratio is not within the acceptable limits of 80-125%.

The 90% confidence intervals for erythro bupropion of ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

Although the 90% confidence intervals for threo bupropion of ln-transformed AUC_t and AUC_i ratios are within the acceptable limits of 80-125%, the 90% confidence interval of ln-transformed C_{max} ratio is not within the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting BE study is unacceptable.

Table 4. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Bupropion

	Test (n=24)		Reference (n=24)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.01	321.58	0.01	292.48	0.84
1.00	42.87	58.61	0.29	422.59	147.49
2.00	65.34	50.14	14.33	217.56	4.56
3.00	73.25	37.86	61.72	83.96	1.19
4.00	75.59	38.40	90.57	54.89	0.83
5.00	69.14	38.02	97.64	33.30	0.71
6.00	56.50	45.80	91.23	54.95	0.62
8.00	41.09	38.36	69.25	42.57	0.59
12.00	35.08	29.16	47.48	44.69	0.74
16.00	27.61	32.18	29.62	49.26	0.93
24.00	15.45	35.11	19.02	51.06	0.81
36.00	7.02	47.56	9.09	49.17	0.77
48.00	5.06	56.91	6.14	56.25	0.82
60.00	3.17	77.16	3.68	77.67	0.86
72.00	2.20	92.65	2.57	98.16	0.86

Hydroxy Bupropion

	Test (n=24)		Reference (n=24)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	73.27	60.32	0.59	489.90	123.92
2.00	160.29	46.10	17.97	160.89	8.92
3.00	240.91	39.23	123.67	73.25	1.95
4.00	309.85	32.49	243.60	45.82	1.27
5.00	347.49	35.93	342.22	39.66	1.02
6.00	378.55	38.99	396.73	31.88	0.95
8.00	379.25	35.48	449.34	32.98	0.84
12.00	384.40	34.59	469.09	33.36	0.82
16.00	375.04	39.15	446.42	29.91	0.84
24.00	374.45	42.43	417.25	37.14	0.90
36.00	282.06	40.50	302.48	38.32	0.93
48.00	224.07	49.89	243.38	42.84	0.92
60.00	149.69	51.14	161.72	41.87	0.93
72.00	121.78	55.63	124.47	48.10	0.98

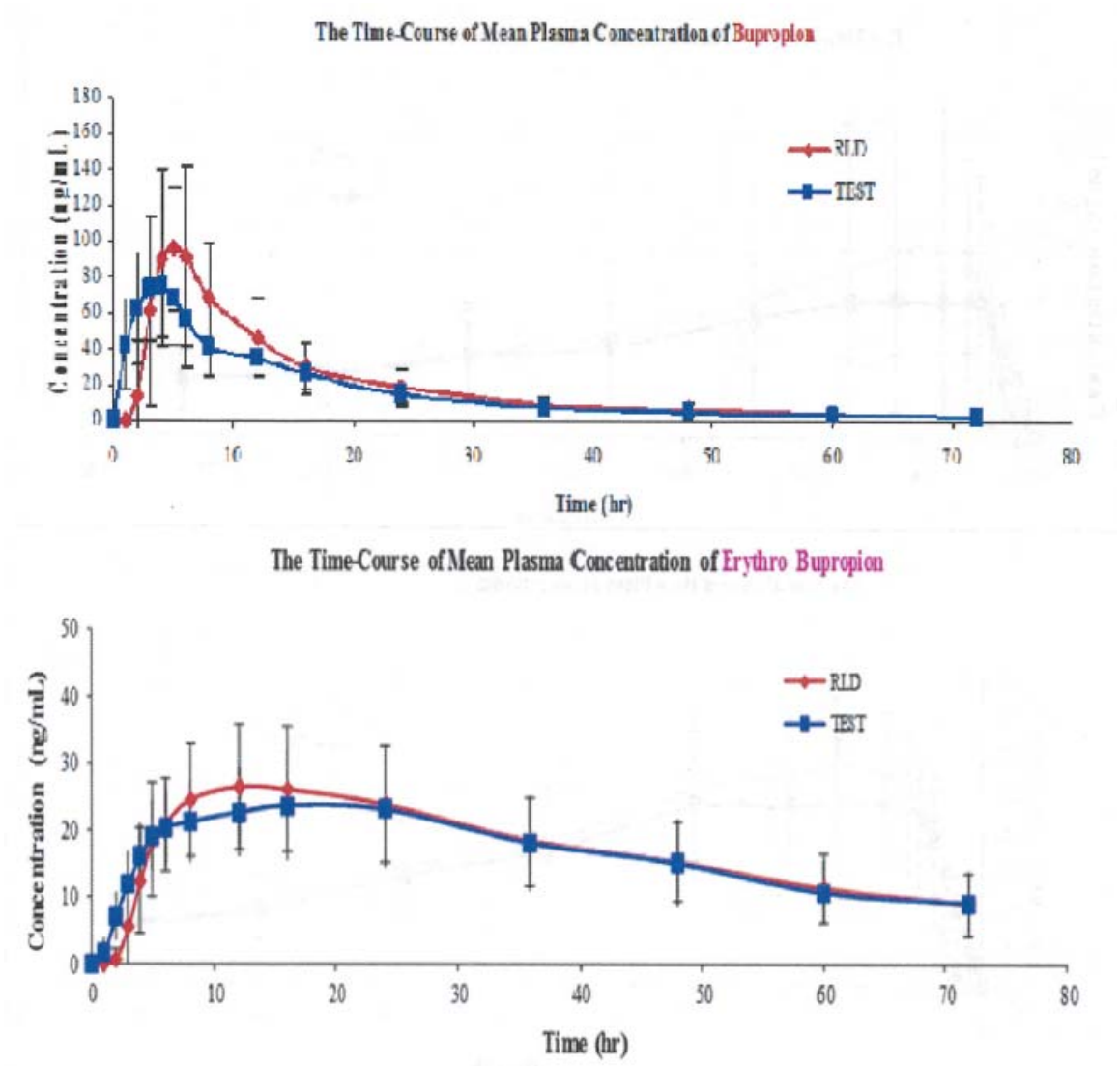
Erythro Bupropion

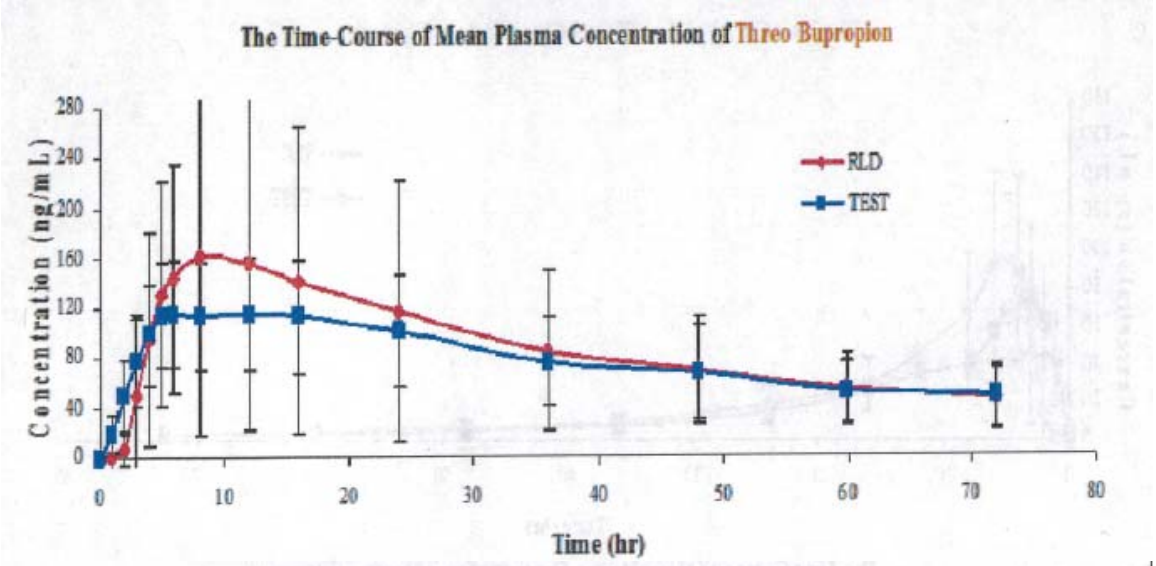
	Test (n=24)		Reference (n=24)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	489.90	0.00	.	.
1.00	1.54	148.27	0.00	.	.
2.00	7.22	48.50	0.60	259.76	12.09
3.00	12.02	38.29	5.60	102.61	2.15
4.00	15.98	30.08	12.34	63.91	1.29
5.00	19.10	27.39	18.64	44.48	1.02
6.00	20.35	27.11	20.72	32.90	0.98
8.00	21.19	29.02	24.47	33.83	0.87
12.00	22.65	28.90	26.71	32.80	0.85
16.00	23.90	32.62	26.04	35.65	0.92
24.00	23.35	34.39	24.37	31.98	0.96
36.00	17.70	40.43	18.51	34.13	0.96
48.00	15.08	43.05	15.04	36.58	1.00
60.00	10.71	43.34	11.16	44.74	0.96
72.00	9.08	53.75	9.08	50.14	1.00

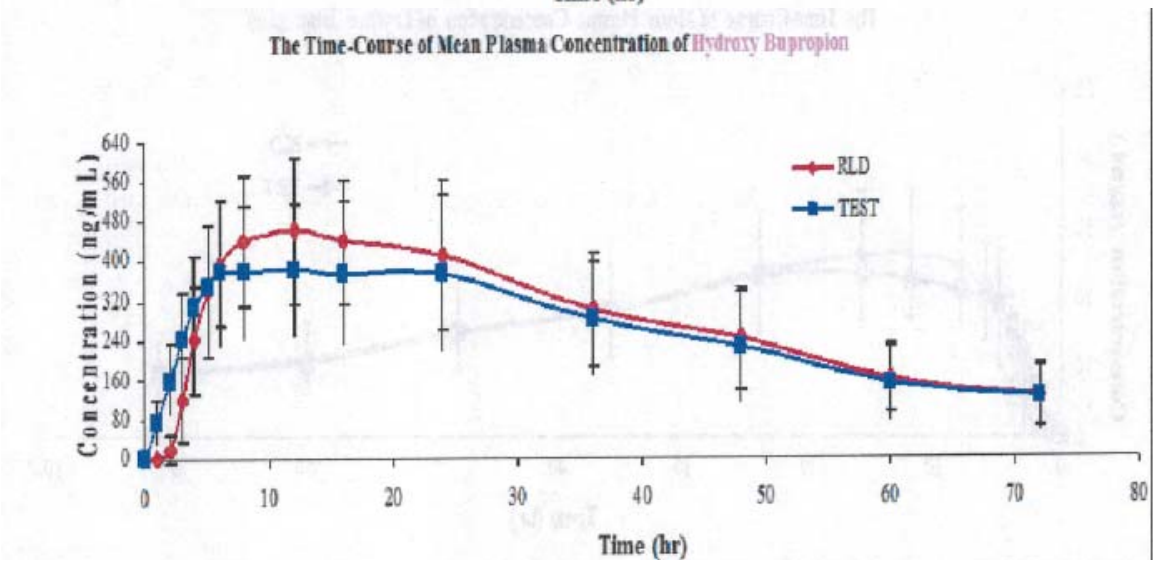
Threo Bupropion

	Test (n=24)		Reference (n=24)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.24	435.42	0.01	426.11	18.15
1.00	19.06	84.86	0.04	317.81	482.15
2.00	50.44	57.53	5.54	237.36	9.10
3.00	78.05	48.07	41.37	98.08	1.89
4.00	98.90	41.42	83.39	67.26	1.19
5.00	113.73	36.95	118.34	47.78	0.96
6.00	114.69	37.15	129.64	36.82	0.88
8.00	113.50	37.76	140.53	42.49	0.81
12.00	114.56	38.70	136.73	44.27	0.84
16.00	112.66	40.87	125.88	46.86	0.89
24.00	101.54	43.84	102.52	44.25	0.99
36.00	76.17	45.55	76.71	40.93	0.99
48.00	66.83	56.99	63.68	39.08	1.05
60.00	51.06	48.40	51.12	43.33	1.00
72.00	47.55	53.21	44.64	49.15	1.07

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study




The Time-Course of Mean Plasma Concentration of Threo Bupropion
Concentration (ng/mL)
280
240
200
160
120
80
40
0
0
10
20
30
40
50
60
70
80
Time (hr)
RLD
TEST


The Time-Course of Mean Plasma Concentration of Hydroxy Bupropion
Concentration (ng/mL)
640
560
480
400
320
240
160
80
0
0
10
20
30
40
50
60
70
80
Time (hr)
RLD
TEST

2. Dissolution Data

On 10/12/2006, in the course of its review of ANDA 077415, the Agency acknowledged the following dissolution method and specifications:

> The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP Apparatus I (basket) at 75 rpm. The test products should meet the following specifications:
>
> 1 hr: 15-35%
> 2 hrs: 25-50%
> 4 hrs: 40-65%
> 8 hrs: 65-90%
> 12 hrs: NLT 80% dissolved

In the current report, the dissolution testing using the above dissolution method was conducted comparing test and reference products (Budeprion XL Tablets, 300 mg versus Wellbutrin XL Tablets, 300 mg). The dissolution testing data are summarized below.

Table 1. Dissolution Data

Dissolution Data for Budeprion XL Tablets at 2 hr.

Test	Specification	Budeprion XL	
Dissolution:			
Wavelength	USP @ 252 nm:	@ 252nm	@ 298nm
% Released at 2 hr.	NMT 20%		
Vessel #1	FDA Approved	32.91	33.91
#2	@ 298nm:	33.29	33.91
#3	25-50%	33.14	33.80
#4		33.67	34.19
#5		33.15	33.69
#6		33.06	33.80
Mean		**33.20**	**33.88**
Min		32.91	33.69
Max		33.67	34.19
SD		0.26	0.17
% CV		0.78	0.51

Dissolution Data for Budeprion XL Tablets at 4 hr.

Test	Specification	Budeprion XL	
Dissolution: **Wavelength** **% Released at 4 hr.**	USP @ 252 nm: 20-45%	@ 252nm	@ 298nm
Vessel #1	FDA Approved	49.25	50.37
#2	@ 298nm:	49.57	50.31
#3	40-65%	49.52	50.20
#4		49.90	50.54
#5		49.37	50.09
#6		49.55	50.48
Mean		**49.53**	**50.33**
Min		49.25	50.09
Max		49.90	50.54
SD		0.22	0.17
% CV		0.45	0.34

Dissolution Data for Budeprion XL Tablets at 8 hr.

Test	Specification	Budeprion XL	
Dissolution:			
Wavelength	USP @ 252 nm:	@ 252nm	@ 298nm
% Released at 8 hr.	65-90%		
Vessel #1	FDA Approved	71.92	72.99
#2	@ 298nm:	71.82	72.65
#3	65-90%	72.22	72.93
#4		72.20	72.82
#5		71.93	72.76
#6		72.02	72.87
Mean		**72.02**	**72.84**
Min		71.82	72.65
Max		72.22	72.99
SD		0.16	0.12
% CV		0.22	0.17

Dissolution Data for Budeprion XL Tablets at 16 hr.

Test	Specification	Budeprion XL	
Dissolution:			
Wavelength	USP @ 252	@ 252nm	@ 298nm
% Released at 16 hr.	nm:		
	NLT 80%		
Vessel #1		97.67	98.89
#2	FDA Approved	96.09	96.92
#3	@ 298nm:	97.77	98.72
#4	12 hrs: NLT	96.96	97.99
#5	80%	97.20	97.99
#6		97.38	98.38
Mean		**97.18**	**98.15**
Min		96.09	96.92
Max		97.77	98.89
SD		0.61	0.71
% CV		0.63	0.72

Dissolution Data for Wellbutrin XL Tablets at 2hr.

Test	Specification	Wellbutrin XL	
Dissolution:			
Wavelength	USP @ 252nm:	@ 252nm	@ 298nm
% Released at 2 hr.	NMT 20%		
Vessel #1		6.17	6.36
#2		1.58	1.67
#3	FDA Approved	6.95	6.92
#4	@ 252 nm:	5.62	5.69
#5	NMT 20%	1.90	1.95
#6		3.91	3.96
Mean		**4.36**	**4.43**
Min		1.58	1.67
Max		6.95	6.92
SD		2.26	2.26
% CV		51.91	51.04

Dissolution Data for Wellbutrin XL Tablets at 4hr.

Test	Specification	Wellbutrin XL	
Dissolution:			
Wavelength	USP @ 252 nm:	@ 252nm	@ 298nm
% Released at 4 hr.	20-45%		
Vessel #1	FDA Approved	34.79	34.61
#2	@ 252 nm:	24.66	24.62
#3	20-45%	34.67	34.61
#4		30.99	31.02
#5		26.57	26.64
#6		32.68	32.64
Mean		**30.73**	**30.69**
Min		24.66	24.62
Max		34.79	34.61
SD		4.24	4.19
% CV		13.81	13.66

Dissolution Data for Wellbutrin XL Tablets at 8hr.

Test	Specification	Wellbutrin XL	
Dissolution:			
Wavelength	USP @ 252 nm:	@ 252nm	@ 298nm
% Released at 8 hr.	65-90%		
Vessel #1	FDA Approved	78.03	77.69
#2	@ 252 nm:	76.01	75.83
#3	[redacted]%	74.30	74.15
#4		71.19	71.07
#5		71.90	71.74
#6		77.95	77.80
Mean		**74.90**	**74.71**
Min		71.19	71.07
Max		78.03	77.80
SD		2.95	2.90
% CV		3.94	3.88

Dissolution Data for Wellbutrin XL Tablets at 16hr.

Test	Specification	Wellbutrin XL	
Dissolution:			
Wavelength	USP @ 252 nm:	@ 252nm	@ 298nm
% Released at 16 hr.	NLT 80%		
Vessel #1	FDA Approved	101.22	101.19
#2	@ 252 nm:	102.76	102.71
#3	NLT 80%	101.11	101.14
#4		99.03	99.11
#5		101.50	101.64
#6		102.52	102.71
Mean		**101.36**	**101.42**
Min		99.03	99.11
Max		102.76	102.71
SD		1.33	1.33
% CV		1.31	1.31

Figure 2. Dissolution Profiles