CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-824

BIOEQUIVALENCE REVIEW

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-824
Reviewer: James E. Chaney
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Roxane Laboratories
Columbus, Ohio
Submission Date:
March 24, 2000

Review of In Vitro Data and Waiver Request

1. Introduction:

The demonstration of bioequivalence of aqueous solution nasal sprays may be accomplished based on: a) Q1 and Q2 sameness of the generic and innovator formulations, and b) equivalent *in vitro* performance of the test product to the reference product.

The comparative performance of the drug delivery devices of the test and reference products may be based on the following tests:

Unit Dose/Content Uniformity
Spray Pattern
Plume Geometry
Droplet Size Distribution by at least two methods
Priming, Loss of Prime, and Tail-Off

The firm has submitted comparative formulation data of its proposed test product and the reference listed drug Stadol® Nasal Spray, 10 mg/mL. The firm conducted comparative *in vitro* testing on the following parameters: unit dose/ content uniformity, spray pattern, plume geometry, droplet size distribution (laser diffraction and cascade impactor), priming, re-priming and tailing-off.

2. Background:

Butorphanol Tartrate Nasal Spray, 10 mg/mL, is indicated for the management of pain when the use of an opioid analgesic is appropriate. The reference listed drug is Stadol®, nasal solution (Bristol-Myers) which is administered using a manual metering device. The product is marketed as a solution provided in 2.5 mL fill bottles. Following priming a bottle delivers 14-15 sprays (100 µL/spray, 1 mg/spray). The drug exerts *in vivo* effect(s) through the systemic circulation following absorption from the nasal cavity.

3. Formulations: (Not to be released under FOI)

Comparative formulations of the reference and the proposed test product are given in Table 1. Based on the data submitted by the sponsor, composition of the proposed test product is qualitatively and quantitatively the same as in the reference product.

4. Drug Products:

Test: Roxane's Butorphanol Nasal Spray, 10 mg/mL. Batch # 999001A of the solution formulation was used for all three sub-lots. Batch size was [redacted] commercial scale, [redacted] which yielded [redacted]. Solution manufactured March 1, 1999; proposed expiration dating is 24 months. The sub-lot numbers were V203079500, V203830900 and V204011600 corresponding to different pumps.

Reference: Bristol-Meyers Squibb's Stadol NS®, 10 mg/mL; Lots 9F10028, 9F13540 and 9F15910. For the reference product, it is not known if the drug product and/or valves are from the same or different lots.

Comparability of Spray Devices

[redacted] developed and provided a nasal spray pump to Roxane Laboratories which was identical to that of the innovator product with the exception of a different [redacted] was used in the test product instead of the [redacted], the exact details of which have not been disclosed to Roxane due to confidentiality reasons. [redacted] no longer offers the innovator's [redacted] formulation as a standard pharmaceutical [redacted]

Drawings of the nasal pump were included in the submission (Section XIII, Attachment XIIIe, pp 1095-1119 of Vol. 5).

5. Procedures and Information Applicable to All Tests

All actuations of the nasal spray products were done using an automatic actuator to actuate the nasal sprays in a reproducible manner. The actuator was a proprietary unit designed by [redacted] for nasal spray actuation. The force used for actuation of the nasal sprays was specified at [redacted] by the sponsor. The Roxane samples consisted of one lot of the drug solution formulation and three lots of pumps. The pumps were assembled onto the bottles at time of testing for both the Roxane product and the Reference product.

For each *in-vitro* test ten (10) units from each of the three sub-lots of the test product and each of the three lots of the reference product were tested. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested.

6. Unit Dose and Uniformity Of Unit Dose

6.1 Sampling Procedure

For the content uniformity portion of the bioequivalency study, 10 units from each lot of product were tested. The data sequence for the content uniformity testing was to record individual actuation weights for actuations 1 through 10 and 21 through 23. Actuations 7 through 10 and 21 through 23 were collected for [redacted] assay. The [redacted] assay values for actuations 8 and 21 were the data sources used to evaluate content uniformity of the product. Analytical method validation data shows that the [redacted] method is linear, selective, accurate, precise (%CV=0.1%) and rugged. The assay is free from interference due to excipients, degradation products and related compounds of the proposed formulation. The assay of butorphanol tartrate has a range [redacted] of the normal assay concentration of 1.0 mg/mL butorphanol (LOQ = [redacted]

6.2 Results

The firm reported content uniformity summary results only for actuations 8 and 21. See Table 2 for the summary data for actuations 8, 9 and 23 as calculated by the reviewer . Overall variability (%CV) and range of within lot %CV's are presented in Table 3.

Comments:

- The firm reported "Beginning" as Actuation # 8 in its summary data. The reviewer calculated summary data for actuation # 9 in addition to # 8 because the patient instructions recommend priming until a fine spray appears (up to 7 to 8 strokes). The reviewer's calculations provided grand mean (N=30) values in addition to mean values for lots. The firm had reported only mean values for lots in its summary data (N=10). The reviewer's means agree with firm's means (N=10).

- Also, the reviewer did the calculations for actuation # 23 that would correspond to the 15th actuation from actuation # 9 in that a bottle delivers 14-15 sprays per the labeling.
- The minimum and maximum values for the test and reference products show that the delivered doses fall within 88-113% of the labeled dose. The draft guidance recommends that based on the 'first tier' of testing (10 units), not more than one unit be outside of the label claim, and none should be outside the
- The differences in the test and reference products at actuation #9 (beginning of unit life) and actuation #23 (end of unit life) are not statistically significant, and the differences in mean (N=30) values are less than or equal to 2.1%. The difference between the test and reference products at actuation #8 (beginning of unit life) is statistically significant. However, the difference in the mean (N=30) values between test and reference is only 1.7%.
- The overall variability and within lot variability are very low and similar for the test and reference products (5.9 %CV or less, Table 3).

7. Spray Pattern

7.1 Method

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6.

15. Recommendation:

The waiver request of *in vivo* bioequivalence requirements for the test product, Roxane Laboratories on its Butorphanol Tartrate Nasal Spray Pump, 10 mg/mL, is denied due to the reasons cited in the above deficiencies.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

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FT INITIALED YCHuang /S/ ate 11/16/2000

for Concur: /S/ Date 11/29/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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Table 1. Formulation (mg/mL), [NOT TO BE RELEASED UNDER FOI]		
Ingredient	**Test**	**Reference**
Butorphanol Tartrate	10	10
Sodium Chloride	[redacted]	[redacted]
Citric Acid	[redacted]	[redacted]
Benzethonium Chloride	[redacted]	[redacted]
Sodium Hydroxide	Adjust pH	Adjust pH
Hydrochloric Acid	Adjust pH	Adjust pH
Water, Purified	Q.S.	Q.S.
PH	5	5

Table 2. Content Uniformity (mg Delivered/Actuation)								
	Statistic	**N**	**Test (mg/Spray)**		**Reference (mg/Spray)**		**T/R**	***P***
			Sub-Lot #	Mean	Lot #	Mean		
Beginning (Spray #8)		10	V203079500	1.039	9F10028	1.053	0.986	
		10	V203830900	1.034	9F13540	1.074	0.963	
		10	204011600	1.078	9F15910	1.078	1.000	
	Grand Mean	30		1.050		1.068	0.983	*0.040*
	%CV	30		4.8		2.8		
	Min	30		[redacted]		[redacted]		
	Max	30		[redacted]		[redacted]		
Beginning (Spray #9)		10	V203079500	1.026	9F10028	1.068	0.961	
		10	V203830900	1.032	9F13540	1.046	0.987	
		10	204011600	1.088	9F15910	1.085	1.002	
	Grand Mean	30		1.049		1.066	0.983	*0.068*
	%CV	30		4.7		4.5		
	Min	30		[redacted]		[redacted]		
	Max	30		[redacted]		[redacted]		
End (Spray #23)		10	V203079500	1.061	9F10028	1.069	0.992	
		10	V203830900	1.039	9F13540	1.077	0.964	
		10	204011600	1.050	9F15910	1.072	0.980	
	Grand Mean	30		1.050		1.073	0.979	*0.434*
	%CV	30		4.0		3.8		
	Min	30		[redacted]		[redacted]		
	Max	30		[redacted]		[redacted]		

Table 3. Overall Variability (%CV) and Range of Within Lot Variability (%CV) from Content Uniformity Data.		
	Overall Variability	**Range of Within Lot %CV's**
Test	4.0-4.8	1.2-6.3
Reference	2.8-4.5	1.4-5.9

Table 4. Spray Pattern Testing Data: Calculated from the Pattern Center (N=30)						
Distance (cm)	Stage	Product	Statistic	Dmax (mm)	Dmin (mm)	Ovality Ratio
3	Begin	Test	Mean	37.510	32.859	1.147
			%CV	7.8	9.1	8.4
		Reference	Mean	35.904	31.278	1.159
			%CV	10.0	8.6	16.6
			T/R	1.045	1.051	0.990
			P	*0.02393*	*0.00575*	*0.38019*
	End	Test	Mean	38.414	34.386	1.121
			%CV	8.3	10.2	5.8
		Reference	Mean	36.345	32.200	1.136
			%CV	9.8	8.6	13.6
			T/R	1.057	1.068	0.987
			P	*0.00452*	*0.00241*	*0.29922*
4	Begin	Test	Mean	45.660	37.728	1.214
			%CV	9.3	8.9	8.8
		Reference	Mean	41.304	34.162	1.223
			%CV	12.9	10.2	19.5
			T/R	1.105	1.104	0.993
			P	*0.00055*	*0.00011*	*0.42132*
	End	Test	Mean	46.282	38.705	1.199
			%CV	8.9	8.5	8.1
		Reference	Mean	42.336	35.455	1.212
			%CV	12.1	11.3	20.2
			T/R	1.093	1.092	0.990
			P	*0.00066*	*0.00121*	*0.39316*
5	Begin	Test	Mean	54.670	43.265	1.266
			%CV	11.2	7.3	10.6
		Reference	Mean	48.037	37.455	1.305
			%CV	15.3	14.6	21.9
			T/R	1.138	1.155	0.970
			P	*0.00008*	*0.00000*	*0.22806*
	End	Test	Mean	55.927	44.913	1.249
			%CV	11.1	10.1	9.1
		Reference	Mean	49.141	39.039	1.284
			%CV	13.8	11.9	23.6
			T/R	1.138	1.150	0.973
			P	*0.00011*	*0.00003*	*0.27083*

Table 5. Overall Variability (%CV) and Range of Within Lot Variability (%CV) From Spray Pattern Data.						
	Overall Variability			Range of Within Lot %CV's		
	Dmax	Dmin	Ovality	Dmax	Dmin	Ovality
Test	7.8-11.2	7.3-10.2	5.8-10.6	3.0-14.6	4.0-12.6	2.9-12.3
Reference	7.8-15.3	8.6-14.6	13.6-23.6	6.6-21.0	5.0-16.2	5.4-28.0

Table 6. Plume Geometry Data (N=30)						
Time (ms)	**View**	**Product**	**Statistic**	**Length (cm)**	**Width (cm)**	**Angle (°)**
20	Front	Test	Mean	15.59	11.26	60.9
			%CV	9.9	13.9	10.9
		Reference	Mean	15.55	10.49	58.5
			%CV	14.3	13.5	10.3
			T/R	1.003	1.074	1.041
			p	*0.470*	*0.024*	*0.072*
	Side	Test	Mean	15.33	11.55	61.5
			%CV	10.4	12.9	10.0
		Reference	Mean	15.557	10.21	58.5
			%CV	13.7	13.4	7.2
			T/R	0.985	1.131	1.051
			p	*0.332*	*0.002*	*0.020*
75	Front	Test	Mean	28.18	16.49	54.6
			%CV	7.2	14.4	13.4
		Reference	Mean	28.63	15.66	50.7
			%CV	7.1	14.0	14.6
			T/R	0.984	1.053	1.076
			p	*0.208*	*0.095*	*0.026*
	Side	Test	Mean	28.19	16.75	54.0
			%CV	7.1	12.6	13.4
		Reference	Mean	28.86	15.32	51.2
			%CV	8.6	12.3	15.5
			T/R	0.977	1.094	1.056
			P	*0.146*	*0.009*	*0.078*
150	Front	Test	Mean	37.33	18.56	54.3
			%CV	8.0	12.9	13.8
		Reference	Mean	38.58	17.24	49.8
			%CV	4.5	13.3	11.7
			T/R	0.967	1.077	1.090
			P	*0.027*	*0.026*	*0.013*
	Side	Test	Mean	36.97	18.88	54.6
			%CV	7.1	11.7	13.0
		Reference	Mean	38.56	17.10	50.3
			%CV	5.0	10.0	9.3
			T/R	0.959	1.105	1.085
			P	*0.006*	*0.004*	*0.009*

Table 7. Overall Variability (%CV) and Range of Within Lot Variability (%CV) From Plume Geometry Data.						
	Overall Variability			Range of Within Lot %CV's		
	Length	Width	Angle	Length	Width	Angle
Test	7.1-10.4	11.7-14.4	10.0-13.8	5.8-11.7	5.4-16.9	7.0-17.1
Reference	4.5-14.3	10.0-14.0	7.2-15.5	3.4-19.6	5.3-17.5	4.9-19.3

Table 8. Firm's Reported Plume Geometry Data for Test Product

Butorphanol Tartrate Summary						
	Plume angle, 20 ms		Plume length, 75 ms		Plume Width, 75 ms	
Pump Number	Front	Side	Front	Side	Front	Side
V204011600 Average	63.5	63.8	28.5	28.3	17.4	18.4
%RSD	8.7	9.5	8.7	7.4	9.0	10.0
V203079500 Average	59.6	61.4	28.6	28.8	15.0	15.4
%RSD	9.7	7.0	6.8	7.6	12.7	5.4
V203830900 Average	59.7	59.3	27.4	27.5	17.1	16.4
%RSD	13.9	12.7	5.8	5.8	16.9	13.6

Table 9. Firm's Reported Plume Geometry Data for Reference Product

Stadol NS Summary						
	Plume angle, 20 ms		Plume length, 75 ms		Plume width, 75 ms	
Lot Number	Front	Side	Front	Side	Front	Side
9F13540 Average	56.3	58.1	29.7	29.4	14.9	15.5
%RSD	7.9	4.9	5.6	4.0	12.1	9.7
9F15910 Average	58.7	57.9	27.8	27.9	15.1	14.3
%RSD	14.4	10.5	8.3	13.1	17.5	11.9
9F10028 Average	60.6	59.6	28.5	29.4	17.0	16.1
%RSD	6.7	5.6	6.1	6.2	9.0	13.1

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Table 10. Droplet Size Distribution Determined By [illegible] Diffraction At Beginning, Middle And End Stages (N=30).

Stage of Unit Life	Distance (cm)	Delay Time (ms)	D_{50}						SPAN					
			Test		Reference				Test		Reference			
			Mean	%CV	Mean	%CV	T/R	*p*	Mean	%CV	Mean	%CV	T/R	*p*
Begin	1	15	53.08	15.2	57.28	12.9	0.93	0.026	1.64	6.0	1.72	9.9	0.95	0.012
Begin	1	45	59.81	12.0	64.91	18.6	0.92	0.025	1.53	5.8	1.63	9.2	0.94	0.004
Begin	1	75	72.95	39.3	70.61	27.3	1.03	0.364	1.54	9.7	1.67	18.2	0.92	0.021
Begin	3	15	45.24	15.3	46.71	14.5	0.97	0.209	1.65	6.3	1.71	25.1	0.96	0.232
Begin	3	45	50.33	13.2	54.42	13.4	0.92	0.016	1.60	4.4	1.62	24.1	0.98	0.348
Begin	3	75	66.02	45.4	63.92	28.4	1.03	0.385	1.57	6.8	1.58	9.1	0.99	0.325
Begin	5	15	40.76	12.6	43.92	9.9	0.93	0.003	1.45	11.1	1.44	14.4	1.00	0.469
Begin	5	45	46.35	12.9	51.95	11.2	0.89	0.000	1.37	10.3	1.36	11.8	1.01	0.368
Begin	5	75	58.20	43.8	64.40	42.4	0.90	0.207	1.46	12.4	1.45	22.2	1.01	0.447
Mean Begin Stage			**54.75**	**19.1**	**57.57**	**15.7**	**0.95**	**--**	**1.53**	**6.1**	**1.58**	**8.3**	**0.97**	**--**
Middle	1	15	51.57	13.5	57.04	15.5	0.90	0.009	1.62	4.8	1.94	47.8	0.83	0.033
Middle	1	45	57.93	13.2	61.94	12.3	0.94	0.032	1.53	4.4	1.71	19.2	0.90	0.004
Middle	1	75	62.08	11.7	65.14	12.9	0.95	0.073	1.53	3.6	1.86	45.7	0.82	0.023
Middle	3	15	42.14	14.6	45.83	14.4	0.92	0.004	1.66	6.1	1.64	14.8	1.01	0.408
Middle	3	45	49.62	17.0	52.47	13.6	0.95	0.049	1.56	6.3	1.55	7.2	1.01	0.231
Middle	3	75	56.47	19.5	57.22	13.2	0.99	0.370	1.56	6.4	1.50	7.5	1.04	0.011
Middle	5	15	41.76	11.2	44.51	14.3	0.94	0.033	1.49	10.3	1.49	23.0	1.01	0.453
Middle	5	45	48.27	11.2	51.80	11.9	0.93	0.007	1.40	11.1	1.38	24.3	1.01	0.408
Middle	5	75	53.10	27.8	55.81	11.8	0.95	0.163	1.43	15.0	1.42	21.2	1.01	0.419
Mean Middle Stage			**51.44**	**13.3**	**54.64**	**12.5**	**0.94**	**--**	**1.53**	**5.4**	**1.61**	**12.1**	**0.95**	**--**
End	1	15	52.49	10.9	58.10	16.1	0.90	0.002	1.63	5.5	2.10	52.4	0.78	0.013
End	1	45	58.44	11.1	63.75	15.9	0.92	0.009	1.56	5.6	1.76	29.9	0.89	0.022
End	1	75	68.01	57.5	67.22	17.1	1.01	0.457	1.55	7.4	1.72	27.7	0.90	0.029
End	3	15	44.63	15.0	47.32	18.4	0.94	0.096	1.64	7.1	1.75	17.1	0.94	0.025
End	3	45	50.79	14.8	54.01	16.7	0.94	0.076	1.56	7.1	1.62	12.4	0.97	0.094
End	3	75	58.35	25.3	58.98	16.6	0.99	0.428	1.59	9.4	1.58	10.6	1.01	0.360
End	5	15	41.41	11.5	42.14	11.5	0.98	0.291	1.53	7.1	1.56	17.0	0.98	0.271
End	5	45	48.19	13.6	50.05	12.5	0.96	0.155	1.42	6.2	1.48	23.4	0.96	0.221
End	5	75	57.77	51.2	53.84	11.4	1.07	0.239	1.45	11.5	1.50	25.7	0.97	0.291
Mean End Stage			**53.34**	**15.4**	**55.05**	**14.4**	**0.97**	**--**	**1.55**	**4.7**	**1.67**	**11.4**	**0.93**	**--**

Table 11. Overall Variability (%CV) and Range of Within Lot Variability (%CV) From Droplet Size Distribution Determined by ' [illegible] at Beginning, Middle and End Stages.				
	Overall Variability		Range of Within Lot %CV's	
	D_{50}	SPAN	D_{50}	SPAN
Test	10.9-57.5	3.6-15	5.5-89.0	2.3-18.9
Reference	9.9-42.4	7.2-52.4	7.2-59.5	2.7-58.0

Table 12. Mean Recovery Data From Five Actuations In Cascade Impaction Study (N=30).									
		Test			Reference				
Sector	Group	Mean	%CV	%/Group	Mean	%CV	%/Group	T/R	*P*
BEGIN	1	5188.83	4.6	0.993	5141.90	10.8	0.992	1.01	*0.34085*
	2	5.21	29.6	0.001	6.84	103.6	0.001	0.76	*0.10733*
	3	33.57	33.7	0.006	34.56	38.4	0.007	0.97	*0.37782*
END	1	4952.02	6.2	0.993	4979.39	4.7	0.992	0.99	*0.34337*
	2	4.01	34.1	0.001	4.59	42.4	0.001	0.87	*0.11064*
	3	30.43	40.0	0.006	33.64	39.2	0.007	0.90	*0.14931*

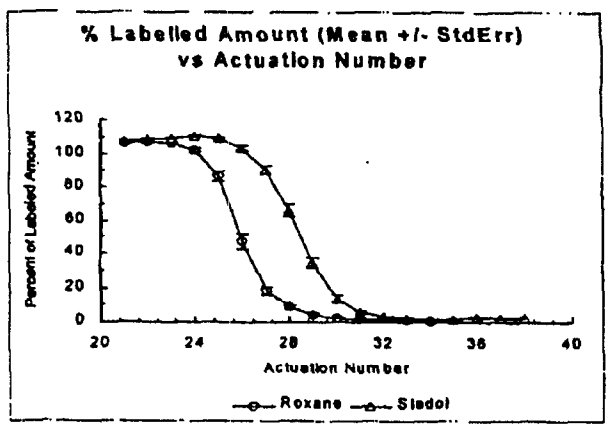
Table 13. Overall Variability (%CV) and Range of Within Lot Variability (%CV) from Recovery Data Following Five Actuations in Cascade Impaction Study.		
	Overall Variability	Range of Within Lot %CV's
Test	4.6-40	1.3-37.5
Reference	4.7-103.6	2.5-136.0

Table 14. Summary of µG Butorphanol Tartrate Per Actuation As Reported By The Firm				
	Beginning of Life		End of Life	
	Roxane	Stadol NS®	Roxane	Stadol NS®
Globe	[illegible]	[illegible]	[illegible]	[illegible]
Adaptor	[illegible]	[illegible]	[illegible]	[illegible]
Preseparator	[illegible]	[illegible]	[illegible]	[illegible]
Sum (Group 1)	[illegible]	[illegible]	[illegible]	[illegible]
Stage 0 (Group 2)	[illegible]	[illegible]	[illegible]	[illegible]
Stages 1-7 (Group 3)	[illegible]	[illegible]	[illegible]	[illegible]

Table 15. Priming/ Repriming Data (mg/Spray)								
	Test			Reference				
Spray #	Mean	%CV	N	Mean	%CV	N	T/R	*p*
7	1.045	6.37	30	1.082	3.81	30	0.966	0.00631
8	1.068	2.84	30	1.076	4.35	30	0.993	0.205262
9	1.049	4.76	30	1.066	4.47	30	0.983	0.068211
12	1.061	3.44	30	1.082	2.43	30	0.980	0.004452
13	1.073	3.15	30	1.098	1.75	30	0.977	0.000533

Table 16. Tail Off Data (mg/spray)							
	Test			Reference			
Spray #	Mean	%CV	N	Mean	%CV	N	T/R
21	1.061	2.98	30	1.073	4.81	30	0.989
22	1.066	2.49	30	1.088	3.56	30	0.980
23	1.062	2.29	30	1.094	2.81	30	0.971
24	1.023	6.26	30	1.107	2.58	30	0.924
25	0.865	19.20	30	1.090	3.89	30	0.794
26	0.470	53.71	30	1.035	8.33	30	0.454
27	0.185	69.12	30	0.903	15.93	30	0.205
28	0.090	62.31	29	0.659	30.84	30	0.137
29	0.045	87.35	29	0.347	47.82	30	0.128
30	0.026	90.67	24	0.139	85.57	30	0.189
31	0.021	72.91	19	0.058	77.75	30	0.359
32	0.019	50.70	7	0.033	52.31	28	0.584
33	0.010	88.88	3	0.026	72.09	24	0.384
34	0.005	-	1	0.020	78.52	17	0.249
35	0.000	-	0	0.020	46.16	8	0.000
36	0.000	-	0	0.028	26.95	2	0.000
37	0.000	-	0	0.026	-	1	0.000
38	0.000	-	0	0.025	-	1	0.000

Figure 1. Plot of Tail Off Data



DEC 4 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-824 APPLICANT: Roxane Laboratories

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please report expiration dates for the three lots of reference product.
2. Please submit representative (at least 20%) computer printout sheets for the [redacted]
3. [redacted] raw data to the Agency for evaluation.
4. Regarding the actuators you did not supply the following information on the test and reference products: [redacted]. Please supply this information.
5. Please provide evidence of rationale for selecting [redacted] as delay times for characterizing [redacted] respectively. The evidence may include plots of percent obscuration or percent transmission as a function of time (ms).
6. You submitted only a hard copy of the raw plume data. In future applications on this dosage form you should submit diskettes of the raw plume data in Microsoft Excel.

Sincerely yours,

/S/

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-824
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney /S/ 11/16/2000
HFD-652/ Y. Huang /S/ 11/16/2000
HFD-655/ GJP Singh /S/ 11/17/2000
HFD-617/ K. Scardi /S/ 11/29/00
for HFD-650/ D. Conne.

V:\FIRMSNZ\ROXANE\LTRS&REV\75824w.300

BIOEQUIVALENCY - DEFICIENCY Submission Date: March 24, 2000

~~WAIVER (WAI)~~
Testing Laboratory:
OTHER (OTH)
- in vitro testing

Strengths 10 mg/mL
Outcome: **IC**

NOTE:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: **Incomplete**

WINBIO COMMENTS:

The *in vitro* performance testing conducted on Roxane Laboratories' Butorphanol Tartrate Nasal Spray Pump, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers) has been found incomplete.

BIOEQUIVALENCY AMENDMENT

ANDA 75-824

DEC 4 2000

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Roxane Laboratories, Inc. TEL: 614-241-4131

ATTN: Sean Alan F.X. Reade, M.A. FAX: 614-276-0321

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 24, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butorphanol Tartrate Nasal Spray, 10mg/ml.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-824 SPONSOR : Roxane Laboratories
DRUG AND DOSAGE FORM: Butorphanol Tartrate Nasal Spray,
STRENGTH(S): 10 mg/mL
TYPES OF STUDIES: *In vitro*

TESTING LABORATORY: ——————

STUDY SUMMARY: Acceptable

DISSOLUTION: NA

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results: Acceptable
First Generic YES New facility NO For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date) Aug 01, 2001	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL: /S/ DATE: 5/21/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: /S/ DATE: 5/21/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

for INITIAL : /S/ DATE : 11/15/2001

Main - JPC 3.1

Butorphanol Tartrate
Nasal Spray, 10 mg/mL
ANDA #75-824
Reviewer: James E. Chaney
V:\FIRMSNZ\ROXANE\LTRS&REV\75824a.D00

Roxane Laboratories
Columbus, Ohio
Submission Date:
December 18, 2000

REVIEW OF ADDENDUM TO ORIGINAL REVIEW OF MARCH 24, 2000 SUBMISSION AND AN AMENDMENT TO THE ORIGINAL DECEMBER 18, 2000 SUBMISSION

1. Addendum To Original Review Of The March 24, 2000 Submission

Methods for statistical analysis of *in vitro* performance data given in the draft NASAL BA/BE guidance are still under development. Therefore, those methods are not completely implemented at this time. The evaluation of the *in vitro* equivalence of the test- and reference product is based on ratios of geometric means and consideration of relative variability (%CV) of test and reference products. In the original review arithmetic means were presented. In this addendum the evaluation of the *in vitro* equivalence of test and reference products is based on ratios of geometric means.

1.1 Unit Spray Content (Unit Dose)

The test/reference geometric mean ratios for the unit spray content (unit dose) were within the limit of 90-111%, stipulated in the draft Nasal BA/BE guidance (Table 1). The variability of the test and reference products was comparable. The unit spray content data are acceptable.

[ ]

1.3 Spray Pattern

With regard to the spray pattern data, the overall variability of the test product was lower than that of the reference product for the parameters Dmax, Dmin and ovality-ratios. The test/reference ratios of the geometric means were within the 90-111% range except ratios for the Dmax and Dmin data at the 5-cm distance (Table 3).

The spray pattern data were also analyzed by the population bioequivalence (PBE) approach outlined in the draft guidance. The statistical methodology based on that approach takes into consideration the relative variability of the test and reference products in determining product equivalence. The PBE analyses were performed by _____ (Attachment I).

Because values of two parameters (i.e., $sigma_{T0}$ - the variance terms offset, and epsilon – the scaling variance) to be used for the methodology outlined in the draft guidance are still under consideration ——————, analysis of the spray pattern data utilized combinations (i.e., $sigma_{T0}$ values of 0.1 and 0.2, and epsilon values of 0.0, 0.01, 0.03, and 0.05, where 0.0 represents the most stringent criterion). In addition the average bioequivalence (ABE) limits of 1.11 and 1.25 were used. With the exception of the 5-cm Dmin data, the test product meets equivalence criterion based on all combinations of ABE, $sigma_{T0}$ and epsilon. However, based on an epsilon value of 0.01, the test product meets equivalence criteria for all three parameters at all three distances. Therefore, the spray pattern data are acceptable.

1.4 Droplet Size Distribution

In its December 18, 2000 amendment in response to deficiency 5 of the bioequivalence review of the original March 24, 2000 submission (See Response to Deficiency 5 in the Amendment section of this review) the sponsor submitted representative plots of %

[ ]

nasal BA/BE guidance.

- The SPAN data were also analyzed in the manner outlined for the D50 data. Based on the analyses, T/R ratios were found to be within the acceptable range of 0.90-1.11.
- The total variability of the D50 data from the test product was comparable to that of the reference product. For the SPAN data, the test product was less variable than the reference product.
- As was done for the spray pattern data, the droplet size distribution data were also analyzed by ——————— (Attachment II). The droplet size distribution data were determined to be acceptable.

1.5 Plume Geometry

Plume geometry was characterized by plume angle, plume height, and plume width for the front and side views of the plume (Table 5). Based on the test/reference geometric mean ratios of the front view data, plume geometric characteristics of the test and reference products are similar (i.e., with the limits of 90-111% stipulated in the draft Nasal BA/BE guidance).

1.6 AddendumTables

Table 1. Content Uniformity (mg Delivered/Actuation)								
	Statistic	N	Test (mg/Spray)		Reference (mg/Spray)		T/R	*P*
			Sub-Lot #	Mean	Lot #	Mean		
Beginning (Spray #8)		10	V203079500	1.039	9F10028	1.053	0.986	
		10	V203830900	1.034	9F13540	1.074	0.963	
		10	204011600	1.078	9F15910	1.078	1.000	
	Grand Mean	30		1.050 (1.049)		1.068 (1.068)	0.983 (0.983)	*0.040*
	%CV	30		4.8		2.8		
	Min	30						
	Max	30						
Beginning (Spray #9)		10	V203079500	1.026	9F10028	1.068	0.961	
		10	V203830900	1.032	9F13540	1.046	0.987	
		10	204011600	1.088	9F15910	1.085	1.002	
	Grand Mean	30		1.049 (1.048)		1.066 (1.066)	0.983 (0.983)	*0.068*
	%CV	30		4.7		4.5		
	Min	30						
	Max	30						
End (Spray #23)		10	V203079500	1.061	9F10028	1.069	0.992	
		10	V203830900	1.039	9F13540	1.077	0.964	
		10	204011600	1.050	9F15910	1.072	0.980	
	Grand Mean	30		1.050 (1.049)		1.073 (1.072)	0.979 (0.979)	*0.434*
	%CV	30		4.0		3.8		
	Min	30						
	Max	30						

Data shown in parenthesis are test/reference ratios based on geometric means.

Table 2. Mean Recovery Data From Five Actuations In Cascade Impaction Study (N=30).									
		Test			Reference				
Sector	Grp	Mean	%CV	%/Grp	Mean	%CV	%/Grp	T/R	*P*
BEGIN	1	5188.83	4.6	99.3	5141.90	10.8	99.2	1.01 (1.01)	*0.34085*
	2	5.21	29.6	0.1	6.84	103.6	0.1	0.76 (0.89)	*0.10733*
	3	33.57	33.7	0.6	34.56	38.4	0.7	0.97 (1.01)	*0.37782*
END	1	4952.02	6.2	99.3	4979.39	4.7	99.2	0.99 (0.99)	*0.34337*
	2	4.01	34.1	0.1	4.59	42.4	0.1	0.87 (0.90)	*0.11064*
	3	30.43	40.0	0.6	33.64	39.2	0.7	0.90 (0.90)	*0.14931*

Data shown in parenthesis are test/reference ratios that are based on geometric means.
Grp = Group.

Table 3. Spray Pattern Testing Data: Calculated from the Pattern Center (N=30)						
Distance (cm)	**Stage**	**Product**	**Statistic**	**Dmax (mm)**	**Dmin (mm)**	**Ovality Ratio**
3	Begin	Test	Mean	37.510	32.859 (32.711)	1.147 (1.143)
			%CV	7.8	9.1	8.4
		Reference	Mean	35.904	31.278	1.159
			%CV	10.0	8.6	16.6
			T/R	[illegible]	[illegible]	[illegible]
			P	*0.02993*	*0.00575*	*0.38019*
	End	Test	Mean	38.414	34.386	1.121
			%CV	8.3	10.2	5.8
		Reference	Mean	36.345	32.200	1.136
			%CV	9.8	8.6	13.6
			T/R	1.057 (1.058)	1.068 (1.066)	0.987 (0.992)
			P	*0.00452*	*0.00241*	*0.29922*
4	Begin	Test	Mean	45.660	37.728	1.214
			%CV	9.3	8.9	8.8
		Reference	Mean	41.304	34.162	1.223
			%CV	12.9	10.2	19.5
			T/R	1.105 (1.110)	1.104 (1.106)	0.993 (1.003)
			P	*0.00055*	*0.00011*	*0.42132*
	End	Test	Mean	46.282	38.705	1.199
			%CV	8.9	8.5	8.1
		Reference	Mean	42.336	35.455	1.212
			%CV	12.1	11.3	20.2
			T/R	1.093 (1.097)	1.092 (1.095)	0.990 (1.001)
			P	*0.00066*	*0.00121*	*0.39316*
5	Begin	Test	Mean	54.670	43.265	1.266
			%CV	11.2	7.3	10.6
		Reference	Mean	48.037	37.455	1.305
			%CV	15.3	14.6	21.9
			T/R	1.138 (1.145)	1.155 (1.164)	0.970 (0.983)
			P	*0.00008*	*0.00000*	*0.22806*
	End	Test	Mean	55.927	44.913	1.249
			%CV	11.1	10.1	9.1
		Reference	Mean	49.141	39.039	1.284
			%CV	13.8	11.9	23.6
			T/R	1.138 (1.141)	1.150 (1.153)	0.973 (0.990)
			P	*0.00011*	*0.00003*	*0.27083*

Data shown in parenthesis are test/reference ratios that are based on geometric means.

Table 4. Droplet Size Distribution Determined By [illegible], At Beginning, Middle And End Stages (N=30).

Stage of Unit Life	Distance (cm)	Delay Time	D50						SPAN					
			Test		Reference				Test		Reference			
			Mean	%CV	Mean	%CV	T/R	*P*	Mean	%CV	Mean	%CV	T/R	*p*
Begin	1	15	53.08	15.2	57.28	12.9	0.93(0.92)	0.026	1.64	6.0	1.72	9.9	0.95(0.95)	0.012
	1	45	59.81	12.0	64.91	18.6	0.92(0.93)	0.025	1.53	5.8	1.63	9.2	0.94(0.94)	0.004
	1	75	72.95	39.3	70.61	27.3	1.03(1.01)	0.364	1.54	9.7	1.67	18.2	0.92(0.93)	0.021
	3	15	45.24	15.3	46.71	14.5	0.97(0.97)	0.209	1.65	6.3	1.71	25.1	0.96(0.98)	0.232
	3	45	50.33	13.2	54.42	13.4	0.92(0.92)	0.016	1.60	4.4	1.62	24.1	0.98(1.00)	0.348
	3	75	66.02	45.4	63.92	28.4	1.03(1.00)	0.385	1.57	6.8	1.58	9.1	0.99(0.99)	0.325
	5	15	40.76	12.6	43.92	9.9	0.93(0.93)	0.003	1.45	11.1	1.44	14.4	1.00(1.01)	0.469
	5	45	46.35	12.9	51.95	11.2	0.89(0.89)	0.000	1.37	10.3	1.36	11.8	1.01(1.01)	0.368
	5	75	58.20	43.8	64.40	42.4	0.90(0.90)	0.207	1.46	12.4	1.45	22.2	1.01(1.02)	0.447
Mean Begin Stage			**54.75**	**19.1**	**57.57**	**15.7**	**0.95**	**--**	**1.53**	**6.1**	**1.58**	**8.3**	**0.97**	**--**
Middle	1	15	51.57	13.5	57.04	15.5	0.90(0.90)	0.009	1.62	4.8	1.94	47.8	0.83(0.88)	0.033
	1	45	57.93	13.2	61.94	12.3	0.94(0.93)	0.032	1.53	4.4	1.71	19.2	0.90(0.91)	0.004
	1	75	62.08	11.7	65.14	12.9	0.95(0.95)	0.073	1.53	3.6	1.86	45.7	0.82(0.87)	0.023
	3	15	42.14	14.6	45.83	14.4	0.92(0.92)	0.004	1.66	6.1	1.64	14.8	1.01(1.01)	0.408
	3	45	49.62	17.0	52.47	13.6	0.95(0.94)	0.049	1.56	6.3	1.55	7.2	1.01(1.01)	0.231
	3	75	56.47	19.5	57.22	13.2	0.99(0.98)	0.370	1.56	6.4	1.50	7.5	1.04(1.04)	0.011
	5	15	41.76	11.2	44.51	14.3	0.94(0.94)	0.033	1.49	10.3	1.49	23.0	1.01(1.02)	0.453
	5	45	48.27	11.2	51.80	11.9	0.93(0.93)	0.007	1.40	11.1	1.38	24.3	1.01(1.03)	0.408
	5	75	53.10	27.8	55.81	11.8	0.95(0.93)	0.163	1.43	15.0	1.42	21.2	1.01(1.01)	0.419
Mean Middle Stage			**51.44**	**13.3**	**54.64**	**12.5**	**0.94**	**--**	**1.53**	**5.4**	**1.61**	**12.1**	**0.95**	**--**
End	1	15	52.49	10.9	58.10	16.1	0.90(0.91)	0.002	1.63	5.5	2.10	52.4	0.78(0.84)	0.013
	1	45	58.44	11.1	63.75	15.9	0.92(0.92)	0.009	1.56	5.6	1.76	29.9	0.89(0.91)	0.022
	1	75	68.01	57.5	67.22	17.1	1.01(0.96)	0.457	1.55	7.4	1.72	27.7	0.90(0.92)	0.029
	3	15	44.63	15.0	47.32	18.4	0.94(0.95)	0.096	1.64	7.1	1.75	17.1	0.94(0.94)	0.025
	3	45	50.79	14.8	54.01	16.7	0.94(0.94)	0.076	1.56	7.1	1.62	12.4	0.97(0.97)	0.094
	3	75	58.35	25.3	58.98	16.6	0.99(0.98)	0.428	1.59	9.4	1.58	10.6	1.01(1.01)	0.360
	5	15	41.41	11.5	42.14	11.5	0.98(0.98)	0.291	1.53	7.1	1.56	17.0	0.98(0.99)	0.271
	5	45	48.19	13.6	50.05	12.5	0.96(0.96)	0.155	1.42	6.2	1.48	23.4	0.96(0.98)	0.221
	5	75	57.77	51.2	53.84	11.4	1.07(1.01)	0.239	1.45	11.5	1.50	25.7	0.97(0.98)	0.291
Mean End Stage			**53.34**	**15.4**	**55.05**	**14.4**	**0.97**	**--**	**1.55**	**4.7**	**1.67**	**11.4**	**0.93**	**--**

Data shown in parenthesis are test/reference ratios that are based on geometric means.

Table 5. Plume Geometry Data (N=30)						
Time (msec)	View	Product	Statistic	Length (cm)	Width (cm)	Angle (°)
20	Front	Test	Mean	15.59	11.26	60.9
			%CV	9.9	13.9	10.9
		Reference	Mean	15.55	10.49	58.5
			%CV	14.3	13.5	10.3
			T/R	1.003 (1.008)	1.074 (1.073)	1.041 (1.040)
			p	*0.470*	*0.024*	*0.072*
	Side	Test	Mean	15.33	11.55	61.5
			%CV	10.4	12.9	10.0
		Reference	Mean	15.557	10.21	58.5
			%CV	13.7	13.4	7.2
			T/R	0.985 (0.989)	1.131 (1.132)	1.051 (1.048)
			p	*0.332*	*0.002*	*0.020*
75	Front	Test	Mean	28.18	16.49	54.6
			%CV	7.2	14.4	13.4
		Reference	Mean	28.63	15.66	50.7
			%CV	7.1	14.0	14.6
			T/R	0.984 (0.984)	1.053 (1.052)	1.076 (1.079)
			p	*0.208*	*0.095*	*0.026*
	Side	Test	Mean	28.19	16.75	54.0
			%CV	7.1	12.6	13.4
		Reference	Mean	28.86	15.32	51.2
			%CV	8.6	12.3	15.5
			T/R	0.977 (0.978)	1.094 (1.093)	1.056 (1.060)
			P	*0.146*	*0.009*	*0.078*
150	Front	Test	Mean	37.33	18.56	54.3
			%CV	8.0	12.9	13.8
		Reference	Mean	38.58	17.24	49.8
			%CV	4.5	13.3	11.7
			T/R	0.967 (0.965)	1.077 (1.078)	1.090 (1.087)
			P	*0.027*	*0.026*	*0.013*
	Side	Test	Mean	36.97	18.88	54.6
			%CV	7.1	11.7	13.0
		Reference	Mean	38.56	17.10	50.3
			%CV	5.0	10.0	9.3
			T/R	0.959 (0.958)	1.105 (1.102)	1.085 (1.081)
			P	*0.006*	*0.004*	*0.009*

Data shown in parenthesis are test/reference ratios that are based on geometric means.

2. Review of Amendment to Original March 24, 2000 Submission

2.1 Deficiency 1:
Please report expiration dates for the three lots of reference product.
Firm's Response:
The expiration dates for the three reference products (Stadol NS® Nasal Spray) are as follows: Lot 9FI0028, 5/31/01; Lot 9F13540, 5/31/01; Lot 9F15910, 6/30/01.
Review's Comment:
The firm's response is acceptable.

2.2 Deficiency 2:
Please submit representative (at least 20%) computer printout sheets for the [redacted] analysis.
Firm's Response:
Representative (20%) computer printouts (data plots) for the [redacted], analysis were submitted.
Review's Comment:
The firm's response is acceptable.

2.3 Deficiency 3:
The quantification for the priming/re-priming and tail-off testing was accomplished by taking individual actuation weights. In these tests, please base your measurements of drug per actuation on a validated [redacted] assay and resubmit the raw data to the Agency for evaluation.
Firm's Response:

Priming/re-priming
Actuations 6 through 8, 13, 14 and 21 were collected for [redacted] assay. The results confirmed that the two formulations are equivalent with respect to priming/re-priming when the amount of drug in each actuation is directly measured by [redacted] (Table 6).

Table 6. Amended Priming/Re-priming Data (mg/Spray) -

	Test			Reference			
Spray #	Mean	%CV	N	Mean	%CV	N	T/R
6	1.032	4.6	31	1.025	4.4	31	1.007
7	1.045	4.0	31	1.035	4.8	31	1.010
8	1.058	4.5	31	1.056	4.9	31	1.002
13	1.073	2.6	31	1.065	2.1	31	1.008
14	1.053	5.2	31	1.067	2.0	31	0.988
21	1.067	3.8	31	1.075	1.5	31	0.993

Tail-off
Actuations 24, 27, 29 and 31 were collected for [redacted] assay. The results presented in this report comparing Roxane's Butorphanol Nasal Spray and Stadol NS have confirmed that the two formulations are equivalent with respect to tailing-off when the amount of drug in each actuation is directly measured by [redacted] Table 7).

Table 7. Amended Tail Off Data (mg/spray) – HPLC							
	Test			Reference			
Spray #	Mean	%CV	N	Mean	%CV	N	T/R
24	0.949	16.6	31	1.068	2.9	31	0.888
27	0.137	109.1	21	0.697	22.2	31	0.197
29	0	-	0	0.194	45.3	25	0
31	0	-	0	0.076	-	1	0

Reviewer's Comment:
The priming/re-priming and tail-off testing based on measurements of drug per actuation using the chromatographic assay is acceptable.

2.4 Deficiency 4:

Firm's Response:

Review's Comment:
The firm's response is acceptable.

2.5 Deficiency 5:

Review's Comment:
The firm's response is acceptable.

2.6 Deficiency 6:
You submitted only a hard copy of the raw plume data. In future applications on this dosage form you should submit diskettes of the raw plume data in Microsoft Excel.
Firm's Response:
The firm acknowledged that in future applications on this dosage form, it will submit diskette copies of the raw plume data in Microsoft Excel.
Review's Comment:
The firm's response is acceptable.

3. Recommendation:

The formulation of the test product is Q1 and Q2 the same as that of the reference product. The *in vitro* testing conducted by Roxane Laboratories comparing its butorphanol tartrate nasal spray (10 mg/mL) and the reference product (Stadol nasal spray, 10 mg/mL) has been found acceptable to the Division of Bioequivalence. In terms of dose delivered per actuation and the size, shape and droplet size distribution of the spray, the test product's performance is similar to that of the reference product. Therefore, the Division of Bioequivalence deems the test product to be equivalent to the reference product in dose delivery and performance of the delivery device.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

/S/

RD INITIALED YCHuang
FT INITIALED YCHuang _____ Date 5/21/01

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Concur: _____ Date 5/22/2001
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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Attachment 1

Non-Profile Bioequivalence

Test: Spray Pattern II
Summary Table

Distance (cm)	BE Variable	Geometric Mean		Geometric Mean Ratio (%)	Standard Deviation		Upper Confidence Bound [1]
		Test	Reference		Reference	T/R Ratio	
3	D_{max}	37.84	35.96	105.24	0.098	0.836	-0.008
	D_{min}	33.45	31.61	105.81	0.091	1.141	-0.001
	Ovality Ratio	1.13	1.14	99.46	0.127	0.547	-0.023
4	D_{max}	45.78	41.50	110.32	0.126	0.746	-0.006
	D_{min}	38.07	34.59	110.06	0.115	0.774	-0.003
	Ovality Ratio	1.20	1.20	100.24	0.163	0.509	-0.039
5	D_{max}	54.97	48.08	114.32	0.147	0.766	-0.002
	D_{min}	43.91	37.89	115.87	0.140	0.659	**0.001** (-0.017)
	Ovality Ratio	1.25	1.27	98.66	0.192	0.498	-0.054

[1] A negative upper confidence bound means the test product passes this bioequivalence test. These 95% upper confidence bounds use the regulatory constants suggested in the draft guidance, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", June 1999; that is, average BE criterion (GMR) of 90/111, $\varepsilon = 0$, and $\sigma_0 = 0.1$. If the bioequivalence test fails using these constants, then the alternate values suggested in the guidance (i.e., $\varepsilon = 0.01$ and the other two unchanged) are reported in parentheses.

Dataset: asprsprtn.xls
3/7/2001

ANDA 75-824

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ASPRAPTRN: Spray Pattern 15:12 Wednesday, March 7, 2001

---------- dm=' 3 / Cmax' ----------

Obs	Sigma T0	epsilon	ASE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
1	0.1	0.00	1.11	1.09	37.8	36.0	105.24	0.08	0.10	0.84	-0.0061	-0.0076	-0.007622
2	0.1	0.00	1.25	4.88	37.8	36.0	105.24	0.08	0.10	0.84	-0.0379	-0.0468	-0.046524
3	0.2	0.00	1.11	0.27	37.8	36.0	105.24	0.08	0.10	0.84	0.0009	-0.0076	-0.007622
4	0.2	0.00	1.25	1.24	37.8	36.0	105.24	0.08	0.10	0.84	-0.0074	-0.0468	-0.046524
5	0.1	0.01	1.11	2.08	37.8	36.0	105.24	0.08	0.10	0.84	-0.0144	-0.0176	-0.017622
6	0.1	0.01	1.25	5.98	37.8	36.0	105.24	0.08	0.10	0.84	-0.0459	-0.0565	-0.056524
7	0.2	0.01	1.11	0.52	37.8	36.0	105.24	0.08	0.10	0.84	-0.0013	-0.0176	-0.017622
8	0.2	0.01	1.25	1.49	37.8	36.0	105.24	0.08	0.10	0.84	-0.0095	-0.0565	-0.056524
9	0.1	0.03	1.11	4.08	37.8	36.0	105.24	0.08	0.10	0.84	-0.0307	-0.0376	-0.037622
10	0.1	0.03	1.25	7.98	37.8	36.0	105.24	0.08	0.10	0.84	-0.0620	-0.0765	-0.076524
11	0.2	0.03	1.11	1.02	37.8	36.0	105.24	0.08	0.10	0.84	-0.0055	-0.0376	-0.037622
12	0.2	0.03	1.25	1.98	37.8	36.0	105.24	0.08	0.10	0.84	-0.0136	-0.0765	-0.076524
13	0.1	0.05	1.11	6.08	37.8	36.0	105.24	0.08	0.10	0.84	-0.0468	-0.0576	-0.057622
14	0.1	0.05	1.25	9.98	37.8	36.0	105.24	0.08	0.10	0.84	-0.0780	-0.0965	-0.096524
15	0.2	0.05	1.11	1.53	37.8	36.0	105.24	0.08	0.10	0.84	-0.0087	-0.0576	-0.057622
16	0.2	0.05	1.25	2.49	37.8	36.0	105.24	0.08	0.10	0.84	-0.0177	-0.0965	-0.096524

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Obs	Sigma TO	epsilon	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	99% UCL G-scaled PBE Criterion	Upper Confidence Bound
17	0.1	0.00	1.11	1.06	33.5	31.6	105.61	0.10	0.09	1.14	0.0017	-0.0009	-0.000892
18	0.1	0.00	1.26	4.98	33.5	31.6	105.61	0.10	0.09	1.14	-0.0260	-0.0396	-0.039794
19	0.2	0.00	1.11	0.27	33.5	31.6	105.61	0.10	0.09	1.14	0.0079	-0.0009	-0.000892
20	0.2	0.00	1.26	1.24	33.5	31.6	105.61	0.10	0.09	1.14	0.0006	-0.0396	-0.039794
21	0.1	0.01	1.11	2.00	33.5	31.6	105.61	0.10	0.09	1.14	-0.0034	-0.0109	-0.010892
22	0.1	0.01	1.26	5.96	33.5	31.6	105.61	0.10	0.09	1.14	-0.0329	-0.0496	-0.049794
23	0.2	0.01	1.11	0.52	33.5	31.6	105.61	0.10	0.09	1.14	0.0060	-0.0109	-0.010892
24	0.2	0.01	1.26	1.49	33.5	31.6	105.61	0.10	0.09	1.14	-0.0013	-0.0496	-0.049794
25	0.1	0.03	1.11	4.09	33.5	31.6	105.61	0.10	0.09	1.14	-0.0196	-0.0309	-0.030892
26	0.1	0.03	1.26	7.96	33.5	31.6	105.61	0.10	0.09	1.14	-0.0466	-0.0696	-0.069794
27	0.2	0.03	1.11	1.02	33.5	31.6	105.61	0.10	0.09	1.14	0.0022	-0.0309	-0.030892
28	0.2	0.03	1.26	1.99	33.5	31.6	105.61	0.10	0.09	1.14	-0.0049	-0.0696	-0.069794
29	0.1	0.06	1.11	6.09	33.5	31.6	105.61	0.10	0.09	1.14	-0.0337	-0.0509	-0.050892
30	0.1	0.06	1.26	9.96	33.5	31.6	105.61	0.10	0.09	1.14	-0.0606	-0.0896	-0.089794
31	0.2	0.06	1.11	1.52	33.5	31.6	105.61	0.10	0.09	1.14	-0.0015	-0.0509	-0.050892
32	0.2	0.06	1.26	2.49	33.5	31.6	105.61	0.10	0.09	1.14	-0.0065	-0.0896	-0.089794

---------- dsw' 3 / Ovality Ratio' ----------

Obs	Sigma TO	epsilon	ASE	FDA PSE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PSE Criterion	95% UCL C-scaled PSE Criterion	Upper Confidence Bound
33	0.1	0.00	1.11	1.09	1.13	1.14	99.46	0.07	0.13	0.55	-0.0229	-0.0191	-0.02291
34	0.1	0.00	1.25	4.00	1.13	1.14	99.46	0.07	0.13	0.55	-0.0750	-0.0500	-0.07504
35	0.2	0.00	1.11	0.27	1.13	1.14	99.46	0.07	0.13	0.55	-0.0119	-0.0101	-0.01906
36	0.2	0.00	1.25	1.24	1.13	1.14	99.46	0.07	0.13	0.56	-0.0250	-0.0500	-0.05798
37	0.1	0.01	1.11	2.09	1.13	1.14	99.46	0.07	0.13	0.55	-0.0363	-0.0291	-0.03634
38	0.1	0.01	1.25	5.96	1.13	1.14	99.46	0.07	0.13	0.55	-0.0884	-0.0500	-0.08842
39	0.2	0.01	1.11	0.52	1.13	1.14	99.46	0.07	0.13	0.55	-0.0153	-0.0291	-0.02906
40	0.2	0.01	1.25	1.46	1.13	1.14	99.46	0.07	0.13	0.55	-0.0264	-0.0500	-0.06798
41	0.1	0.03	1.11	4.00	1.13	1.14	99.46	0.07	0.13	0.55	-0.0831	-0.0481	-0.08313
42	0.1	0.03	1.25	7.98	1.13	1.14	99.46	0.07	0.13	0.55	-0.1152	-0.0500	-0.11818
43	0.2	0.03	1.11	1.02	1.13	1.14	99.46	0.07	0.13	0.55	-0.0220	-0.0481	-0.04906
44	0.2	0.03	1.25	1.98	1.13	1.14	99.46	0.07	0.13	0.55	-0.0351	-0.0500	-0.06798
45	0.1	0.05	1.11	6.08	1.13	1.14	99.46	0.07	0.13	0.56	-0.0809	-0.0681	-0.08988
46	0.1	0.05	1.25	9.98	1.13	1.14	99.46	0.07	0.13	0.55	-0.1419	-0.1000	-0.14193
47	0.2	0.05	1.11	1.52	1.13	1.14	99.46	0.07	0.13	0.55	-0.0287	-0.0681	-0.06908
48	0.2	0.05	1.25	2.49	1.13	1.14	99.46	0.07	0.13	0.55	-0.0418	-0.1000	-0.10796

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---------- dm=' 4 / Dmax' ----------

Obs	Sigma TO	epsilon	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
49	0.1	0.00	1.11	1.06	45.8	41.5	110.32	0.09	0.13	0.75	-0.0062	-0.0015	-0.00817
50	0.1	0.00	1.25	4.98	45.8	41.5	110.32	0.09	0.13	0.75	-0.0567	-0.0404	-0.05973
51	0.2	0.00	1.11	0.27	45.8	41.5	110.32	0.09	0.13	0.75	0.0054	-0.0015	-0.00147
52	0.2	0.00	1.25	1.24	45.8	41.5	110.32	0.09	0.13	0.75	-0.0063	-0.0404	-0.04036
53	0.1	0.01	1.11	2.09	45.8	41.5	110.32	0.09	0.13	0.75	-0.0200	-0.0115	-0.01986
54	0.1	0.01	1.25	5.98	45.8	41.5	110.32	0.09	0.13	0.75	-0.0720	-0.0604	-0.07196
55	0.2	0.01	1.11	0.52	45.8	41.5	110.32	0.09	0.13	0.75	0.0018	-0.0115	-0.01147
56	0.2	0.01	1.25	1.49	45.8	41.5	110.32	0.09	0.13	0.75	-0.0118	-0.0504	-0.05036
57	0.1	0.03	1.11	4.09	45.8	41.5	110.32	0.09	0.13	0.75	-0.0498	-0.0315	-0.04986
58	0.1	0.03	1.25	7.96	45.8	41.5	110.32	0.09	0.13	0.75	-0.0984	-0.0704	-0.09840
59	0.2	0.03	1.11	1.02	45.8	41.5	110.32	0.09	0.13	0.75	-0.0052	-0.0315	-0.03147
60	0.2	0.03	1.25	1.99	45.8	41.5	110.32	0.09	0.13	0.75	-0.0187	-0.0704	-0.07038
61	0.1	0.05	1.11	6.09	45.8	41.5	110.32	0.09	0.13	0.75	-0.0734	-0.0515	-0.07344
62	0.1	0.05	1.25	9.96	45.8	41.5	110.32	0.09	0.13	0.75	-0.1247	-0.0904	-0.12474
63	0.2	0.05	1.11	1.52	45.8	41.5	110.32	0.09	0.13	0.75	-0.0122	-0.0515	-0.05147
64	0.2	0.05	1.25	2.49	45.8	41.5	110.32	0.09	0.13	0.75	-0.0255	-0.0904	-0.09036

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Obs	Sigma TO	epsilon	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
65	0.1	0.00	1.11	1.09	38.1	34.6	110.06	0.09	0.11	0.77	-0.0031	-0.0010	-0.00314
66	0.1	0.00	1.25	4.98	38.1	34.6	110.06	0.09	0.11	0.77	-0.0471	-0.0399	-0.04711
67	0.2	0.00	1.11	0.27	38.1	34.6	110.06	0.09	0.11	0.77	0.0068	-0.0010	-0.00098
68	0.2	0.00	1.25	1.24	38.1	34.6	110.06	0.09	0.11	0.77	-0.0050	-0.0389	-0.03987
69	0.1	0.01	1.11	2.09	38.1	34.6	110.06	0.09	0.11	0.77	-0.0147	-0.0110	-0.01489
70	0.1	0.01	1.25	5.98	38.1	34.6	110.06	0.09	0.11	0.77	-0.0582	-0.0499	-0.05818
71	0.2	0.01	1.11	0.82	38.1	34.6	110.06	0.09	0.11	0.77	0.0036	-0.0110	-0.01096
72	0.2	0.01	1.25	1.49	38.1	34.6	110.06	0.09	0.11	0.77	-0.0079	-0.0499	-0.04987
73	0.1	0.03	1.11	4.09	38.1	34.6	110.06	0.09	0.11	0.77	-0.0372	-0.0310	-0.03721
74	0.1	0.03	1.25	7.98	38.1	34.6	110.06	0.09	0.11	0.77	-0.0802	-0.0699	-0.08022
75	0.2	0.03	1.11	1.02	38.1	34.6	110.06	0.09	0.11	0.77	-0.0024	-0.0310	-0.03096
76	0.2	0.03	1.25	1.99	38.1	34.6	110.06	0.09	0.11	0.77	-0.0136	-0.0699	-0.06987
77	0.1	0.05	1.11	6.09	38.1	34.6	110.06	0.09	0.11	0.77	-0.0594	-0.0510	-0.05939
78	0.1	0.05	1.25	9.98	38.1	34.6	110.06	0.09	0.11	0.77	-0.1022	-0.0899	-0.10220
79	0.2	0.05	1.11	1.52	38.1	34.6	110.06	0.09	0.11	0.77	-0.0082	-0.0510	-0.05096
80	0.2	0.05	1.25	2.49	38.1	34.6	110.06	0.09	0.11	0.77	-0.0193	-0.0899	-0.06987

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Attachment II
Droplet Size Distribution
Summary Table

BE Measure	Distance (cm)	Delay (msec)	Geometric Mean Test	Geometric Mean Reference	Geometric Mean Ratio (%)	Standard Deviation Reference	Standard Deviation T/R Ratio	Upper Confidence Bound †
D50	1	15	51.94	56.93	91.23	0.135	0.978	-0.005
		45	58.30	62.89	92.70	0.138	0.895	-0.012
		75	64.87	66.67	97.29	0.165	1.524	0.020
								(-0.004)
	3	15	43.52	46.11	94.38	0.147	1.037	-0.011
		45	49.70	53.11	93.57	0.138	1.098	-0.005
		75	58.05	58.97	98.43	0.182	1.394	0.010
								(-0.020)
	5	15	41.05	43.23	94.95	0.117	0.992	-0.007
		45	47.26	50.92	92.80	0.116	1.060	-0.001
		75	53.60	56.61	94.68	0.198	1.414	0.017
								(-0.019)
Span	1	15	1.63	1.83	89.06	0.273	0.196	-0.119
		45	1.54	1.67	91.99	0.157	0.341	-0.034
		75	1.54	1.69	90.65	0.221	0.319	-0.071
	3	15	1.64	1.68	97.86	0.146	0.455	-0.032
		45	1.57	1.58	99.42	0.121	0.520	-0.022
		75	1.57	1.5 5	101.35	0.088	0.865	-0.011
	5	15	1.48	1.48	100.46	0.160	0.611	-0.036
		45	1.39	1.38	100.49	0.158	0.597	-0.036
		75	1.44	1.43	100.59	0.177	0.717	-0.038

† 95% upper confidence bound uses the regulatory constants suggested in the draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", June 1999

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Attachment II (cont)

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metric=D50 distance=1 delay=15

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
1	0.1	0.00	0.1	1.11	1.089	51.94	56.93	91.225	0.132	0.135	0.978	-0.0050	0.0022	-0.00505
2	0.1	0.00	0.1	1.25	4.979	51.94	56.93	91.225	0.132	0.135	0.978	-0.0673	-0.0367	-0.06730
3	0.2	0.00	0.2	1.11	0.272	51.94	56.93	91.225	0.132	0.135	0.978	0.0065	0.0022	0.00222
4	0.2	0.00	0.2	1.25	1.245	51.94	56.93	91.225	0.132	0.135	0.978	-0.0076	-0.0367	-0.03668
5	0.1	0.01	0.1	1.11	2.089	51.94	56.93	91.225	0.132	0.135	0.978	-0.0213	-0.0078	-0.02127
6	0.1	0.01	0.1	1.25	5.979	51.94	56.93	91.225	0.132	0.135	0.978	-0.0831	-0.0467	-0.08311
7	0.2	0.01	0.2	1.11	0.522	51.94	56.93	91.225	0.132	0.135	0.978	0.0043	-0.0078	-0.00778
8	0.2	0.01	0.2	1.25	1.495	51.94	56.93	91.225	0.132	0.135	0.978	-0.0117	-0.0467	-0.04668
9	0.1	0.03	0.1	1.11	4.089	51.94	56.93	91.225	0.132	0.135	0.978	-0.0532	-0.0278	-0.05319
10	0.1	0.03	0.1	1.25	7.979	51.94	56.93	91.225	0.132	0.135	0.978	-0.1147	-0.0667	-0.11466
11	0.2	0.03	0.2	1.11	1.022	51.94	56.93	91.225	0.132	0.135	0.978	-0.0040	-0.0278	-0.02778
12	0.2	0.03	0.2	1.25	1.995	51.94	56.93	91.225	0.132	0.135	0.978	-0.0197	-0.0667	-0.06668
13	0.1	0.05	0.1	1.11	6.089	51.94	56.93	91.225	0.132	0.135	0.978	-0.0848	-0.0478	-0.08484
14	0.1	0.05	0.1	1.25	9.979	51.94	56.93	91.225	0.132	0.135	0.978	-0.1462	-0.0867	-0.14616
15	0.2	0.05	0.2	1.11	1.522	51.94	56.93	91.225	0.132	0.135	0.978	-0.0121	-0.0478	-0.04778
16	0.2	0.05	0.2	1.25	2.495	51.94	56.93	91.225	0.132	0.135	0.978	-0.0278	-0.0867	-0.08668

metric=D50 distance=1 delay=45

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
17	0.1	0.00	0.1	1.11	1.089	58.30	62.89	92.699	0.123	0.138	0.895	-0.0119	-0.0040	-0.011892
18	0.1	0.00	0.1	1.25	4.979	58.30	62.89	92.699	0.123	0.138	0.895	-0.0767	-0.0429	-0.076702
19	0.2	0.00	0.2	1.11	0.272	58.30	62.89	92.699	0.123	0.138	0.895	0.0021	-0.0040	-0.003978
20	0.2	0.00	0.2	1.25	1.245	58.30	62.89	92.699	0.123	0.138	0.895	-0.0145	-0.0429	-0.042880
21	0.1	0.01	0.1	1.11	2.089	58.30	62.89	92.699	0.123	0.138	0.895	-0.0287	-0.0140	-0.028732
22	0.1	0.01	0.1	1.25	5.979	58.30	62.89	92.699	0.123	0.138	0.895	-0.0932	-0.0529	-0.093211
23	0.2	0.01	0.2	1.11	0.522	58.30	62.89	92.699	0.123	0.138	0.895	-0.0022	-0.0140	-0.013978

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Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2373

metric=D50 distance=1 delay=45

(continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
24	0.2	0.01	0.2	1.25	1.495	58.30	62.89	92.699	0.123	0.138	0.895	-0.0188	-0.0529	-0.05288
25	0.1	0.03	0.1	1.11	4.089	58.30	62.89	92.699	0.123	0.138	0.895	-0.0620	-0.0340	-0.06198
26	0.1	0.03	0.1	1.25	7.979	58.30	62.89	92.699	0.123	0.138	0.895	-0.1262	-0.0729	-0.12618
27	0.2	0.03	0.2	1.11	1.022	58.30	62.89	92.699	0.123	0.138	0.895	-0.0108	-0.0340	-0.03398
28	0.2	0.03	0.2	1.25	1.995	58.30	62.89	92.699	0.123	0.138	0.895	-0.0272	-0.0729	-0.07288
29	0.1	0.05	0.1	1.11	6.089	58.30	62.89	92.699	0.123	0.138	0.895	-0.0950	-0.0540	-0.09502
30	0.1	0.05	0.1	1.25	9.979	58.30	62.89	92.699	0.123	0.138	0.895	-0.1591	-0.0929	-0.15910
31	0.2	0.05	0.2	1.11	1.522	58.30	62.89	92.699	0.123	0.138	0.895	-0.0192	-0.0540	-0.05398
32	0.2	0.05	0.2	1.25	2.495	58.30	62.89	92.699	0.123	0.138	0.895	-0.0355	-0.0929	-0.09288

metric=D50 distance=1 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
33	0.1	0.00	0.1	1.11	1.089	64.87	66.67	97.292	0.251	0.165	1.524	0.0202	0.0369	0.02024
34	0.1	0.00	0.1	1.25	4.979	64.87	66.67	97.292	0.251	0.165	1.524	-0.0736	-0.0020	-0.07357
35	0.2	0.00	0.2	1.11	0.272	64.87	66.67	97.292	0.251	0.165	1.524	0.0408	0.0369	0.03693
36	0.2	0.00	0.2	1.25	1.245	64.87	66.67	97.292	0.251	0.165	1.524	0.0164	-0.0020	-0.00198
37	0.1	0.01	0.1	1.11	2.089	64.87	66.67	97.292	0.251	0.165	1.524	-0.0043	0.0269	-0.00434
38	0.1	0.01	0.1	1.25	5.979	64.87	66.67	97.292	0.251	0.165	1.524	-0.0972	-0.0120	-0.09723
39	0.2	0.01	0.2	1.11	0.522	64.87	66.67	97.292	0.251	0.165	1.524	0.0345	0.0269	0.02693
40	0.2	0.01	0.2	1.25	1.495	64.87	66.67	97.292	0.251	0.165	1.524	0.0102	-0.0120	-0.01198
41	0.1	0.03	0.1	1.11	4.089	64.87	66.67	97.292	0.251	0.165	1.524	-0.0524	0.0069	-0.05241
42	0.1	0.03	0.1	1.25	7.979	64.87	66.67	97.292	0.251	0.165	1.524	-0.1444	-0.0320	-0.14437
43	0.2	0.03	0.2	1.11	1.022	64.87	66.67	97.292	0.251	0.165	1.524	0.0219	0.0069	0.00693
44	0.2	0.03	0.2	1.25	1.995	64.87	66.67	97.292	0.251	0.165	1.524	-0.0020	-0.0320	-0.03198
45	0.1	0.05	0.1	1.11	6.089	64.87	66.67	97.292	0.251	0.165	1.524	-0.0998	-0.0131	-0.09982

Attachment II (cont)

---------- metric=D50 distance=1 delay=75 ----------
(continued)

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
46	0.1	0.05	0.1	1.25	9.979	64.87	66.67	97.292	0.251	0.165	1.524	-0.1914	-0.0520	-0.19136
47	0.2	0.05	0.2	1.11	1.522	64.87	66.67	97.292	0.251	0.165	1.524	0.0095	-0.0131	-0.01307
48	0.2	0.05	0.2	1.25	2.495	64.87	66.67	97.292	0.251	0.165	1.524	-0.0142	-0.0520	-0.05198

---------- metric=D50 distance=3 delay=15 ----------

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
49	0.1	0.00	0.1	1.11	1.089	43.52	46.11	94.383	0.152	0.147	1.037	-0.0110	-0.0003	-0.01096
50	0.1	0.00	0.1	1.25	4.979	43.52	46.11	94.383	0.152	0.147	1.037	-0.0851	-0.0392	-0.08514
51	0.2	0.00	0.2	1.11	0.272	43.52	46.11	94.383	0.152	0.147	1.037	0.0051	-0.0003	-0.00033
52	0.2	0.00	0.2	1.25	1.245	43.52	46.11	94.383	0.152	0.147	1.037	-0.0140	-0.0392	-0.03924
53	0.1	0.01	0.1	1.11	2.089	43.52	46.11	94.383	0.152	0.147	1.037	-0.0302	-0.0103	-0.03024
54	0.1	0.01	0.1	1.25	5.979	43.52	46.11	94.383	0.152	0.147	1.037	-0.1040	-0.0492	-0.10403
55	0.2	0.01	0.2	1.11	0.522	43.52	46.11	94.383	0.152	0.147	1.037	0.0001	-0.0103	-0.01033
56	0.2	0.01	0.2	1.25	1.495	43.52	46.11	94.383	0.152	0.147	1.037	-0.0188	-0.0492	-0.04924
57	0.1	0.03	0.1	1.11	4.089	43.52	46.11	94.383	0.152	0.147	1.037	-0.0683	-0.0303	-0.06829
58	0.1	0.03	0.1	1.25	7.979	43.52	46.11	94.383	0.152	0.147	1.037	-0.1417	-0.0692	-0.14175
59	0.2	0.03	0.2	1.11	1.022	43.52	46.11	94.383	0.152	0.147	1.037	-0.0097	-0.0303	-0.03033
60	0.2	0.03	0.2	1.25	1.995	43.52	46.11	94.383	0.152	0.147	1.037	-0.0284	-0.0692	-0.06924
61	0.1	0.05	0.1	1.11	6.089	43.52	46.11	94.383	0.152	0.147	1.037	-0.1061	-0.0503	-0.10610
62	0.1	0.05	0.1	1.25	9.979	43.52	46.11	94.383	0.152	0.147	1.037	-0.1794	-0.0892	-0.17942
63	0.2	0.05	0.2	1.11	1.522	43.52	46.11	94.383	0.152	0.147	1.037	-0.0193	-0.0503	-0.05033
64	0.2	0.05	0.2	1.25	2.495	43.52	46.11	94.383	0.152	0.147	1.037	-0.0380	-0.0892	-0.08924

Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2375

metric=D50 distance=3 delay=45

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
65	0.1	0.00	0.1	1.11	1.089	49.70	53.11	93.572	0.152	0.138	1.098	-0.0047	0.0035	-0.00473
66	0.1	0.00	0.1	1.25	4.979	49.70	53.11	93.572	0.152	0.138	1.098	-0.0702	-0.0354	-0.07022
67	0.2	0.00	0.2	1.11	0.272	49.70	53.11	93.572	0.152	0.138	1.098	0.0095	0.0035	0.00352
68	0.2	0.00	0.2	1.25	1.245	49.70	53.11	93.572	0.152	0.138	1.098	-0.0074	-0.0354	-0.03538
69	0.1	0.01	0.1	1.11	2.089	49.70	53.11	93.572	0.152	0.138	1.098	-0.0218	-0.0065	-0.02181
70	0.1	0.01	0.1	1.25	5.979	49.70	53.11	93.572	0.152	0.138	1.098	-0.0868	-0.0454	-0.08684
71	0.2	0.01	0.2	1.11	0.522	49.70	53.11	93.572	0.152	0.138	1.098	0.0051	-0.0065	-0.00648
72	0.2	0.01	0.2	1.25	1.495	49.70	53.11	93.572	0.152	0.138	1.098	-0.0117	-0.0454	-0.04538
73	0.1	0.03	0.1	1.11	4.089	49.70	53.11	93.572	0.152	0.138	1.098	-0.0554	-0.0265	-0.05539
74	0.1	0.03	0.1	1.25	7.979	49.70	53.11	93.572	0.152	0.138	1.098	-0.1200	-0.0654	-0.12000
75	0.2	0.03	0.2	1.11	1.022	49.70	53.11	93.572	0.152	0.138	1.098	-0.0036	-0.0265	-0.02648
76	0.2	0.03	0.2	1.25	1.995	49.70	53.11	93.572	0.152	0.138	1.098	-0.0202	-0.0654	-0.06538
77	0.1	0.05	0.1	1.11	6.089	49.70	53.11	93.572	0.152	0.138	1.098	-0.0887	-0.0465	-0.08867
78	0.1	0.05	0.1	1.25	9.979	49.70	53.11	93.572	0.152	0.138	1.098	-0.1531	-0.0854	-0.15310
79	0.2	0.05	0.2	1.11	1.522	49.70	53.11	93.572	0.152	0.138	1.098	-0.0122	-0.0465	-0.04648
80	0.2	0.05	0.2	1.25	2.495	49.70	53.11	93.572	0.152	0.138	1.098	-0.0287	-0.0854	-0.08538

metric=D50 distance=3 delay=75

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
81	0.1	0.00	0.1	1.11	1.089	58.05	58.97	98.432	0.254	0.182	1.394	0.0098	0.0325	0.00979
82	0.1	0.00	0.1	1.25	4.979	58.05	58.97	98.432	0.254	0.182	1.394	-0.1049	-0.0064	-0.10487
83	0.2	0.00	0.2	1.11	0.272	58.05	58.97	98.432	0.254	0.182	1.394	0.0349	0.0325	0.03250
84	0.2	0.00	0.2	1.25	1.245	58.05	58.97	98.432	0.254	0.182	1.394	0.0051	-0.0064	-0.00641
85	0.1	0.01	0.1	1.11	2.089	58.05	58.97	98.432	0.254	0.182	1.394	-0.0202	0.0225	-0.02018
86	0.1	0.01	0.1	1.25	5.979	58.05	58.97	98.432	0.254	0.182	1.394	-0.1339	-0.0164	-0.13388
87	0.2	0.01	0.2	1.11	0.522	58.05	58.97	98.432	0.254	0.182	1.394	0.0271	0.0225	0.02250

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Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2376

metric=D50 distance=3 delay=75

(continued)

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
88	0.2	0.01	0.2	1.25	1.495	58.05	58.97	98.432	0.254	0.182	1.394	-0.0024	-0.0164	-0.01641
89	0.1	0.03	0.1	1.11	4.089	58.05	58.97	98.432	0.254	0.182	1.394	-0.0790	0.0025	-0.07895
90	0.1	0.03	0.1	1.25	7.979	58.05	58.97	98.432	0.254	0.182	1.394	-0.1917	-0.0364	-0.19173
91	0.2	0.03	0.2	1.11	1.022	58.05	58.97	98.432	0.254	0.182	1.394	0.0118	0.0025	0.00250
92	0.2	0.03	0.2	1.25	1.995	58.05	58.97	98.432	0.254	0.182	1.394	-0.0174	-0.0364	-0.03641
93	0.1	0.05	0.1	1.11	6.089	58.05	58.97	98.432	0.254	0.182	1.394	-0.1371	-0.0175	-0.13706
94	0.1	0.05	0.1	1.25	9.979	58.05	58.97	98.432	0.254	0.182	1.394	-0.2494	-0.0564	-0.24944
95	0.2	0.05	0.2	1.11	1.522	58.05	58.97	98.432	0.254	0.182	1.394	-0.0033	-0.0175	-0.01750
96	0.2	0.05	0.2	1.25	2.495	58.05	58.97	98.432	0.254	0.182	1.394	-0.0322	-0.0564	-0.05641

metric=D50 distance=5 delay=15

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
97	0.1	0.00	0.1	1.11	1.089	41.05	43.23	94.950	0.116	0.117	0.992	-0.0074	-0.0047	-0.007380
98	0.1	0.00	0.1	1.25	4.979	41.05	43.23	94.950	0.116	0.117	0.992	-0.0540	-0.0436	-0.054013
99	0.2	0.00	0.2	1.11	0.272	41.05	43.23	94.950	0.116	0.117	0.992	0.0027	-0.0047	-0.004716
100	0.2	0.00	0.2	1.25	1.245	41.05	43.23	94.950	0.116	0.117	0.992	-0.0093	-0.0436	-0.043618
101	0.1	0.01	0.1	1.11	2.089	41.05	43.23	94.950	0.116	0.117	0.992	-0.0195	-0.0147	-0.019509
102	0.1	0.01	0.1	1.25	5.979	41.05	43.23	94.950	0.116	0.117	0.992	-0.0659	-0.0536	-0.065879
103	0.2	0.01	0.2	1.11	0.522	41.05	43.23	94.950	0.116	0.117	0.992	-0.0004	-0.0147	-0.014716
104	0.2	0.01	0.2	1.25	1.495	41.05	43.23	94.950	0.116	0.117	0.992	-0.0123	-0.0536	-0.053618
105	0.1	0.03	0.1	1.11	4.089	41.05	43.23	94.950	0.116	0.117	0.992	-0.0434	-0.0347	-0.043429
106	0.1	0.03	0.1	1.25	7.979	41.05	43.23	94.950	0.116	0.117	0.992	-0.0896	-0.0736	-0.089570
107	0.2	0.03	0.2	1.11	1.022	41.05	43.23	94.950	0.116	0.117	0.992	-0.0066	-0.0347	-0.034716
108	0.2	0.03	0.2	1.25	1.995	41.05	43.23	94.950	0.116	0.117	0.992	-0.0184	-0.0736	-0.073618
109	0.1	0.05	0.1	1.11	6.089	41.05	43.23	94.950	0.116	0.117	0.992	-0.0672	-0.0547	-0.067181

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Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2377

metric=D50 distance=5 delay=15
(continued)

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
110	0.1	0.05	0.1	1.25	9.979	41.05	43.23	94.950	0.116	0.117	0.992	-0.1132	-0.0936	-0.11323
111	0.2	0.05	0.2	1.11	1.522	41.05	43.23	94.950	0.116	0.117	0.992	-0.0127	-0.0547	-0.05472
112	0.2	0.05	0.2	1.25	2.495	41.05	43.23	94.950	0.116	0.117	0.992	-0.0244	-0.0936	-0.09362

metric=D50 distance=5 delay=45

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
113	0.1	0.00	0.1	1.11	1.089	47.26	50.92	92.799	0.123	0.116	1.060	-0.0014	0.0012	-0.00136
114	0.1	0.00	0.1	1.25	4.979	47.26	50.92	92.799	0.123	0.116	1.060	-0.0471	-0.0377	-0.04705
115	0.2	0.00	0.2	1.11	0.272	47.26	50.92	92.799	0.123	0.116	1.060	0.0086	0.0012	0.00117
116	0.2	0.00	0.2	1.25	1.245	47.26	50.92	92.799	0.123	0.116	1.060	-0.0032	-0.0377	-0.03773
117	0.1	0.01	0.1	1.11	2.089	47.26	50.92	92.799	0.123	0.116	1.060	-0.0133	-0.0088	-0.01330
118	0.1	0.01	0.1	1.25	5.979	47.26	50.92	92.799	0.123	0.116	1.060	-0.0586	-0.0477	-0.05862
119	0.2	0.01	0.2	1.11	0.522	47.26	50.92	92.799	0.123	0.116	1.060	0.0056	-0.0088	-0.00883
120	0.2	0.01	0.2	1.25	1.495	47.26	50.92	92.799	0.123	0.116	1.060	-0.0052	-0.0477	-0.04773
121	0.1	0.03	0.1	1.11	4.089	47.26	50.92	92.799	0.123	0.116	1.060	-0.0367	-0.0288	-0.03672
122	0.1	0.03	0.1	1.25	7.979	47.26	50.92	92.799	0.123	0.116	1.060	-0.0817	-0.0677	-0.08170
123	0.2	0.03	0.2	1.11	1.022	47.26	50.92	92.799	0.123	0.116	1.060	-0.0006	-0.0288	-0.02883
124	0.2	0.03	0.2	1.25	1.995	47.26	50.92	92.799	0.123	0.116	1.060	-0.0122	-0.0677	-0.06773
125	0.1	0.05	0.1	1.11	6.089	47.26	50.92	92.799	0.123	0.116	1.060	-0.0599	-0.0488	-0.05989
126	0.1	0.05	0.1	1.25	9.979	47.26	50.92	92.799	0.123	0.116	1.060	-0.1047	-0.0877	-0.10472
127	0.2	0.05	0.2	1.11	1.522	47.26	50.92	92.799	0.123	0.116	1.060	-0.0066	-0.0488	-0.04883
128	0.2	0.05	0.2	1.25	2.495	47.26	50.92	92.799	0.123	0.116	1.060	-0.0181	-0.0877	-0.08773

Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2378

metric=D50 distance=5 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
129	0.1	0.00	0.1	1.11	1.089	53.60	56.61	94.680	0.279	0.198	1.414	0.0166	0.0456	0.01665
130	0.1	0.00	0.1	1.25	4.979	53.60	56.61	94.680	0.279	0.198	1.414	-0.1196	0.0067	-0.11961
131	0.2	0.00	0.2	1.11	0.272	53.60	56.61	94.680	0.279	0.198	1.414	0.0464	0.0456	0.04564
132	0.2	0.00	0.2	1.25	1.245	53.60	56.61	94.680	0.279	0.198	1.414	0.0110	0.0067	0.00674
133	0.1	0.01	0.1	1.11	2.089	53.60	56.61	94.680	0.279	0.198	1.414	-0.0190	0.0356	-0.01898
134	0.1	0.01	0.1	1.25	5.979	53.60	56.61	94.680	0.279	0.198	1.414	-0.1541	-0.0033	-0.15407
135	0.2	0.01	0.2	1.11	0.522	53.60	56.61	94.680	0.279	0.198	1.414	0.0372	0.0356	0.03564
136	0.2	0.01	0.2	1.25	1.495	53.60	56.61	94.680	0.279	0.198	1.414	0.0021	-0.0033	-0.00326
137	0.1	0.03	0.1	1.11	4.089	53.60	56.61	94.680	0.279	0.198	1.414	-0.0888	0.0156	-0.08884
138	0.1	0.03	0.1	1.25	7.979	53.60	56.61	94.680	0.279	0.198	1.414	-0.2227	-0.0233	-0.22273
139	0.2	0.03	0.2	1.11	1.022	53.60	56.61	94.680	0.279	0.198	1.414	0.0191	0.0156	0.01564
140	0.2	0.03	0.2	1.25	1.995	53.60	56.61	94.680	0.279	0.198	1.414	-0.0157	-0.0233	-0.02326
141	0.1	0.05	0.1	1.11	6.089	53.60	56.61	94.680	0.279	0.198	1.414	-0.1578	-0.0044	-0.15784
142	0.1	0.05	0.1	1.25	9.979	53.60	56.61	94.680	0.279	0.198	1.414	-0.2912	-0.0433	-0.29120
143	0.2	0.05	0.2	1.11	1.522	53.60	56.61	94.680	0.279	0.198	1.414	0.0011	-0.0044	-0.00436
144	0.2	0.05	0.2	1.25	2.495	53.60	56.61	94.680	0.279	0.198	1.414	-0.0333	-0.0433	-0.04326

metric=Span distance=1 delay=15

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
145	0.1	0.00	0.1	1.11	1.089	1.627	1.827	89.055	0.053	0.273	0.196	-0.1188	-0.0576	-0.11882
146	0.1	0.00	0.1	1.25	4.979	1.627	1.827	89.055	0.053	0.273	0.196	-0.3732	-0.0965	-0.37324
147	0.2	0.00	0.2	1.11	0.272	1.627	1.827	89.055	0.053	0.273	0.196	-0.0649	-0.0576	-0.06491
148	0.2	0.00	0.2	1.25	1.245	1.627	1.827	89.055	0.053	0.273	0.196	-0.1291	-0.0965	-0.12905
149	0.1	0.01	0.1	1.11	2.089	1.627	1.827	89.055	0.053	0.273	0.196	-0.1844	-0.0676	-0.18439
150	0.1	0.01	0.1	1.25	5.979	1.627	1.827	89.055	0.053	0.273	0.196	-0.4385	-0.1065	-0.43851
151	0.2	0.01	0.2	1.11	0.522	1.627	1.827	89.055	0.053	0.273	0.196	-0.0815	-0.0676	-0.08147

Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2379

metric=Span distance=1 delay=15

(continued)

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
152	0.2	0.01	0.2	1.25	1.495	1.627	1.827	89.055	0.053	0.273	0.196	-0.1455	-0.1065	-0.14546
153	0.1	0.03	0.1	1.11	4.089	1.627	1.827	89.055	0.053	0.273	0.196	-0.3151	-0.0876	-0.31512
154	0.1	0.03	0.1	1.25	7.979	1.627	1.827	89.055	0.053	0.273	0.196	-0.5690	-0.1265	-0.56902
155	0.2	0.03	0.2	1.11	1.022	1.627	1.827	89.055	0.053	0.273	0.196	-0.1144	-0.0876	-0.11443
156	0.2	0.03	0.2	1.25	1.995	1.627	1.827	89.055	0.053	0.273	0.196	-0.1782	-0.1265	-0.17822
157	0.1	0.05	0.1	1.11	6.089	1.627	1.827	89.055	0.053	0.273	0.196	-0.4457	-0.1076	-0.44568
158	0.1	0.05	0.1	1.25	9.979	1.627	1.827	89.055	0.053	0.273	0.196	-0.6995	-0.1465	-0.69950
159	0.2	0.05	0.2	1.11	1.522	1.627	1.827	89.055	0.053	0.273	0.196	-0.1473	-0.1076	-0.14726
160	0.2	0.05	0.2	1.25	2.495	1.627	1.827	89.055	0.053	0.273	0.196	-0.2109	-0.1465	-0.21094

metric=Span distance=1 delay=45

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
161	0.1	0.00	0.1	1.11	1.089	1.540	1.674	91.991	0.054	0.157	0.341	-0.0338	-0.0209	-0.03379
162	0.1	0.00	0.1	1.25	4.979	1.540	1.674	91.991	0.054	0.157	0.341	-0.1169	-0.0598	-0.11687
163	0.2	0.00	0.2	1.11	0.272	1.540	1.674	91.991	0.054	0.157	0.341	-0.0161	-0.0209	-0.02094
164	0.2	0.00	0.2	1.25	1.245	1.540	1.674	91.991	0.054	0.157	0.341	-0.0371	-0.0598	-0.05984
165	0.1	0.01	0.1	1.11	2.089	1.540	1.674	91.991	0.054	0.157	0.341	-0.0552	-0.0309	-0.05525
166	0.1	0.01	0.1	1.25	5.979	1.540	1.674	91.991	0.054	0.157	0.341	-0.1381	-0.0698	-0.13815
167	0.2	0.01	0.2	1.11	0.522	1.540	1.674	91.991	0.054	0.157	0.341	-0.0215	-0.0309	-0.03094
168	0.2	0.01	0.2	1.25	1.495	1.540	1.674	91.991	0.054	0.157	0.341	-0.0425	-0.0698	-0.06984
169	0.1	0.03	0.1	1.11	4.089	1.540	1.674	91.991	0.054	0.157	0.341	-0.0979	-0.0509	-0.09792
170	0.1	0.03	0.1	1.25	7.979	1.540	1.674	91.991	0.054	0.157	0.341	-0.1807	-0.0898	-0.18067
171	0.2	0.03	0.2	1.11	1.022	1.540	1.674	91.991	0.054	0.157	0.341	-0.0323	-0.0509	-0.05094
172	0.2	0.03	0.2	1.25	1.995	1.540	1.674	91.991	0.054	0.157	0.341	-0.0532	-0.0898	-0.08984
173	0.1	0.05	0.1	1.11	6.089	1.540	1.674	91.991	0.054	0.157	0.341	-0.1405	-0.0709	-0.14048

Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2380

metric=Span distance=1 delay=45
(continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
174	0.1	0.05	0.1	1.25	9.979	1.540	1.674	91.991	0.054	0.157	0.341	-0.2232	-0.1098	-0.22318
175	0.2	0.05	0.2	1.11	1.522	1.540	1.674	91.991	0.054	0.157	0.341	-0.0431	-0.0709	-0.07094
176	0.2	0.05	0.2	1.25	2.495	1.540	1.674	91.991	0.054	0.157	0.341	-0.0639	-0.1098	-0.10984

metric=Span distance=1 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
177	0.1	0.00	0.1	1.11	1.089	1.535	1.694	90.653	0.071	0.221	0.319	-0.0711	-0.0360	-0.07114
178	0.1	0.00	0.1	1.25	4.979	1.535	1.694	90.653	0.071	0.221	0.319	-0.2332	-0.0749	-0.23319
179	0.2	0.00	0.2	1.11	0.272	1.535	1.694	90.653	0.071	0.221	0.319	-0.0367	-0.0360	-0.03671
180	0.2	0.00	0.2	1.25	1.245	1.535	1.694	90.653	0.071	0.221	0.319	-0.0777	-0.0749	-0.07767
181	0.1	0.01	0.1	1.11	2.089	1.535	1.694	90.653	0.071	0.221	0.319	-0.1129	-0.0460	-0.11294
182	0.1	0.01	0.1	1.25	5.979	1.535	1.694	90.653	0.071	0.221	0.319	-0.2747	-0.0849	-0.27473
183	0.2	0.01	0.2	1.11	0.522	1.535	1.694	90.653	0.071	0.221	0.319	-0.0473	-0.0460	-0.04730
184	0.2	0.01	0.2	1.25	1.495	1.535	1.694	90.653	0.071	0.221	0.319	-0.0881	-0.0849	-0.08813
185	0.1	0.03	0.1	1.11	4.089	1.535	1.694	90.653	0.071	0.221	0.319	-0.1962	-0.0660	-0.19618
186	0.1	0.03	0.1	1.25	7.979	1.535	1.694	90.653	0.071	0.221	0.319	-0.3578	-0.1049	-0.35779
187	0.2	0.03	0.2	1.11	1.022	1.535	1.694	90.653	0.071	0.221	0.319	-0.0683	-0.0660	-0.06834
188	0.2	0.03	0.2	1.25	1.995	1.535	1.694	90.653	0.071	0.221	0.319	-0.1090	-0.1049	-0.10900
189	0.1	0.05	0.1	1.11	6.089	1.535	1.694	90.653	0.071	0.221	0.319	-0.2793	-0.0860	-0.27929
190	0.1	0.05	0.1	1.25	9.979	1.535	1.694	90.653	0.071	0.221	0.319	-0.4408	-0.1249	-0.44083
191	0.2	0.05	0.2	1.11	1.522	1.535	1.694	90.653	0.071	0.221	0.319	-0.0893	-0.0860	-0.08927
192	0.2	0.05	0.2	1.25	2.495	1.535	1.694	90.653	0.071	0.221	0.319	-0.1298	-0.1249	-0.12985

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Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2381

metric=Span distance=3 delay=15

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
193	0.1	0.00	0.1	1.11	1.089	1.644	1.680	97.859	0.067	0.146	0.455	-0.0319	-0.0235	-0.03188
194	0.1	0.00	0.1	1.25	4.979	1.644	1.680	97.859	0.067	0.146	0.455	-0.1006	-0.0624	-0.10055
195	0.2	0.00	0.2	1.11	0.272	1.644	1.680	97.859	0.067	0.146	0.455	-0.0174	-0.0235	-0.02348
196	0.2	0.00	0.2	1.25	1.245	1.644	1.680	97.859	0.067	0.146	0.455	-0.0346	-0.0624	-0.06238
197	0.1	0.01	0.1	1.11	2.089	1.644	1.680	97.859	0.067	0.146	0.455	-0.0495	-0.0335	-0.04954
198	0.1	0.01	0.1	1.25	5.979	1.644	1.680	97.859	0.067	0.146	0.455	-0.1182	-0.0724	-0.11819
199	0.2	0.01	0.2	1.11	0.522	1.644	1.680	97.859	0.067	0.146	0.455	-0.0219	-0.0335	-0.03348
200	0.2	0.01	0.2	1.25	1.495	1.644	1.680	97.859	0.067	0.146	0.455	-0.0390	-0.0724	-0.07238
201	0.1	0.03	0.1	1.11	4.089	1.644	1.680	97.859	0.067	0.146	0.455	-0.0848	-0.0535	-0.08484
202	0.1	0.03	0.1	1.25	7.979	1.644	1.680	97.859	0.067	0.146	0.455	-0.1535	-0.0924	-0.15348
203	0.2	0.03	0.2	1.11	1.022	1.644	1.680	97.859	0.067	0.146	0.455	-0.0307	-0.0535	-0.05348
204	0.2	0.03	0.2	1.25	1.995	1.644	1.680	97.859	0.067	0.146	0.455	-0.0479	-0.0924	-0.09238
205	0.1	0.05	0.1	1.11	6.089	1.644	1.680	97.859	0.067	0.146	0.455	-0.1201	-0.0735	-0.12013
206	0.1	0.05	0.1	1.25	9.979	1.644	1.680	97.859	0.067	0.146	0.455	-0.1888	-0.1124	-0.18877
207	0.2	0.05	0.2	1.11	1.522	1.644	1.680	97.859	0.067	0.146	0.455	-0.0395	-0.0735	-0.07348
208	0.2	0.05	0.2	1.25	2.495	1.644	1.680	97.859	0.067	0.146	0.455	-0.0567	-0.1124	-0.11238

metric=Span distance=3 delay=45

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
209	0.1	0.00	0.1	1.11	1.089	1.572	1.581	99.417	0.063	0.121	0.520	-0.0218	-0.0191	-0.021782
210	0.1	0.00	0.1	1.25	4.979	1.572	1.581	99.417	0.063	0.121	0.520	-0.0700	-0.0580	-0.069975
211	0.2	0.00	0.2	1.11	0.272	1.572	1.581	99.417	0.063	0.121	0.520	-0.0116	-0.0191	-0.019114
212	0.2	0.00	0.2	1.25	1.245	1.572	1.581	99.417	0.063	0.121	0.520	-0.0237	-0.0580	-0.058016
213	0.1	0.01	0.1	1.11	2.089	1.572	1.581	99.417	0.063	0.121	0.520	-0.0342	-0.0291	-0.034182
214	0.1	0.01	0.1	1.25	5.979	1.572	1.581	99.417	0.063	0.121	0.520	-0.0824	-0.0680	-0.082355
215	0.2	0.01	0.2	1.11	0.522	1.572	1.581	99.417	0.063	0.121	0.520	-0.0147	-0.0291	-0.029114

Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2382

metric=Span distance=3 delay=45

(continued)

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
216	0.2	0.01	0.2	1.25	1.495	1.572	1.581	99.417	0.063	0.121	0.520	-0.0266	-0.0660	-0.06602
217	0.1	0.03	0.1	1.11	4.089	1.572	1.581	99.417	0.063	0.121	0.520	-0.0590	-0.0491	-0.05895
218	0.1	0.03	0.1	1.25	7.979	1.572	1.581	99.417	0.063	0.121	0.520	-0.1071	-0.0880	-0.10711
219	0.2	0.03	0.2	1.11	1.022	1.572	1.581	99.417	0.063	0.121	0.520	-0.0210	-0.0491	-0.04911
220	0.2	0.03	0.2	1.25	1.995	1.572	1.581	99.417	0.063	0.121	0.520	-0.0330	-0.0880	-0.08802
221	0.1	0.05	0.1	1.11	6.089	1.572	1.581	99.417	0.063	0.121	0.520	-0.0837	-0.0691	-0.08371
222	0.1	0.05	0.1	1.25	9.979	1.572	1.581	99.417	0.063	0.121	0.520	-0.1319	-0.1080	-0.13186
223	0.2	0.05	0.2	1.11	1.522	1.572	1.581	99.417	0.063	0.121	0.520	-0.0272	-0.0691	-0.06911
224	0.2	0.05	0.2	1.25	2.495	1.572	1.581	99.417	0.063	0.121	0.520	-0.0392	-0.1080	-0.10802

metric=Span distance=3 delay=75

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
225	0.1	0.00	0.1	1.11	1.089	1.567	1.547	101.351	0.076	0.088	0.865	-0.0079	-0.0111	-0.011132
226	0.1	0.00	0.1	1.25	4.979	1.567	1.547	101.351	0.076	0.088	0.865	-0.0345	-0.0500	-0.050034
227	0.2	0.00	0.2	1.11	0.272	1.567	1.547	101.351	0.076	0.088	0.865	-0.0022	-0.0111	-0.011132
228	0.2	0.00	0.2	1.25	1.245	1.567	1.547	101.351	0.076	0.088	0.865	-0.0090	-0.0500	-0.050034
229	0.1	0.01	0.1	1.11	2.089	1.567	1.547	101.351	0.076	0.088	0.865	-0.0148	-0.0211	-0.021132
230	0.1	0.01	0.1	1.25	5.979	1.567	1.547	101.351	0.076	0.088	0.865	-0.0413	-0.0600	-0.060034
231	0.2	0.01	0.2	1.11	0.522	1.567	1.547	101.351	0.076	0.088	0.865	-0.0039	-0.0211	-0.021132
232	0.2	0.01	0.2	1.25	1.495	1.567	1.547	101.351	0.076	0.088	0.865	-0.0107	-0.0600	-0.060034
233	0.1	0.03	0.1	1.11	4.089	1.567	1.547	101.351	0.076	0.088	0.865	-0.0285	-0.0411	-0.041132
234	0.1	0.03	0.1	1.25	7.979	1.567	1.547	101.351	0.076	0.088	0.865	-0.0549	-0.0800	-0.080034
235	0.2	0.03	0.2	1.11	1.022	1.567	1.547	101.351	0.076	0.088	0.865	-0.0074	-0.0411	-0.041132
236	0.2	0.03	0.2	1.25	1.995	1.567	1.547	101.351	0.076	0.088	0.865	-0.0141	-0.0800	-0.080034
237	0.1	0.05	0.1	1.11	6.089	1.567	1.547	101.351	0.076	0.088	0.865	-0.0421	-0.0611	-0.061132

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Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2383

---------- metric=Span distance=3 delay=75 ----------
(continued)

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
238	0.1	0.05	0.1	1.25	9.979	1.567	1.547	101.351	0.076	0.088	0.865	-0.0686	-0.1000	-0.10003
239	0.2	0.05	0.2	1.11	1.522	1.567	1.547	101.351	0.076	0.088	0.865	-0.0109	-0.0611	-0.06113
240	0.2	0.05	0.2	1.25	2.495	1.567	1.547	101.351	0.076	0.088	0.865	-0.0176	-0.1000	-0.10003

---------- metric=Span distance=5 delay=15 ----------

Obs	Sigma TO	epsilon	Sigma TO	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
241	0.1	0.00	0.1	1.11	1.089	1.484	1.477	100.460	0.098	0.160	0.611	-0.0359	-0.0228	-0.03593
242	0.1	0.00	0.1	1.25	4.979	1.484	1.477	100.460	0.098	0.160	0.611	-0.1212	-0.0617	-0.12118
243	0.2	0.00	0.2	1.11	0.272	1.484	1.477	100.460	0.098	0.160	0.611	-0.0179	-0.0228	-0.02277
244	0.2	0.00	0.2	1.25	1.245	1.484	1.477	100.460	0.098	0.160	0.611	-0.0394	-0.0617	-0.06168
245	0.1	0.01	0.1	1.11	2.089	1.484	1.477	100.460	0.098	0.160	0.611	-0.0579	-0.0328	-0.05788
246	0.1	0.01	0.1	1.25	5.979	1.484	1.477	100.460	0.098	0.160	0.611	-0.1431	-0.0717	-0.14307
247	0.2	0.01	0.2	1.11	0.522	1.484	1.477	100.460	0.098	0.160	0.611	-0.0235	-0.0328	-0.03277
248	0.2	0.01	0.2	1.25	1.495	1.484	1.477	100.460	0.098	0.160	0.611	-0.0448	-0.0717	-0.07168
249	0.1	0.03	0.1	1.11	4.089	1.484	1.477	100.460	0.098	0.160	0.611	-0.1017	-0.0528	-0.10169
250	0.1	0.03	0.1	1.25	7.979	1.484	1.477	100.460	0.098	0.160	0.611	-0.1868	-0.0917	-0.18684
251	0.2	0.03	0.2	1.11	1.022	1.484	1.477	100.460	0.098	0.160	0.611	-0.0345	-0.0528	-0.05277
252	0.2	0.03	0.2	1.25	1.995	1.484	1.477	100.460	0.098	0.160	0.611	-0.0558	-0.0917	-0.09168
253	0.1	0.05	0.1	1.11	6.089	1.484	1.477	100.460	0.098	0.160	0.611	-0.1455	-0.0728	-0.14548
254	0.1	0.05	0.1	1.25	9.979	1.484	1.477	100.460	0.098	0.160	0.611	-0.2306	-0.1117	-0.23061
255	0.2	0.05	0.2	1.11	1.522	1.484	1.477	100.460	0.098	0.160	0.611	-0.0454	-0.0728	-0.07277
256	0.2	0.05	0.2	1.25	2.495	1.484	1.477	100.460	0.098	0.160	0.611	-0.0668	-0.1117	-0.11168

Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2384

metric=Span distance=5 delay=45

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
257	0.1	0.00	0.1	1.11	1.089	1.391	1.384	100.494	0.094	0.158	0.597	-0.0357	-0.0230	-0.03574
258	0.1	0.00	0.1	1.25	4.979	1.391	1.384	100.494	0.094	0.158	0.597	-0.1194	-0.0619	-0.11943
259	0.2	0.00	0.2	1.11	0.272	1.391	1.384	100.494	0.094	0.158	0.597	-0.0181	-0.0230	-0.02304
260	0.2	0.00	0.2	1.25	1.245	1.391	1.384	100.494	0.094	0.158	0.597	-0.0391	-0.0619	-0.06195
261	0.1	0.01	0.1	1.11	2.089	1.391	1.384	100.494	0.094	0.158	0.597	-0.0573	-0.0330	-0.05729
262	0.1	0.01	0.1	1.25	5.979	1.391	1.384	100.494	0.094	0.158	0.597	-0.1409	-0.0719	-0.14092
263	0.2	0.01	0.2	1.11	0.522	1.391	1.384	100.494	0.094	0.158	0.597	-0.0235	-0.0330	-0.03304
264	0.2	0.01	0.2	1.25	1.495	1.391	1.384	100.494	0.094	0.158	0.597	-0.0445	-0.0719	-0.07195
265	0.1	0.03	0.1	1.11	4.089	1.391	1.384	100.494	0.094	0.158	0.597	-0.1003	-0.0530	-0.10030
266	0.1	0.03	0.1	1.25	7.979	1.391	1.384	100.494	0.094	0.158	0.597	-0.1839	-0.0919	-0.18390
267	0.2	0.03	0.2	1.11	1.022	1.391	1.384	100.494	0.094	0.158	0.597	-0.0343	-0.0530	-0.05304
268	0.2	0.03	0.2	1.25	1.995	1.391	1.384	100.494	0.094	0.158	0.597	-0.0553	-0.0919	-0.09195
269	0.1	0.05	0.1	1.11	6.089	1.391	1.384	100.494	0.094	0.158	0.597	-0.1433	-0.0730	-0.14328
270	0.1	0.05	0.1	1.25	9.979	1.391	1.384	100.494	0.094	0.158	0.597	-0.2269	-0.1119	-0.22686
271	0.2	0.05	0.2	1.11	1.522	1.391	1.384	100.494	0.094	0.158	0.597	-0.0451	-0.0730	-0.07304
272	0.2	0.05	0.2	1.25	2.495	1.391	1.384	100.494	0.094	0.158	0.597	-0.0660	-0.1119	-0.11195

metric=Span distance=5 delay=75

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
273	0.1	0.00	0.1	1.11	1.089	1.436	1.427	100.594	0.127	0.177	0.717	-0.0384	-0.0202	-0.03845
274	0.1	0.00	0.1	1.25	4.979	1.436	1.427	100.594	0.127	0.177	0.717	-0.1413	-0.0591	-0.14126
275	0.2	0.00	0.2	1.11	0.272	1.436	1.427	100.594	0.127	0.177	0.717	-0.0166	-0.0202	-0.02019
276	0.2	0.00	0.2	1.25	1.245	1.436	1.427	100.594	0.127	0.177	0.717	-0.0426	-0.0591	-0.05909
277	0.1	0.01	0.1	1.11	2.089	1.436	1.427	100.594	0.127	0.177	0.717	-0.0649	-0.0302	-0.06495
278	0.1	0.01	0.1	1.25	5.979	1.436	1.427	100.594	0.127	0.177	0.717	-0.1676	-0.0691	-0.16764
279	0.2	0.01	0.2	1.11	0.522	1.436	1.427	100.594	0.127	0.177	0.717	-0.0233	-0.0302	-0.03019

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Attachment II (cont)

ALL 10:58 Tuesday, March 20, 2001 2385

---------- metric=Span distance=5 delay=75 ----------
(continued)

Obs	Sigma T0	epsilon	Sigma T0	ABE	FDA PBE limit	Geom Mean T	Geom Mean R	exp(DELTA)* 100	SigmaTT (Total T Std Dev)	SigmaTR (Total R Std Dev)	Ratio: sigTT / sigTR	95% UCL R-scaled PBE Criterion	95% UCL C-scaled PBE Criterion	Upper Confidence Bound
280	0.2	0.01	0.2	1.25	1.495	1.436	1.427	100.594	0.127	0.177	0.717	-0.0492	-0.0691	-0.06909
281	0.1	0.03	0.1	1.11	4.089	1.436	1.427	100.594	0.127	0.177	0.717	-0.1178	-0.0502	-0.11778
282	0.1	0.03	0.1	1.25	7.979	1.436	1.427	100.594	0.127	0.177	0.717	-0.2204	-0.0891	-0.22037
283	0.2	0.03	0.2	1.11	1.022	1.436	1.427	100.594	0.127	0.177	0.717	-0.0367	-0.0502	-0.05019
284	0.2	0.03	0.2	1.25	1.995	1.436	1.427	100.594	0.127	0.177	0.717	-0.0625	-0.0891	-0.08909
285	0.1	0.05	0.1	1.11	6.089	1.436	1.427	100.594	0.127	0.177	0.717	-0.1705	-0.0702	-0.17053
286	0.1	0.05	0.1	1.25	9.979	1.436	1.427	100.594	0.127	0.177	0.717	-0.2731	-0.1091	-0.27309
287	0.2	0.05	0.2	1.11	1.522	1.436	1.427	100.594	0.127	0.177	0.717	-0.0499	-0.0702	-0.07019
288	0.2	0.05	0.2	1.25	2.495	1.436	1.427	100.594	0.127	0.177	0.717	-0.0757	-0.1091	-0.10909

BIOEQUIVALENCY COMMENTS

ANDA: 75-824 APPLICANT: Roxane Laboratories

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-824
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney
HFD-652/ Y. Huang
HFD-655/ GJP Singl
HFD-617/ K. Scardina
HFD-650/ D. Connc

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BIOEQUIVALENCY - ACCEPTABLE

Submission Date: December 18, 2000

STUDY AMENDMENT (STA)

Strengths:
Outcome: AC

NOTE:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:

The *in vitro* performance testing conducted on Roxane Laboratories' Butorphanol Tartrate Nasal Spray Pump, 10 mg/mL comparing it with the reference product, Stadol®, nasal solution (Bristol-Myers) has been found acceptable.

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-824 SPONSOR : Roxane Laboratories
DRUG AND DOSAGE FORM: Butorphanol Tartrate Nasal Spray,
STRENGTH(S): 10 mg/mL
TYPES OF STUDIES: *In vitro*

TESTING LABORATORY: _____

STUDY SUMMARY: Acceptable

DISSOLUTION: NA

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results: Acceptable
First Generic YES New facility NO For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date) Aug 01, 2001	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL /S/ DATE: 5/21/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: /S/ DATE: 5/21/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

for INITIAL: /S/ DATE: 11/15/2001

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-824 SPONSOR : Roxane Laboratories
DRUG AND DOSAGE FORM: Butorphanol Tartrate Nasal Spray,
STRENGTH(S): 10 mg/mL
TYPES OF STUDIES: *In vitro*

TESTING LABORATORY: ——————

STUDY SUMMARY: Based on an acceptable response from Roxane to the Form 483 from the DSI inspection the study remains acceptable.

DISSOLUTION: NA

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results: Acceptable
First Generic YES New facility NO For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date) 7/27/01	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL: /S/ DATE: 10/26/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: /S/ DATE: 10/26/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL: /S/ DATE: 11/13/01

CC: ANDA 75-824
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DIVISION FILE
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DRUG FILE

HFD-652/ J. Chaney /S/ 10/26/2001
HFD-652/ Y. Huang /S/ 10/26/2001
HFD-617/ K. Scardina
HFD-650/ D. Conner /S/ 11/13/01
HFD-48 S. Subraman

V:\FIRMSNZ\ROXANE\LTRS&REV\75824ins.801

BIOEQUIVALENCY - ACCEPTABLE

1. OTHERS (OTH) - US Document Dated August 2, 2001 (1)

   Strength: 10 mg/mL
   (Audit Report Submitted August 1, 2001)
   Outcome: AC

2. STUDY AMENDMENT (STA)

   Strength: 10 mg/mL
   (Amendment in response to DSI report Submitted October 8, 2001)
   Outcome: AC

NOTE:

IC - Incomplete
AC - Acceptable
UN - Unacceptable
NC - No Action

Outcome Decision: AC - Acceptable

WINBIO COMMENT: Based on an acceptable response from Roxane to the Form 483 from the DSI inspection the study remains acceptable.

BIOEQUIVALENCY COMMENTS

ANDA: 75-824 APPLICANT: Roxane Laboratories

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

8/2/01
10/8/01
DSI
Report

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secret and/or

confidential

commercial

information

BIOEQUIVALENCY ACCEPTABLE

ANDA: 75-824 APPLICANT: Roxane Laboratories

DRUG PRODUCT: Butorphanol Tartrate Nasal Spray, 10 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please be advised for the future that (1) per 21 CFR 320.63 you should assure the proper retention of samples by the testing laboratories and clinics for all bioavailability or bioequivalence studies and (2) in your bioequivalence studies you should consistently follow parameters established during pre-study method validations.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

1ST

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research