

Data from FEV₁ Measurements for the Study Validation

Methacholine PD₂₀ (mg)

Subject#	Treatment	Reviewer	Sponsor
1 (AM visit)	Ref.	0.0491	0.0439
1 (PM visit)	Ref.	0.0588	0.0589
2	Ref.	0.021	0.021
3	Test	0.0289	0.025
4	Ref.	0.0542	0.0540

Data from All Visits
(the following from PM visits only)

Methacholine PD₂₀ (mg)

Subject#	Treatment	Reviewer	Sponsor
3	Test	0.2008	0.2010
5	Ref.	0.5831	0.3852
10	Test	0.0170	0.0152
18	Test	0.4409	0.3570
27	Ref.	1.2465	1.2430

Comment:

Based on the data provided, the reviewer cannot confirm some of the reported post-albuterol PD₂₀ values. Note that, in the absence of the number of breaths associated with each methacholine dose, five breaths were assumed. (please see the Deficiency Section).

M. Statistical Analysis and Comparative In Vivo Performance:

As recommended by the 1994 OGD interim Guidance, the post-albuterol PD₂₀ values of the in vivo performance of the test and reference listed products were used as the primary basis for bioequivalence evaluation. Data on the Drug Activity Ratios (DAR) have been analyzed and used as a secondary parameter for future reference.

The methacholine PD₂₀ measured after the albuterol dose of the test product was compared to the same measurement after the reference product. The ratios of the post-albuterol PD₂₀ to the pre-albuterol PD₂₀, Drug Activity ratio (DAR) for each treatment were also compared. The within product variances were also computed.

Individual subject PD₂₀ values for the test and reference products are given in Table #1. The effect of length of time between two treatments of a given product on the stability of post-albuterol PD₂₀ is given in Table #2 (the table shows the number of days between successive treatments of test and reference products). The relationship between length of dosing interval on the PD₂₀ ratios of its first and second replicate treatments is given in Table #3.

Results of the relationship between length of dosing interval (in days) and the PD₂₀ ratios of its first and second replicate treatments are displayed in Figure #1. This analysis was conducted to determine whether shorter intervals decreased variability in response.

The results of linear regression analysis indicated that there was no correlation between the length of dosing interval (in days) and the ratio of PD₂₀ values for either product. Shorter intervals did not result in PD₂₀ ratios closer to unity.

There are two ways to assess bioequivalence of MDI drugs based on pharmacodynamic measurements: (a) "response scale", and (b) "dose scale". In the "response scale" assessment, 90% confidence intervals are calculated for ratios of the test and reference products' values for a given pharmacodynamic metric, which is PD₂₀ for the bronchoprovocation study under review. The "dose scale" assessment method involves extrapolation of the pharmacodynamic response to the dose axis, and calculation of the 90% confidence intervals for the bioavailability of the test product relative to that of the reference product. The agency has previously approved albuterol MDI studies based on either "response scale" or "dose scale".

In the present submission both the in vivo pharmacodynamic study and data analysis were conducted based on the 1994 OGD interim guidance. The statistical analysis that was used to determine bioequivalence of the test and reference products was based on the response scale approach.

It should be noted that "dose scale" assessment of bioequivalence is not necessary for this biostudy for the following reasons:

1. The firm has conducted the present study based on the 1994 OGD interim guidance which requires each subject to demonstrate dose response before inclusion of the subject in the study.
2. The biostudy has shown the ability of the subjects that were enrolled to distinguish between pharmacodynamic responses (PD_{20}) to one and two actuations of the reference product, the characteristic that is known as the "good detector".
3. Most of subjects have shown a minimum twofold ratio of response to two actuations relative to one actuation of Ventolin® Inhalation Aerosol.
4. The biostudy included spirometric controls for each study day to minimize the variability in drug response.

DATA AND STATISTICAL ANALYSIS:

The statistical analysis to determine bioequivalence of the test and reference products was based on the "response scale". Analyses of the data were performed by the Division of Biometrics, HFD-700.

The following statistical approaches were applied:

1. Conventional analyses employed for replicate design-based bioequivalence studies.
2. Scaling of the bioequivalence interval based on the intra-subject variability of the reference product.

The evaluation analyses are described below:

1. **Conventional analyses employed for replicate design-based bioequivalence studies:**

The conventional analyses were performed with and without using the pre-albuterol PD_{20} as covariate. These analyses were carried out for log-transformed (Ln) post-albuterol PD_{20} and Drug Activity Ratio (DAR). In these analyses, two models were considered: (1) a model that assumed no period effect, and (2) a model that assumed that period effects might be present. Analyses were carried out using SAS PROC MIXED. The results of these analyses are summarized below in terms of point estimates and 90% confidence intervals for the ratio of test product average response over reference product average response.

a. Response Scale-Conventional Analyses without use of Pre-albuterol PD₂₀ as Covariate

Model	Ln(Post-Albuterol PD ₂₀)		Ln (DAR)	
	Test/Ref	90% CI	Test/Ref	90% CI
No Period Effect	80.90%	67.52, 96.92	89.49%	73.12, 109.52
With period Effect	81.14%	67.79, 97.12	89.68%	72.99, 110.19

Comments:

- i. Results of conventional analyses with or without period effect showed that the 90% confidence intervals for the log-transformed PD₂₀ fall within the range of % previously considered by OGD for the approval of generic albuterol MDI's.
- ii. Drug Activity Ratios (DAR) were calculated as secondary data analyses recommended in the OGD interim guidance. The DAR analysis is intended to assist an evaluation of adjustment of postdose PD₂₀ for the baseline PD₂₀ obtained on the same day. In addition, it serves as a potential future reference in the development of a bioequivalence standard for albuterol inhalation aerosols.
- iii. Note: The 1994 OGD interim guidance states that the primary data analysis of given bioequivalence data should be based on postdose PD₂₀. These data are considered pivotal.

b. Response Scale-Conventional Analyses with use of Pre-albuterol PD₂₀ as Covariate

Several analyses were carried out in which Ln(pre-albuterol PD₂₀) was used as a covariate. Point estimates and 90% confidence intervals using this approach were always the same for Ln-post albuterol PD₂₀ and Ln-DAR. The specific values of the 90% confidence limits depended on which factors were included in the statistical model. For this study, the lower limit of the 90% confidence interval ranged from % to %, and the upper limit of the 90% confidence interval ranged from % to %, for the various models used. Thus, all of the confidence intervals obtained using Ln(pre-albuterol PD₂₀) as a covariate fell within the limits

of μ .

2. **Scaling Of Bioequivalence Limits to the Reference Product Within-Subject Standard Deviation:**

Two analyses were carried out for this scaling approach. The purpose of the two analyses is to assess whether bioequivalence had been demonstrated if the bioequivalence limits are scaled to the reference product within-subject standard deviation. These analyses used bootstrap methodology [specifically, the Bias-Corrected and Accelerated (BCa) method as described in the 1993 textbook of Efron and Tibshirani, 100,000 bootstrap samples per run] to obtain 90% confidence intervals for the quantity,

$$[\text{Ln}(\mu\text{T}) - \text{Ln}(\mu\text{R})] / \sigma_{\text{WR}}$$

where: μT is the population geometric mean response for the Test product, μR is the population geometric mean response for the reference product, and σ_{WR} is the reference product within-subject standard deviation on the log scale. In the first analysis, it was assumed that there were no period effects in the study (Without Period Effect). In the second analysis, the analysis allowed for period effects (With Period Effect).

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The 90% bootstrap confidence limits

Model	Metric	90% bootstrap confidence Limits (Ln-Units)
Without Period Effect	Post-albuterol PD ₂₀	-0.6935, -0.0658
	DAR	-0.5287, 0.1385
With Period Effect	Post-albuterol PD ₂₀	-0.7625, -0.0504
	DAR	-0.5673, 0.1790

The bioequivalence limits to which these confidence intervals are compared are plus-or-minus $(\ln 1.25)/\sigma_{w0}$. For the choices of $\sigma_{w0} = 0.30, 0.25$ and 0.20 , these limits are as follows:

σ_{w0}	$(\ln 1.25)/\sigma_{w0}$	Bioequivalence Limits (Ln-units)
0.30	0.7438	-0.7438, 0.7438
0.25	0.8926	-0.8926, 0.8926
0.20	1.1157	-1.1157, 1.1157

Comments:

- i. The scaling of bioequivalence limits become less stringent as the value of σ_{w0} is decreased, and more stringent as the value of σ_{w0} is increased. Thus, a $\sigma_{w0} = 0.25$ provides wider bioequivalence limits than does $\sigma_{w0} = 0.30$.
- ii. The confidence interval for the primary PD₂₀ pharmacodynamic parameter analyzed without period effect falls within the limits corresponding to $\sigma_{w0} = 0.30$. When analyzed with a period effect, this parameter fails to fall within the limits corresponding to $\sigma_{w0} = 0.30$. It would pass the test for

$\sigma_{w0}=0.293$. Thus, both the products would pass the test for the less stringent limit of $\sigma_{w0} = 0.25$.

SUMMARY OF THE STATISTICAL ANALYSIS:

1. The bioequivalence evaluation for this study is based on "response scale".
2. For the pivotal post-dose PD₂₀ data, the test product meets the OGD interim standard bioequivalence interval criteria of \bar{V} % set for albuterol metered dose inhalers. These criteria are based on data analyses with and without the assumption of period effects and with and without the use of pre-albuterol PD₂₀ as covariate.
3. An alternative analysis, based on scaling the bioequivalence limits to the reference product's within-subject standard deviation, was conducted. The 90% confidence interval limits for the pivotal post-dose PD₂₀ data assuming no period effects fell within the limits corresponding to $\sigma_{w0} = 0.30$. However, when period effects were assumed, the 90% confidence interval does not fall within the limit corresponding to $\sigma_{w0} = 0.30$. The product would however, pass the test for $\sigma_{w0} = 0.293$ or lower, a less stringent bioequivalence limit.
4. The above analyses are contingent upon validation of data requested in the Deficiency Section.

V. SAFETY EVALUATION STUDY:

The in vivo safety evaluation study conducted by A.L. Laboratories on its drug product, albuterol inhalation aerosol, 90 µg per actuation, lot #6403, comparing it to Ventolin® manufactured by Allen & Hanburys (a Division of Glaxo), has been found acceptable by the Division of Bioequivalence. (Based on the medical officer's review, in volume B9.1) .

VI. DEFICIENCIES:

The following items are needed for completion of the evaluation of the in vivo bioequivalence study. These items should be provided on paper copies (spread sheets) as well as on a floppy diskette (ASCII format):

1. Complete raw data for all FEV₁ measurements, during screening and subject inclusion phases, and during the replicate design treatment phase for the 25 subjects used in the bioequivalence

study. This should include baseline FEV₁ measurements for each study day including subject screening and inclusion phase, as well as all FEV₁ measurements associated with each and every challenge dose. The number of breaths of methacholine associated with each and every challenge dose should also be reported.

These data should include:

A. Raw data on subject inclusion qualification criteria showing that there was a minimum eight-fold increase over baseline in response to two actuations of Ventolin[®] Inhalation Aerosol and a minimum twofold ratio of response to two actuations relative to one actuation of Ventolin[®] Inhalation Aerosol. Include an example(s) of the method of calculation that was used for subject inclusion qualification criteria.

B. With regard to the data on the individual FEV₁ efforts for the bronchoprovocation study (Data submitted by the firm on June 19, 1995, in two tables, located in volume B9.1, p #05-#25).

i. For **Table #1** (baseline FEV₁ data prior to morning and afternoon challenges for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

ii. For **Table #2** (raw FEV₁ data for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

2. Please provide the equation that was used to estimate the Post-albuterol PD₂₀ (cumulative mg). In addition, the firm should provide examples of its calculations for this value for a number of subjects. These examples should include subjects who had relatively high and relatively low post-albuterol PD₂₀ values.
3. In the validation report section (Vol. A8.1, page #116), the firm is requested to provide equations and its calculations for subject #1, both morning and afternoon visits.
4. The raw data for the challenge studies should include the actual date of dosing of the treatment phase, gender and age, body weight, height, and predicted FEV₁ for age, gender and height, in addition to the data on baseline, saline control and FEV₁ at each challenge dose.

VII. RECOMMENDATION:

The in vivo bioequivalence study conducted by A.L. Laboratories on its drug product, albuterol inhalation aerosol, 90 µg per actuation, lot #6403, comparing it to Ventolin® manufactured by Allen & Hanburys (a Division of Glaxo), has been found incomplete by the Division of Bioequivalence for the deficiencies cited above.

The firm should be informed of the deficiencies and recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

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FT INITIALED RMHATRE

/S/

9/3/96

Concur: _____ */S/* _____ Date: *9/3/96*

fu Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 73-045 (original, duplicate), HFD-600 (Hare), HFD-630,
HFD-658 (Mhatre, Wahba), Drug File, Division File

ANDA: 73-045

Table # 1

PharmaKinetics Laboratories, Inc.
 Albuterol Metered Dose Inhaler
 Bronchoprovocation Study #135-01-10647

Daily Baseline Qualification Criteria During Bioequivalence Testing (A,B)

Subject	Qual Day Qual			Product	Visit Date	Visit	Baseline FEV1	% (FEV1/ Pred FEV1) [1]	%Chg FEV1 /Qual Day FEV1 [2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1 [3]	% (Pre-A PD20/ .Qual Day PD20) [4]	Pre- Albuterol PD20	Post- Albuterol PD20	Post-A PD20/ Pre-A PD20
	Pred FEV1	Pre-A PD20	Day FEV1												
101	3.93	0.0463	3.87	R	16MAY94	1	3.83	97	-1	3.83	0.0				
				R	18MAY94	1A	3.91	99	1	3.87	-1.0	167.0	0.0773	0.1840	2.4
				T	24MAY94	2	4.21	107	9	4.21	0.0	99.4	0.0460	0.0680	1.5
				T	02JUN94	3	3.90	99	1	3.81	-2.3	57.7	0.0267	0.1294	4.8
102	4.32	0.0442	3.62	R	08JUN94	4	3.79	96	-2	3.66	-3.4	89.2	0.0413	0.1270	3.1
				T	18MAY94	1	3.53	82	-2	3.36	-4.8	79.6	0.0352	0.3670	10.4
				R	15JUN94	2	3.49	81	-4	3.49	0.0	126.2	0.0558	0.1850	3.3
				R	21JUN94	3	3.62	84	0	3.66	1.1	58.1	0.0257	0.5930	23.1
103	3.97	0.0160	4.21	T	28JUN94	4	3.79	88	5	3.79	0.0	140.3	0.0620	0.2320	3.7
				R	20MAY94	1	4.17	105	-1	4.13	-1.0	455.0	0.0728		
				R	23MAY94	1A	3.74	94	-11	3.62	-3.2	91.3	0.0146	0.1790	12.3
				T	25MAY94	2	3.91	98	-7	3.83	-2.0	120.0	0.0192	0.2010	10.5
104	4.32	0.1820	3.87	T	07JUN94	3	3.83	96	-9	3.70	-3.4	80.6	0.0129		
				T	14JUN94	3A	4.09	103	-3	4.04	-1.2	63.1	0.0101	0.0652	6.5
				R	17JUN94	4	4.21	106	0	4.02	-4.5	269.4	0.0431		
				R	22JUN94	4A	4.26	107	1	4.13	-3.1	117.5	0.0188	0.1590	8.5
105	3.31	0.0788	2.81	T	23MAY94	1	3.83	89	-1	3.83	0.0	76.9	0.1400	6.8360	48.8
				R	25MAY94	2	3.70	86	-4	3.70	0.0	321.9	0.5858		
				R	31MAY94	2A	3.77	87	-3	3.90	3.4	56.9	0.1035	2.6840	25.9
				R	03JUN94	3	3.70	86	-4	3.70	0.0	89.6	0.1630	3.8360	23.5
105	3.31	0.0788	2.81	T	07JUN94	4	3.79	88	-2	3.87	2.1	168.8	0.3072	5.8000	18.9
				T	17JUN94	1	3.11	94	11	3.06	-1.6	223.4	0.1760		
				T	20JUN94	1A	2.81	85	0	2.89	2.8	106.7	0.0841	0.3138	3.7
				R	22JUN94	2	2.85	86	1	2.85	0.0	105.2	0.0829	0.3852	4.6
				R	29JUN94	3	2.77	84	-1	2.85	2.9	97.2	0.0766	0.7540	9.8

[A] Subjects were excluded from the study on a particular day if:

- [1] the baseline FEV1 was < 70% of predicted
- [2] there was a greater than 12% change in FEV1 from the qualifying day FEV1
- [3] there was a greater than 10% drop in FEV1 post-saline administration
- [4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400% (# - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20

[B] The abbreviations used on this listing are: Pred-Predicted, Pre-A-Pre-Albuterol, Post-A-Post-Albuterol, Base-Baseline Qual Day-Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

ANDA : 73-034

Table # 1
(Continue)

PharmaKinetics Laboratories, Inc.
Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647

Daily Baseline Qualification Criteria During Bioequivalence Testing (A,B)

Subject	Qual Day Qual			Product	Visit Date	Visit	Baseline FEV1	% (FEV1/ Pred FEV1) [1]	%Chg FEV1 /Qual Day FEV1[2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1 [3]	% (Pre-A PD20/ Qual Day PD20) [4]	Pre- Albuterol PD20	Post- Albuterol PD20	Post-A PD20/ Pre-A PD20
	Pred FEV1	Pre-A PD20	Day FEV1												
106	2.56	0.0782	2.13	T	06JUL94	4	2.72	82	-3	2.68	-1.5	105.7	0.0833	0.5530	6.6
				R	22JUN94	1	2.13	83	0	2.13	0.0	44.5	0.0348	0.4108	11.8
				T	07JUL94	2	2.17	85	2	2.13	-1.8	109.0	0.0852	0.8012	9.4
				T	12JUL94	3	2.00	78	-6	2.04	2.0	73.7	0.0576	1.3692	23.8
108	4.57	0.2310	3.73	R	14JUL94	4	2.17	85	2	2.04	-6.0	120.2	0.0940	1.4044	14.9
				R	10AUG94	1	3.66	80	-2	3.57	-2.5	162.8	0.3760	1.0390	2.8
				T	12AUG94	2	3.70	81	-1	3.66	-1.1	79.7	0.1840	1.1010	6.0
				T	15AUG94	3	3.62	79	-3	3.62	0.0	274.9	0.6350		
109	4.57	0.0770	4.94	T	16AUG94	3A	3.62	79	-3	3.53	-2.5	168.4	0.3890	1.6940	4.4
				R	22AUG94	4	3.60	79	-3	3.47	-3.6	168.4	0.3890	3.6180	9.3
				T	18AUG94	1	4.68	102	-5	4.81	2.8	248.1	0.1910		
				T	23AUG94	1A	4.85	106	-2	4.77	-1.6	94.8	0.0730	1.0390	14.2
110	3.84	0.0066	3.57	R	26AUG94	2	4.72	103	-4	4.68	-0.8	90.9	0.0700	0.4240	6.1
				R	31AUG94	3	4.77	104	-3	4.60	-3.6	213.0	0.1640		
				R	02SEP94	3A	4.85	106	-2	4.77	-1.6	129.5	0.0997	2.3940	24.0
				T	06SEP94	4	4.85	106	-2	4.77	-1.6	95.3	0.0734	1.5260	20.8
113	3.23	0.1770	2.79	R	19AUG94	1	3.53	92	-1	3.40	-3.7	215.2	0.0142		
				R	23AUG94	1A	2.68	70	-25						
				R	30AUG94	1B	3.23	84	-10	3.19	-1.2	145.5	0.0096	0.0317	3.3
				T	08SEP94	2	3.28	85	-8	3.23	-1.5	106.1	0.0070	0.0152	2.2
113	3.23	0.1770	2.79	T	15SEP94	3	3.66	95	3	3.53	-3.6	103.0	0.0068	0.0466	6.9
				R	20SEP94	4	3.66	95	3	3.49	-4.6	378.8	0.0250		
				R	27SEP94	4A	3.49	91	-2	3.23	-7.4	140.9	0.0093	0.0529	5.7
				R	15SEP94	1	2.40	74	-14						
R	06OCT94	1A	2.64	82	-5	2.67	1.1	41.2	0.0730	0.5370	7.4				

[A] Subjects were excluded from the study on a particular day if:

- [1] the baseline FEV1 was < 70% of predicted
- [2] there was a greater than 12% change in FEV1 from the qualifying day FEV1
- [3] there was a greater than 10% drop in FEV1 post-saline administration
- [4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400%
(# - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20

[B] The abbreviations used on this listing are: Pred=Predicted, Pre-A=Pre-Albuterol, Post-A=Post-Albuterol, Base=Baseline Qual Day=Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

ANDA: 73-045

Table # 1
(Continue)

PharmaKinetics Laboratories, Inc.
Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647

Daily Baseline Qualification Criteria During Bioequivalence Testing (A,B)

Subject	Qual Day Qual			Visit	Date	Visit	Baseline FEV1	% (FEV1/ Pred [1])	%Chg FEV1 /Qual Day [2]	Saline FEV1	%Chg Saline FEV1 /Base [3]	% (Pre-A PD20/ Qual Day [4])	Pre- Albuterol PD20	Post- Albuterol PD20	Post-A PD20/ Pre-A PD20
	Pred FEV1	Pre-A PD20	Day FEV1												
114	2.99	0.0070	3.29	T	13OCT94	2	2.76	85	-1	2.76	0.0	102.3	0.1810	1.4800	8.2
				T	10NOV94	3	2.57	80	-8	2.69	4.7	48.6	0.0860	0.6080	7.1
				R	17NOV94	4	2.71	84	-3	2.72	0.4	138.4	0.2450	0.5400	2.2
				T	22OCT94	1	3.54	118	8	3.47	-2.0	328.6	0.0230		
				T	24OCT94	1A	3.25	109	-1	3.08	-5.2	285.7	0.0200		
				T	29OCT94	1B	3.00	100	-9	2.87	-4.3	300.0	0.0210	0.0210	1.0
				R	12NOV94	2	3.09	103	-6	3.12	1.0	128.6	0.0090	0.0360	4.0
				R	29NOV94	3	3.20	107	-3	2.54	-20.6				
115	3.62	0.0280	3.04	R	03DEC94	3A	3.26	109	-1	3.29	0.9	228.6	0.0160	0.0330	2.1
				T	05DEC94	4	3.30	110	0	3.41	3.3	228.6	0.0160	0.0140	0.9
				R	08NOV94	1	2.56	71	-16						
				R	14NOV94	1A	3.14	87	3	3.02	-3.8	235.7	0.0660	0.3140	4.8
				T	07DEC94	2	3.04	84	0	2.94	-3.3	246.4	0.0690	0.1530	2.2
				T	04JAN95	3	2.77	77	-9	2.56	-7.6	114.3	0.0320	0.0860	2.7
				R	13JAN95	4	3.26	90	7	3.09	-5.2	67.9	0.0190	0.1070	5.6
				T	09NOV94	1	2.27	91	-11	2.20	-3.1	50.0	0.0090	0.0270	3.0
116	2.49	0.0180	2.55	R	11NOV94	2	2.24	90	-12	2.18	-2.7	44.4	0.0080	0.0580	7.3
				R	22NOV94	3	2.25	90	-12	2.31	2.7	94.4	0.0170	0.2610	15.4
				T	30NOV94	4	2.55	102	0	2.48	-2.7	155.6	0.0280	0.1520	5.4
				R	17NOV94	1	3.45	88	-3	3.49	1.2	301.9	1.0840	5.0400	4.6
				T	28NOV94	2	3.49	89	-2	3.32	-4.9	201.7	0.7240	1.0050	1.4
				T	30NOV94	3	3.45	88	-3	3.49	1.2	217.8	0.7820	0.8110	1.0
				R	02DEC94	4	3.53	90	-1	3.36	-4.8	790.0	2.8360		
				R	14DEC94	4A	3.49	89	-2	3.32	-4.9	228.4	0.8200	1.5200	1.9
118	2.75	0.0960	2.89	T	23NOV94	1	2.94	107	2	2.85	-3.1	53.1	0.0510	0.3570	7.0

[A] Subjects were excluded from the study on a particular day if:

- [1] the baseline FEV1 was < 70% of predicted
- [2] there was a greater than 12% change in FEV1 from the qualifying day FEV1
- [3] there was a greater than 10% drop in FEV1 post-saline administration
- [4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400% (8 - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20

[B] The abbreviations used on this listing are: Pred-Predicted, Pre-A-Pre-Albuterol, Post-A-Post-Albuterol, Base-Baseline Qual Day-Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

ANDA : 73-045

Table #1
(Continue)

PharmaKinetics Laboratories, Inc.
Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647

Daily Baseline Qualification Criteria During Bioequivalence Testing (A,B)

Subject	Qual Day Qual			Product	Visit Date	Visit	Baseline FEV1	% (FEV1/ Pred FEV1) [1]	%Chg FEV1 /Qual Day FEV1 [2]	%Chg Saline FEV1 /Base FEV1 [3]	% (Pre-A PD20/ Qual Day PD20) [4]	Pre- Albuterol PD20	Post- Albuterol PD20	Post-A PD20/ Pre-A PD20	
	Pred FEV1	Pre-A PD20	Day Qual FEV1												
119	4.48	0.0200	3.72	R	28NOV94	2	2.64	96	-9	2.60	-1.5	18.0	0.0173		
				R	02DEC94	2A	2.85	104	-1	2.77	-2.8	190.6	0.1830	0.6770	3.7
				R	05DEC94	3	2.72	99	-6	2.72	0.0	176.0	0.1690	0.4250	2.5
				T	07DEC94	4	3.02	110	4	2.89	-4.3	136.5	0.1310	0.9490	7.2
				T	01DEC94	1	3.37	75	-9	3.37	0.0	70.0	0.0140	0.0180	1.3
				R	03DEC94	2	3.45	77	-7	3.42	-0.9	210.0	0.0420	0.0540	1.3
				R	29DEC94	3	3.22	72	-13						
				R	09JAN95	3A	3.12	70	-16						
				R	11JAN95	3B	3.52	79	-5	3.30	-6.3	105.0	0.0210	0.0770	3.7
				T	18JAN95	4	3.59	80	-3	3.53	-1.7	130.0	0.0260	0.0370	1.4
121	4.33	0.0500	3.74	T	20DEC94	1	3.71	86	-1	3.74	0.8	164.0	0.0820	0.2570	3.1
				R	22DEC94	2	3.70	85	-1	3.61	-2.4	272.0	0.1360	0.1030	0.8
				R	11JAN95	3	4.15	96	11	4.09	-1.4	368.0	0.1840	0.1750	1.0
				T	17JAN95	4	2.14	49	-43						
				T	23JAN95	4A	4.01	93	7	3.86	-3.7	170.0	0.0850		
				T	27JAN95	4B	3.74	86	0	3.80	1.6	166.0	0.0830	0.1620	2.0
122	3.97	0.1320	3.41	R	10JAN95	1	3.24	82	-5	3.30	1.9	136.4	0.1800	0.5650	3.1
				T	25JAN95	2	3.02	76	-11	2.92	-3.3	112.9	0.1490	0.1600	1.1
				T	01FEB95	3	3.03	76	-11	2.89	-4.6	57.6	0.0760	0.1440	1.9
				R	03FEB95	4	2.94	74	-14						
				R	13FEB95	4A	2.75	69	-19						
				R	21MAR95	4B	3.07	77	-10	2.92	-4.9	243.2	0.3210	0.4610	1.4
123	3.46	0.5020	3.17	R	18JAN95	1	2.90	84	-9	2.78	-4.1	67.3	0.3380	1.5360	4.5
				T	25JAN95	2	2.66	77	-16						
				T	27JAN95	2A	2.67	77	-16						

[A] Subjects were excluded from the study on a particular day if:

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- [3] there was a greater than 10% drop in FEV1 post-saline administration
- [4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400% (# - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20

[B] The abbreviations used on this listing are: Pred-Predicted, Pre-A-Pre-Albuterol, Post-A-Post-Albuterol, Base-Baseline Qual Day-Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

ANDA : 73-045

Table # 1
(Continue)

PharmaKinetics Laboratories, Inc.
Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647

Daily Baseline Qualification Criteria During Bioequivalence Testing (A,B)

Subject	Pred FEV1	Qual Day Pre-A PD20	Qual Day FEV1	Product	Visit Date	Visit	Baseline FEV1	% (FEV1/ Pred FEV1) [1]	%Chg FEV1 /Qual Day FEV1 [2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1 [3]	% (Pre-A PD20/ Qual Day PD20) [4]	Pre- Albuterol PD20	Post- Albuterol PD20	Post-A PD20/ Pre-A PD20
124	2.69	0.2860	3.49	T	81JAN95	2B	2.81	81	-11	2.73	-2.8	46.4	0.2330	3.3020	14.2
				T	02FEB95	3	2.83	82	-11	2.73	-3.5	59.8	0.3000	1.1390	3.8
				R	07FEB95	4	2.92	84	-8	2.90	-0.7	25.1	0.1260	0.9050	7.2
				T	07MAR95	1	3.29	122	-6	3.26	-0.9	99.0	0.2830	1.6920	6.0
				R	14MAR95	2	3.44	128	-1	3.41	-0.9	187.4	0.5360	0.5360	1.0
125	3.33	0.0480	2.77	R	21MAR95	3	3.21	119	-8	3.07	-4.4	113.6	0.3250	2.2610	7.0
				T	27MAR95	4	3.23	120	-7	3.18	-1.5	95.1	0.2720	1.5600	5.7
				R	14MAR95	1	2.65	80	-4	2.82	6.4	87.5	0.0420	0.0990	2.4
				T	20MAR95	2	2.72	82	-2	2.66	-2.2	87.5	0.0420	0.1950	4.6
126	4.27	0.0480	3.72	T	27MAR95	3	2.71	81	-2	2.70	-0.4	58.3	0.0280	0.1610	5.8
				R	04APR95	4	2.59	78	-6	2.69	3.9	72.9	0.0350	0.1860	5.3
				T	31MAR95	1	3.76	88	1	3.59	-4.5	166.7	0.0800	0.3520	4.4
				R	05APR95	2	3.58	84	-4	3.53	-1.4	120.8	0.0580	0.5610	9.7
				R	07APR95	3	3.71	87	0	3.78	1.9	120.8	0.0580	0.3900	6.7
127	3.38	0.2160	3.39	T	12APR95	4	3.97	93	7	4.06	2.3	116.7	0.0560	0.5000	8.9
				T	01APR95	1	3.35	99	-1	3.27	-2.4	77.8	0.1680	1.3360	8.0
				R	08APR95	2	3.33	99	-2	3.37	1.2	87.0	0.1880	1.2430	6.6
				R	11APR95	3	3.21	95	-5	3.15	-1.9	98.6	0.2130	2.2840	10.7
				T	22APR95	4	3.13	93	-8	3.26	4.2	85.2	0.1840	0.6050	3.3
128	3.71	0.0160	2.95	R	01APR95	1	2.81	76	-5	2.91	3.6	143.8	0.0230	0.1660	7.2
				T	08APR95	2	2.85	77	-3	2.80	-1.8	181.3	0.0290	0.0890	3.1
				T	13APR95	3	2.83	76	-4	2.80	-1.1	168.8	0.0270	0.0860	3.2
				R	22APR95	4	2.69	73	-9	2.62	-2.6	500.0	0.0800		
				R	29APR95	4A	2.67	72	-9	2.64	-1.1	93.8	0.0150	0.1250	8.3
129	3.18	0.2220	3.47	R	03APR95	1	3.27	103	-6	3.32	1.5	132.9	0.2950	1.2470	4.2

[A] Subjects were excluded from the study on a particular day if:

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- [3] there was a greater than 10% drop in FEV1 post-saline administration
- [4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400% (8 - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20

[B] The abbreviations used on this listing are: Pred=Predicted, Pre-A=Pre-Albuterol, Post-A=Post-Albuterol, Base=Baseline Qual Day=Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

ANDA : 73-045

Table #1
(Continue)

PharmaKinetics Laboratories, Inc.
Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647
Daily Baseline Qualification Criteria During Bioequivalence Testing (A,B)

Subject	Pred FEV1	Qual Day Pre-A PD20	Qual Day FEV1 Product	Visit Date	Visit	Baseline FEV1	% (FEV1/ Pred FEV1) {1}	%Chg FEV1 /Qual Day FEV1 {2}	Saline FEV1	%Chg Saline FEV1 /Base FEV1 {3}	% (Pre-A PD20/ .Qual Day Albuterol PD20) {4}	Pre- Albuterol PD20	Post- Albuterol PD20	Post-A PD20/ Pre-A PD20	
				T	05APR95	2	3.47	109	0	3.36	-3.2	105.9	0.2350	0.5380	2.3
				T	11APR95	3	3.24	102	-7	3.22	-0.6	144.1	0.3200	1.2530	3.9
				R	13APR95	4	3.34	105	-4	3.35	0.3	169.4	0.3760	1.1850	3.2

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[A] Subjects were excluded from the study on a particular day if:

- [1] the baseline FEV1 was < 70% of predicted
- [2] there was a greater than 12% change in FEV1 from the qualifying day FEV1
- [3] there was a greater than 10% drop in FEV1 post-saline administration
- [4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400%
(# - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20

[B] The abbreviations used on this listing are: Pred-Predicted, Pre-A-Pre-Albuterol, Post-A-Post-Albuterol, Base-Baseline
Qual Day-Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

ANDA # 73-045

Table # 2

number of days
between treatments



Study subject	Study seq	#135-01-1 product	Bioequivalence vdate	Phase ivisit	Visit isvisit	Meeting : Qualificati		Criteria 1		Criteria 1 sfv1	Criteria 1 sfv1	Criteria 1 sfv1
						pd20	apd20	fev1	sfv1			
101	2	2	18-May-94	1A		1	0.0773	0.184	3.91	3.87	0	
101	2	1	24-May-94		2	2	0.046	0.068	4.21	4.21	-6	
101	2	1	2-Jun-94		3	3	0.0267	0.1294	3.9	3.81	-15	
101	2	2	8-Jun-94		4	4	0.0413	0.127	3.79	3.66	-21	
102	1	1	18-May-94		1	1	0.0352	0.367	3.53	3.36	0	
102	1	2	15-Jun-94		2	2	0.0558	0.185	3.49	3.49	-28	
102	1	2	21-Jun-94		3	3	0.0257	0.593	3.62	3.66	-34	
102	1	1	28-Jun-94		4	4	0.062	0.232	3.79	3.79	-41	
103	2	2	23-May-94	1A		1	0.0146	0.179	3.74	3.62	0	
103	2	1	25-May-94		2	2	0.0192	0.201	3.91	3.83	-2	
103	2	1	14-Jun-94	3A		3	0.0101	0.0652	4.09	4.04	-22	
103	2	2	22-Jun-94	4A		4	0.0188	0.159	4.26	4.13	-30	
104	1	1	23-May-94		1	1	0.14	6.836	3.83	3.83	0	
104	1	2	31-May-94	2A		2	0.1035	2.684	3.77	3.9	-8	
104	1	2	3-Jun-94		3	3	0.163	3.836	3.7	3.7	-11	
104	1	1	7-Jun-94		4	4	0.3072	5.8	3.79	3.87	-15	
105	1	1	20-Jun-94	1A		1	0.0841	0.3138	2.81	2.89	0	
105	1	2	22-Jun-94		2	2	0.0829	0.3852	2.85	2.85	-2	
105	1	2	29-Jun-94		3	3	0.0766	0.754	2.77	2.85	-9	
105	1	1	6-Jul-94		4	4	0.0833	0.553	2.72	2.68	-16	
106	2	2	22-Jun-94		1	1	0.0348	0.4108	2.13	2.13	0	
106	2	1	7-Jul-94		2	2	0.0852	0.8012	2.17	2.13	-15	
106	2	1	12-Jul-94		3	3	0.0576	1.3692	2	2.04	-20	
106	2	2	14-Jul-94		4	4	0.094	1.4044	2.17	2.04	-22	
108	2	2	10-Aug-94		1	1	0.376	1.039	3.66	3.57	0	
108	2	1	12-Aug-94		2	2	0.184	1.101	3.7	3.66	-2	
108	2	1	16-Aug-94	3A		3	0.389	1.894	3.62	3.53	-6	
108	2	2	22-Aug-94		4	4	0.389	3.818	3.6	3.47	-12	
109	1	1	23-Aug-94	1A		1	0.073	1.039	4.85	4.77	0	
109	1	2	26-Aug-94		2	2	0.07	0.424	4.72	4.68	-3	
109	1	2	2-Sep-94	3A		3	0.0997	2.394	4.85	4.77	-10	
109	1	1	6-Sep-94		4	4	0.0734	1.526	4.85	4.77	-14	
110	2	2	30-Aug-94	1B		1	0.0096	0.0317	3.23	3.19	0	
110	2	1	8-Sep-94		2	2	0.007	0.0152	3.28	3.23	-9	
110	2	1	15-Sep-94		3	3	0.0068	0.0466	3.66	3.53	-16	
110	2	2	27-Sep-94	4A		4	0.0093	0.0529	3.49	3.23	-28	
113	2	2	6-Oct-94	1A		1	0.073	0.537	2.84	2.67	0	
113	2	1	13-Oct-94		2	2	0.181	1.48	2.76	2.76	-7	
113	2	1	10-Nov-94		3	3	0.086	0.608	2.57	2.69	-35	
113	2	2	17-Nov-94		4	4	0.245	0.54	2.71	2.72	-42	
114	1	1	29-Oct-94	1B		1	0.021	0.021	3	2.87	0	
114	1	2	12-Nov-94		2	2	0.009	0.036	3.09	3.12	-14	
114	1	2	3-Dec-94	3A		3	0.016	0.033	3.26	3.29	-35	
114	1	1	5-Dec-94		4	4	0.016	0.014	3.3	3.41	-37	
115	2	2	14-Nov-94	1A		1	0.066	0.314	3.14	3.02	0	
115	2	1	7-Dec-94		2	2	0.069	0.153	3.04	2.94	-23	
115	2	1	4-Jan-95		3	3	0.032	0.086	2.77	2.56	-51	
115	2	2	13-Jan-95		4	4	0.019	0.107	3.26	3.09	-60	
116	1	1	9-Nov-94		1	1	0.009	0.027	2.27	2.2	0	

number of days
between treatments



Table # 2
(Continue)

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116	1	2	11-Nov-94	2	2	0.008	0.058	2.24	2.18	-2
116	1	2	22-Nov-94	3	3	0.017	0.261	2.25	2.31	-13
116	1	1	30-Nov-94	4	4	0.028	0.152	2.55	2.48	-21
117	2	2	17-Nov-94	1	1	1.084	5.04	3.45	3.49	0
117	2	1	28-Nov-94	2	2	0.724	1.005	3.49	3.32	-11
117	2	1	30-Nov-94	3	3	0.782	0.811	3.45	3.49	-13
117	2	2	14-Dec-94 4A		4	0.82	1.52	3.49	3.32	-27
118	1	1	23-Nov-94	1	1	0.051	0.357	2.94	2.85	0
118	1	2	2-Dec-94 2A		2	0.183	0.677	2.85	2.77	-9
118	1	2	5-Dec-94	3	3	0.169	0.425	2.72	2.72	-12
118	1	1	7-Dec-94	4	4	0.131	0.949	3.02	2.89	-14
119	1	1	1-Dec-94	1	1	0.014	0.018	3.37	3.37	0
119	1	2	3-Dec-94	2	2	0.042	0.054	3.45	3.42	-2
119	1	2	11-Jan-95 3B		3	0.021	0.077	3.52	3.3	-41
119	1	1	18-Jan-95	4	4	0.026	0.037	3.59	3.53	-48
121	1	1	20-Dec-94	1	1	0.082	0.257	3.71	3.74	0
121	1	2	22-Dec-94	2	2	0.136	0.103	3.7	3.61	-2
121	1	2	11-Jan-95	3	3	0.184	0.175	4.15	4.09	-22
121	1	1	27-Jan-95 4B		4	0.083	0.162	3.74	3.8	-38
122	2	2	10-Jan-95	1	1	0.18	0.565	3.24	3.3	0
122	2	1	25-Jan-95	2	2	0.149	0.16	3.02	2.92	-15
122	2	1	1-Feb-95	3	3	0.076	0.144	3.03	2.89	-22
122	2	2	21-Mar-95 4B		4	0.321	0.461	3.07	2.92	-70
123	2	2	18-Jan-95	1	1	0.338	1.536	2.9	2.78	0
123	2	1	31-Jan-95 2B		2	0.233	3.302	2.81	2.73	-13
123	2	1	2-Feb-95	3	3	0.3	1.139	2.83	2.73	-15
123	2	2	7-Feb-95	4	4	0.126	0.905	2.92	2.9	-20
124	1	1	7-Mar-95	1	1	0.283	1.692	3.29	3.26	0
124	1	2	14-Mar-95	2	2	0.536	0.536	3.44	3.41	-7
124	1	2	21-Mar-95	3	3	0.325	2.261	3.21	3.07	-14
124	1	1	27-Mar-95	4	4	0.272	1.56	3.23	3.18	-20
125	2	2	14-Mar-95	1	1	0.042	0.099	2.65	2.82	0
125	2	1	20-Mar-95	2	2	0.042	0.195	2.72	2.66	-6
125	2	1	27-Mar-95	3	3	0.028	0.161	2.71	2.7	-13
125	2	2	4-Apr-95	4	4	0.035	0.186	2.59	2.69	-21
126	1	1	31-Mar-95	1	1	0.08	0.352	3.76	3.59	0
126	1	2	5-Apr-95	2	2	0.058	0.561	3.58	3.53	-5
126	1	2	7-Apr-95	3	3	0.058	0.39	3.71	3.78	-7
126	1	1	12-Apr-95	4	4	0.056	0.5	3.97	4.06	-12
127	1	1	1-Apr-95	1	1	0.168	1.336	3.35	3.27	0
127	1	2	8-Apr-95	2	2	0.188	1.243	3.33	3.37	-7
127	1	2	11-Apr-95	3	3	0.213	2.284	3.21	3.15	-10
127	1	1	22-Apr-95	4	4	0.184	0.605	3.13	3.26	-21
128	2	2	1-Apr-95	1	1	0.023	0.166	2.81	2.91	0
128	2	1	8-Apr-95	2	2	0.029	0.089	2.85	2.8	-7
128	2	1	13-Apr-95	3	3	0.027	0.086	2.83	2.8	-12
128	2	2	29-Apr-95 4A		4	0.015	0.125	2.67	2.64	-28
129	2	2	3-Apr-95	1	1	0.295	1.247	3.27	3.32	0
129	2	1	5-Apr-95	2	2	0.235	0.538	3.47	3.36	-2
129	2	1	11-Apr-95	3	3	0.32	1.253	3.24	3.22	-8
129	2	2	13-Apr-95	4	4	0.376	1.185	3.34	3.35	-10

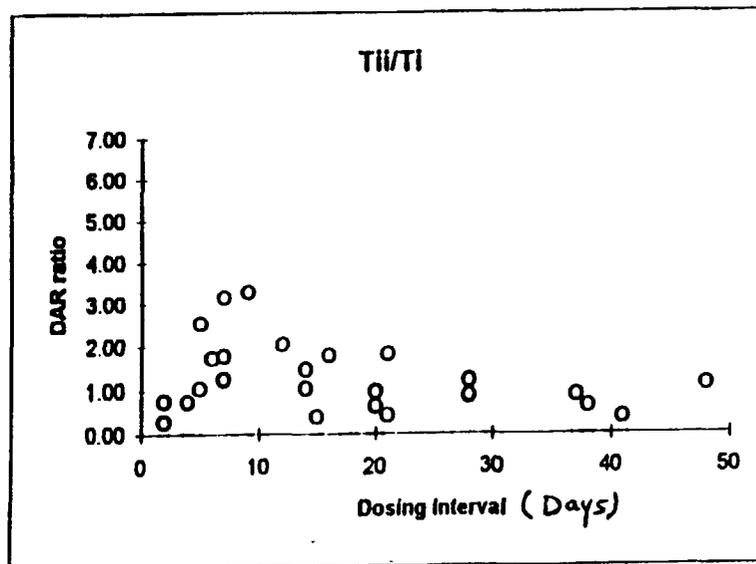
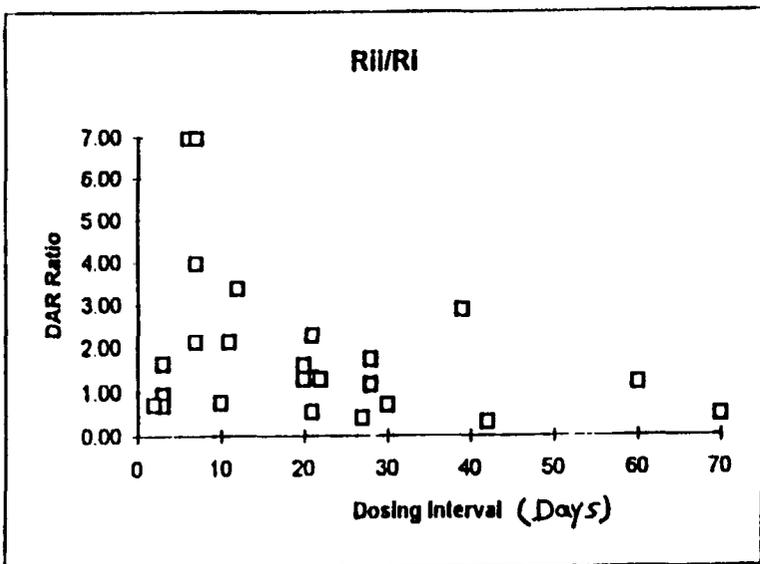
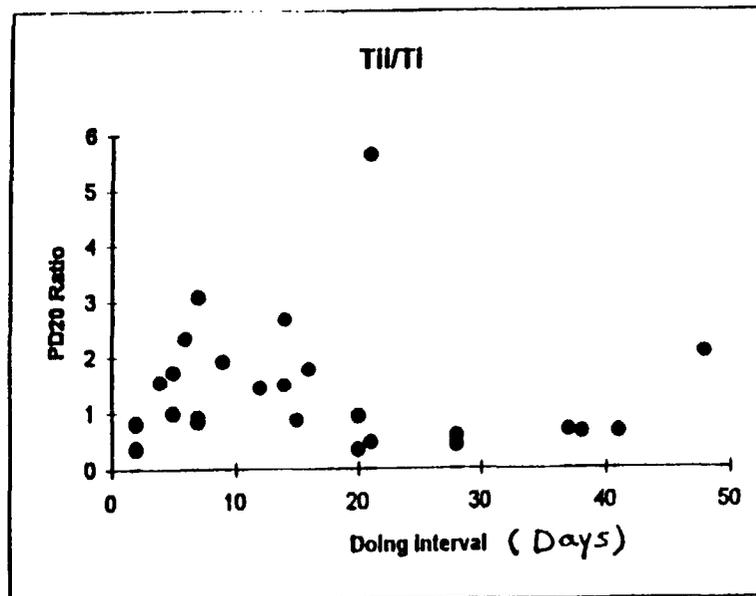
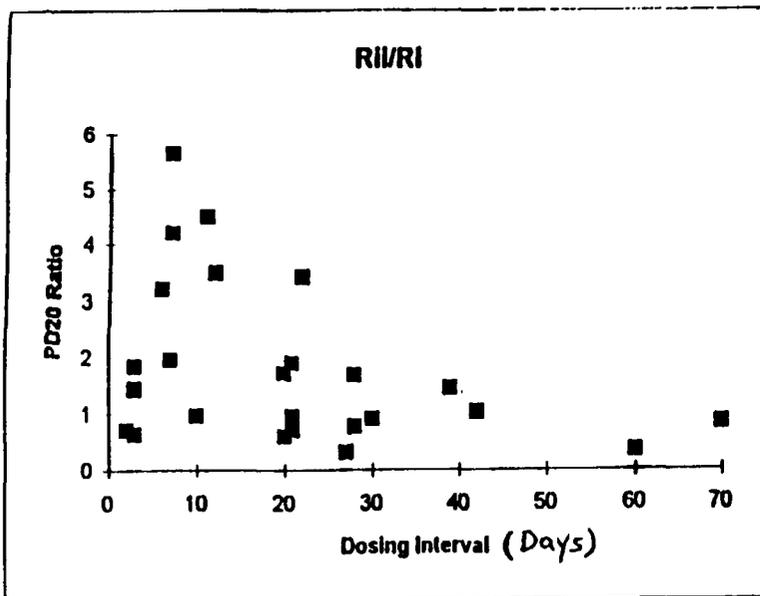
Table # 3

Ratios of PD20 & DAR values for the test and reference products at one actuation and time intervals between the replicate doses (ANDA #73045)

SUB	Time Interval (days) (Tii-Ti)	Tii/Ti		Time Interval (days) (Rii-Ri)	Rii/Ri	
		PD20	DAR		PD20	DAR
101	9					
102	41					
103	20					
104	15					
105	16					
106	5					
108	4					
109	14					
110	7					
113	28					
114	37					
115	28					
116	21					
117	2					
118	14					
119	48					
121	38					
122	7					
123	2					
124	20					
125	7					
126	12					
127	21					
128	5					
129	6					
Mean	17.08	1.39	1.28	20.8	1.8	1.88
STD	13.09	1.16	0.82	17.50	1.45	1.79
%CV	77	83	64	84	81	95
Min						
Max						

Ti Test product response, first dose
 Tii Test product response, second dose
 Ri Reference product response, first dose
 Rii Reference product response, second dose

Ratios of PD20 & D/...
 products at or...
 between the replicate doses (ANDA #73045)



- Ti Test product response, first dose
- Tii Test product response, second dose
- Ri Reference product response, first dose
- Rii Reference product response, second dose

JUL 17 1996

Albuterol Inhalation Aerosol

A.L. Laboratories

90 µg/actuation

ANDA 73-045

Reviewer: Z.Z. Wahba

73045s.695

Submission Dates:

June 12, 1995

June 22, 1995

Review of a Pharmacodynamic Study
and In Vitro Study Data
for Bioequivalence Determination

I. OBJECTIVE:

To review the comparative in vivo and in vitro performance studies A.L. Laboratories' Albuterol Metered Dose Inhaler (MDI) relative to that of the reference listed drug, Ventolin^R Inhalation Aerosol Inhaler.

II. IN VIVO COMPARATIVE STUDY:

SUMMARY OF STUDY DESIGN:

Clinical study project #135-01-10647

A. Protocol Title:

A bronchoprovocation study comparing two formulations of Albuterol Metered-Dose Aerosol Inhaler in patients with mild to moderate asthma.

B. Sponsor:

A.L. Laboratories, Inc.
The Johns Hopkins Bayview
Research Campus
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224

C. Clinical Facility:

✓

✓ Principle Investigator:
Project Director:

D. Study Period:

May 1994 to May 1995

E. Study design:

Randomized, two-treatment, four-period, two-sequence, crossover double blind study on four separate days, employing 25 mild to moderate asthma patients. A single

dose (90 µg/actuation) was administered during each treatment period.

Treatment Sequences:

Period	Visit 1	Visit 2	Visit 3	Visit 4
Sequence 1	T	R	R	T
Sequence 2	R	T	T	R

T=test product R=reference product

F. Treatment Plan:

a. Bioequivalence Study Products:

i. Test Product:

Albuterol Metered Dose Inhaler
90 µg/actuation
Manufacturer: CCL Laboratories Ltd. Rvncorn,
Chshire, England for A.L. Laboratories, Inc.
Lot #6403

ii. Reference Product:

Ventolin^R (Albuterol Metered Dose Inhaler)
90 µg/actuation
Manufacturer: Allen & Hanburys, Division of Glaxo
Lot #Z31383LS
Expiration Date: March 1996

b. Other Drug Products:

i. Screening for the Dose Response:

Ventolin^R Aerosol Inhaler
90 µg/actuation
Manufacturer: Allen & Hanburys, a Division of
Glaxo
Lot #Z31443MS, Expiration Date: March 1996
Lot #Z31473MS, Expiration Date: March 1996
Lot #4ZPA183, Expiration Date: December 1996

ii. Challenge Testing:

Product: Methacholine chloride (Provocholine^R)
100 mg/5 mL vial for reconstitution
Manufacturer: Roche Laboratories
Lot #0033, Expiration Date: April 1, 1995
Lot #0038, Expiration Date: November 1, 1995

G. Brief Summary of the Study Conduct:

Drug Administration

Patients were trained in the correct use of the MDI prior to each day's testing. For actual dosing, patients were required to place the inhaler in their mouths with their lips forming a seal around the mouthpiece. Patients were

required to activate the MDI at the same time, starting a slow sustained inhalation over a 6-9 second period. After inhalation patients were required to hold their breath for 8-10 seconds before a controlled exhalation. The investigator and patients remained blinded as to which treatment was administered during each period.

Dosing was performed for each patient at approximately the same time for each treatment period. On methacholine challenge days, dosing with albuterol MDI occurred 15 minutes prior to initiation of the methacholine challenge test.

Baseline Qualification

Patients were required to perform repeated baseline FEV₁s at the start of each day. In most cases, three baseline FEV₁s were within 5% of each other.

Each study day consisted of a pre-albuterol methacholine challenge followed at least 3 hours later by administration of the assigned albuterol treatment and a post-albuterol methacholine challenge. Each dosing period was separated by at least 24 hours.

Before proceeding with the albuterol treatment on each day, subjects were required to meet the following baseline criteria:

- a. An FEV₁ \geq 80% of predicted value for age, height and gender.
- b. An FEV₁ within 12% of the qualifying FEV₁
- c. FEV, due to the saline control not less than a 10% decrease from baseline FEV₁.
- d. A pre-albuterol PD₂₀ within a four-fold dilution (25-400%) of the qualifying PD₂₀ (see Deviation from Subject Inclusion Criteria section).

The methacholine PD₂₀ measured after the albuterol dose of the test product was compared to the same measurement after the reference product. The ratios of the post-albuterol PD₂₀ to the pre-albuterol PD₂₀ for each treatment were also compared. The within product variances were also computed.

H. Subjects:

A total of 87 patient volunteers were screened for the study. Twenty-nine met the inclusion/exclusion criteria. Of the 58 patients who failed screening, 24 had baseline FEV₁s less than 80% of predicted value, 10 failed to demonstrate a suitable airway response to doses of methacholine below 4 mg/mL, 19 failed to meet the necessary airway responsiveness to one and two actuations of albuterol

and 5 patients were ineligible because of medical issues (4 were over-weight, 1 was taking concomitant medication).

Twenty-nine subjects met the dose-response criteria for entry into the bioequivalence study. However, only twenty-five subjects completed the bioequivalence study. Four subjects (#107, #111, #112 and #120) did not complete the bioequivalence study for various reasons (for details see Vol. #8.1, p #076).

**APPEARS THIS WAY
ON ORIGINAL**

Demographic Information

<p>The total number of patients screened for the study</p>	<p>The firm mentioned that 87 patients were screened but the firm's demographic table provided information for 84 patients only. Males= 34 Females= 50</p>
<p>Number of patients who failed screening and were discontinued</p>	<p>58 subjects failed screening: <u>Details</u> a. 24 subjects had baseline FEV₁s less than 80% of predicted value b. 10 subjects failed to demonstrate a suitable airway response to doses of methacholine below 4 mg/mL c. 19 subjects failed to meet the necessary airway responsiveness to one or two actuations of albuterol d. 5 Subjects were ineligible because of medical issues (4 were over-weight and 1 was taking concomitant medication).</p>
<p>Number of Patients who passed the inclusion/exclusion and screening criteria for entry the biostudy</p>	<p>29 patients Males= 15 Females= 14</p>
<p>Number of patients who completed the biostudy</p>	<p>25 patients (#101-106, 108-110, 113-119, and 121-129) completed the biostudy. Males= 12 Females= 13 Out of 29 patients only 4 patients (#107, 111, 112 and 120) did not complete the study for various reasons (for details see Vol. #8.1, p #076)</p>

I. Deviation from Subject Inclusion Criteria:

1. Subject #103 did not meet the criteria of $(PD_{20} \text{ after 2 actuations}) / (\text{baseline } PD_{20}) \geq 8.0$ and $(PD_{20} \text{ after 2 actuations}) / (PD_{20} \text{ after 1 actuation}) \geq 2.0$, the ratio were 7.4 and 1.8, respectively.
2. Subject #108 did not meet the criteria of $(PD_{20} \text{ after 2 actuations}) / (\text{baseline } PD_{20}) \geq 8.0$ and $(PD_{20} \text{ after 2 actuations}) / (PD_{20} \text{ after 1 actuation}) \geq 2.0$, the ratio were 6.4 and 1.9, respectively.
3. Subject #119 did not meet the criteria of $(PD_{20} \text{ after 2 actuations}) / (\text{baseline } PD_{20}) \geq 8.0$, the ratio was 7.7.
4. There was a number of baseline PD_{20} on some study days that showed values outside the range of 50-200% of the qualifying day PD_{20} .

J. Visits Plan:

The twenty-five subjects who completed the biostudy did so in a minimum of 4 and a maximum of 7 visits. Eight, nine, five and three subjects completed the study in 4, 5, 6 and 7 visits, respectively.

- K. Adverse Events:** (page #087, vol. 8.1)
See Attachment #1

L. Study Validation:

Four subjects (#101, 102, 103 and 105) were used to evaluate the intra- and interday precision of the methacholine challenge method. Intraday precision was evaluated by comparing two baseline methacholine challenges conducted at an interval of at least three hours. Interday precision was measured by comparing the baseline evaluation of the patient on five different days (see Attachment #2).

M. DATA ANALYSIS:

The statistical analysis for 25 subjects are presented in the following table.

Statistical Analysis Results (n=25)

Measurements (Logarithms)	Test Mean (Antiln)	Ref. Mean (Antiln)	T/R	Signif. (alpha=0.05)	Power%	90% C.I.
Pre-albuterol PD ₂₀	-2.65715 (0.070*)	-2.55713 (0.078*)	0.90	NS	71	0.79-1.03
Post-albuterol PD ₂₀	-1.15123 (0.316*)	-0.94227 (0.390*)	0.81	NS	<50	0.68-0.98
Post-/Pre- albuterol PD ₂₀	1.50592 (4.508*)	1.61487 (5.027*)	0.90	NS	<50	0.73-1.10

Based on least squares means of logarithmically transformed data.
* mg of methacholine required to invoke the PD₂₀ response.

General Comments on the Statistical Analysis Data of the 25 Subjects:

1. For Intra-subject, Within-Product Variability (n=25):
The within subject variances in post-albuterol PD₂₀ were 0.26698 and 0.27514 for the test and reference products, respectively (see page #063, vol. 8.1). The within subject variances in pre-albuterol PD₂₀ were 0.11777 and 0.19072 for the test and reference products, respectively. The within subject variations in post-albuterol PD₂₀/pre-albuterol PD₂₀ were 0.22352 and 0.31539, respectively.
2. For Inter-subject, Within-Product Variability (n=25):
The within subject variances in post-albuterol PD₂₀ were 2.25197 and 1.57096 for the test and reference products, respectively (see page #064, vol. 8.1). The within subject variances in pre-albuterol PD₂₀ were 1.3030 and 1.52300 for the test and reference products, respectively. The within subject variations in post-albuterol PD₂₀/pre-albuterol PD₂₀ were 0.59767 and 0.40107, respectively.

2. Test Product (AL Labs)

Nominal dose ex-valve:

Weight albuterol per canister:

Number of theoretical doses:

Table #1
Comparative formulations
(Weight of Ingredient per Actuation)

Ingredients	Test*	Reference**	T/R
Albuterol, USP	μg	μg	
Oleic Acid, NF	μg	μg	
Trichloromonofluoromethane, NF (Propellant 11)	mg	mg	
Dichlorodifluoromethane, NF (Propellant 12)	mg	mg	
Total mg/Canister***	mg	mg	

* 90 μg per dose delivered to patient, approximately 10% retained on mouthpiece.

* Includes a % %) overage to deliver a minimum of 200 doses per canister.

* The information of the test product was provided in Volume #A1.1, page #0093 and volume #A10.1

** The information of the RLD was provided in NDA #18-473, Volume #8.1, Annual Report R-08, Section C, covering the period of 01 June 1984 to 31 May 1985.

*** Obtained by addition of the four ingredients.

Table #2
Comparative formulations
(Weight of Ingredient per Canister)

Ingredients	Test*	Reference**	T/R
Albuterol, USP	mg	mg	
Oleic Acid, NF	mg	mg	
Trichloromonofluoromethane, NF (Propellant 11)	mg	mg	
Dichlorodifluoromethane, NF (Propellant 12)	mg	mg	
Total mg/Canister***	mg	mg	

* 90 µg per dose delivered to patient, approximately 10% retained on mouthpiece.

* Includes a () % () % overage to deliver a minimum of 200 doses per canister.

** The information of the RLD was provided in NDA #18-473, Volume #8.1, Annual Report R-08, Section C, covering the period of 01 June 1984 to 31 May 1985.

*** Obtained by addition of the four ingredients.

Table #3
Comparative formulations
(Weight of Ingredient per %)

Ingredients	Test Prod. Theoretical Content per shot*	Test Prod. Quantity as % of Total**	Reference Prod. Quantity as % of Total***
Albuterol, USP	µg	%	%
Oleic Acid, NF	µg	%	%
Trichloromonofluoromethane, NF	mg	%	%
Dichlorodifluoromethane, NF	mg	%	%
Total	mg	%	%

*90 µg per dose delivered to patient, approximately 10% retained on mouthpiece.

** The formulation of the test product provided in ANDA #73-045, volume #1.1, page #0093.

***The formulation of the RLD was provided in NDA #18-473, volume #8.1, Annual Report R-08, Section C, covering the period of June 01, 1984 to May 31, 1985.

Comments on the formulation:

- a. The formulation provided in volume 1.1, Section 5, p. 93, indicates an overage of (% $\frac{1}{2}$). It is not clear whether the overage applies to drug only or to all ingredients.
- b. The actual, theoretical batch size and the number of filled canisters manufactured are not clear in the submission.
- c. The randomization process used to select test product canisters for the comparative *in vitro* bioequivalence testing, as well as for the *in vivo* bioequivalence study was not provided.

C. Particle Size:

The Division of Bioequivalence guidance (June 27, 1989) requests particle size determination by at least two different methods, with the cascade impactor data considered as pivotal.

The firm determined the particle size by using the following methods: Cascade Impactor, Malvern Laser, and Twin Impinger.

1. Cascade Impactor

The cascade impactor apparatus (USP 23, Chapter 601) is used to determine the following:

- (1) The total mass of drug released from the inhalation aerosol.
- (2) The quantity of drug collected at each location of the cascade impactor device.
- (3) The mass median aerodynamic diameter (MMAD; the diameter above and below which lies 50% of mass of the particles).
- (4) The geometric standard deviation (GSD).

The firm used the cascade impactor with the following specification:

Number of stages: 5
Atomizing chamber: USP 23 metal throat

Flow rate: L/min

Assay Method

r

The results of the cascade impactor analysis for MMAD and GSD are given below:

Table #4
Mass Median Aerodynamic Diameter (MMAD)
(in microns)

Shot #	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean	Range	%CV	Mean	Range	%CV
Start 6-30 (n=3)	2.62		12.7	2.32		3.3
Middle 91- 115 (n=3)	2.55		7.07	2.32		2.49
End 176-200 (n=3)	2.58		2.96	2.37		2.44

Table #5
Geometric Standard Deviation (GSD)
(in microns)

Shot #	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean	Range	%CV	Mean	Range	%CV
Start (n=3) 6-30	2.05		21.7	1.72		19.99
Middle (n=3) 91-115	2.11		21.3	1.73		21.53
End (n=3) 176-200	2.38		19.1	1.74		23.89

Table #6
Total Mass of Drug Released from the Inhalation Aerosol
(in μg)

Shot #	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean	Range	%CV	Mean	Range	%CV
Start (n=3) 6-30	2.83	✓	14.23	2.57	✓	1.60
Middle (n=3) 91-115	2.92		11.17	2.60		5.78
End (n=3) 176-200	2.94		21.09	2.46	✓	1.43

Comments on Cascade Impactor:

- a. The firm's 12 June 1995 *in vitro* data submission, Vol A8.2, provides particle size data by cascade impactor. Pages 565 and 567 lists amounts of drug deposited on various stages of the impactor. The firm is requested to provide complete mass data on laboratory worksheets for each of the 18 observations for test and reference products, including amount of drug on the valve, actuator, and atomizing chamber, and date each study was performed.
- b. The cascade impactor is calibrated at _____ L/minute. The firm used a flow rate of _____ L/minute. USP 23 <601> specifies that the flow rate through the cascade impactor should be within 2% of that specified by the manufacturer.
- c. The respirable dose and respirable fraction data based on drug less than _____ microns for each cascade impactor study were not given.
- d. Percentage material balance as defined in USP 23 <601> for each cascade impactor study was not given.

2. Malvern Laser

The sampling tube dimensions are:

Diameter at base of tube: 6mm (interior); 8 mm (exterior)

Diameter at top of tube: 51mm (interior); 55 mm (exterior)

Length of tube: 45 cm

Distance from the beam: \lceil cm

Distance above the beam: \lrcorner mm

Table #7
Particle Size Delivered from
the Actuator (Mouthpiece) Laser
(in microns)

Shot #	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean	Range	%CV	Mean	Range	%CV
Start (n=3) 6-30	3.27	\lceil	4.0	2.92	\lceil	6.5
Middle (n=3) 91-115	3.21		3.5	2.97		8.0
End (n=3) 176-200	3.21	\lrcorner	3.4	2.90	\lrcorner	2.5

Comments on Malvern Laser:

The particle size distribution data by Malvern Laser are missing information regarding the methodology (Volume A8.2, pp. 568-605) using \lceil . If this method for sizing aerosols is a standardized, validated method, the firm needs to provide references and other relevant information. The firm needs to comment on the effect of spraying every two or five seconds, which is more frequent than the labeled interval between successive doses, on the resultant particle size distribution. In addition, explain on the effect of spraying with the canister held in a near-horizontal position rather than the labeled near-vertical position.

3. Twin Impinger (Deposition of Emitted Dose)

The firm employed the Twin Impinger (single stage impactor apparatus 2, USP Chapter <601> Aerosols/Physical Tests) to determine the deposition of the emitted dose. Drug deposited on on stage 2 is less than \lceil microns. Data are expressed as the percentage of drug in stage \lceil (Upper chamber) and stage \lrcorner (the lower chamber). The equations are presented on page #613, volume #8.2.

Table #8
Particle Size Delivered from the Actuator
(% Deposition of Emitted Dose)

Deposition Stage (number of cans)	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean (%)	Range	%CV	Mean (%)	Range	%CV
Deposition Stage 1 (n=5)	46.01		7.9	34.13		9.8
Deposition Stage 2 (n=5)	49.03		3.0	58.40		4.7

Comment on the Twin Impinger Study:

Regarding the twin stage impinger study (Volume A8.2, pp. 606-615), the firm should provide the amount of drug in both the upper and lower stages for each canister, and the average shot dose as determined by Method (per). In addition, the respirable fraction for each canister for the data should be provided.

D. Spray Pattern

The spray pattern and plume geometry are used to characterize the performance of the valve and actuator.

The spray pattern was determined on one spray per each of three canisters of test and RLD at each of three distances. Each can was placed in actuator and positioned, 2.5, 5.0 and 7.5 cm away and parallel to a 20 cm X 20 cm spray. spray was fired (the canister was shaken before each spray) for each measurement. The resulting spots were viewed under UV light and the spray pattern was outlined with a pencil. Longest and shortest diameters of the spot were measured and the mean diameter was calculated.

Table #9
✓ Spray Pattern

	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)			
		Mean	Range	%CV	Mean	Range	%CV
2.5 cm Spray Pattern Diameter (cm)	Shortest (3 cans)	15		17.6	16		11.9
	Longest (3 cans)	17		15.6	18.3		3.1
	Mean (3 cans, 6 shots)	16		16.2	17.2		3.4
5.0 cm Spray Pattern Diameter (cm)	Shortest (3 cans)	15		6.7	15.7		16.1
	Longest (3 cans)	18.7		3.1	16.3		9.4
	Mean (3 cans, 6 shots)	16.8		3.4	16		12.5
7.5 cm Spray Pattern Diameter (cm)	Shortest (3 cans)	15.7		9.8	16.7		2.5
	Longest (3 cans)	19		5.3	22		7.9
	Mean (3 cans, 6 shots)	17.3		4.4	19.3		14.2

**✓
Comment on Spray Pattern:**

The comparative spray pattern profiles are inadequate. Accurate measurements cannot be assured based on the photocopies provided in Volume A8.2, pp. 619-620. In the experience of the Division of Bioequivalence, spray patterns from an inhalation aerosol do not exhibit the irregular patterns shown on pp. 619-20. The firm is requested to provide photographs of the UV spots for review, along with a complete listing of the experimental procedure, including the number of actuations fired to waste between each experiment.

E. Plume Geometry:

The firm stated the following: plume geometry testing was not performed since it is believed that no quantitative data or conclusion can be made from comparative photographs of aerosol clouds. The basis of an equivalence claim is more appropriately made on desposition of the dose delivered rather than its \sqrt spray pattern (see the firm's letter dated June 12, 1995).

Comments on Plume Geometry:

It should be noted that the 1989 guidance for the In Vitro portion of Bioequivalence Requirments for Albuterol MDI encourages the sponsor to submit data on plume geometry for the test and reference products to the agency, eventhough it is optional.

F. Potency

Potency is defined as the average amount of drug delivered per spray. The results are expressed as percent of labeled amount of drug delivered from the mouthpiece per spray.

Three random cans were tested. The cans were weighed and shots were sampled at the beginning (10-11), middle (100-101) and end (199-200) sprays. The loss in each canister weight was recorded.

Table #10
Potency as measured by Amount of Drug Delivered,
weight loss data are also listed

	Test Product (Batch #6403)				Reference Product (Batch #Z31383LS)			
	Shots #	Mean	Range	%CV	Mean	Range	%CV	Mean T/R
Drug Deliver ed (μ g)	Sprays 11-12 (3 cans)	82.76		2.0	91.15		1.4	0.91
	Sprays 100-101 (3 cans)	93.95		4.0	101.98		4.8	0.92
	Sprays 199-200 (3 cans)	107.4		1.3	98.73		1.6	1.09

Weight Loss (mg)	Sprays 11-12 (3 cans)	87	1.8	85	1.2	1.02
	Sprays 100-101 (3 cans)	86.8	2.0	84.9	2.2	1.02
	Sprays 199-200 (3 cans)	86.1	2.3	84.4	1.4	1.02

Comments on Potency Study:

The Potency section of Volume A8.2 provides comparative data for only three canisters of test and reference products, instead of the ten canisters recommended by the 1989 *In Vitro* Guidance. No conclusions can be drawn from the data of three canisters. The firm is requested to provide comparative unit spray content for ten canisters of the test and ten canisters of the reference products used in the *in vivo* bioequivalence study, determined within the expiration dating of the products. The lot number of the reference listed drug does not correspond to that of the bioequivalence lot number. The firm is requested to confirm that these data are based on Test Method

The firm has used three cans to determine the drug potency. The 1989 guidance requests potency determination for ten test and ten reference canisters.

IV. IN VITRO DEFICIENCIES:

1. The firm's 12 June 1995 *in vitro* data submission, Vol A8.2, provides particle size data by cascade impactor. Pages 565 and 567 lists amounts of drug deposited on various stages of the impactor. The firm is requested to provide complete mass data on laboratory worksheets for each of the 18 studies for test and reference products, including amount of drug on the valve, actuator, and atomizing chamber, and date each study was performed. Please provide legible representative plots of these studies showing the computation of MMAD and GSD.
2. The Andersen cascade impactor is calibrated at L/minute. The firm used a flowrate of L/minute. USP 23 <601> specifies that the flowrate through the cascade impactor should be within 2% of that specified by the manufacturer. Please comment. Please state the model number of the cascade impactor.

3. ✓ Cascade impactor validation tests in Volume 7.1, "Drug Product Specifications and Tests" are dated November 1994. Do these validation data apply to the comparative data summarized in Volume A8.2, pp. 565, 567?
4. The firm is requested to provide respirable dose and respirable fraction data based on drug less than ✓ microns for each ✓ cascade impactor study. These data should be computed as described in USP 23, <601>.
5. Percentage material balance as defined in USP 23 <601> should be provided for each ✓ cascade impactor study. The mass of formulation delivered and the concentration of drug in the formulation should also be provided, along with the quantities in each individual canister used to compute these average mass and concentration values.
6. Regarding the batch record, please indicate the actual and theoretical batch size, including the number of filled canisters manufactured.
7. The firm is requested to provide an explanation of the randomization process used to select test product canisters for the comparative *in vitro* bioequivalence testing, as well as for the *in vivo* bioequivalence study.
8. The formulation provided in volume 1.1, Section 5, p. 93, indicates an overage of _____ % (____ %). Please clarify whether the overage applies to drug only or to all ingredients. If to all ingredients, does the product include an additional overage of drug only?
9. The Potency section of Volume A8.2 provides comparative data for only three canisters of test and reference products, instead of the ten canisters recommended by the 1989 *In Vitro* Guidance. In addition to estimation of mean drug delivery at beginning, middle and end of canister life, these ten canister data are also used to assure conformity to uniformity of unit spray content specifications (USP <905>). No conclusions can be drawn from the data of three canisters. The firm is requested to provide comparative unit spray content for ten canisters of the test and ten canisters of the reference products used in the *in vivo* bioequivalence study, determined within the expiration dating of the products. The lot number of the reference listed drug does not correspond to that of the bioequivalence lot number. The firm is requested to confirm that these data were based on Test Method _____
10. Comparative ✓ spray pattern profiles are inadequate. Accurate measurements cannot be assured based on the photocopies

provided in Volume A8.2, pp. 619-620. In the experience of the Division of Bioequivalence, spray patterns from an inhalation aerosol do not exhibit the irregular patterns shown on pp. 619-20. The firm is requested to provide photographs of the UV spots for review, along with a complete listing of the experimental procedure, including the number of actuations fired to waste between each experiment.

11. Regarding the particle size distribution data by Malvern Laser, please provide information regarding the methodology (Volume A8.2, pp. 568-605) using the . If this method for sizing aerosols is a standardized, validated method, please provide references and other relevant information. Please comment on the effect of spraying every two or five seconds, which is more frequent than the labeled interval between successive doses, on the resultant particle size distribution. Please comment on the effect of spraying with the canister held in a near-horizontal position rather than the labeled near-vertical position.
12. Regarding the twin stage impinger study (Volume A8.2, pp. 606-615), please provide the amount of drug in both the upper and lower stages for each canister, and the average shot dose as determined by Method . In addition, please provide respirable fraction for each canister for the data tabulated on p. 615, as defined in USP 23, <601>, Single-stage Impactor Apparatus 2.
13. The firm is advised that review of *in vitro* data is ongoing and additional questions may arise pending completion of this review.

V. Issues need to be answered for making the decision:

1. **Regarding Statistical Issues**
 - a. The number of days between treatments were different from one subject to another. The highest range was 48 days and lowest range was 2 days between two successive visits. It is clear from the study, some treatments were done at longer intervals as compared to others. The question is: Do longer intervals have an effect on the outcome of the statistical analysis?
 - b. An issue has been raised that deals with residual effects (i.e. carry over effects). Should the possibility of residual effects such as the case of blood level concentration be considered in the evaluation of MDI drugs?

VI. RECOMMENDATION:

At the present time the 1994 guidance does not specify the conference interval range value for Albuterol MDI. The status of approval of Albuterol should be based solely on the outcome of the medical and safety evaluation (Division of Pulmonary Drug Products, HFD-570), the statistical analysis (Division of Biometrics, HFD-700) and the firm's response to the in vitro deficiencies that are identified above. The firm should be informed of the deficiencies cited above (the in vitro deficiencies #1-13)).

ISI

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED /RMHATRE
FT INITIALED /RMHATRE

ISI

7/16/96

Concur: _____ Date: 2/12/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 73-045 (original, duplicate), HFD-600 (Hare), HFD-630,
HFD-658 (Mhatre, Wahba), Drug File, Division File

APR 18 1989

Albuterol
90 mcg inhalation aerosol
ANDA #73-045
Reviewer: Marilyn N. Martinez
Wang #6127f

1.1
Superpharm Corporation
Bayshore, New York
Submission dated:
December 23, 1988

REVIEW OF A PROTOCOL AND IN-VITRO DATA

OBJECTIVE:

The firm has submitted the following data for review:

- a. the bioequivalence protocol for an ongoing clinical study. The firm states that this protocol has been informally reviewed by the Food and Drug Administration and has been revised to include Agency suggestions.
- b. in-vitro data for the two production batches of the proposed drug product, Albuterol Aerosol Inhaler, 90 mcg, and one batch each of the listed products, Proventil Inhaler (Schering) and Ventolin Inhaler (Glaxo).
- c. comparative [✓]spray pattern study.

It should be noted that Superpharm Corporation is authorized to act as the U.S. agent on behalf of Generics (UK) Limited in all matters pertaining to this ANDA. Superpharm Corporation will function as the U.S. contact/liason between Generics (UK) Limited and the FDA both prior to and subsequent to product approval.

PROTOCOL:

TITLE: Comparative 3-way double-blind, randomized, clinical efficacy study between albuterol (Generics (U.K.) Ltd.) and Proventil (Schering) and Ventolin (Glaxo) 90 mcg metered dose albuterol inhalers.

DESIGN: randomized, 3-way, double blind clinical trial using the double dummy technique for subject and technician blinding.

BLINDING TECHNIQUE: on each of the three study days, each patient will inhale 2 puffs of an active aerosol and 2 puffs of the other two placebo aerosols. All three will be sequentially inhaled at 30-second intervals. The actuator sequence will be consistent across study days for any given study subject.

A sample subject dosing schedule is defined as follows:

	<u>ALBUTEROL</u>	<u>VENTOLIN</u>	<u>PROVENTIL</u>
<u>DAY 1</u>	ACTIVE	PLACEBO	PLACEBO
<u>DAY 2</u>	PLACEBO	ACTIVE	PLACEBO
<u>DAY 3</u>	PLACEBO	PLACEBO	ACTIVE

Neither the patients nor the technicians performing the tests will know the identity of the respective canisters.

DOSE: 180 mcg (2 puffs)

SUBJECTS: 60 male and female volunteers, ages 18-60 years, presenting with uncomplicated stable asthma will be employed in the study. Patients will be selected on the basis of a typical history of asthma and the prior observation of an increase in FEV₁ of at least 7% that of control values. Patients will be studied on three different days, 2 to 7 days apart.

Subjects are permitted to take their chronic asthma medications. However, they must refrain from taking the following preparations in accordance to the indicated washout schedule:

.inhaled beta-adrenergic agonist	at least 8 hours
.oral beta-adrenergic agonist	at least 12 hours
.lung inhaled cromolyn sodium	at least 30 days
.antihistamines	at least 48 hours
.hydroxyzine	at least 96 hours
.xanthines a) taken bid	at least 24 hours
b) taken q24h	at least 48 hours
.calcium channel blockers	at least 48 hours
.beta blockers	at least 24 hours
.anticholinergic eye drops	at least 24 hours
.alpha-adrenergic agonist	at least 12 hours
.aspirin and non-steroidal anti-inflammatory drugs	at least 7 days

Patients on stable doses of systemic or aerosol steroids will not be excluded and the steroids will be maintained at the same dose during the study.

INCLUSION CRITERIA:

- .nonsmokers for at least 6 months prior to the study
- .males and nonpregnant females who are 18-60 years of age and who are within +10% of the ideal weight for their height, age and gender (Metropolitan Life Insurance Bulletin, 1983)
- .mild to moderate chronic asthmatics (FEV₁ = 50-85% of predicted)

EXCLUSION CRITERIA:

- .history of cardiovascular, renal, neurologic, liver or endocrine disease
- .intolerance to aerosolized beta₂-adrenergic agonists
- .history of hypersensitivity to any of the ingredients of the metered dose inhalers
- .evidence of respiratory tract infection within 6 weeks prior to the study
- .history of status asthmaticus, cystic fibrosis or bronchiectasis
- .inability to tolerate the temporary withdrawal of current asthma medication

RESTRICTIONS:

- .use of caffeine-containing foods and beverages must be prohibited at least 12 hours prior to and throughout the study
- .subjects should be instructed to refrain both from lying down or engaging in strenuous exercise throughout the 6 hour test period

BASELINE MEASUREMENTS:

Verification that the FEV₁ predose is within $\pm 15\%$ the of baseline value between study days. If the FEV₁ is not within $\pm 15\%$, the patient will be rescheduled for another day or excluded from the investigation.

STUDY DAY PROCEDURES:

Electronic spirometer attached to a fast response X-Y plotter and to a timer for the measurement of FEV₁.

On each day, maximum expiratory flow volume curves and FEV₁ will be obtained in triplicate before and after the administration of the consecutive three types of aerosols (one active plus two placebos) at 5, 15, 30, 60, 90, 120, 180, 240, 300 and 360 minutes. Predose FEV₁ will be done at the same time in the morning for each subject throughout the study. The data will be reduced and analyzed as forced vital capacity (FVC) and FEV₁. The maximum expiratory flow-volume curves will be performed on consecutive maneuvers, superimposing one curve over the other without removing the mouthpiece to insure measurement reproducibility.

Respiratory rate, pulse rate and blood pressure will be taken immediately before each pulmonary function measurement. A 12-lead ECG will be done 60 minutes post-dose.

ONE PUFF STUDY PROTOCOL

With the exception of the following revisions, the firm may use a protocol similar to that employed in the two puff study:

1. the inclusion and exclusion criteria indicated by the firm, are acceptable with the following revisions:
 - a) subjects should not have received an investigational drug within 30 days prior to the current study
 - b) subjects must not be currently taking oral corticosteroids

In addition, the recommended drug washout should include the following criteria:

- | | |
|----------------------------|------------------|
| a) inhaled corticosteroids | at least 30 days |
| b) anticholinergics | at least 7 |
2. the study population should include 8 subjects presenting with an FEV₁ of % of predicted and 32 subjects with FEV₁ of % of predicted. The severity of the disease condition should be established under drug washout conditions (see Appendix 2 of the Division Albuterol Guidance dated February 9, 1989).
 3. the firm has indicated that it is currently using the double dummy technique for blinding of subjects and technical support staff. The firm may wish to consider canister camouflag in their supplemental study.
 4. the firm is advised to refer to the Division of Bioequivalence Guidance for In-Vivo Bioequivalence Studies of Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers), dated February 9, 1989, for more details regarding the recommended in-vivo test procedures and the corresponding method of data analysis.
- b. both for the one puff and two puff data sets, the following data evaluation procedures are recommended:

1. for each treatment group, the following information should be included in the final study report (individual subject data and related statistics:
 - a) onset of the therapeutic response
 - b) duration of the therapeutic response
 - c) AUC calculated from the onset of the response to hour 3
 - d) AUC calculated from the onset of the response to the time of corresponding with the termination of the response
 - e) $FEV_{1\text{ max}}$ (the peak bronchodilatory response)
 - f) TMAX
 - g) $FEV_{1\text{ values}}$ at all measurement times within each evaluation period

For additional details regarding these parameters, refer to the aforementioned Division Guidance.

2. the firm should statistically compare the therapeutic efficacy of the three products at each of the two dosing levels using a three-way ANOVA which includes the error attributable to subjects(seq), period, treatment and compares the effect of sequence as a between-subject error term. All three treatments should be compared simultaneously. However, the data for the two dosing levels SHOULD NOT BE POOLED. Separate statistical evaluation should be performed for the data generated with one puff and two puffs.

Pairwise comparisons for each parameter should include the determination of the 90% confidence intervals around the difference between any 2 products relative to some reference mean (Proventil or Ventolin). Generics LTD may also wish to include the profile analysis described in their current submission.

- c. the data generated in accordance with the original Generic LTD protocol will be used for comparing the clinical efficacy of 2 puffs of the Generics's albuterol canister against that effected by 2 puffs of Ventolin or Proventil. However, the following subjects should be dropped from the study:
 1. subjects whose dose of systemic corticosteroids changed during the course of the study period
 2. asthmatics whose predose $FEV_{1\text{ values}}$ exceeds 80% of predicted.

To accomodate other differences between the firm's study design versus that currently recommended by the Division of Bioequivalence, the firm is requested to submit 2 sets of data analysis:

1. including all study subjects
2. omitting those subjects who do not meet the exclusion and inclusion criteria listed in the Division of Bioequivalence study Guidance, dated February 9, 1989.

If subject selection has not as yet been completed, the firm is requested to recruit several patients whose predose FEV₁ is within the range of % of predicted. In addition, for all study subjects, the firm is should delineate those patients whose predose FEV₁ fall within % of predicted and those which are % of predicted.

RECOMMENDATIONS:

The protocol for a proposed bioavailability study comparing the test product with Proventil (Schering) and Ventolin (Glaxo) is acceptable provided that the firm incorporated the comments in the protocol.

The firm should be informed of the above Recommendations and Comments.

/S/

Marilyn N. Martinez, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED FPELSOR
FT INITIALED FPELSOR

/S/

Concur:

/S/
S.V. Dighe Ph.D.
Director, Division of Bioequivalence

Date:

4/17/89.

cc. ANDA #73-045 original, HFD-230, HFD-200 (Hare), HFD-22 (Hooton), HFD-255 (Martinez, Pelsor), Drug File

Albuterol Inhaler
90 mcg/inhalation
ANDA # 73-045
Reviewer: W.P. Adams
Wang # 5727f

Generics (UK) Limited
U.S. Agent:
Superpharm Corporation
Bayshore, NY
Submission Date:
December 23, 1988

Review of In Vitro Data

I. BACKGROUND

A protocol for the firm's in vivo bioequivalence study was previously reviewed (Drug File Date, April 18, 1989); the bioequivalence study is currently under review.

In vitro data for two test product lots and lots of the two reference products were submitted. Initial data, as well as stability data (ambient and % RH for 4, 8 and 12 weeks) were submitted. From a Bioequivalence point of view, only the initial data pertaining to particle size, spray pattern and potency will be reviewed. Other data should be reviewed by chemists in the Division of Generic Drugs.

II. PRODUCT INFORMATION

<u>Firm</u>	<u>Product</u>	<u>Lot No.</u> ¹	<u>Production Size</u>
Generics (UK)	Inhaler	291E1 ²	(cans
Generics (UK)	Inhaler	293E1	└ cans
Allen & Hanburys (Div. Glaxo)	Ventolin ^R	Z12927NA ²	Production
Schering	Proventil ^R	7BBS460 ²	Production

¹All products packaged in canister size NLT 200 inhalations

²Batches used for the bioequivalence study

The test product manufactured by Generics (UK) in UK has been marketed for over 3 years and is currently approved and distributed in 10 countries.

The firm should state that the two reference products were purchased in the US and intended for US distribution.

III. PARTICLE SIZE

A. AUTOMATIC IMAGE ANALYSIS

Ref: G.W. Hallworth and R.R. Hamilton, "Size analysis of metered suspension pressurized aerosols with the Quantimet 720," J. Pharm. Pharmacol. (1976), 28, 890-897.

Laboratory: {

Particle size distributions for 3 canisters each of the above-stated four products were determined. 108 sprays (3 groups of 36 sprays each) from a particular canister were discharged into the Hallworth and Hamilton settling drum containing microscope slides placed at the bottom of the drum. Following a settling period, slides were examined by an automatic image analysis system, the LeMont OASYS^R Optical Analysis System. A scanner transforms the image on the microscope slide to a series of electrical pulses. The width and height of the pulses are proportional to the size and grey level of the particles. Particles were classified by count into ranges of equivalent circular diameters. The smallest particle that could be analyzed by the system is 4 microns.

Data are summarized on the following page (Automatic Image Analysis Data Summary).

**APPEARS THIS WAY
ON ORIGINAL**

AUTOMATIC IMAGE ANALYSIS DATA SUMMARY

<u>Product</u>	<u>Lot</u>	<u>Equiv. Circular Diameter (microns)¹</u>				<u>Range</u>	<u>Cumulative Frequency Percent</u>		
		<u>Can</u>	<u>Mean</u>	<u>Median</u>	<u>SD²</u>		<u>NMT 5 microns</u>	<u>NMT 10 microns</u>	<u>NMT 20 microns</u>
Ventolin (Allen & Hanburys)	212927NA	1	3.7	3.4	2.2	f	77.3	98.8	100
		2	3.5	3.3	2.0		80.7	99.1	100
		3	3.6	3.2	2.0		81.9	98.6	100
			(3.6) ³	(3.3) ³					
Proventil (Schering)	7BBS460	1	3.0	2.3	2.4		86.2	97.2	100
		2	4.0	3.8	2.0		75.1	99.1	100
		3	3.3	3.0	2.0		83.0	99.3	100
			(3.4)	(3.0)					
Generics (UK)	291E1	1	3.6	3.4	1.5		85.6	99.7	100
		2	3.7	3.5	1.5		85.4	99.5	100
		3	3.6	3.4	1.5		84.3	99.8	100
			(3.6)	(3.4)					
Generics (UK)	293E1	1	3.7	3.5	1.5		83.5	99.8	100
		2	3.9	3.8	1.5		80.6	99.4	100
		3	3.5	3.2	1.5		83.3	99.8	100
			(3.7)	(3.5)					

¹The firm's Procedure No. S0188-001, Dated November 1, 1988 (Vol 1.2, p. 516) states that the total number of sprays will be . Neither SOP S0188-001 nor the procedure followed for the above data indicated the number of slides examined or whether all fields of view on each slide were examined by the OASYS System.

²The firm reported "RMS Dev," assumed by the reviewer to be S.D.

³Mean data for three cans are given in parentheses.

These data indicate similar equivalent circular diameters as determined by
 Based upon the mean data of three canisters, the
 two test lots exhibit similar mean and median diameters (by count) to the
 reference products. Ranges of particle sizes are also similar. Based upon
 S.D., the particle size distributions of the two test lots are tighter than
 those of the reference products.

The two test lots meet the firm's finished product specifications (Vol. 1.2,
 p. 514):

Median diameter:	microns		
Cumulative frequency percent:	NLT	% up to	microns
	NLT	% up to	microns
	NLT	% up to	microns

The above data and specifications are intended for pre-approval information
 only. Post-approval, this method will not be used.

B. ✓ CASCADE IMPACTOR

Equipment and operating conditions were as follows:

Cascade impactor:	✓	stage single orifice unit with diameters of	% cutoff	a 5 microns
Sampling chamber:		Human-shaped mouthpiece plus 4 liter perspex chamber		
Airflow rate:		1 liter/min		
No. sprays per study:		Entire contents of two canisters, discharged sequentially		
Determination of drug on each stage:		By weight		
No. of studies:		5		
Product studied:		Test lot no. 291		
Laboratory:		[]		

Study director:

The test product contains _____ mg albuterol and _____ mg oleic acid per
 canister. For each study using two canisters, _____ mg albuterol and _____ mg
 oleic acid are discharged.

The following data were obtained for test lot 291:

<u>Study No.</u>	<u>MMAD</u> ¹	<u>SGSD</u> ²	<u>Mass Recovered</u> <u>on 5 Stages (mg)</u>	<u>%</u> <u>Recovery</u> ³
1	✓ 1.84	1.53	0.193	0.38
2	1.94	1.90	0.215	0.42
3	2.27	2.11	0.321	0.63
4	1.75	1.43	0.197	0.39
5	1.73	0.996	0.661	1.30

¹MMAD (mass median aerodynamic diameter)

²GSD (geometric standard deviation)

³Based on a total mass of _____ mg sprayed into the system

The firm's finished product specifications for MMAD are (Vol. 1.2, p. 514):

microns MMAD microns

The above data and specifications are intended for pre-approval information only. Post-approval, this method will not be used.

The ✓ cascade impactor experiments did not include data for the reference products. In addition, it did not include other measurements described in the In Vitro Guidance for this product.

C. LIGHT SCATTERING LASER

Laser: ✓ Malvern particle size analyzer, version M4.1
 63 mm focal length lens
 5.0 mm beam length
 0.0416 obscuration
 pia (powders in air) type experiment

Laboratory:

Procedure: Following 8 priming sprays, sample measurement is initiated, spraying every 5 seconds until sample measurement is complete. SOP 0188-001 (November 1, 1988) does not state the number of spray pulses over which the data is averaged.

No. of canisters: Particle sizing was performed on 5 individual aerosol canisters of test lot no. 291 and no. 293, but only 2 canisters of each of the reference products.

IV. ✓ SPRAY PATTERN AND PLUME GEOMETRY

Laboratory:

Study director:

The firm provided plume geometry data examining cone angle at the MDI exit port (0" downstream) and sizes of droplets at the leading edge and back end of the spray (measured 3" downstream from the exit port).

<u>Product</u>	<u>Lot no.</u> ¹	<u>Cone Angle</u> (degrees)	<u>Droplet Size (Microns)</u>	
			<u>Front</u>	<u>Back</u>
Proventil 1	--	20	✓ 50-100	75-100
Proventil 2	--	25	Intermed-125	Intermed
Proventil 3	--	15	75-100	Intermed-125
Ventolin 1	--	15	150-200	Intermed
Ventolin 2	--	25	50-100	50-75
Ventolin 3	--	25	75-100	Intermed
Generics (UK) 1	--	17	Intermed	Fine-150
Generics (UK) 2	--	17	Intermed	Intermed-150
Generics (UK) 3	--	15	25-75	150

¹Lot nos. not provided

In addition to providing lot numbers, the firm should indicate whether the three tests on each product represent three different canisters or 3 tests on the same canister. Discharge of priming shots should be stated if performed.

The above data suggest that cone angles for the test product are intermediate between those of the two reference products. In addition, the back end of the test spray appears to have somewhat wider range of particle sizes than those of the reference products.

No ✓ spray pattern data were provided.

V. POTENCY

The firm's "shot dose" method uses a 1 liter separatory funnel placed in a horizontal plane and containing a cotton pledget at the base. A vacuum pump draws 250 mm Hg vacuum through the funnel. The MDI with actuator is placed at the mouth of the funnel and individual sprays are discharged. Following actuation, the amount of albuterol free base discharged into the funnel is determined by chemical assay. The canister is weighed prior to and after each actuation. As with the USP Unit ✓ Spray Content method, the amount of drug deposited in the actuator is not assayed. Thus, the amount of drug delivered from the mouthpiece is determined.

A. Micrograms of drug delivered from the mouthpiece (ranges of single shot data)

Amounts of albuterol discharged into the funnel from single shots were determined at 10 stations (11, 12, 51, 52, 101, 102, 151, 152, 181 and 182) from individual product canisters. The single shot ranges over the 10 shots are tabulated below.

<u>Product</u>	<u>Lot No.</u>	<u>Mcg albuterol/shot</u>		
		<u>Can 1</u>	<u>Can 2</u>	<u>Can 3</u>
Generics (UK)	291E1			
Generics (UK)	293E1			
Allen & Hanburys (Div. Glaxo)	Z12927NA			
Schering	7BBS460			

*Second lowest shot was mcg albuterol

The firm's finished product specifications for the single shot data are mcg albuterol/shot. The above data and specifications are intended for pre-approval information only. Post-approval, the method will not be used.

Based upon the above results, the upper limit of the range is too high and should be lowered to MMT mcg. The firm should include single shot testing in its QC testing, either computed on single doses or as the mean of two shots, as suggested in the In Vitro Guidance (see B below).

B. Micrograms of drug delivered from the mouthpiece (single shot data based on mean of two shots)

<u>Product</u>	<u>Lot No.</u>	<u>Station No.¹</u>	<u>Can 1</u>	<u>Can 2</u>	<u>Can 3</u>	<u>Mean</u>
✓ Generics (UK)	291E1	11-12				83.5
		51-52				84.7
		101-102				82.4
		151-152				85.6
		181-182				87.0
		Grand mean				84.6
Generics (UK)	293E1	11-12				77.6
		51-52				77.7
		101-102				78.3
		151-152				75.4
		181-182				72.8
		Grand mean				76.4

Allen & Hanburys (Div. Glaxo)	Z12927NA	11-12	92.1
		51-52	86.8
		101-102	68.9
		151-152	91.6
		<u>181-182</u>	<u>93.4</u>
		Grand mean	86.6
Schering	7BBS460	11-12	86.9
		51-52	84.6
		101-102	86.2
		151-152	86.6
		<u>181-182</u>	<u>87.0</u>
		Grand mean	86.3

¹Each datum represents the mean of two sprays which were individually collected and assayed.

²Spray 101, Can 1 = 83.7 mcg; spray 102, Can 1 = 12.9 mcg. However, the total weight loss of the canister for each of these shots was normal.

As an alternative to finished product specifications based upon single shot data (A above), the firm may set specifications based upon the mean of two shots.

C. Weight loss per spray

Product	Lot No. ¹	Station No.	Mean mg/shot from		
			Can 1	Can 2	Mean
✓ Generics (UK)	293E1	11-12			80.1
		51-52			80.1
		101-102			82.9
		151-152			82.2
		<u>181-182</u>			<u>81.8</u>
		Grand mean			81.4
Allen & Hanburys (Div. Glaxo)	Z12927NA	11-12			85.5
		51-52			85.9
		101-102			87.8
		151-152			86.8
		<u>181-182</u>			<u>86.1</u>
		Grand mean			86.4
Schering	7BBS460	11-12			84.3
		51-52			83.5
		101-102			84.5
		151-152			84.4
		<u>181-182</u>			<u>85.0</u>
		Grand mean			84.3

¹Data not provided for test product lot 291E1.

D. Micrograms of drug delivered from the mouthpiece (10 shot data)

As a QC procedure, the firm plans to use a procedure similar to that used for the single shot data, except that 10 shots are collected into the funnel and the total drug assayed. The table below summarizes mean 10 shot data collected 5 times per canister (each datum represents the mean of 50 shots) for 3 canisters of each product.

<u>Product</u>	<u>Lot No.</u>	<u>Mean mcg/shot from¹</u>			<u>Mean</u>
		<u>Can 1</u>	<u>Can 2</u>	<u>Can 3</u>	
Generics (UK)	291E1				90.9
Generics (UK)	293E1				88.5
Allen & Hanburys (Div. Glaxo)	Z12927NA				91.8
Schering	7BBS460				95.7

¹S0188-001 (November 1, 1988) does not state whether drug deposited in the actuator is included in these values.

The individual 10 shot data and the proposed QC specifications (mcg albuterol per shot) will not be reviewed by the Division of Bioequivalence since these data are to be reviewed by chemists in the Division of Generic Drugs.

The single shot data (B above) suggest that the amount of drug delivered per shot from test product lot # 293E1 is low relative to test lot # 291E1 and the two reference product lots. Mean lot 293E1 test/Allen & Hanburys and lot 293E1/Schering ratios are 0.882 and 0.885, respectively. However, the corresponding ratios based upon 10 shot data (D above) are 0.964 and 0.925, which are acceptable.

IV. COMMENTS

1. The firm is requested to provide batch records for test product lots 291E1 and 293E1. The firm should provide documentation that the lots of the two reference products (Allen & Hanburys lot Z12927NA and Schering lot 7BBS460) were purchased in the United States and intended for U.S. distribution.
2. The automatic image analysis experimental procedure is not fully described. The procedure on p. 47, Vol. 1.3, states that sprays per sample are used; p. 516, Vol. 1.2 states that sprays per sample are used. This inconsistency should be corrected. The number of slides examined per experiment should be stated. Whether data from all fields of view on the slides were examined with the OASYS system should be stated. Page 48, Vol. 1.3, reports RMS Dev. This term should be defined and its equation submitted. How this term differs from Std. Dev. should be described.

3. The ✓ cascade impactor data are incomplete since data for the reference products are missing. In addition, the following questions should be addressed.
 - a. p. 72, Vol. 1.3 states that a 4 liter "perspex" chamber and human mouthpiece were used and that the flow rate was 1 liter per min. Pages 516-517, Vol. 1.2 state that a 10 liter chamber and flow rate of 1.05 liters per min were used. No mention is made of a human mouthpiece. These discrepancies should be corrected and a drawing or photograph of the entire apparatus with dimensions should be submitted.
 - b. the entire contents of two canisters of the test product were discharged into the ✓ cascade impactor, resulting in an average collection (5 experiments) of under 1% of total mass (excluding propellants). In all experiments, mass balance should be obtained, quantifying drug on actuator, on sampling chamber, on sampling plates and walls and on filter. Mass balance requires a chemical assay. In addition to possible analytical balance sensitivity problems when measuring as little as 11 mcg of drug plus surfactant, during the prolonged period of time necessary to discharge 400 + shots there is the possibility of drawing airborne contaminants into the cascade impactor, which would alter results.
 - c. the very low (under 1%) recovery may be related to the very low flow rate (1 liter/min). The firm is requested to provide information regarding the use of the ✓ cascade impactor at this low flow rate and to describe its calibration procedure of % cutoff diameters using beads or other medium. A ✓ cascade impactor of not less than six stages with a particle size range of about microns should be used.
 - d. the Division of Bioequivalence In Vitro Guidance for Albuterol Inhalation Aerosols should be consulted for additional details.
4. ✓ Light scattering laser testing data should be submitted using three canisters of test and reference products. Testing should be conducted at the beginning, middle and end of each products labeled number of actuations. Additional details are provided in the Division of Bioequivalence In Vitro Guidance. Raw data outputs from the ✓ Malvern laser should be submitted for all experiments. Complete experimental details should be provided.
5. The data submitted from ✓ . provide plume geometry information only. ✓ Spray pattern data must be provided with complete identification by lot number.
6. From a bioequivalence point of view, potency data on the test product lots 291E1 and 293E1 and the reference product lots are acceptable at this time.

7. The particle size and [✓]spray pattern data should be provided for the test product lot 291E1 and reference products lots Z12927NA and 7BBS460 that were used in the in vivo bioequivalence study. Data on test product lot 293E1 may also be provided if desired by the firm.

VII. RECOMMENDATION

The in vitro data submitted by Generics (UK), [Superpharm Corporation, U.S. Agent] on its Albuterol 90 mcg/inhalation, not less than (NLT) 200 spray Inhaler, lot # 291E1, comparing it to Allen & Hanburys (Division Glaxo) Ventolin[®] 90 mcg/inhalation, NLT 200 spray Inhaler, lot # Z12927NA and to Schering Proventil[®] 90 mcg/inhalation, NLT 200 spray Inhaler, lot # 7BBS460, have been found incomplete by the Division of bioequivalence. The firm should submit the information requested in Comments 1-7.

The firm should be advised of the Comments and Recommendation.

/S/

Wallace P. Adams, Ph.D.
Division of Bioequivalence
Review Branch III

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Concur: _____ */S/* _____ 6/28/89.

S.V. Dighe, Ph.D.
Director
Division of Bioequivalence

cc: ANDA # 73-045 original, HFD-230, HFD-200 (Hare), HFD-22 (Hooton),
HFD-258 (Mhatre, Adams), Drug File