

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-538

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-538
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 ug per Spray
Applicant Name	Apotex Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	February 28, 2005
Amendment Date(S)	August 12, 2005
Reviewer	Hoainhon Nguyen
First Generic	No
File Location	V:\firmsam\apotex\ltrs&rev\77538N0205.doc

I. Executive Summary

This is an Electronic Submission.

The firm has submitted a single-dose bioequivalence PK study, a clinical endpoint bioequivalence study, and in vitro bioequivalence studies comparing its test product, Fluticasone Propionate Nasal Spray, 50 µg per spray, with the RLD product, Flonase® Nasal Spray (Aqueous Suspension), 50 µg per spray, manufactured by GlaxoSmithKline.

The fasting study was a single-dose, two-way crossover study using 45 male and 54 female normal healthy volunteers given a dose of 200 µg. The results (point estimate, 90% CI) of the fasting BE study are LAUC_t of 0.99, 91.3-107.9; LAUC_i of 1.08, 97.2-120.7; LC_{max} of 1.01, 94.0-109.4. The fasting PK/BE study is **acceptable**.

The *in-vitro* equivalence studies are **incomplete** due to deficiencies concerning method validation data for some of the *in-vitro* tests. The firm should address the deficiencies.

The clinical endpoint bioequivalence study is currently under review with the OGD Clinical Group.

The application is **incomplete**.

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III. Submission Summary

A. Drug Product Information

Test Product	Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray
Reference Listed Drug (RLD) Product	Flonase® (Fluticasone Propionate) Nasal Spray (Aqueous Suspension), 50 ug per spray
RLD Product's Manufacturer	GlaxoSmithKline
NDA No.	20-121
RLD Product's Approval Date	October 19, 1994
Indication	Flonase® Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

B. PK Information

Bioavailability

Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2% (Electronic PDR).

T_{max}

Approximately 2 hours based on the PK studies of ANDA Nos. 76-504 (Roxane; 10/03/02) and (b) (4)

Metabolism

The only circulating inactive metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway (Electronic PDR).

Excretion

Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites (Electronic PDR).

Half-life

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours (Electronic PDR).

Dosage and Administration

The recommended starting dosage in adults is 2 sprays in each nostril once daily (total daily dose, 200 ug). The same dosage divided into 100 ug given twice daily is also effective. The maximum total daily dosage should not exceed 2 sprays in each nostril (total dose: 200 ug/day) (Electronic PDR).

Relevant OGD or DBE History

1. To date, the following ANDAs were submitted to the DBE for review:

- 76-504 (Roxane; 10/03/02)
- (b) (4)
- [REDACTED]
- [REDACTED]

The firms submitted an *in vivo* PK/BE study, *in vitro* testing, and a clinical endpoint BE study for each of the ANDA above. The DBE reviewed the PK/BE study and *in vitro* testing results. For the PK/BE study, the 90% confidence interval criteria were applied to $\ln C_{max}$, $\ln AUC_t$ and $\ln AUC_{\infty}$. For the *in vitro* testing, the DBE used the acceptance criteria that require the ratio of test to reference geometric means for each of the measured parameters to be within 90-110%.

2. Control Document #03-361 (b) (4) ; 05/06/03) addressed the DBE's recommendations concerning the PK/BE requirements for the drug product. The DBE specifically recommended the following concerning measurement of AUC_t and C_{max} :

"The AUC_t should be based on at least four consecutive nonzero plasma concentration values. The AUC computation should be terminated at the last quantifiable plasma concentration before the first zero (BLQ) value following these four or more values. The PK analysis should include only those subjects that meet this rule for both periods, i.e., for both Test product and RLD.

“The Cmax should be computed as the maximum plasma concentration that occurs among the values used to compute the AUCt. A second maximum concentration that may occur after the data points used in the computation of AUCt [i.e., following the above mentioned zero (BLQ) value] is not the Cmax of interest.”

3. Currently, the DBE uses different acceptance criteria for the *in vitro* testing results. The new acceptance criteria, applied to the data submitted in the current submission, uses a confidence approach that is based on population bioequivalence and outlined under “In Vitro BE Data: Nonprofile Analyses Using a Confidence Interval Approach” section in the draft April 2003 *Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.

Agency Guidance

Revised Draft Guidance For Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, April 2003.

Drug Specific Issues (if any)

None.

C. Contents of Submission

Table 1

Study Types	Yes/No?	How many?
Single-dose bioequivalence study (PK study)	Yes.	1
In-Vitro equivalence studies	Yes.	6
Clinical endpoint study	Yes.	1

Table 2 Lots used in the above In-Vivo and In-Vitro studies are as follows:

Study Types	RLD Product Lot No.	Date of Expiration	Test Product Lot No.	Date of Manufacture
Single-dose bioequivalence study (PK study)	C099476	02/06	GN4297*	05/10/04
In-Vitro equivalence studies	C099476	02/06	GN4297*	05/10/04
	3L058	10/05	GN5442	05/27/04
	C091877	10/05	GN5444	03/24/04

* These lots were used in the in vitro and in vivo studies

D. Pre-Study Bioanalytical Method Validation

Fluticasone Propionate in Human Plasma (EDTA) Validation
MDS PS Study 27983-01

VALIDATION SUMMARY		
Analyte	Fluticasone Propionate	
Matrix (Anticoagulant)	Human Plasma (EDTA)	
BAM Number	BAM 27983-01	
Assay Method	LC-MS/MS	
Detector	(b) (4)	
Assay Volume Required	1.0 mL	
Standard Curve Range	1.00 – 50.0 pg/mL	
Regression Type	Linear (1/x)	
Quantitation Method	Peak Area Ratio	
LLOQ Validation Samples	Precision (%)	Accuracy (%)
Inter-batch	15.7	100
Intra-batch	7.8	107
Quality Control Samples	Precision (%)	Accuracy (%)
Inter-batch	Low	97
	Medium	99
	High	100
Intra-batch	Low	99
	Medium	99
	High	99
Recovery	Recovery (%)	
Analyte	Low	89
	High	87
Internal Standard	91	
Long-term Stability	47 weeks at -20°C	
Short-term Stability	23 hours at ambient temperature, under white light	
Freeze and Thaw Stability	6 cycles at -20°C	
Stock Solution Stability	203 days in methanol at -20°C	
Internal Standard Stock Stability	203 days in methanol at -20°C	
Processed Sample Integrity	52 hours at 5°C	
Batch Size (Intra-batch)	110 injections	
Dilution Integrity	DF = 5	
Post-preparative Stability	78 hours at 5°C	

NOTE: The data from the summary table above were verified with the data submitted in individual validation summary tables from the prestudy validation report.

1. Internal standard was (b) (4)
2. QC range was 1.00 – 37.5 pg/mL (1.00, 3.00, 15.0, 37.5 pg/mL)

E. In-Vivo Study

Single-Dose Bioequivalence Study (PK Study)

Study Summary	
Study No.	AA23357
Study design	Randomized, Single-Dose, Two-Way Crossover
No. of subjects enrolled	100
No. of subjects completed	100
No. of subjects analyzed	99*
Subjects (Healthy/Patients?)	Healthy
Sex(es) included for subjects that completed the study(how many?)	Male: 45 Female: 54
Test product	Fluticasone Propionate Nasal Spray Aqueous Suspension
Reference (RLD) product	Flonase® (Fluticasone Propionate) Nasal Spray Aqueous Suspension
Strength tested	50 ug per spray
Dose	200 µg (50 µg spray X2 in each nostril)

*NOTE: Subject #29 had a nosebleed 32 minutes after dosing in Period I. Since this event occurred before the expected Tmax (approximately 2 hours), the adverse event was expected to affect the absorption of fluticasone for this subject. For this reason, the samples of Subject #29 were not analyzed and not included in the study analysis.

Summary of Statistical Data (N=99)		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC0-t	0.99	91.3-107.9
LAUC _∞	1.08	97.2-120.7
LCmax	1.01	94.0-109.4
Summary of Statistical Data (N=99) – Supportive Analysis*		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC0-t	0.96	86.4-106.5
LCmax	1.01	94.0-109.4

*NOTE: In the supportive analysis, AUCt and Cmax were calculated as specified in the DBE recommendation stated in Control Document No. 03-361 (See the DBE History section of this review):
“The AUCt should be based on at least four consecutive nonzero plasma concentration values. The AUC computation should be terminated at the last quantifiable plasma concentration before the first zero (BLQ) value following these four or more values. The PK analysis should include only those subjects that meet this rule for both periods, i.e., for both Test product and RLD.
“The Cmax should be computed as the maximum plasma concentration that occurs among the values used to compute the AUCt. A second maximum concentration that may occur after the data points used in the computation of AUCt [i.e., following the above mentioned zero (BLQ) value] is not the Cmax of interest.”
 In the main analysis, AUCt, AUCinfinity and Cmax were calculated with all data points included, whereas in the supportive analysis, any non-zero data point following the first zero (BLQ) value was excluded.

Reanalysis of Study Samples Additional information in Appendix, Table 4								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays*		Actual number		% of total assays*	
	T	R	T	R	T	R	T	R
There was no PK repeat.								

Reviewer's Comments:

All samples were repeated for analytical reasons. No recalculation was necessary.

Comment on the Bioequivalence Study (PK Study):

The 90% confidence intervals for lnCmax, lnAUCt and lnAUCinfinity (main analysis only) were within the acceptable limits of [80.0;125.0] in the main and supportive analysis. The bioequivalence study conducted under fasting conditions is **acceptable**.

F. Formulation

Location in appendix

Section B

Inactive ingredients within IIG Limits (Yes or No?)

Yes. The test and RLD products are Q1/Q2.

Formulation is acceptable (Yes or No?)

Yes.

G. In-Vitro Equivalence Studies

The following studies were submitted by the firm to demonstrate the equivalence of in-vitro performance between the test and RLD products:

1. Spray Content Uniformity Through Container Life
2. Droplet Size Distribution by Laser Diffraction
3. Particle Size Distribution by Cascade Impactor
4. Spray Pattern
5. Plume Geometry
6. Priming and Repriming

Comments on the In-Vitro Equivalence Studies:

H. Waiver Request N/A

I. Deficiency Comments

- **Deficiency Comments on the Single-Dose Bioequivalence Study (PK Study):** None
- **Deficiency Comments on the In-Vitro Equivalence Studies:**

1. Automated Spray Pump Actuation Systems:

SOP No. GM-143 refers to three pump actuation systems: Automated Spray Pump Actuation Station ((b) (4)), (b) (4) Nasal Spray Pump Actuation Station (b) (4) and (b) (4) ((b) (4)). It is not clear which system was used for the following tests: Single Actuation Content, Spray Pattern, Priming and Repriming tests. The firm is asked to identify the pump actuation systems used for these tests, the pump parameters for each of these tests. In addition, the DBE requests that the firm confirms that the operation parameters used for the test and reference products are the same. Although the test and reference products may have the same type of metering nasal pump (i.e., (b) (4)), the resistance of different pumps within the same type may be different. However, it is essential that the operation parameters for the test and reference pumps are the same for the purpose of accurate comparison.

2. For Single Actuation Content Test:

(i) Since most of the spray content data are based on the weight of each spray, the calibration and validation of the weighing procedure should be reported.

(ii) The HPLC assay method only included one working standard. The firm should provide validation data (linearity, precision and accuracy) for standard curves of at least 5 standard concentrations which bracket the concentration of the working standard.

3. Particle Size Distribution by Cascade Impactor Test:

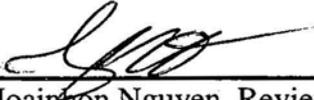
The firm did not submit any validation data for the standard curves of the concentration range of 0.36-1.68 µg/mL and the QCs for this concentration range.

J. Recommendations

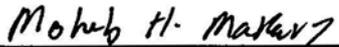
1. The single-dose bioequivalence study (PK study) conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, Lot No. GN4297, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, Lot No. C099476, manufactured by GlaxoSmithKline, is **acceptable**.
2. The In-Vitro equivalence studies conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, manufactured by

GlaxoSmithKline, are **incomplete** due to the reasons cited in the Deficiency Comments above.

The firm should be informed of the Deficiency Comments.



Hoainhon Nguyen, Review Branch I, Review Date 3/30/06



Moheb H. Makary, Ph.D., Team Leader, Review Branch I, Review Date 3/30/06



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs 4/3/06

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IV. Appendix

A. Single-Dose Bioequivalence Study (PK Study) Review

Study Information			
Sponsor	Apotex Inc.		
Study Number	AA23357		
Study Title	Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Apotex Inc. and GlaxoSmithKline (Flonase®) 50 µg/actuation Fluticasone Propionate Nasal Spray Following a 200 µg Dose in Healthy Adult Volunteers under Fasting Conditions		
Clinical Site	MDS Pharma Services Saint-Laurent, Montreal Quebec, Canada		
Principal Investigator	Gaetano Morelli, Ph.D.		
Dosing Dates	Group	Period I	Period II
	I (#1-34)	10/30/04	11/06/04
	II (#35-68)	11/07/04	11/14/04
	III (#69-100)	11/13/04	11/20/04
Analytical Site	MDS Pharma Services Lincoln, NE		
Analytical Director	(b) (6), M.S.		
Analysis Dates	11/23/04-02/03/05		
Storage Period (Number of days from the first day of sample collection through the last day of the sample analysis)	113 days		

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 µg per spray	Flonase® Nasal Spray (Aqueous Suspension), 50 µg per spray
Manufacturer	Apotex Inc.	GlaxoSmithKline
Batch/Lot No.	GN4297*	C099476*
Manufacture Date	05/10/04	NA
Expiration Date	NA	02/06
Strength	50 µg per spray	50 µg per spray
Dosage Form	Nasal Spray	Nasal Spray
Batch Size	(b) (4) units	NA
Assayed Potency	97.1%	99.8%
Content Uniformity	97% (mean beginning and mean end); range=93-101%	Not Provided
Formulation	See Appendix Section B	See Appendix Section B
Route of Administration	Nasal	Nasal
Dose Administered	Single-dose of 200 µg**	Single-dose of 200 µg**

*These lots were also used in the *in vitro* testing.

**Subjects received a single 200 µg dose of either Treatment A or B administered as 2 sprays (one cycle) in nostrils. Two cycles were to be administered, one cycle every minute (beginning of the first cycle to the beginning of the second cycle), for a total of 4 sprays (2 in each nostril) under fasting conditions.

Study Design	2-Way Crossover
No. of Centers	1
No. of Groups	3
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
Washout Period	7 days
Randomization Scheme	See below.
Blood Sampling Times	At pre-dose and at 0.25,0.5, 0.75, 1.0, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 18 and 24 hours post-dose.
Blood Volume Collected/Sample	2x 10 mL
Blood Sample Processing/Storage	Samples were collected in blood collection tubes containing EDTA and processed on ice. Plasma samples were separated by centrifugation and stored at -20°C until assayed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Confinement	Subjects were confined from the night prior to dosing until the 8 hour blood sample was collected.
Safety Monitoring	Subjects were monitored by qualified personnel.

Subject Randomization



77538randomization.pdf

Table 1 Demographics of Study Subjects (N=100)

5.2 Demographic Information

Demographic Summary for All Subjects

Trait		Female	Male	Overall
Gender	Female	55		55
	Male		45	45
Race	Asian	1	1	2
	Black		5	5
	Caucasian	54	39	93
Frame Size	Small	9	17	26
	Medium	44	27	71
	Large	2	1	3
Age	Mean	34	38	36
	S.D.	11	9	10
	Minimum	19	21	19
	Maximum	54	52	54
	N	55	45	100
Weight (kg)	Mean	61.1	75.5	67.6
	S.D.	7.2	7.3	10.2
	Minimum	49.0	57.5	49.0
	Maximum	82.0	91.4	91.4
	N	55.0	45.0	100.0
Height (cm)	Mean	165	176	170
	S.D.	7	6	9
	Minimum	151	162	151
	Maximum	182	190	190
	N	55	45	100

Dropout Information

There was no dropout.

Table 2 Study Adverse Events

Adverse Event Description	# in Test Group	# in RLD Group
Dizziness	2	
Feels hot	1	1
Nausea	3	2
Headache	3	3
Vomited		1
Feels warm	1	
Loose stools		1
Sleepy	1	
Pain in upper right nostril		1
Congested right nostril		1
Nose bleed		1
Itchiness	1	
Runny nose	1	
Swollen at venipuncture site, right arm	1	1
Pain at venipuncture site, left arm		1
Visual disturbance		1
Bruise at venipuncture site, left arm	1	1
Swollen right hand	1	
Total:	16	15

None of the adverse events was serious.

Protocol Deviations

There was no significant protocol deviation that appeared to have compromised the integrity of the study.

Comments: Deviations in blood sampling were corrected by using the actual sampling times if the deviation was greater than 5% (in the reviewer's analysis).

Table 3 Assay Validation: Within-Study

QC Conc. (pg/mL)	Fluticasone Propionate			
	3.00 (n=207)	6.00 (n=207)	15.0 (n=205)	37.5 (n=203)
Inter-day Precision (% CV)	9.4	6.6	5.0	4.6
Inter-day Accuracy (%)	96.0	95.8	96.0	96.5
Cal. Standards Conc. (pg/mL)	1.00, 2.00, 5.00, 10.0, 20.0, 30.0, 40.0, 50.0			
Inter-day Precision (% CV)	3.0-7.4			
Inter-day Accuracy (%)	99-104			
Range of r Values	0.9911-0.9999			

Comments on Within-Study Assay: Acceptable

Were 20% of Chromatograms included?	Yes.
Random Selection of Serial Chromatograms	No.
Any interfering peaks?	No.

Comments on Chromatograms: Acceptable

Table 4 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
SOP GL-BIO-10603-01	09/01/04	Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

Comments: The assay validation data are acceptable.

Table 5 Arithmetic Mean Pharmacokinetic Parameters (N=99)

Parameter	Units	Test		Reference		T/R
		Mean	% CV	Mean	% CV	
AUC _{0-t}	pg*hr/mL	44.99	54	48.05	63	0.94
AUC _∞	pg*hr/mL	64.13	55	65.77	66	0.98
C _{max}	pg/mL	7.244	46	7.264	52	1.00
T _{max}	hr	1.58	60	1.61	87	0.98
T _{1/2}	hr	9.99	54	8.83	56	1.13
kel	hr ⁻¹	0.0948	64	0.108	62	0.88

Table 6 Least Square Geometric Means and 90% Confidence Intervals (N=99)

Parameter	Test	Reference	T/R	90% CI
AUC _{0-t}	39.07	39.37	0.99	91.3-107.9
AUC _∞	59.76	55.18	1.08	97.2-120.7
C _{max}	6.590	6.500	1.01	94.0-109.4

Table 7 Least Square Geometric Means and 90% Confidence Intervals (N=99)**Supportive Analysis***

Parameter	Test	Reference	T/R	90% CI
AUC _{0-t}	36.52	38.07	0.96	86.4-106.5
C _{max}	6.590	6.500	1.01	94.0-109.4

***NOTE:** In the supportive analysis, AUC_t and C_{max} were calculated as specified in the DBE recommendation stated in Control Document No. 03-361 (See the DBE History section of this review): *“The AUC_t should be based on at least four consecutive nonzero plasma concentration values. The AUC computation should be terminated at the last quantifiable plasma concentration before the first zero (BLQ) value following these four or more values. The PK analysis should include only those subjects that meet this rule for both periods, i.e., for both Test product and RLD. “The C_{max} should be computed as the maximum plasma concentration that occurs among the values used to compute the AUC_t. A second maximum concentration that may occur after the data points used in the computation of AUC_t [i.e., following the above mentioned zero (BLQ) value] is not the C_{max} of interest.”* In the main analysis, AUC_t, AUC_∞ and C_{max} were calculated with all data points included, whereas in the supportive analysis, any non-zero data point following the first zero (BLQ) value was excluded.

Table 8 Additional Study Information (Main Analysis)

Root mean square error, AUC _{0-t}	0.355241
Root mean square error, AUC _∞	0.311347
Root mean square error, C _{max}	0.320556
K _{el} and AUC _∞ determined for how many subjects?	64 of 99 for Test treatment; 70 of 99 for Reference treatment
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as C _{max}	0
Were the subjects dosed as more than one group?	Yes. The group*treatment term was statistically insignificant for lnC _{max} , lnAUC _t and lnAUC _{infinity} and was dropped from the final main and supportive analyses (See SAS Output)

Comments on Pharmacokinetic and Statistical Analysis: Acceptable.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The 90% confidence intervals for lnC_{max}, lnAUC_t and lnAUC_{infinity} (main analysis only) were within the acceptable limits of [80.0;125.0] in the main and supportive analysis. The bioequivalence study conducted under fasting conditions is **acceptable**.

Table 9 Mean Plasma Concentrations of Fluticasone Propionate (pg/mL)**Test Treatment**

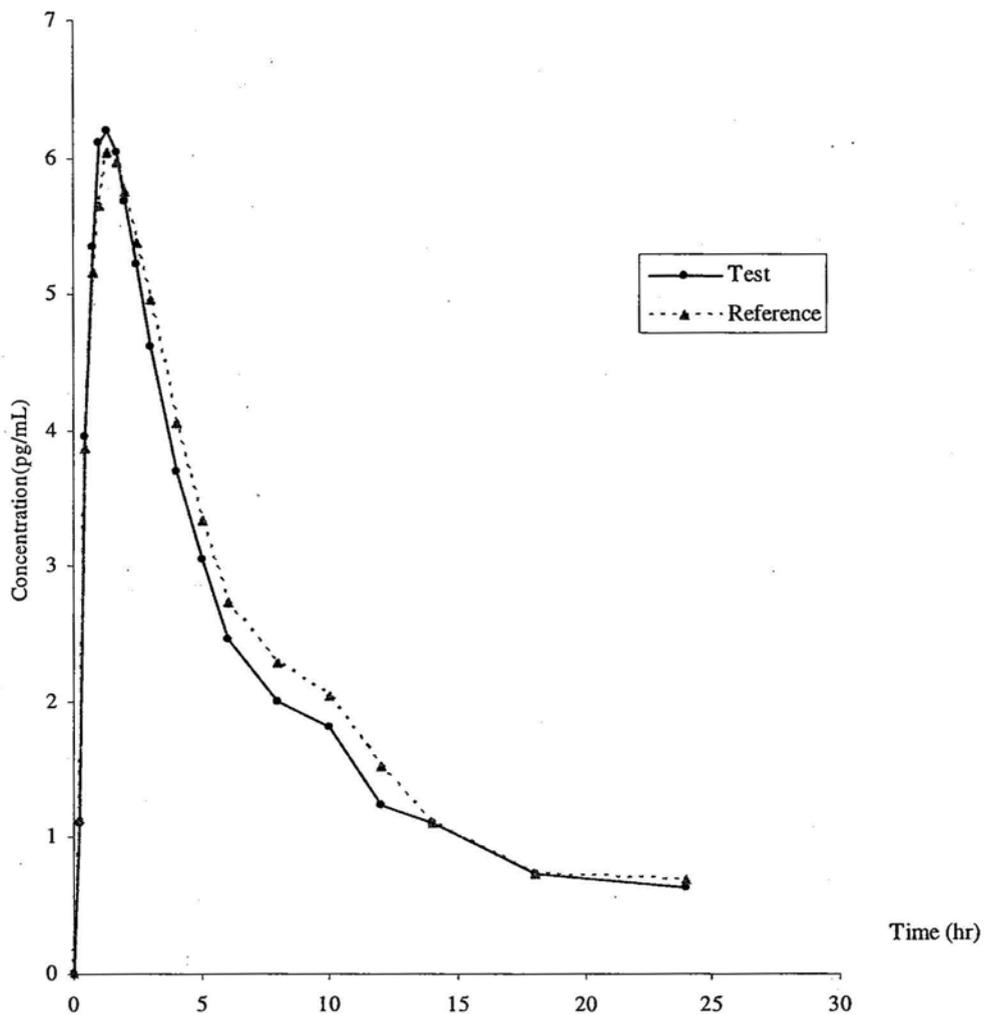
Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	99	0.000	0.000	0.000	0.000
Hour0.25	99	1.102	1.256	0.000	6.050
Hour0.50	99	3.946	2.156	0.000	10.500
Hour0.75	99	5.340	2.662	1.030	17.300
Hour1	99	6.107	2.954	1.790	20.600
Hour1.33	99	6.195	2.839	1.610	18.000
Hour1.67	99	6.036	3.015	0.000	19.800
Hour2	99	5.676	2.489	1.630	15.700
Hour2.50	99	5.224	2.233	1.790	11.900
Hour3	99	4.620	2.000	1.450	12.300
Hour4	99	3.701	1.748	1.080	9.220
Hour5	99	3.051	1.891	0.000	12.900
Hour6	99	2.454	1.553	0.000	13.200
Hour8	99	2.003	1.483	0.000	11.900
Hour10	99	1.808	1.307	0.000	10.300
Hour12	99	1.236	0.962	0.000	4.050
Hour14	99	1.113	1.102	0.000	6.850
Hour18	99	0.726	0.957	0.000	5.200
Hour24	99	0.637	0.845	0.000	4.420

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	99	0.000	0.000	0.000	0.000
Hour0.25	99	1.140	1.246	0.000	4.270
Hour0.50	99	3.865	2.084	0.000	9.510
Hour0.75	99	5.160	2.418	1.290	12.900
Hour1	99	5.655	2.545	1.740	15.300
Hour1.33	99	6.030	2.955	2.410	17.200
Hour1.67	99	5.962	3.266	2.000	19.600
Hour2	99	5.751	3.373	2.260	20.200
Hour2.50	99	5.371	3.275	1.800	23.500
Hour3	99	4.962	3.161	1.710	23.400
Hour4	99	4.053	2.570	0.000	15.600
Hour5	99	3.329	1.999	0.000	12.400
Hour6	99	2.724	1.639	0.000	8.990
Hour8	99	2.280	2.042	0.000	15.400
Hour10	99	2.035	1.866	0.000	11.200
Hour12	99	1.522	1.280	0.000	6.960
Hour14	99	1.103	1.107	0.000	5.810
Hour18	99	0.727	0.960	0.000	4.110
Hour24	99	0.684	0.873	0.000	3.580

Figure 1

Fluticasone Mean Plasma Concentrations
Single Dose Fasting Study



Formulation Comparison of the Test and RLD Products: (NOT TO BE RELEASED UNDER FOI)

Test Product			RLD Product ♦			
Ingredient	mg per Spray	%	Ingredient	mg per Spray	%	% Diff.
Fluticasone Propionate (micronized)	0.050	0.05	Fluticasone Propionate (micronized)	0.050	0.05	0
Polysorbate 80, NF (b) (4)	(b) (4)	(b) (4)	Polysorbate 80, NF	(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF			(b) (4) (Microcrystalline Cellulose and Carboxymethylcellulose Sodium), NF			
Dextrose (b) (4) USP			Dextrose (b) (4) , USP			
Benzalkonium Chloride (b) (4) NF?EP			Benzalkonium Chloride Solution NF (b) (4)			
Phenylethyl Alcohol, USP			Phenylethyl Alcohol, USP			
Water (b) (4)	To 100 mg	0.25	Water (Purified), USP	To 100 mg	0.25	0
Total	100 mg Suspension	100	Total	100 mg Suspension	100	(b) (4)

♦: From Reviews of NDA 20-121 submitted on 3/26/93 (review date: 6/20/94) and 7/30/99 (review date: 10/20/99).

B.2 Test Device

100 uL (b) (4) Nasal Spray Pump Components; Metering Nasal Pump with (b) (4) Gasket: 20 mm		
Component	Materials	Supplier
Pump Body	(b) (4)	(b) (4)
Floating Gasket		
Spring Support		
Spring Cap		
Return Spring		
Stem		
Piston		
Stem Spring		
Ferrule		
Stem Gasket		
Neck Gasket		
Dip Tube		

B.2.1 Test and Reference Device Comparison

	Test Product	RLD Product
Family		(b) (4)
Dose (mcl)		
Ferrule diameter (mm)		
Crimp type		
Ferrule Finish		
Neck Gasket		
Spring		
Diptube		
Body		
Spring Support		
Spring Cap		
Stem		
Piston		

Further pump comparison data are given in the following attachment:



77538pumpcomparison.pdf

Comments: The test and reference devices appear similar.

C. In-Vitro Equivalence Studies

Objective:

To demonstrate equivalence in the in-vitro performance between Fluticasone Propionate Nasal Spray (aqueous suspension), 50 ug by Apotex Inc. and Flonase® Nasal Spray (aqueous suspension), 50 ug by GlaxoSmithKline.

Site of Studies:

Apotex Inc.
Richmond Hill, Ontario, Canada

Study Director:

Not provided.

Analytical Director:

Not provided.

Test Dates:

Not provided.

Guidance:

The firm stated that the In-Vitro tests were performed in accordance with the April 2003 "Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action".

Test and Reference Listed Drug (RLD) Products:

Samples tested in the study were 10 bottles randomly selected from each of 3 lots of the Reference Listed Drug (RLD) product, Flonase® Nasal Spray, and 10 bottles from each of 3 lots of the test product, Fluticasone Propionate Nasal Spray. The lot numbers are as follows:

Lot No.	Manuf. Date	Exp. Date
Test GN4297	03/24/04	
Test GN5442	03/24/04	
Test GN5444	03/24/04	
Ref. 3L058		10/05
Ref. C091877		10/05
Ref. C099476		02/06

Automated/Manual Actuations:

All tests were performed by mechanically actuating the pump using automated mechanical actuation systems manufactured by (b) (4) and (b) (4). The tests were performed in a blinded manner. (SOPs: GM-143 Operation of the Automated Spray Pump Actuation Stations (effective 04/30/04) and PD Re. No. 21 Blinding Procedure for Bioavailability and Bioequivalence Studies for Nasal Spray Product (effective 10/11/2000))

TABLE 1 - Pump Specific Parameters used in the Operation of the (b) (4) Automated Spray Pump Actuation Station (b) (4)

Parameters	(b) (4)
Dose Time (msec)	
Return Time (msec)	
Hold Time (sec)	
Actuation Force (kg)	

TABLE 2 - Typical Pump Specific Parameters used in the Operation of the
 (b) (4) Nasal Spray Pump Actuation Station

Parameter	(b) (4)
Actuation Force (kg)	(b) (4)
Force Rise Time (sec)	(b) (4)
Hold Time (sec)	(b) (4)
Force Fall Time (sec)	(b) (4)
Spray Delay (sec)	(b) (4)
Minimum Travel Distance (mm)	(b) (4)
Maximum Travel Time (sec)	(b) (4)
Trigger Signal Delay (sec)	(b) (4)
Number of Sprays	(b) (4)

TABLE 3 - Pump Specific Parameters used in the Operation of the
 (b) (4) Nasal Spray Pump Actuation Station

Parameters	(b) (4)
Initial Delay Time (msec)	(b) (4)
Final Delay Time (msec)	(b) (4)
Hold Time (msec)	(b) (4)
Velocity (mm/s)	(b) (4)
Acceleration (mm/s ²)	(b) (4)

Comments: SOP No. GM-143 refers to three pump actuation systems: Automated Spray Pump Actuation Station (b) (4) (b) (4) Nasal Spray Pump Actuation Station (b) (4) and (b) (4) (b) (4). It is not clear which system was used for the following tests: Single Actuation Content, Spray Pattern, Priming and Repriming tests. The firm is asked to identify the pump actuation systems used for these tests, the pump parameters for each of these tests. In addition, the DBE requests that the firm confirms that the operation parameters used for the test and reference products are the same. Although the test and reference products may have the same type of metering nasal pump (i.e., (b) (4)), the resistance of different pumps within the same type may be different. However, it is essential that the operation parameters for the test and reference pumps are the same for the purpose of accurate comparison.

1. Spray Content Uniformity Through Container Life (Single Actuation Content):

Assay Method:

A HPLC assay method was used for the Spray Content Uniformity (SOP No. TM-1174 Assay of Fluticasone Propionate Per Spray and Total Number of Sprays Per Bottle Delivered From Actuator in Fluticasone Propionate Nasal Spray (effective 10/26/2000)). The method used one working standard of 0.002 mg/mL for comparison. CV% for the peak area of 5 consecutive injections was NMT 2%; The percent recovery for the Check Standard, which was the working standard placed at the end of the analysis, was within 97%-103% based on the mean of initial 5 injections of the working standard.

The assay was calculated as follows:

$$\text{Assay } (\mu\text{g/spray}) = (A_t/A_s) \times (W_s/100) \times (1/100) \times (25/1) \times (P/100) \times 1000$$

$$\% \text{ label claim} = \text{Assay} \times (100/\text{LC})$$

where:

A_t = Peak Area of the sample

A_s = Peak Area of the reference standard

W_s = Weight of the reference standard

P = Assay of the Reference Standard on "as is" (%) basis

LC = Label claim (50 $\mu\text{g/spray}$)

Test Procedure:

The Flonase® label recommends "wasting" of the first six actuations for priming. Testing was performed following priming actuations (1-6), at the beginning of bottle life (actuation: # 7) and at the end of bottle life (actuation: # 126). The bottle was shaken and each single actuation was collected into an inverted 25 mL volumetric flask, and was assayed for Fluticasone Propionate content as per method outlined above.

Results:

The results of PBE analysis for the Single Actuation Content (SAC) test are in the following attachment.



77538SAC.doc

Comments: (i) The weight of each spray was included in the result tables for the first 20 measurements of each bottle, in addition to the assay of each spray to demonstrate that weight alone can be used to determine the drug content of each spray. For the first 20 measurements of each bottle, the assay value as calculated based on the weight of individual spray and the assay results of each lot ("assay-weight") was compared with the direct assay value ("assay-LC"). The remaining results of the ten bottles of each lot were given as "assay-weight" only.

The firm stated that "there is good correlation between the quantity of drug delivered per spray obtained by weight, and that obtained by the assay using an HPLC method, with equal or better RSD. An extensive amount of time and chemicals is required to prepare and analyze HPLC samples, not to mention that it did not increase the accuracy of the final result but rather, runs the chance of errors during sample preparation." The reviewer agrees with the firm's statement based on the data submitted.

(ii) Since most of the spray content data are based on the weight of each spray, the calibration and validation of the weighing procedure should be reported.

(iii) The HPLC assay method only included one working standard. The firm should provide validation data (linearity, precision and accuracy) for standard curves of at least 5 standard concentrations which bracket the concentration of the working standard.

(iv) The PBE results show that the test product passed the SAC test.

2. Droplet Size Distribution by Laser Diffraction

Measurement Method:

The droplet size distribution was measured using a (b) (4) Particle Sizer) (b) (4), synchronized with (b) (4) Automated Spray Pump Actuation Station. A (b) (4) vacuum fan system (b) (4) was also used. (SOP GM-155 Determination of Spray Droplet Size Distribution for Nasal Spray Products Using the (b) (4) Sizer)

The droplet size determination was performed at the beginning and end of use life of the product at two distances, (b) (4) and (b) (4), from the orifice of the pump to the laser beam. Measurements were taken only at fully developed phase.

Representative plots (about 20%) of pump units actuated at the two distances from the laser source were submitted, with the stable fully developed phase constituting the sampling point. The firm has also submitted the data of D10, D50, D90 and SPAN. Based on the current draft of the Nasal BA/BE guidance, bioequivalence evaluation is based on D50 and SPAN data at the fully formed phase.

Procedure:

Background check was performed and scattering reduction was set prior to testing according to the manufacturer's recommendation. The pump was primed at least 5 full sprays for fresh bottle and 1 spray for previously primed bottled using the automated actuation station. A (b) (4) fan was mounted above the laser beam and directly over the tip of the actuator of the bottle and turned on prior to actuation. Data from 3 sprays were collected at 3 phases, Plume Formation, Fully Developed Plume and Plume Dissipation. The droplet size of the Fully Developed Plume was calculated from the average of three particle size distribution histograms (at percent transmission range of 65-75%, with the transmission value reported for each average scan). Scan duration was 40 ms.

Results:

The results of PBE analysis for the Droplet Size Distribution by Laser Diffraction test are in the following attachments.



77538DropletSizeD5
0Dist3.doc



77538DropletSizeD5
0Dist6.doc



77538DropletSizeSP
ANDist3.doc



77538DropletSizeSP
ANDist6.doc

Comments: (i) The PBE results show that the test product passed the Droplet Size Distribution by Laser Diffraction test.

3. Particle Size Testing by (b) (4) Cascade Impactor

Measurement Method:

Cascade impaction performed on the beginning use of the product was done by grouping the analysis of drugs deposited on various stages of the impactor as recommended in the Nasal BA/BE guidance. (SOP PD-084 Determination of Aerodynamic Particle Size Distribution in Fluticasone Propionate Nasal Spray (0.05%) using (b) (4) Cascade Impactor and (b) (4) Automated Spray Pump Actuation Station)

The multistage cascade impactor was connected to a vacuum pump on one end and, on the other end, to a 5 liter Glass Adaptor which was aligned over the Actuator Nozzle, which was in turn installed onto the Automated Actuation Station. The pooled mass of droplets <9 µm, the mass of droplets >9 µm and mass balance accountability were reported.

An HPLC /UV assay method was used to quantitate the amount of drug from samples grouped into droplet sizes. All samples were filtered with a 0.2 µm membrane syringe filter. The calibration standards used were 0.36, 0.60, 1.20 and 1.68 µg/mL, and the LOQ standard was 0.0072 µg/mL. The acceptance criteria was that the coefficient of determination (R^2) from the linear regression analysis should be NLT 0.98. The same

standards were used at the end of multiple sample analysis, as QCs, and the acceptance criteria were for the recovery (%) for the slope to be within 95-105% based on the slope of the initial linear regression analysis.

Procedure:

The test and reference products were actuated into the Glass Adaptor, which was used in place of the USP throat. The air flow of the apparatus was set at 28.3 liters/min. A total of 10 actuations (#7-16) at the beginning of the life stage of each bottle were used in each experiment. The stages were disassembled and each component was rinsed with diluent, filtered and assayed.

Particle Size Range Groups:

Drug deposited in the cascade impactor was grouped as follows:

Group #	Component (Size of Particles)	Aerodynamic Diameter (μm)
1	Collar, Glass Adaptor, Inlet Cone, Stage 0, Actuator	>9.0
2	Stage 1	<9.0
3	Stages 2-7	(b) (4)

Validation: Reproducibility of the method was demonstrated in the attachment below:



77538cascadevalidat
ion-pd-084.pdf

Results:

The results of PBE analysis for the Droplet Size Distribution by Cascade Impaction test are in the following attachments. **NOTE:** Group 1 in the PBE analysis report below represents the pooled mass of drug deposited on *all lower stages* (Stage 1 and Stages 2-7) with *size of particles less than 9 microns* (Groups #2 and 3 combined from the table above). Group 2 in the PBE analysis report below represents the total mass of drug collected on *all stages*.



77538CascadeGROU
P1smalldroplets.doc



77538CascadeGROU
P2alldroplets.doc

Comments: (i) The firm did not submit any validation data for the standard curves of the concentration range of 0.36-1.68 µg/mL and the QCs for this concentration range.

(ii) The test product did not pass the PBE criteria for the pooled mass of drug in small droplets (<9 microns)(Group 1 in the PBE analysis report). However, according to the current draft Nasal Guidance, it was stated that "For BE, the mass of drug in small droplets for the T (test) product would be less than or equivalent to the corresponding mass of drug from the R (reference) product. The comparative test addresses a potential safety concern – an excess of small droplets due to T relative to R might deliver to regions beyond the nose excipients with possible adverse pulmonary effects. The CI test for nasal sprays is not intended to provide PSD (Particle Size Distribution) of drug or aerosolized droplets." The T/R arithmetic mean ratio was 0.9093, and the T/R geometric mean ratio was 0.9139, therefore, the mass of drug in small droplets for the T was less than the corresponding mass of drug from the R product. Based on the above statements from the Nasal Guidance, the CI test results, therefore, are considered acceptable.

(NOTE: Similar conclusion was reached for the CI test for ANDA (b) (4) See v:\firmsnz (b) (4) \trs&rev\ (b) (4) a1005.doc)

(iii) The test product passed the PBE criteria for the total mass of drug collected at all stages and accessories (Group 2 in the PBE analysis report). The 90% CI for the total mass was [103.5, 106.7] and within the acceptable limits of [85.0-115.0] specified by the current draft Nasal Guidance.

4. Spray Pattern

Measurement Method:

The spray pattern determination was performed with the impaction thin-layer chromatography method. (SOP TM-1297 Spray Pattern Determination for Fluticasone Propionate Nasal Spray) Spray pattern were collected at two distances, (b) (4) and (b) (4) at the beginning sprays of the unit. A non-specific reagent, (b) (4), was selected for visualizing the spray pattern with no significant interferences reported. (Drug-specific reagents were tried but without success) automated spray pump actuation system was used in the test. 20% of the spray pattern images were submitted electronically.

Procedure:

The TLC plate holder was adjusted to the tested distance, (b) (4) or (b) (4), from the nasal applicator tip. The pump was tested at the beginning of the life stage (spray 7-11) of the bottle using the Automated Spray Pump Actuation Station. The TLC aluminum sheet was sprayed with spray reagent, heated to dry and for visualization. The spray pattern was photocopied in colors immediately. To determine the spray pattern, an outline of the area of the spray pattern was drawn. The estimated center of mass (COM) was obtained by drawing a circle that best fits the inner area of the pattern using a compass and the compass scale transparency. The maximum diameter (Dmax) and the minimum diameter

(Dmin) were drawn intersecting the COM and measured in centimeters to an accuracy of 1 decimal place. Ovality was calculated as Dmax/Dmin ratio.

Validation: Reproducibility of the method was demonstrated in the data below:

2.1 Repeatability:

The method precision repeatability was determined by measuring 6 individual spray patterns from the same pump (Batch #GM7577) of the same lot (Batch #GN4297) at distances of (b) (4), (b) (4) and (b) (4) between the tip of the actuator and the TLC aluminum sheet. Two sprays were collected at the distance of (b) (4). The mean of Dmax, Dmin and Ovality (Dmax/Dmin) were calculated and tabulated (TABLE 1).

TABLE 1 - Repeatability

Distance:	(b) (4)			(b) (4)			(b) (4)		
Spray No.	Dmax (cm)	Dmin (cm)	Ovality	Dmax (cm)	Dmin (cm)	Ovality	Dmax (cm)	Dmin (cm)	Ovality
1	(b) (4)								
2									
3									
4									
5									
6									
Mean:	2.8	2.4	1.173	2.8	2.5	1.142	3.7	3.4	1.089
CV (%):	1.8	1.7	2.8	2.9	3.9	2.3	3.3	3.6	0.3
Reference: DJ10040052, p.69									

2.2 Intermediate Precision:

The intermediate precision was determined by a second chemist measuring 6 individual spray patterns for 2 consecutive days from the same pump (Batch #GM7577) of the same lot (Batch #GN4297) used in section 2.1 at distances of (b) (4) and (b) (4) between the tip of the actuator and the TLC aluminum sheet. Two sprays were collected at the distance of (b) (4). The mean of Dmax, Dmin and Ovality (Dmax/Dmin) of each day were calculated and tabulated (TABLE 2).

TABLE 2 - Intermediate Precision

DAY 1:	(b) (4)			(b) (4)			(b) (4)		
Pump No.	Dmax (cm)	Dmin (cm)	Ovality	Dmax (cm)	Dmin (cm)	Ovality	Dmax (cm)	Dmin (cm)	Ovality
1	(b) (4)								
2									
3									
4									
5									
6									
Mean:	2.8	2.6	1.050	3.0	2.6	1.142	3.6	3.3	1.091
CV (%):	2.9	2.0	1.9	2.1	5.8	4.9	1.8	1.9	1.9
DAY 2:	(b) (4)			(b) (4)			(b) (4)		
Pump No.	Dmax (cm)	Dmin (cm)	Ovality	Dmax (cm)	Dmin (cm)	Ovality	Dmax (cm)	Dmin (cm)	Ovality
1	(b) (4)								
2									
3									
4									
5									
6									
Mean:	2.8	2.6	1.085	2.8	2.4	1.131	3.5	3.3	1.071
CV (%):	1.8	2.1	1.6	4.4	5.7	1.9	2.3	0	2.3
Reference: JM10040075, p.92									

Results:

The results of PBE analysis for the Spray Pattern test are in the following attachments.



77538SprayPatternO
valityDist3.doc



77538SprayPatternO
valityDist6.doc



77538SprayPatternD
MAXDist3.doc



77538SprayPatternD
MAXDist6.doc

Comments: (i) The validation data showed acceptable reproducibility.
(ii) The test product passed the PBE criteria for the Spray Pattern test for parameters Ovality and Dmax at distances of (b) (4) and (b) (4)

5. Plume Geometry by Laser Imaging:

Measurement Method:

The geometry of the spray plume was characterized by measuring the plume angle at one side view position (90°), as well as the width and height of the plume at the fully developed phase. The (b) (4) instrument from (b) (4) ((b) (4) Spray Characterization System and (b) (4) Automated Nasal Spray Actuator) was used to capture the entire spray plume over the entire actuation of the pump. However, the width and angle are measured at the fully developed phase only. (SOP PD-103 Characterization of Plume Geometry for Nasal Spray Using (b) (4) Spray Characterization System)

Individual angle and width data obtained per unit were submitted. In addition, 20% of the electronic *snapshot* images were also provided.

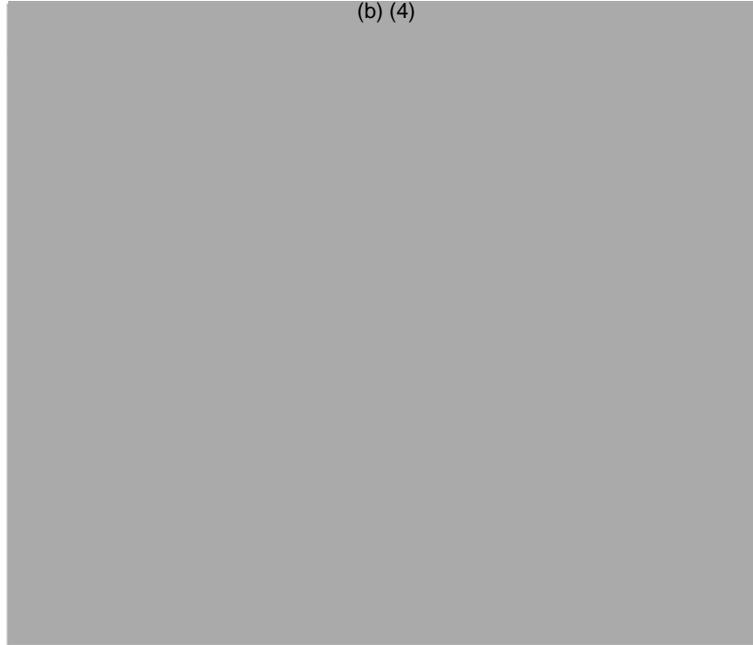
Note: No individual plume height data were submitted. Plume height was recorded with each electronic image of the plume. However, the firm's definition of plume height was different from that of the Nasal BA/BE draft guidance: According to the SOP PD-103, the plume height is the intersect-vertex distance which was the same as the greater of the 2 distances selected for spray pattern or (b) (4), whereas the guidance defines plume height as "the distance from the actuator orifice to the leading edge of the plume". Due to subjectivity in the measurement of plume height, the DBE currently does not request the plume height data.

Procedure:

The plume geometry data was measured at the beginning of unit life at a single view (90 degree angle). Image calibration was carried out prior to the start of the experiment and after changing camera or laser position. Approximately 500 snapshot frames were obtained per actuation, and frames desired for processing were selected using manual mode. The delay time of a snapshot was selected in the fully developed phase of the plume (approximately 40 ms). (b) (4)'s Plume Geometry Tool was used for measurement of the plume angle. The Tool assisted in drawing of the nominal line of the flow (vertical line up from the tip of the actuator and through the vertex of the plume), the perpendicular normal line (positioned near the top of the high intensity region of the spray (approximately 20 mm above vertex) for determination of the particle intensity profile (NLT 20%), as well as the left and right arms of the plume angle. For determination of the width of the plume, the perpendicular normal line was placed at approximately (b) (4) (the greater of the 2 distances selected for spray pattern). Plume angle and plume width (at (b) (4)) were calculated automatically based on selected positions of the arms and height.

Typical Actuator Parameters (based on the information accompanying the electronic snapshot images submitted)

(b) (4)



Validation: Reproducibility of the method was demonstrated in the data below:

Table 2 System Precision Ninety Degree Orientation

Orientation: 90 degree									
	Plume Formation			Intermediate Spray			Plume Dissipation		
Spray #	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)
1	(b) (4)								
2									
3									
4									
5									
6									
Mean:	82.9	19.23	10.56	88.9	22.62	12.46	78.9	11.69	6.92
%CV:	2.8	8.3	2.4	1.1	3.3	4.4	5.7	8.0	7.3

Table 4 Intra-Day Precision Ninety Degree Orientation

Orientation: 90 degree										
QC#5631		Plume Formation			Intermediate Spray			Plume Dissipation		
Bottle #	Spray #	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)
1	1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	2									
2	1									
	2									
3	1									
	2									
4	1									
	2									
5	1									
	2									
6	1									
	2									
Mean:		86.0	15.16	8.82	90.6	23.03	13.26	76.6	10.46	6.13
%CV:		8.5	24.3	12.7	5.7	11.3	12.5	10.4	27.6	23.8

Table 6 Inter-Day Precision Ninety Degree Orientation

Orientation: 90 degree										
		Plume Formation			Intermediate Spray			Plume Dissipation		
Day #	Spray #	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)
1	1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	2									
	3									
	4									
	5									
	6									
2	1									
	2									
	3									
	4									
	5									
	6									
3	1									
	2									
	3									
	4									
	5									
	6									
Mean:		88.6	16.20	10.55	94.2	20.35	14.27	83.7	10.18	7.72
%CV:		5.7	15.5	4.5	4.5	9.0	10.6	6.0	18.8	11.7

Table 8 Inter-Lot Precision Ninety Degree Orientation

Orientation: 90 degree																				
Lot #	Bottle #	Spray #	Plume Formation			Intermediate Spray			Plume Dissipation											
			Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)									
QC#5631	1	1	(b) (4)																	
	2	2																		
QC#5630	1	1																		
	2	2																		
QC#5632	1	1																		
	2	2																		
		Mean:										88.1	14.80	8.59	92.2	22.33	12.56	77.3	11.03	5.62
		%CV:										9.8	29.7	19.6	8.8	29.0	13.0	10.7	28.5	22.0

Table 10 Intermediate Precision Ninety Degree Orientation

Orientation: 90 degree									
Spray #	Plume Formation			Intermediate Spray			Plume Dissipation		
	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)
1	(b) (4)								
2									
3									
4									
5									
6									
Mean:	80.5	15.64	8.82	85.3	25.85	12.00	79.2	13.59	7.34
%CV:	6.9	13.4	10.5	2.8	1.1	9.6	2.8	18.8	14.6

Table 11 Summary Comparison for Intermediate Precision

Orientation: 0 degree									
	Plume Formation			Intermediate Spray			Plume Dissipation		
Chemist #	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)
1	(b) (4)								
2									
% Diff	6.9	19.0	10.5	6.5	5.6	3.5	3.9	2.0	3.2
Orientation: 90 degree									
	Plume Formation			Intermediate Spray			Plume Dissipation		
Chemist #	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)	Overall Angle	Height (mm)	Width (mm)
1	(b) (4)								
2									
% Diff	2.9	18.7	16.5	4.0	12.5	3.7	0.4	14.0	5.7

Results:

Overall Treatment Summary of Arithmetic Means

Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	64.05	30	5.33	68.70	50.20
WIDTH	44.09	30	5.66	48.80	37.40

Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	64.57	30	3.29	68.50	60.30
WIDTH	44.67	30	7.78	55.00	36.90

Within-Batch Summary of Arithmetic Means

BATCH=3L058 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	64.38	10	3.15	67.20	60.20
WIDTH	44.89	10	4.27	47.70	42.00

BATCH=C091877 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	63.47	10	8.44	68.70	50.20
WIDTH	43.52	10	7.65	48.80	37.40

BATCH=C099476 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	64.30	10	3.18	67.50	60.10
WIDTH	43.86	10	4.66	46.50	40.90

BATCH=GN4297 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	63.43	10	2.05	64.80	61.60
WIDTH	42.75	10	6.91	47.70	36.90

BATCH=GN5442 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	65.22	10	3.17	68.40	62.30
WIDTH	46.42	10	8.75	55.00	42.00

BATCH=GN5444 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	65.06	10	3.89	68.50	60.30
WIDTH	44.84	10	5.55	49.40	42.00

Between-Batch Summary of Arithmetic Means**Reference Product**

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	64.05	3	0.79	64.38	63.47
WIDTH	44.09	3	1.62	44.89	43.52

Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
ANGLE	64.57	3	1.53	65.22	63.43
WIDTH	44.67	3	4.12	46.42	42.75

Treatment Geometric Means and Point Estimates

NAME	LSMEANTEST	GEOMEANTEST	LSMEANREF	GEOMEANREF	Probt	POINTESTIMATE
LANGLE	4.16723	64.5364	4.15816	63.9539	0.4536	1.00911
LWIDTH	3.79644	44.5425	3.78466	44.0206	0.5022	1.01186

Comments: (i) The ratios of the test geometric mean to reference geometric mean for plume angle and plume width are 1.01 and 1.01, respectively, and within the 90-111% limits.

(ii) The variability observed in the measurement of plume length, plume width, and plume angle for the test product is comparable to the reference product.

The plume geometry test is acceptable.

6. Priming and Repriming

The draft guidance states that “For nasal sprays and some nasal aerosols, the R product labeling (package insert and/or patient package insert) describes the number of actuations to prime the product on initial use and on repriming following one or more periods of nonuse (e.g., 24 hours and 7 days following last dose). For these products, we request priming and repriming data for T and R products.”

The package insert for Flonase® Nasal Spray states that “It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (6 actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each 16-g bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.” Because of these insert statements, the firm submitted priming and repriming data as requested.

The priming data were based on the emitted dose of the single actuation at beginning life stage (*dose #7*) for each of the 10 bottles of each lot tested. The guidance specifies the acceptance criteria for priming data: “For ANDAs, priming would be established providing that the geometric mean of emitted dose of the 30 canisters or bottles calculated from the SAC data at B lifestage falls within 95-105 percent of label claim. Repriming would be similarly established based on a single actuation following the specified number of repriming actuations in the R product labeling.” For the repriming study of the current ANDA, repriming data were based on the SAC data for the first and second sprays following a 7-day period of non-use in vertical position (*doses #65 and 66*).

The assay method for priming and repriming samples was the same as the method used in the Spray Content Uniformity test (SOP TM-1174).

A. Priming Results:

NOTE: In the tables below, LCASSAY represents results that were calculated based on HPLC assay values whereas WTASSAY represents results that were calculated based on sample weights and potency assay of tested lots.

Summary of Overall Priming Arithmetic Means

Spray #7

Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	93.69	30	2.84	98.60	86.70
WTASSAY	96.87	30	2.48	100.20	89.50

Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	96.14	30	3.13	105.20	90.00
WTASSAY	97.71	30	1.16	100.50	95.30

**Within-Batch Summary of Arithmetic Means
Spray #7**

BATCH=3L058 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	92.99	10	3.33	96.60	86.70
WTASSAY	95.86	10	3.01	99.00	89.50

BATCH=C091877 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	94.37	10	2.62	97.50	89.90
WTASSAY	97.82	10	2.44	100.00	92.40

BATCH=C099476 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	93.70	10	2.64	98.60	90.40
WTASSAY	96.94	10	1.60	100.20	94.90

BATCH=GN4297 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	95.92	10	1.86	98.30	92.80
WTASSAY	97.57	10	1.11	99.10	95.30

BATCH=GN5442 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	97.14	10	4.79	105.20	90.00
WTASSAY	98.27	10	1.42	100.50	95.50

BATCH=GN5444 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	95.37	10	1.67	97.70	93.40
WTASSAY	97.29	10	0.69	98.30	96.20

**Between-Batch Summary of Arithmetic Means
Spray #7**

Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	93.69	3	0.74	94.37	92.99
WTASSAY	96.87	3	1.01	97.82	95.86

Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	96.14	3	0.94	97.14	95.37
WTASSAY	97.71	3	0.52	98.27	97.29

**Treatment Geometric Means and Point Estimates
Spray #7**

NAME	LSMEANTEST	GEOMEANTEST	LSMEANREF	GEOMEANREF	Probt	POINTESTIMATE
LLCASSAY	4.56538	96.0987	4.53956	93.6497	0.4536	1.02615
LWTASSAY	4.58194	97.7036	4.57310	96.8440	0.5022	1.00888

Comments: (i) The ratios of the test geometric mean to reference geometric mean for SAC at Spray #7, based on HPLC assay and sample weight*lot assay, are 1.03 and 1.01, respectively, and within the 90-111% limits.

(ii) The variability observed in the measurement of priming for the test product is comparable to the reference product.

The priming test is acceptable.

B. Repriming Results:

NOTE: In the tables below, LCASSAY represents results that were calculated based on HPLC assay values whereas WTASSAY represents results that were calculated based on sample weights and potency assay of tested lots.

Spray #65 represents the first spray following non-use period of 7 days at the vertical position. As seen in the summary of overall arithmetic means below, the SAC at this spray did not reach 90% LC for either test or reference product. The summary data for Spray #66, therefore, were also included.

Summary of Overall Priming Arithmetic Means

Spray #65

Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	83.61	30	3.98	90.70	77.20
WTASSAY	80.83	30	2.03	83.30	77.00

Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	86.37	30	3.39	94.60	80.50
WTASSAY	82.46	30	1.75	85.60	78.90

Treatment Geometric Means and Point Estimates

Spray #65

NAME	LSMEANTEST	GEOMEANTEST	LSMEANREF	GEOMEANREF	Probt	POINTESTIMATE
LLCASSAY	4.45813	86.3258	4.42540	83.5462	0.0011	1.03327
LWTASSAY	4.41212	82.4443	4.39215	80.8138	0.0001	1.02018

Summary of Overall Priming Arithmetic Means

Spray #66

Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	97.56	30	2.13	103.70	94.00
WTASSAY	97.88	30	1.53	100.70	94.70

Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	98.98	30	3.07	105.80	93.30
WTASSAY	98.04	30	1.70	100.30	94.60

**Within-Batch Summary of Arithmetic Means
Spray #66**

BATCH=3L058 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	98.06	10	2.01	100.70	94.00
WTASSAY	97.66	10	1.32	99.80	95.20

BATCH=C091877 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	97.65	10	1.40	99.30	95.30
WTASSAY	98.53	10	1.40	100.10	95.90

BATCH=C099476 Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	96.96	10	2.83	103.70	94.50
WTASSAY	97.46	10	1.77	100.70	94.70

BATCH=GN4297 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	99.20	10	2.71	104.90	95.60
WTASSAY	97.35	10	1.84	100.00	94.60

BATCH=GN5442 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	99.59	10	4.25	105.80	93.30
WTASSAY	98.20	10	2.09	100.30	94.90

BATCH=GN5444 Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	98.15	10	1.84	100.60	93.80
WTASSAY	98.56	10	0.84	99.80	96.80

**Between-Batch Summary of Arithmetic Means
Spray #66**

Reference Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	97.56	3	0.57	98.06	96.96
WTASSAY	97.88	3	0.58	98.53	97.46

Test Product

Variable	Mean	N	Coeff of Variation	Maximum	Minimum
LCASSAY	98.98	3	0.75	99.59	98.15
WTASSAY	98.04	3	0.63	98.56	97.35

**Treatment Geometric Means and Point Estimates
Spray #65**

NAME	LSMEANTEST	GEOMEANTEST	LSMEANREF	GEOMEANREF	Probt	POINTESTIMATE
LLCASSAY	4.59447	98.9354	4.58022	97.5354	0.0398	1.01435
LWTASSAY	4.58520	98.0229	4.58366	97.8722	0.7152	1.00154

Comments: (i) Although the RLD insert states that "It is necessary to prime the pump before first use or after a period of non-use (1 week or more)", the repriming data showed that only one spray was required following a non-use period of 7 days at the vertical position. At the second repriming spray (Spray #66), the ratios of the test geometric mean to reference geometric mean for SAC, based on HPLC assay and sample weight*lot assay, are 1.01 and 1.00, respectively, and within the 90-111% limits.

(ii) In addition, at the first spray following the non-use period (Spray #65), although the SAC did not reach 90% LC, the ratios of the test geometric mean to reference geometric mean, based on HPLC assay and sample weight*lot assay, are 1.03 and 1.02, respectively, and also within the 90-111% limits.

(iii) The variability observed in the measurement of repriming for the test product is comparable to the reference product.

(iv) As seen in the priming data also, the LCASSAY and WTASSAY data provided comparable results. It appears that the weighing method is equivalent to the LC assay method for priming and repriming tests.

The repriming test is acceptable.

E. SAS Output:

1. Main Analysis (With Group*Treatment Term Included)



77538FASTMAIN.txt

2. Main Analysis (Without Group*Treatment Term)



77538FASTMAINWO
GRPTRT.txt

3. Supportive Analysis (With Group*Treatment Term Included)



77538FASTSUPPORT
IVE.txt

4. Supportive Analysis (Without Group*Treatment Term)



77538FASTSUPPORT
IVEWGRPTRT.txt

5. PBE Analysis Output

See the test outputs under each of individual test summaries above.

CC: ANDA (b) (4) - 77-538
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

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Endorsements: (Final with Dates)
HFD-652/HNguyen *AVC 3/30/06*
HFD-652/MMakary *MMH 3/30/06*
HFD-650/DPConner *AVC 4/3/06*

BIOEQUIVALENCY - INCOMPLETE

Submission Date : 02-28-05
& 08-12-05

- | | | | | | |
|----|--|-----------|-------|----------|----|
| 1. | Single-Dose PK Study
Clinical:
MDS Pharma Services
Saint-Laurent, Montreal
Quebec, Canada

Analytical:
MDS Pharma Services
Lincoln, NE | Strength: | 50 ug | Outcome: | AC |
| 2. | In-Vitro equivalence study | Strength: | 50 ug | Outcome: | IC |
| 3. | In-Vitro equivalence study | Strength: | 50 ug | Outcome: | IC |
| 4. | In-Vitro equivalence study | Strength: | 50 ug | Outcome: | IC |
| 5. | In-Vitro equivalence study | Strength: | 50 ug | Outcome: | IC |

OUTCOME DECISION: IC - Incomplete; AC - Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-538
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 ug per Spray
Applicant Name	Apotex Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	April 20, 2006
Amendment Date(S)	
Reviewer	Hoainhon Nguyen
First Generic	No
File Location	V:\firmsam\apotex\ltrs&rev\77538a0406.doc

I. Executive Summary

The firm has submitted the current amendment in response to the DBE's deficiency comments communicated in the letter dated April 12, 2006. The firm's current responses are not adequate. The firm should provide additional assay validation data for the HPLC methods used in the Single Actuation Content and Cascade Impaction tests.

The application is **incomplete**.

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III. Submission Summary

A. Drug Product Information

Test Product Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray

Reference Listed Drug (RLD) Product Flonase® (Fluticasone Propionate) Nasal Spray (Aqueous Suspension), 50 ug per spray

RLD Product's Manufacturer GlaxoSmithKline

NDA No. 20-121

RLD Product's Approval Date October 19, 1994

Indication Flonase® Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

B. PK Information

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Amendment	Yes.	1

D. In-Vivo Study

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

Single-Dose Bioequivalence Study (PK Study)

Study Summary	
Study No.	AA23357
Study design	Randomized, Single-Dose, Two-Way Crossover
No. of subjects enrolled	100
No. of subjects completed	100
No. of subjects analyzed	99*
Subjects (Healthy/Patients?)	Healthy
Sex(es) included for subjects that completed the study(how many?)	Male: 45 Female: 54
Test product	Fluticasone Propionate Nasal Spray Aqueous Suspension
Reference (RLD) product	Flonase® (Fluticasone Propionate) Nasal Spray Aqueous Suspension
Strength tested	50 ug per spray
Dose	200 µg (50 µg spray X2 in each nostril)

*NOTE: Subject #29 had a nosebleed 32 minutes after dosing in Period I. Since this event occurred before the expected Tmax (approximately 2 hours), the adverse event was expected to affect the absorption of fluticasone for this subject. For this reason, the samples of Subject #29 were not analyzed and not included in the study analysis.

Summary of Statistical Data (N=99)		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC0-t	0.99	91.3-107.9
LAUC∞	1.08	97.2-120.7
LCmax	1.01	94.0-109.4
Summary of Statistical Data (N=99) – Supportive Analysis*		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC0-t	0.96	86.4-106.5
LCmax	1.01	94.0-109.4

*NOTE: In the supportive analysis, AUCt and Cmax were calculated as specified in the DBE recommendation stated in Control Document No. 03-361 (See the DBE History section of this review):
“The AUCt should be based on at least four consecutive nonzero plasma concentration values. The AUC computation should be terminated at the last quantifiable plasma concentration before the first zero (BLQ) value following these four or more values. The PK analysis should include only those subjects that meet this rule for both periods, i.e., for both Test product and RLD.
“The Cmax should be computed as the maximum plasma concentration that occurs among the values used to compute the AUCt. A second maximum concentration that may occur after the data points used in the computation of AUCt [i.e., following the above mentioned zero (BLQ) value] is not the Cmax of interest.”
 In the main analysis, AUCt, AUCinfinity and Cmax were calculated with all data points included, whereas in the supportive analysis, any non-zero data point following the first zero (BLQ) value was excluded.

Comment on the Bioequivalence Study (PK Study):

The 90% confidence intervals for lnCmax, lnAUCt and lnAUCinfinity (main analysis only) were within the acceptable limits of [80.0;125.0] in the main and supportive analysis. The bioequivalence study conducted under fasting conditions is **acceptable**.

E. Formulation

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

G. In-Vitro Equivalence Studies

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

H. Firm's Responses to DBE's Deficiency Comments:

The following deficiency comments were communicated to the firm in the letter dated April 12, 2006:

Deficiency Comments on the In-Vitro Equivalence Studies:

1. Automated Spray Pump Actuation Systems:

SOP No. GM-143 refers to three pump actuation systems: Automated Spray Pump Actuation Station ((b) (4)), (b) (4) Nasal Spray Pump Actuation Station (b) (4) and (b) (4) (b) (4)). It is not clear which system was used for the following tests: Single Actuation Content, Spray Pattern, Priming and Repriming tests. The firm is asked to identify the pump actuation systems used for these tests, the pump parameters for each of these tests. In addition, the DBE requests that the firm confirms that the operation parameters used for the test and reference products are the same. Although the test and reference products may have the same type of metering nasal pump (i.e., (b) (4)), the resistance of different pumps within the same type may be different. However, it is essential that the operation parameters for the test and reference pumps are the same for the purpose of accurate comparison.

2. For Single Actuation Content Test:

(i) Since most of the spray content data are based on the weight of each spray, the calibration and validation of the weighing procedure should be reported.

(ii) The HPLC assay method only included one working standard. The firm should provide validation data (linearity, precision and accuracy) for standard curves of at least 5 standard concentrations which bracket the concentration of the working standard.

3. Particle Size Distribution by Cascade Impactor Test:

The firm did not submit any validation data for the standard curves of the concentration range of 0.36-1.68 µg/mL and the QCs for this concentration range.

In the current amendment, the firm has provided the following responses:

1. The tests for Single Actuation Content, Priming/Repriming and Spray Pattern all used the (b) (4) automated actuation station ((b) (4)). The (b) (4) pump station parameters used for the (b) (4) system are as follows:

Actuation Force: (b) (4)
 Dose Time: (b) (4)
 Return Time: (b) (4)
 Hold Time: (b) (4)

2. (i) An amendment to the validation of test method TM-1174 has been completed to include the validation of the spray weighing. A copy of the amendment is provided in section 3.2 P.5.3. The calibration of the weighing balance is done every 3 months and a calibration check of the analytical balance is done daily.

(ii) The HPLC assay validation data are summarized in the tables below.

TABLE 1a - Linearity of Detector Response for Assay per Dose

(%) Theory	Concentration of Fluticasone Propionate (mg/mL)	Observed Area	Concentration Response (x 10 ³)
50	9.896 x 10 ⁻⁴	77.79089	78.6
60	1.188 x 10 ⁻³	93.03547	78.3
80	1.583 x 10 ⁻³	124.36947	78.6
100	1.979 x 10 ⁻³	155.07731	78.4
120	2.375 x 10 ⁻³	186.48831	78.5
150	2.969 x 10 ⁻³	233.18645	78.5
For Concentration Response: Mean:			78.5
CV (%):			0.1
Coefficient of Determination (R ²):			1.0000
y-Intercept:			1.19909 x 10 ⁻¹
Slope:			78.6 x 10 ³

TABLE 1b - Precision at the Extremes of the Range

Injection No.	Observed Area	
Level (%):	50	150
1	(b) (4)	
2		
3		
4		
5		
Mean: CV (%):	77.81438 0.1	232.96503 0.1

TABLE 1c - Accuracy (Recovery) Test

(%) Theory	Theoretical Concentration (mcg/mL)	Average Recovered Concentration (mcg/mL)	Recovery (%)	Mean Recovery (%)
50	10.64000	10.74600	101.0	101.0
	10.43600	10.52804	100.9	
	10.52000	10.63188	101.1	
100	20.03600	19.96546	99.6	100.3
	19.56400	20.03307	102.4	
	19.99600	19.79576	99.0	
150	30.00800	30.04200	100.1	99.7
	29.63200	29.66261	100.1	
	29.992300	29.62384	98.8	

TABLE 1d - Repeatability Precision

Sample No.	(%) Assay
1	(b) (4)
2	
3	
4	
5	
6	
Mean: CV (%):	107.4 0.4

TABLE 1d (cont.) - Intermediate Precision

	(%) Assay	(%) Assay
	Instrument: HPLC (Unit #28) Column: (b) (4) Serial No.: (b) (4)	Instrument: HPLC (Unit #26) Column: (b) (4) Serial No.: (b) (4)
Mean:	107.4	106.4

3. Validation data for the Cascade Impaction test method (PD-084) is provided in Table 2 below.

TABLE 2 – Linearity of Detector Response for Cascade Impaction

Level (%)	Concentration of Fluticasone Propionate (µg/mL)	Observed Area (Mean)	Concentration Response
LOQ (1%)	0.01219	1.21669	99.84326
12.5	0.15232	14.12837	92.75453
25	0.30465	28.36941	93.12132
50	0.60930	56.50677	92.74047
100	1.21859	112.61317	92.41268
160	1.94974	181.98936	93.34032
For Concentration Response: Mean: CV (%)			94.03543 3.0
Coefficient of Determination (R ²) Y-intercept: Slope:			0.99996 -0.129112 93.15243

J. DBE's Comments for Firm's Current Responses:

1. The firm's response to Deficiency #1 is acceptable.
2. The firm should submit representative data for a daily calibration check of the analytical balance. In addition, the firm should submit the amended test method (TM-1174) with the section 3.2.P.5.3. included for validation of the spray weighing. The standard and QC data for the HPLC assay validation are acceptable.
3. The data of the standard curve used in the Cascade Impaction test are acceptable. However, the firm should submit the data of QCs, separate from the standard data, for 3 concentrations within the concentration range of the standard curve, to demonstrate that the assay performs with acceptable precision and accuracy. The QC data may be submitted in the similar format as that of Table 1c presented in the firm's response #2 (ii) above.

I. Deficiency Comments:

1. For the validation of the HPLC assay used in the Single Actuation Content test, the firm should submit representative data for a daily calibration check of the analytical balance. In addition, the firm should submit the amended test method (TM-1174) with the section 3.2.P.5.3. included for validation of the spray weighing.
2. For the validation of the HPLC assay used in the Cascade Impaction test, the data of the standard curve used in the Cascade Impaction test are acceptable. However, the firm should submit the data of QCs, separate from the standard data, for 3 concentrations within the concentration range of the standard curve, to demonstrate that the assay performs with acceptable precision and accuracy. The QC data may be submitted in a similar format as that of Table 1c, presented in the firm's response #2 (ii) concerning the validation of the HPLC assay used in the Single Actuation Content test above.

K. Recommendations

1. The single-dose bioequivalence study (PK study) conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, Lot No. GN4297, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, Lot No. C099476, manufactured by GlaxoSmithKline, is **acceptable**. (See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc)
2. The In-Vitro equivalence studies conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, manufactured by GlaxoSmithKline, are **incomplete** due to the reasons cited in the Deficiency Comments 1-2 above.

The firm should be informed of the Deficiency Comments.

 5/18/06

Hoainhon Nguyen, Review Branch I, Review Date

 5/18/06

Moheb H. Makary, Ph.D., Team Leader, Review Branch I, Review Date

  5/18/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-538
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 ug per Spray
Applicant Name	Apotex Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	June 13, 2006
Amendment Date(S)	
Reviewer	Hoainhon Nguyen
First Generic	No
File Location	V:\firmsam\apotex\ltrs&rev\77538a0606.doc

I. Executive Summary

The firm has submitted the current amendment in response to the DBE's deficiency comments communicated in the letter dated May 23, 2006. The firm's current responses are not satisfactory. The firm is informed of the deficiency comments.

A For-Cause DSI inspection is also requested to verify the validity of the *in vitro* testing in general, and the Cascade Impaction test, in particular.

The application is **incomplete**.

II. Table of Contents

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III. Submission Summary

A. Drug Product Information

Test Product Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray

Reference Listed Drug (RLD) Product Flonase® (Fluticasone Propionate) Nasal Spray (Aqueous Suspension), 50 ug per spray

RLD Product's Manufacturer GlaxoSmithKline

NDA No. 20-121

RLD Product's Approval Date October 19, 1994

Indication Flonase® Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

B. PK Information

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Amendment	Yes.	1

D. In-Vivo Study

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

Single-Dose Bioequivalence Study (PK Study)

Study Summary	
Study No.	AA23357
Study design	Randomized, Single-Dose, Two-Way Crossover
No. of subjects enrolled	100
No. of subjects completed	100
No. of subjects analyzed	99*
Subjects (Healthy/Patients?)	Healthy
Sex(es) included for subjects that completed the study(how many?)	Male: 45 Female: 54
Test product	Fluticasone Propionate Nasal Spray Aqueous Suspension
Reference (RLD) product	Flonase® (Fluticasone Propionate) Nasal Spray Aqueous Suspension
Strength tested	50 ug per spray
Dose	200 µg (50 µg spray X2 in each nostril)

*NOTE: Subject #29 had a nosebleed 32 minutes after dosing in Period I. Since this event occurred before the expected T_{max} (approximately 2 hours), the adverse event was expected to affect the absorption of fluticasone for this subject. For this reason, the samples of Subject #29 were not analyzed and not included in the study analysis.

Summary of Statistical Data (N=99)		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC _{0-t}	0.99	91.3-107.9
LAUC _∞	1.08	97.2-120.7
LC _{max}	1.01	94.0-109.4
Summary of Statistical Data (N=99) – Supportive Analysis*		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC _{0-t}	0.96	86.4-106.5
LC _{max}	1.01	94.0-109.4

*NOTE: In the supportive analysis, AUC_t and C_{max} were calculated as specified in the DBE recommendation stated in Control Document No. 03-361 (See the DBE History section of this review):
“The AUC_t should be based on at least four consecutive nonzero plasma concentration values. The AUC computation should be terminated at the last quantifiable plasma concentration before the first zero (BLQ) value following these four or more values. The PK analysis should include only those subjects that meet this rule for both periods, i.e., for both Test product and RLD.

“The C_{max} should be computed as the maximum plasma concentration that occurs among the values used to compute the AUC_t. A second maximum concentration that may occur after the data points used in the computation of AUC_t [i.e., following the above mentioned zero (BLQ) value] is not the C_{max} of interest.”

In the main analysis, AUC_t, AUC_∞ and C_{max} were calculated with all data points included, whereas in the supportive analysis, any non-zero data point following the first zero (BLQ) value was excluded.

Comment on the Bioequivalence Study (PK Study):

The 90% confidence intervals for lnC_{max}, lnAUC_t and lnAUC_{infinity} (main analysis only) were within the acceptable limits of [80.0;125.0] in the main and supportive analysis. The bioequivalence study conducted under fasting conditions is **acceptable**.

E. Formulation

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

G. In-Vitro Equivalence Studies

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

H. Firm's Responses to DBE's Deficiency Comments:

The following deficiency comments were communicated to the firm in the letter dated May 23, 2006:

"1. For the validation of the HPLC assay used in the Single Actuation Content test, please submit representative data for a daily calibration check of the analytical balance. In addition, please submit the amended test method (TM-1174) with the section 3.2.P.5.3. included for validation of the spray weighing.

2. For the validation of the HPLC assay used in the Cascade Impaction test, the data of the standard curve are acceptable. However, to demonstrate that the assay performs with acceptable precision and accuracy, please submit the data of QCs, separate from the standard data, for at least 3 concentrations within the concentration range of the standard curve. The QC data may be submitted in a similar format as that of Table 1c, presented in your current response #2 (ii) for the validation of the HPLC assay used in the Single Actuation Content test."

In the current amendment, the firm has provided the following responses:

1. The firm has submitted representative data for the daily calibration check of the analytical balance used during the time of the Single Actuation Content testing (July 2004 – August 2004). In addition, the revised test method TM-1174, with sections for spray weighing and spray weighing validation added, was submitted as requested.



RevisedTM1174.pdf



TM1174ValidationAmendment.pdf

2. The firm has submitted the following HPLC assay validation data for the Cascade Impaction test.



77538CascadeValidationTables.pdf

J. DBE’s Deficiency Comments for Firm’s Current Responses:

1. The firm’s response to Deficiency #1 is adequate concerning the representative daily calibration check data and the added procedure for validation of spray weighing. However, from the SOP entitled “Amendment of Validation for Assay of Fluticasone per Spray in Fluticasone Propionate Nasal Spray, 50 µg/spray” (generated 04/17/2006) and the SOP entitled “Assay of Fluticasone Propionate Per Spray and Total Number of Sprays per Bottle Delivered from Actuator in Fluticasone Propionate Nasal Spray” (generated 05/29/2006), it is not clear to which part of which SOP the “section 3.2.P.5.2” was referred. No such “section” was found in either of the two documents submitted. Please clarify the reference of “section 3.2.P.5.2.”.

2. The firm’s response to Deficiency #2 is not acceptable. Based on the calibration curve data submitted in the previous amendment dated April 20, 2006 (as shown in the table below), the concentration range of the standard curve used for the assay of droplet content in the Cascade Impaction test was 0.15232 – 1.94974 µg/mL. However, the QC concentrations used in the same assay, submitted in the current amendment per the DBE’s request, were 250, 500 and 750 µg/mL. The QC concentrations should have been within the concentration range of the standard curve. The HPLC assay, therefore, is not considered adequately validated. The data generated for the Cascade Impaction test are not considered valid.

TABLE 2 – Linearity of Detector Response for Cascade Impaction

Level (%)	Concentration of Fluticasone Propionate (µg/mL)	Observed Area (Mean)	Concentration Response
LOQ (1%)	0.01219	1.21669	99.84326
12.5	0.15232	14.12837	92.75453
25	0.30465	28.36941	93.12132
50	0.60930	56.50677	92.74047
100	1.21859	112.61317	92.41268
160	1.94974	181.98936	93.34032
For Concentration Response:			
Mean:			94.03543
CV (%)			3.0
Coefficient of Determination (R ²)			0.99996
Y-intercept:			-0.129112
Slope:			93.15243

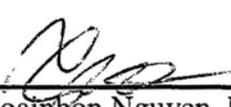
3. **Request for a For-Cause DSI inspection:** The DBE had twice requested the firm to submit HPLC validation data for the Cascade Impaction test, in the letters dated April 13, 2006 and May 23, 2006. The firm also had a telephone communication with the DBE's PM, Aaron Sigler, for clarification of the May 23, 2006 deficiency letter. However, the firm's response to this particular deficiency remains unsatisfactory to date. Due to the difficulty in obtaining validation data for the *in vitro* testing of the test product, especially the Cascade Impaction test, the DBE is requesting a for-cause DSI audit of the *in vitro* testing.

K. Recommendations

1. The In-Vitro equivalence studies conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, manufactured by GlaxoSmithKline, are **incomplete** due to the reasons cited in the Deficiency Comments 1-2 above.

2. A For-Cause DSI inspection is requested for the reasons cited in the Deficiency Comment 3 above.

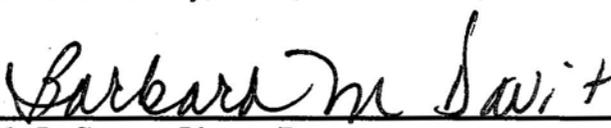
The firm should be informed of the Deficiency Comments.

 6/29/06

Hoainhon Nguyen, Review Branch I, Review Date

FER  6/29/2006

Moheb H. Makary, Ph.D., Team Leader, Review Branch I, Review Date

  6/30/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-538

APPLICANT: Apotex Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray
(Aqueous Suspension), 50 ug

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

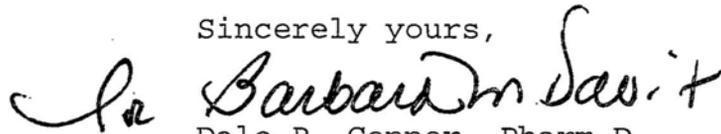
1. Your response to Deficiency #1 is adequate concerning the representative daily calibration check data and the added procedure for validation of spray weighing. However, from the SOP entitled "Amendment of Validation for Assay of Fluticasone per Spray in Fluticasone Propionate Nasal Spray, 50 µg/spray" (generated 04/17/2006) and the SOP entitled "Assay of Fluicasone Propionate Per Spray and Total Number of Sprays per Bottle Delivered from Actuator in Fluticasone Propionate Nasal Spray" (generated 05/29/2006), it is not clear to which part of which SOP the "section 3.2.P.5.2" was referred. No such "section" was found in either of the two documents submitted. Please clarify the reference of "section 3.2.P.5.2."

2. Your response to Deficiency #2 is not acceptable. Based on the calibration curve data submitted in the previous amendment dated April 20, 2006 (shown in the table below), the concentration range of the standard curve used for the assay of droplet content in the Cascade Impaction test was [REDACTED] ^{(b) (4)} µg/mL. However, the QC concentrations used in the same assay, submitted in the current amendment per our request, were 250, 500 and 750 µg/mL. The QC concentrations should have been within the concentration range of the standard curve. The HPLC assay, therefore, is not considered adequately validated. The data generated for the Cascade Impaction test are not considered valid.

TABLE 2 – Linearity of Detector Response for Cascade Impaction

Level (%)	Concentration of Fluticasone Propionate (µg/mL)	Observed Area (Mean)	Concentration Response
LOQ (1%)	(b) (4)	1.21669	(b) (4)
12.5	(b) (4)	14.12837	(b) (4)
25	(b) (4)	28.36941	(b) (4)
50	(b) (4)	56.50677	(b) (4)
100	(b) (4)	112.61317	(b) (4)
160	(b) (4)	181.98936	(b) (4)
For Concentration Response:			
Mean:			94.03543
CV (%)			3.0
Coefficient of Determination (R ²)			0.99996
Y-intercept:			-0.129112
Slope:			93.15243

Sincerely yours,



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

CC: ANDA 77-538
ANDA DUPLICATE
DIVISION FILE
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V:\firmsam\apotex\ltrs&rev\77538a0606.doc

Endorsements: (Final with Dates)

HFD-652/HNguyen *ONE 6/29/06*

HFD-652/MMakary

HFD-650/DPConner *BMD 6/30/06*

ln

[Signature] 6/29/06

BIOEQUIVALENCY – DEFICIENCIES

Submission Date : 06-13-06

1. Study Amendment (STA)

Strength: 50 ug

Outcome: IC

OUTCOME DECISION: IC – Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-538
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 ug per Spray
Applicant Name	Apotex Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	July 20, 2006
Amendment Date(S)	
Reviewer	Hoainhon Nguyen
First Generic	No
File Location	V:\firmsam\apotex\ltrs&rev\77538a0706.doc

I. Executive Summary

The firm has submitted the current amendment in response to the DBE's deficiency comments communicated in the letter dated May 23, 2006. The firm's current responses are satisfactory. The *in vivo* and *intro* studies are now acceptable.

A For-Cause DSI inspection has been requested to verify the validity of the *in vitro* testing in general, and the Cascade Impaction test, in particular (See the previous review, v:\firmsam\apotex\ltrs&rev\77538a0606.doc).

The application is **incomplete** pending the results of the DSI inspection.

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J. DBE's Deficiency Comments for Firm's Current Responses:.....	6
1. The firm's response to Deficiency #1 is satisfactory.....	6
K. Recommendations	6

III. Submission Summary

A. Drug Product Information

Test Product Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray

Reference Listed Drug (RLD) Product Flonase[®] (Fluticasone Propionate) Nasal Spray (Aqueous Suspension), 50 ug per spray

RLD Product's Manufacturer GlaxoSmithKline

NDA No. 20-121

RLD Product's Approval Date October 19, 1994

Indication Flonase[®] Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

B. PK Information

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Amendment	Yes.	1

D. In-Vivo Study

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

Single-Dose Bioequivalence Study (PK Study)

Study Summary	
Study No.	AA23357
Study design	Randomized, Single-Dose, Two-Way Crossover
No. of subjects enrolled	100
No. of subjects completed	100
No. of subjects analyzed	99*
Subjects (Healthy/Patients?)	Healthy
Sex(es) included for subjects that completed the study(how many?)	Male: 45 Female: 54
Test product	Fluticasone Propionate Nasal Spray Aqueous Suspension
Reference (RLD) product	Flonase® (Fluticasone Propionate) Nasal Spray Aqueous Suspension
Strength tested	50 ug per spray
Dose	200 µg (50 µg spray X2 in each nostril)

*NOTE: Subject #29 had a nosebleed 32 minutes after dosing in Period I. Since this event occurred before the expected Tmax (approximately 2 hours), the adverse event was expected to affect the absorption of fluticasone for this subject. For this reason, the samples of Subject #29 were not analyzed and not included in the study analysis.

Summary of Statistical Data (N=99)		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC0-t	0.99	91.3-107.9
LAUC_∞	1.08	97.2-120.7
LCmax	1.01	94.0-109.4
Summary of Statistical Data (N=99) – Supportive Analysis*		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC0-t	0.96	86.4-106.5
LCmax	1.01	94.0-109.4

*NOTE: In the supportive analysis, AUC_t and C_{max} were calculated as specified in the DBE recommendation stated in Control Document No. 03-361 (See the DBE History section of this review):
“The AUC_t should be based on at least four consecutive nonzero plasma concentration values. The AUC computation should be terminated at the last quantifiable plasma concentration before the first zero (BLQ) value following these four or more values. The PK analysis should include only those subjects that meet this rule for both periods, i.e., for both Test product and RLD.

“The C_{max} should be computed as the maximum plasma concentration that occurs among the values used to compute the AUC_t. A second maximum concentration that may occur after the data points used in the computation of AUC_t [i.e., following the above mentioned zero (BLQ) value] is not the C_{max} of interest.”

In the main analysis, AUC_t, AUC_∞ and C_{max} were calculated with all data points included, whereas in the supportive analysis, any non-zero data point following the first zero (BLQ) value was excluded.

Comment on the Bioequivalence Study (PK Study):

The 90% confidence intervals for lnC_{max}, lnAUC_t and lnAUC_{infinity} (main analysis only) were within the acceptable limits of [80.0;125.0] in the main and supportive analysis. The bioequivalence study conducted under fasting conditions is **acceptable**.

E. Formulation

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

G. In-Vitro Equivalence Studies

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

H. Firm's Responses to DBE's Deficiency Comments:

The following deficiency comments were communicated to the firm in the letter dated July 14, 2006:

"1. Your response to Deficiency #1 is adequate concerning the representative daily calibration check data and the added procedure for validation of spray weighing. However, from the SOP entitled "Amendment of Validation for Assay of Fluticasone per Spray in Fluticasone Propionate Nasal Spray, 50 µg/spray" (generated 04/17/2006) and the SOP entitled "Assay of Fluticasone Propionate Per Spray and Total Number of Sprays per Bottle Delivered from Actuator in Fluticasone Propionate Nasal Spray" (generated 05/29/2006), it is not clear to which part of which SOP the "section 3.2.P.5.2" was referred. No such "section" was found in either of the two documents submitted. Please clarify the reference of "section 3.2.P.5.2."

2. Your response to Deficiency #2 is not acceptable. Based on the calibration curve data submitted in the previous amendment dated April 20, 2006 (shown in the table below), the concentration range of the standard curve used for the assay of droplet content in the Cascade Impaction test was [REDACTED] ^{(b) (4)} µg/mL. However, the QC concentrations used in the same assay, submitted in the current amendment per our request, were 250, 500 and 750 µg/mL. The QC concentrations should have been within the concentration range of the standard curve. The HPLC assay, therefore, is not considered adequately validated. The data generated for the Cascade Impaction test are not considered valid."

In the current amendment, the firm has provided the following responses:

1. The reference to section 3.2.P.5.2 was to identify the location of the information in module 3 of the eCTD, not a specific step in the procedure. Within section 3.2.P.5.2 of the eCTD is test method TM-1174 that was revised in the amendment dated June 13, 2006 to include the procedure for spray weighing.

The corresponding validation for the spray weighing procedure was provided as an amendment to validation report TM-1174 in the amendment dated April 20, 2006. This validation report is located in module 3 of the eCTD in section 3.2.P.5.3.

2. The firm informed the DBE that the previous validation data was based on *the total spiked amount not on the concentration*. To demonstrate that the QC concentrations used in the assay were within the linear range of calibration curve ((b) (4) $\mu\text{g/mL}$), the firm has revised the previous response to express the same set of data as concentration (See Tables 1 and 2 in the file attached below). In order to determine that the HPLC assay used in the cascade impaction test (PD-084) performs with acceptable precision, the data of QCs at 3 concentration levels within the linear concentration range of the standard curve are provided in Table 1. In order to determine that the HPLC assay used in the cascade impaction test performs with acceptable accuracy, a mixture of Fluticasone Propionate Raw Material (Batch No. 05ST75MHQ00022, manufactured by (b) (4)) and Placebo (Lot No. 04020604) containing analyte concentrations at the (b) (4) $\mu\text{g/mL}$; (b) (4) $\mu\text{g/mL}$ and (b) (4) $\mu\text{g/mL}$ were prepared and analysed as per PD-084 method. The mean recovery is shown in Table 2.

TABLE 1: Precision of the Method at the Extremes of the Range

Injection No.	Observed Area		
	(Concentration $\mu\text{g/mL}$)	(Concentration $\mu\text{g/mL}$)	(Concentration $\mu\text{g/mL}$)
1	(b) (4)	(b) (4)	(b) (4)
2	(b) (4)	(b) (4)	(b) (4)
3	(b) (4)	(b) (4)	(b) (4)
4	(b) (4)	(b) (4)	(b) (4)
5	(b) (4)	(b) (4)	(b) (4)
6	(b) (4)	(b) (4)	(b) (4)
Mean	45749	91479	137547
CV (%)	0.3	0.3	0.1

Table 2: Accuracy (Recovery)

Theoretical Concentration ($\mu\text{g/mL}$)	Recovered Concentration ($\mu\text{g/mL}$)	Recovery (%)	Mean Recovery (%)
(b) (4)	(b) (4)	(b) (4)	99.8
(b) (4)	(b) (4)	(b) (4)	97.1
(b) (4)	(b) (4)	(b) (4)	97.9

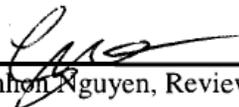
J. DBE's Deficiency Comments for Firm's Current Responses:

1. The firm's response to Deficiency #1 is satisfactory.
2. The firm's response to Deficiency #2 is satisfactory. It should be noted that the firm's original reporting of the assay QCs as *the total spiked amounts* is not usual or conventional. The data as submitted in the current amendment are acceptable and will be verified through the For-Cause DSI inspection currently requested and in progress.

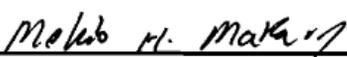
The *in vitro* and *in vivo* studies are now considered **acceptable**. However, the application is **incomplete** pending the results of the DSI inspection.

K. Recommendations

1. The *in-vitro* equivalence studies conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, manufactured by GlaxoSmithKline, are **acceptable**.
2. The *in vivo* bioequivalence study conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, manufactured by GlaxoSmithKline, has been found **acceptable** previously (See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc).
3. The application is **incomplete** pending the results of the For-Cause DSI inspection.

 8/18/06

Hoainhon Nguyen, Review Branch I, Review Date

 8/21/06

Moheb H. Makary, Ph.D., Team Leader, Review Branch I, Review Date

Ua  8/22/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-538

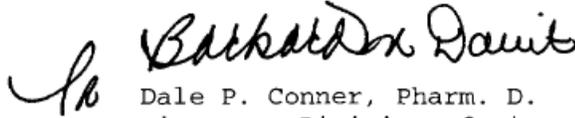
APPLICANT: Apotex Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray (Aqueous Suspension),
50 µg/Spray

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

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

Sincerely yours,

A handwritten signature in black ink, appearing to read "Dale P. Conner". The signature is written in a cursive style with a large initial "D".

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

CC: ANDA 77-538
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

V:\firmsam\apotex\ltrs&rev\77538a0706.doc

Endorsements: (Final with Dates)

HFD-652/HNguyen *PHC*
HFD-652/MMakary *MMM 8/21/06*
HFD-650/DPConner *BMD 8/22/06*



BIOEQUIVALENCY – ACCEPTABLE

Submission Date : 07-20-06

1. Study Amendment (STA)

Strength: 50 ug
Outcome: AC

OUTCOME DECISION: AC – Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-538
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 ug per Spray
Applicant Name	Apotex Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	July 20, 2006
Amendment Date(S)	
Reviewer	Hoainhon Nguyen
First Generic	No
File Location	DFS

I. Executive Summary

This is an addendum to the review V:\firmsam\apotex\ltrs&rev\77538a0706.doc. The purpose of the addendum is to request additional information concerning the assay validation for the Cascade Impaction test. A For-Cause DSI inspection has previously been requested to verify the validity of the *in vitro* testing in general, and the Cascade Impaction test in particular. As of this date, the DSI inspection has not been carried out but all other aspects of the application have been reviewed and found acceptable. Since the DSI could not schedule the inspection promptly due to resource issues, the DBE is requesting additional information from the firm for further verification of the Cascade Impaction test *in place of* the inspection. The additional information includes all relevant SOP's, all raw assay validation data, chromatograms and copies of notebooks used in the validation of the HPLC assay for the Cascade Impaction test.

The application is **incomplete** pending the satisfactory review of the additional information requested above.

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III. Submission Summary

A. Drug Product Information

Test Product Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray

Reference Listed Drug (RLD) Product Flonase® (Fluticasone Propionate) Nasal Spray (Aqueous Suspension), 50 ug per spray

RLD Product's Manufacturer GlaxoSmithKline

NDA No. 20-121

RLD Product's Approval Date October 19, 1994

Indication Flonase® Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

B. PK Information

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Amendment	Yes.	1

D. In-Vivo Study

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

Single-Dose Bioequivalence Study (PK Study)

Study Summary	
Study No.	AA23357
Study design	Randomized, Single-Dose, Two-Way Crossover
No. of subjects enrolled	100
No. of subjects completed	100
No. of subjects analyzed	99*
Subjects (Healthy/Patients?)	Healthy
Sex(es) included for subjects that completed the study(how many?)	Male: 45 Female: 54
Test product	Fluticasone Propionate Nasal Spray Aqueous Suspension
Reference (RLD) product	Flonase® (Fluticasone Propionate) Nasal Spray Aqueous Suspension
Strength tested	50 ug per spray
Dose	200 µg (50 µg spray X2 in each nostril)

*NOTE: Subject #29 had a nosebleed 32 minutes after dosing in Period I. Since this event occurred before the expected Tmax (approximately 2 hours), the adverse event was expected to affect the absorption of fluticasone for this subject. For this reason, the samples of Subject #29 were not analyzed and not included in the study analysis.

Summary of Statistical Data (N=99)		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC0-t	0.99	91.3-107.9
LAUC _∞	1.08	97.2-120.7
LCmax	1.01	94.0-109.4
Summary of Statistical Data (N=99) – Supportive Analysis*		
Parameter	Point Estimate	90% Confidence Interval (CI)
LAUC0-t	0.96	86.4-106.5
LCmax	1.01	94.0-109.4

*NOTE: In the supportive analysis, AUCt and Cmax were calculated as specified in the DBE recommendation stated in Control Document No. 03-361 (See the DBE History section of this review):
“The AUCt should be based on at least four consecutive nonzero plasma concentration values. The AUC computation should be terminated at the last quantifiable plasma concentration before the first zero (BLQ) value following these four or more values. The PK analysis should include only those subjects that meet this rule for both periods, i.e., for both Test product and RLD.
“The Cmax should be computed as the maximum plasma concentration that occurs among the values used to compute the AUCt. A second maximum concentration that may occur after the data points used in the computation of AUCt [i.e., following the above mentioned zero (BLQ) value] is not the Cmax of interest.”
In the main analysis, AUCt, AUCinfinity and Cmax were calculated with all data points included, whereas in the supportive analysis, any non-zero data point following the first zero (BLQ) value was excluded.

Comment on the Bioequivalence Study (PK Study):

The 90% confidence intervals for $\ln C_{max}$, $\ln AUC_t$ and $\ln AUC_{\infty}$ (main analysis only) were within the acceptable limits of [80.0;125.0] in the main and supportive analysis. The bioequivalence study conducted under fasting conditions is **acceptable**.

E. Formulation

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

G. In-Vitro Equivalence Studies

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

H. Firm's Responses to DBE's Deficiency Comments:

The following deficiency comments were communicated to the firm in the letter dated July 14, 2006:

"1. Your response to Deficiency #1 is adequate concerning the representative daily calibration check data and the added procedure for validation of spray weighing. However, from the SOP entitled "Amendment of Validation for Assay of Fluticasone per Spray in Fluticasone Propionate Nasal Spray, 50 µg/spray" (generated 04/17/2006) and the SOP entitled "Assay of Fluticasone Propionate Per Spray and Total Number of Sprays per Bottle Delivered from Actuator in Fluticasone Propionate Nasal Spray" (generated 05/29/2006), it is not clear to which part of which SOP the "section 3.2.P.5.2" was referred. No such "section" was found in either of the two documents submitted. Please clarify the reference of "section 3.2.P.5.2".

2. Your response to Deficiency #2 is not acceptable. Based on the calibration curve data submitted in the previous amendment dated April 20, 2006 (shown in the table below), the concentration range of the standard curve used for the assay of droplet content in the Cascade Impaction test was (b) (4) µg/mL. However, the QC concentrations used in the same assay, submitted in the current amendment per our request, were 250, 500 and 750 µg/mL. The QC concentrations should have been within the concentration range of the standard curve. The HPLC assay, therefore, is not considered adequately validated. The data generated for the Cascade Impaction test are not considered valid."

In the current amendment, the firm has provided the following responses:

1. The reference to section 3.2.P.5.2 was to identify the location of the information in module 3 of the eCTD, not a specific step in the procedure. Within section 3.2.P.5.2 of the eCTD is test method TM-1174 that was revised in the amendment dated June 13, 2006 to include the procedure for spray weighing.

The corresponding validation for the spray weighing procedure was provided as an amendment to validation report TM-1174 in the amendment dated April 20, 2006. This validation report is located in module 3 of the eCTD in section 3.2.P.5.3.

2. The firm informed the DBE that the previous validation data was based on *the total spiked amount not on the concentration*. To demonstrate that the QC concentrations used in the assay were within the linear range of calibration curve (b) (4) $\mu\text{g/mL}$), the firm has revised the previous response to express the same set of data as concentration (See Tables 1 and 2 in the file attached below). In order to determine that the HPLC assay used in the cascade impaction test (PD-084) performs with acceptable precision, the data of QCs at 3 concentration levels within the linear concentration range of the standard curve are provided in Table 1. In order to determine that the HPLC assay used in the cascade impaction test performs with acceptable accuracy, a mixture of Fluticasone Propionate Raw Material (Batch No. 05ST75MHQ00022, manufactured by (b) (4)) and Placebo (Lot No. 04020604) containing analyte concentrations at the (b) (4) $\mu\text{g/mL}$; (b) (4) $\mu\text{g/mL}$ and (b) (4) $\mu\text{g/mL}$ were prepared and analysed as per PD-084 method. The mean recovery is shown in Table 2.

TABLE 1: Precision of the Method at the Extremes of the Range

Injection No.	Observed Area		
	(Concentration $\mu\text{g/mL}$)	(Concentration $\mu\text{g/mL}$)	(Concentration $\mu\text{g/mL}$)
1	(b) (4)	(b) (4)	(b) (4)
2	(b) (4)	(b) (4)	(b) (4)
3	(b) (4)	(b) (4)	(b) (4)
4	(b) (4)	(b) (4)	(b) (4)
5	(b) (4)	(b) (4)	(b) (4)
6	(b) (4)	(b) (4)	(b) (4)
Mean	45749	91479	137547
CV (%)	0.3	0.3	0.1

Table 2: Accuracy (Recovery)

Theoretical Concentration ($\mu\text{g/mL}$)	Recovered Concentration ($\mu\text{g/mL}$)	Recovery (%)	Mean Recovery (%)
(b) (4)	(b) (4)	(b) (4)	99.9
(b) (4)	(b) (4)	(b) (4)	97.1
(b) (4)	(b) (4)	(b) (4)	97.9

J. DBE's Deficiency Comments for Firm's Current Responses:

1. The firm's response to Deficiency #1 is satisfactory.
2. The firm's response to Deficiency #2 is satisfactory. It should be noted that the firm's original reporting of the assay QCs as *the total spiked amounts* is not usual or conventional. The data as submitted in the current amendment are acceptable. Because of the unusual and unconventional manner in which the validation data were obtained and submitted to the Agency, the reviewer has requested a For-Cause DSI inspection to verify the firm's current responses (See the DSI request on file).

As of this date, the DSI inspection has not been carried out but all other aspects of the application have been reviewed and found acceptable. Since the DSI could not schedule the inspection promptly due to resource issues, the DBE is requesting additional information from the firm for further verification of the Cascade Impaction test *in place of* the inspection. (See the emails attached for further discussion concerning the DSI request.) The additional information requested from the firm at this time includes all relevant SOP's, all raw assay validation data, all actual Cascade Impaction sample data obtained by HPLC, chromatograms and copies of *notebooks* used in the validation of the HPLC assay for the Cascade Impaction test. The firm should make sure the address of the laboratory, the name of the analyst(s), their training records, the approval(s) by the laboratory supervisor(s), the dates of the validation as well as the dates of the Cascade Impaction sample analyses, and any deviations from the validation SOPs are clearly documented.

The application is **incomplete** pending the satisfactory review of the additional information requested above.

REVIEWER'S NOTE: Without an onsite inspection, any additional information requested can not be *completely* verified.

K. Recommendations

1. The *in-vitro* equivalence studies conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, manufactured by GlaxoSmithKline, are **incomplete** due to the Deficiency comments above.

NOTE: At this time, the For-Cause DSI inspection remains pending.

VI. Appendix

Emails Concerning the DSI Inspection:

From: Davit, Barbara M
Sent: Wednesday, July 18, 2007 1:47 PM
To: Makary, Moheb H; Nguyen, Hoainhon T
Cc: Sigler, Aaron; Sanchez, Aida L
Subject: FW: ANDA 77538, Apotex's fluticasone propionate nasal spray
Hoai:

As per Bob's email, please ask for additional information about the analytical method validation QC studies, such the actual dates on which they were conducted, etc., and any other information that will put your mind at ease. You can do this as an addendum to the review.

Thanks!

Barbara

From: West, Robert L
Sent: Wednesday, July 18, 2007 1:09 PM
To: Davit, Barbara M
Cc: Sigler, Aaron; Chuh, Esther
Subject: RE: ANDA 77538, Apotex's fluticasone propionate nasal spray

Barbara/Aaron:

Thanks for discussing this issue.

You note below that eventually, the ANDA holder did supply the data we asked for. With regard to when Apotex ran the standard curves and quality control samples, we should ask Apotex to answer this question, and we should be comfortable with their reply. If they answer it the way we want, I think we should accept their answer and move forward.

Bob

From: Davit, Barbara M
Sent: Wednesday, July 18, 2007 1:02 PM
To: West, Robert L
Cc: Conner, Dale P; Sigler, Aaron; Sanchez, Aida L; Nguyen, Hoainhon T; Makary, Moheb H
Subject: ANDA 77538, Apotex's fluticasone propionate nasal spray

Bob:

Aaron sent us an email indicating that you are asking about the status of the pending DSI inspection.

DBE would like to ask you whether we should cancel the pending inspection or not, as the application is up for approval. Here are the arguments for and against canceling the inspection:

Arguments for canceling the inspection:

- All 7 in vitro bioequivalence tests were acceptable.
- The PK bioequivalence study was acceptable.
- The bioequivalence study with clinical endpoints was acceptable.
- The assay validation submitted in support of one of the in vitro tests (cascade impaction) was initially not acceptable, but was later found acceptable. This is the assay for which the reviewer requested a DSI inspection.
- The cascade impaction test, for which the inspection was requested, is one of only 7 in vitro tests, and is a qualitative rather than quantitative test.
- Apotex has a good inspection history.
- DSI has not yet schedule the inspection.

Arguments for allowing the inspection to proceed:

- The QC data used to support the cascade impaction comparative in vitro test was obtained using an unconventional approach.
- The reviewer asked Apotex three times to explain why it ran the assay the way that it did.
- Eventually, Apotex supplied the data that the reviewer asked for.
- It is not clear if Apotex ran the standard curves and quality control samples supporting the assay before or after the cascade impaction test was completed.
- Because Apotex did not send us the data we requested right away, and had to be asked three times, the reviewer thought it prudent to request an inspection to determine how the assay was really run.

Please let us know how to proceed on this application.

Thanks,

Barbara

Barbara M. Davit, Ph.D., J.D.
Deputy Director
Division of Bioequivalence
Office of Generic Drugs
CDER/FDA
240-276-8782

From: Sigler, Aaron
Sent: Wednesday, July 18, 2007 10:07 AM
To: Conner, Dale P; Davit, Barbara M; Makary, Moheb H; Nguyen, Hoainhon T
Cc: Sanchez, Aida L
Subject: RE: APOTEX'S ANDA 77-538 FOR FLUTICASONE NASAL SPRAY

Attachments: 77538a0706.doc

Hi all,

This application is essentially ready for approval. However, we do have a DSI inspection requested for the in-vitro testing. I'd like to generate an appropriate response for Bob, as to the current necessity of the DSI inspection.

Hoai had tried a number of times to get the accurate in-vitro testing data from the firm. After three attempts, I requested a "for-cause" inspection. However, subsequent to my DSI request, the firm submitted data that while unorthodox, was sufficient to find the application acceptable to DBE. However, overall acceptability is still pending the inspection. Below is our last set of comments for the ANDA:

J. DBE's Deficiency Comments for Firm's Current Responses:

1. The firm's response to Deficiency #1 is satisfactory.

2. The firm's response to Deficiency #2 is satisfactory. It should be noted that the firm's original reporting of the assay QCs as *the total spiked amounts* is not usual or conventional. The data as submitted in the current amendment are acceptable and will be verified through the For-Cause DSI inspection currently requested and in progress.

The *in vitro* and *in vivo* studies are now considered **acceptable**. However, the application is **incomplete** pending the results of the DSI inspection.

I'd like to generate some internal dialogue as to how I best can respond to Bob. DSI has not scheduled the inspection, but there have been acceptable inspections in the past. Enclosed is the final review.

Thanks,

Aaron



77538a0706.doc
(861 KB)

From: West, Robert L
Sent: Wednesday, July 18, 2007 7:31 AM
To: Sigler, Aaron
Subject: RE: APOTEX'S ANDA 77-538 FOR FLUTICASONE NASAL SPRAY

Based upon what appears to be a favorable history at Apotex, would it be worth having another telephone conference with the firm to resolve the remaining issues?

Bob

From: Sigler, Aaron
Sent: Wednesday, July 18, 2007 7:21 AM
To: West, Robert L
Cc: Chuh, Esther
Subject: RE: APOTEX'S ANDA 77-538 FOR FLUTICASONE NASAL SPRAY

Hi Bob,

I discussed the issue with Hoai. In summary, the issue is that Hoai lacks faith in some of the data submitted b/c the firm was inconsistent despite numerous attempts on her part to gain some clarification. She would like DSI to be at the site to look at the records.

Given this issue, DBE had requested a For Cause inspection, not routine.

Feel free to call me at your convenience for any additional information. 240-276-8775.

Thanks,

Aaron

From: West, Robert L
Sent: Tuesday, July 17, 2007 7:22 AM
To: Sigler, Aaron
Cc: Chuh, Esther
Subject: APOTEX'S ANDA 77-538 FOR FLUTICASONE NASAL SPRAY

Aaron:

This is a follow up to our conversation last week concerning the completion of the statistical review for this ANDA and what to do about the pending DSI inspection. For a number of reasons we discussed, I believe that you were going to put together a memo to address this issue. In addition, Bernice Tao of Apotex has informed me that the Apotex facility that conducted the in-vitro testing (spray pattern determination, plume geometry, etc.) for this ANDA is:

Apotex Inc.
380 Elgin Mills Road, East
Richmond Hill, Ontario
Canada, L4C 5H2

She claims that this same facility was also used for in-vitro testing for the following ANDAs:

75-499 Butorphanol Tartrate Nasal Spray
76-703 Desmopressin Acetate Nasal Solution
76-156 Ipratropium Bromide Nasal Spray, 0.03%
76-155 Ipratropium Bromide Nasal Spray, 0.06%

For my information, why are we waiting for DSI to inspect for Fluticasone, when we've already approved the 4 ANDAs noted above?

Thanks,

Bob

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-538

APPLICANT: Apotex Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray (Aqueous Suspension),
50 µg/Spray

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies concerning *in-vitro* studies have been identified:

In the current amendment, you informed the DBE that the previous HPLC assay validation data for the Cascade Impaction test were reported based on *the total spiked amount not on the concentration*. We found the manner in which the validation data obtained and presented to the Agency rather unusual and unconventional. For the purpose of further verification of the HPLC assay validation data used in the Cascade Impaction test, we are requesting the following additional information:

Please submit all relevant SOP's, all raw assay validation data, all actual Cascade Impaction sample data obtained by HPLC, chromatograms and copies of notebooks used in the validation of the HPLC assay for the Cascade Impaction test. Please be sure the address of the laboratory, the name of the analyst(s), their training records, the approval(s) by the laboratory supervisor(s), the dates of the validation as well as the dates of the Cascade Impaction sample analyses, and any deviations from the validation SOPs are clearly documented.

Sincerely yours,

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

CC: ANDA 77-538
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

V:\firmsam\apotex\ltrs&rev\77538a0706.doc

BIOEQUIVALENCE – INCOMPLETE

Submission Date : 07-20-06

1. Addendum

Strength: 50 ug
Outcome: IC (WC)

OUTCOME DECISION: IC – Incomplete; WC – Without Credit

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

/s/

Hoainhon T. Nguyen
7/25/2007 05:07:49 PM
BIOPHARMACEUTICS

Moheb H. Makary
7/26/2007 06:35:41 AM
BIOPHARMACEUTICS

Barbara Davit
7/26/2007 03:27:26 PM
BIOPHARMACEUTICS