CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077570

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-570
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 mcg per Spray
Applicant Name	Hi Tech Pharmacal Co. Inc.
Address	369 Bayview Avenue Amityville, NY 11701 Contact: Elan Bar 631-789-8228 ext. 4108 (phone) 631-789-8229 631-789-8429 (fax)
Submission Date(s)	Feb. 7, 2005 (refused to file) April 14, 2005 (file)
Amendment Date(S)	NA
Reviewer	Bing V. Li, Ph.D.
First Generic	No

I. Executive Summary

Hi Tech Pharmacal submitted a single-dose bioequivalence study, a clinical endpoint bioequivalence study, and in vitro bioequivalence studies comparing its test product, fluticasone propionate nasal spray (Aqueous Suspension), 50 mcg per spray with the RLD product, Flonase® Nasal Spray (Aqueous Suspension), 50 mcg per spray, manufactured by GlaxoSmithKline.

The single-dose bioequivalence study (PK study) is **incomplete** due to the deficiencies summarized under "Deficiency Comments on the Single-Dose Bioequivalence Study".

The In-Vitro equivalence studies are also **incomplete** due to the deficiencies summarized under the "Deficiency Comments on the In-Vitro Equivalence Studies".

The clinical endpoint bioequivalence study is currently being reviewed by the OGD Clinical Group.

The application is **incomplete**.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per spray
Reference Listed Drug (RLD) Product	Flonase® (Fluticasone Propionate) Nasal Spray (Aqueous Suspension), 50 mcg 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).
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 mcg). The same dosage divided into 100 mcg given twice daily is also effective. The maximum total daily dosage should not exceed 2 sprays in each nostril (total dose: 200 mcg/day) (Electronic PDR).
Relevant OGD or DBE History	Besides ANDA 76-504 (Roxane) which has been approved on Feb 22, 2006, there were three previous submissions for fluticasone propionate nasal spray 50 mcg/spray: (b) (4) (b) (4).
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

Study Types	Yes/No?	How many?
Single-dose bioequivalence study (PK study)	Yes	1
In-Vitro equivalence studies	Yes	8
Clinical endpoint study	Yes	1

D. Pre-Study Bioanalytical Method Validation

Not reported.

Reviewer's Comment: The firm did not submit the Pre-Study Bioanalytical Method Validation report for the in vivo BE study sample analysis. The firm needs to submit this information.

E. In-Vivo Study

Single-Dose Bioequivalence Study (PK Study)

Study Summary	
Study No.	10322808
Study design	Single-dose, two period, two treatment, crossover
No. of subjects enrolled	72
No. of subjects completed	70
No. of subjects analyzed	68 (subject 49 and 54 were exclude from the statistical analysis)*
Subjects (Healthy/Patients?)	None tobacco using, healthy adults
Sex(es) included for subjects that completed the study (how many?)	Male: 49 Female: 21
Test product	Fluticasone Propionate 50 mcg/spray Nasal Spray
Reference (RLD) product	Flonase® (Fluticasone Propionate) Nasal Spray, 50 mcg/spray
Strength tested	50 mcg per spray
Dose	200 mcg (2 x 50 mcg in each nostril)

* subject 49 was dropped from the statistical analysis as he deviated from the protocol by receiving less than half of the required dose of Treatment B (reference) in Period 2 of the study. Subject 54 had plasma concentrations of fluticasone in her pre-dose plasma samples that were greater than 5% Cmax in both study periods.

Group 1 (n=35)

Summary of Statistical Analysis, Fasting Bioequivalence Study			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		Low	**Upper**
AUC∞	1.07	91.96	123.43
AUC0-t	1.04	92.49	116.15
Cmax	1.05	97.44	113.92

Group 2 (n=33)

Summary of Statistical Analysis, Fasting Bioequivalence Study			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		Low	**Upper**
AUC∞	1.19	96.42	**147.97**
AUC0-t	1.20	107.07	**133.58**
Cmax	1.22	111.33	**134.69**

Reviewer's Comments:

1. The above results are based on the reviewer's calculations. Since subjects were dosed in two groups, the Group-by-Treatment interaction term was used in the model. A statistically significant ($p<0.1$) of Group-by-Treatment interaction was observed for LCmax. The DBE considers the groups as two separate studies, which may have different outcomes. Therefore, the reviewer analyzed the data in two separate groups. The results indicated that the 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{\infty}$ and LC_{max} are within the acceptable limits of 80-125% for group 1 (35 subjects) but not for group 2 (33 subjects). In control #98-392 (see attachment), it is stated that "*if the Group-by-Treatment interaction is statistically significant (p<0.1), DBE requested that equivalence be demonstrated in one of the groups, provided that the group meets minimum requirements for a complete bioequivalence study*".

2. Although the subjects in the study were from the same geographic region and have the same demographic profiles, they were not enrolled in the study at the same time. The subjects enrolled in group 2 were screened after the beginning of the fasting study for group 1. There were 15 days in between the dosing of the two groups. Therefore, individual statistical analysis is performed for each group.

3. Treatment group 2 (N=33) did not meet BE statistical criteria. The 90% confidence intervals for $LAUC_{0-t}$ and $LAUC_{\infty}$ and LC_{max} are not within the acceptable 80-125% range for fluticasone. The results of group 2 may be due to high variability in the BE parameters from this drug product and/or the study group was underpowered.

4. The reviewer also analyzed the data keeping all subjects in one group. The results are as follows and agrees with the firm's results:

Summary of Statistical Analysis, Fasting Bioequivalence Study, firm's results			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		Low	**Upper**
AUC_{∞}	1.11	98.88	123.88
AUC0-t	1.11	102.77	120.34
Cmax	1.14	106.63	120.81

Reanalysis of Study Samples:

There is no PK repeats.

Comment on the Bioequivalence Study (PK Study): The study is incomplete due to the reasons given in the Deficiency section.

F. Formulation

Location in appendix	Section B
Inactive ingredients within IIG Limits (Yes or No?)	Yes
Formulation is acceptable (Yes or No?)	No. (Refer to Appendix, section B for details)

G. In-Vitro Equivalence Studies

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

1. Single Actuation Content through Container Life
2. Spray Pattern using Laser Image (non impaction automated analysis)
3. Spray Pattern using Thin Layer Chromatography (TLC) impaction manual analysis
4. Particle Size Distribution by Microscopy
5. Particle Size Distribution by Cascade Impactor
6. Droplet Size Distribution by Laser Diffraction
7. Plume Geometry
8. Priming and Repriming

Particle Size Distribution by Microscopy study is not reviewed in this report.

H. Waiver Request

None.

I. Deficiency Comments

A. Deficiency Comments on the Single-Dose Bioequivalence Study (PK Study):

1. The firm did not submit the Pre-Study Bioanalytical Method Validation report for the *in vivo* BE study sample analysis. The firm needs to submit this information. In addition, the firm is advised to submit its validation results in a summary table as shown below:

Analyte name	
Internal Standard	
Method description	
QC range	
Standard curve range	
Limit of quantitation	
Average recovery of Drug (%)	
Average Recovery of Int. Std (%)	
QC between-run precision range (CV%)	
QC between-run accuracy range (%)	
QC within-run precision range (CV %)	
QC within-run accuracy range (%)	
Bench-top stability (hrs)	
Stock stability (hours)	
Processed stability (hrs)	
Freeze-thaw stability (cycles)	
Long-term storage stability (days)	
Dilution integrity	
Specificity	
SOP (s)	

2. The firm did not submit its SOP dealing with reassays for the biostudy analysis. The firm should submit this information.

B. Deficiency Comments Applicable to All In-Vitro Equivalence Studies:

1. The firm did not provide the information about the expiration date of the RLD lot Nos. C089155 and C089150 used in the in-vitro studies and the manufacture date and/or expiration date for the test product lot Nos.301700 and 303700.

2. The firm did not submit the information about the device components (container, pump, actuator, protection cap, and protective packages) of the test product. The firm is advised to submit a side-by-side comparison of the test and reference products, of the components of the container and closure system, listing brand and model, dimensions of critical components, and engineering drawings.

3. The firm did not provide the information about the study site, study director and the analytical director for the in-vitro studies.

4. The validation report (method # TM-0122, blue jacket, p 5085) for "Quantitation of Fluticasone Propionate in Fluticasone Propionate Aqueous Nasal Spray (Assay and Assay per Dose) and in Fluticasone Propionate Raw Material (Assay)" did not include the information of Limit of Quantitation and QC concentrations.

5. The firm's electronic data were removed from EDR because of the unacceptable format (refer to Attachment for EDR's records). The Division of Bioequivalence has recently issued a standard data format for the in vitro studies for Nasal spray products. The firm should resubmit its data based on the DBE's recommended format as shown in the Additional Attachment section.

Deficiency Comment for Single Actuation Content through Container Life:

1. The firm is advised to provide a summary table for its Single Actuation Content through Container Life study results of both the test and reference products as shown below:

		Mean			Variability (%CV)		Ratio of Means TEST/RLD		P Value
Product (test or reference)	**Sector (Beginning or Ending)**	**Arith.**	**Geo.**	**Within-Lot**	**Between-Lot**	**Total**	**Arith.**	**Geo.**	
		(N=30)	**(N=30)**	**(N=10)**	**(N=3)**	**(N=30)**	**(N=30)**	**(N=30)**	

Deficiency Comments for Spray Pattern Analysis using Laser Image:

1. The firm used automated pattern recognition measurement for the image analysis. The description about the automated pattern recognition system in the method is not clear. The firm should clarify that using this system, the perimeter of the TRUE shape of the spray pattern was determined, the center of mass (COM) or center of gravity (COG) was identified, and the Dmin and Dmax that passed through COG were measured based on the TRUE shape of the images.

2. The firm is advised to provide a summary table for its Spray Pattern by Laser Image study results of both the test and reference products as shown below:

					Variability (%CV)			TEST/REF		
Products (test or reference)	**Sector (B or E)**	**Distance**	**Parameter (Dmin, Dmax, Ovality)**	**Mean**	**Within-Lot**	**Between-lot**	**Total**	**Arith Mean**	**Geo Mean**	**P Value**
				(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

Deficiency Comments for Spray Pattern using Thin Layer Chromatography (TLC) Impaction Manual Analysis:

1. Quantitation of spray patterns was not performed correctly. The firm fitted an ellipse and determined the Dmax and Dmin based on the fitted area within the ellipse (Vol 1.9, p 2959). The firm should clarify whether the D_{max} and D_{min} measurements were taken from the TRUE perimeters of the patterns or from the ellipses fitted to the pattern. If the data were based on the latter, the firm should provide data based on the TRUE shape of the patterns.

2. The firm did not use an automated actuator for spray pattern study using Thin-Layer Chromatograph (TLC). The firm should explain why an automated actuator was not used for this test.

3. The firm is advised to provide a summary table for its Spray Pattern by TLC study results of both the test and reference products as shown below:

					Variability (%CV)			TEST/REF		
PROD (T or R)	**Sector (B or E)**	**Distance**	**Parameter (Dmin, Dmax, Ovality)**	**Mean**	**Within-Lot**	**Between-lot**	**Total**	**Arith Mean**	**Geo Mean**	**P Value**
				(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

Deficiency Comments for Droplet Size Distribution by Laser Diffraction

1. The firm did not specify that the instrument was operated within the manufacturer recommended obscuration or percent transmission (%T) range.
2. The firm did not submit its protocol or SOP which states the criterion of selecting the plateau region at which droplet size data was determined. This criterion should be established prior to the study and implemented consistently during the study.
3. The firm is advised to provide a summary table for its droplet size distribution study results (D50 and Span) of the test and reference products as shown below:

Droplet Size Distribution (D50 or SPAN Data)

				Variability (%CV)			TEST/REF		
PROD (T or R)	**Sector (B or E)**	**Distance**	**Mean**	**Within-Lot**	**Between-lot**	**Total**	**Arith Mean**	**Geo Mean**	**P Value**
			(N = 30)	**(N=10)**	**(N=3)**	**(N=30)**	**(N=30)**	**(N=30)**	
		Dist. 1							
		Dist. 2							

Deficiency Comments for Particle Size Distribution by Cascade Impactor

1. The firm did not provide the flow rate of the apparatus (liters/min).
2. The firm should note that the Cascade Impaction Studies on the nasal sprays are conducted to determine the amount of drug in small droplets (< 9 µm, below the top stage). Since the amount of drug deposited below the top stage is of primary interest, the drug deposition should be categorized in two groups. Group 1 should include all drug deposited below the top stage which are < 9 µm in size (stage 1 through F, according to the cascade Impactor schematic shown in Vol. 1.9, p 2949). Group 2 should include the total mass of drug collected on all stages and accessories.
3. The firm's electronic data for particle size distribution by Cascade Impactor was removed from EDR because of the unacceptable format. The firm should resubmit its data in the DBE's recommended format (refer to Deficiency Comment in General section for data format). It should be noted that Table 6 can be modified according to the different type of Cascade Impactor used in the study. Nevertheless, the firm should provide data for particle size less than 9 µm and the total mass data.

4. The firm is advised to provide a summary table for its particle size determination by Cascade Impaction study results (in Mass and % of Labeled Claim) of both the test and reference products as shown below:

PROD. (T or R)	SECTOR (B or E)	Mean	Variability (%CV)			TEST/REF		
			Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
		(N=30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=3)0	
		Group 1						
		Group 2						

Deficiency Comments for Plume Geometry by Laser Imaging:

1. The firm did not provide documentation showing that the plume is fully developed at the selected delay time.
2. The firm is advised to provide a summary table for its plume geometry study results, including the plume length, width and angle of the test and reference products as shown below:

Plume Geometry Data

			Variability (%CV)			TEST/REF		
PROD. (T or R)	Plume Stage (B or E)	Mean	Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
		(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

Deficiency Comments for Priming and Repriming Study

1. In the testing method for priming and repriming study experiment part B (Vol. 1.9, p 2944), the firm stated that "*prime the pump by pressing down until a fine mist comes out of the nozzle*". The firm did not mention the number of sprays required for achieving such fine mist. The firm should specify the number of spray required for priming.
2. The firm is advised to provide a summary table for its prime and reprime study results of both the test and reference products as shown below:

Priming and Repriming Data

			Variability (%CV)			TEST/REF		
PROD. (T or R)	Spray #	Mean	Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
		(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

J. Recommendations

1. The pharmacokinetic bioequivalence study # 10322808 submitted for Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per spray by Hi Tech Pharmacal Co. Inc., comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 mcg per spray manufactured by GlaxoSmithKline, is **incomplete** due to deficiencies summarized under "Deficiency Comments on the Single-dose Bioequivalence study (PK Study)".

2. The In-Vitro equivalence studies submitted for Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per spray by Hi Tech Pharmacal Co. Inc. comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 mcg per spray manufactured by GlaxoSmithKline, are **incomplete** due to deficiencies summarized under "Deficiency Comments Applicable for All In-Vitro Equivalence Studies".

The firm should be informed of the deficiency comments and recommendations.

IV. Appendix

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

a). Study Design

Study Information	
Sponsor	Hi-Tech Pharmacal Co., Inc.
Study Number	10322808
Study Title	A Study to Evaluate the Relative Bioavailability Study of Two Fluticasone Propionate 50 mcg/actuation Nasal Spray in Healthy Adult Subjects
Clinical Site	Novum Pharmaceutical Research Services, Pittsburgh, PA 15206
Principal Investigator	Shirley Ann Kennedy, M. D.
Dosing Date	Group 1: 03/06/04; 03/13/04 Group 2: 03/20/04; 03/27/04
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	April 01, 2004 to May 4, 2004
Storage Period (Number of days from the first day of sample collection through the last day of the sample analysis)	59 days

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Fluticasone Propionate 50 mcg/spray Nasal Spray	Flonase® (Fluticasone Propionate) Nasal Spray, 50 mcg/spray
Manufacturer	Hi-Tech Pharmacal Co., Inc.	GlaxoSmithKline
Batch/Lot No.	302-700 (same lot used for in vitro study)	C089739 (same lot used for in vitro study)
Manufacture Date	Not reported	NA
Expiration Date	11/05	08/05
Strength	50 mcg per spray	50 mcg per spray
Dosage Form	Nasal Spray	Nasal Spray
Batch Size	Not reported	N/A
Production Batch Size	Not reported	N/A
Assayed Potency	100%	Not reported
Spray Content Uniformity (Assay per dose)	Beginning: 51 mcg/dose (range 45-59 mcg/dose) End: 51 mcg /dose, (range 45-55 mcg/ml)	Beginning: 47 mcg/dose (range 44-50 mcg/dose) End: 47 mcg /dose, (range 46-49 mcg/ml)
Route of Administration	Nasal	Nasal
Dose Administered	Single-dose of 200 mcg: 1 X 100 mcg spray per nostril for a total of 4 sprays per subject; the time of the first actuation to the final actuation was not exceed 1 min	Single-dose of 200 mcg: 1 X 100 mcg spray per nostril for a total of 4 sprays per subject; the time of the first actuation to the final actuation was not exceed 1 min

No. of Groups	2 Group I: subjects 1-36 Group I: Subjects 37-72
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
Washout Period	7 days
Randomization Scheme	AB: 1, 4, 6, 7, 10, 12, 14, 16, 17, 19, 21, 23, 26, 27, 29, 32, 34, 36, 38, 39, 41, 43, 46, 48, 49, 51, 54, 55, 58, 60, 62, 63, 66, 67, 69, 71 BA: 2, 3, 5, 8, 9, 11, 13, 15, 18, 20, 22, 24, 25, 28, 30, 31, 33, 35, 37, 40, 42, 44, 45, 47, 50, 52, 53, 56, 57, 59, 61, 64, 65, 68, 70, 72
Blood Sampling Times	At pre-dose, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, and 24 hours post-dose (19 samples)
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Blood samples are collected in Vacutainers containing K3-EDTA. Stored at -20˚C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 1**
Fasting	Overnight fast of at least 10 hours
Confinement	Subjects were confined from the night prior to dosing until 24 hours after dosing
Safety Monitoring	Vital signs were monitored prior to dosing and 2 hours after dosing.

b) Clinical Results

Table 1 Demographics of Study Subjects

For all subjects:

Age, Years		Weight		Age Groups		Gender		Race	
				Range	N	Sex	N	Category	N
				<18	0.00			Caucasian	62.86
Mean	27.24	Mean	159.81	18-40	81.43	Male	68.57	Afr. Amer.	31.43
SD	10.32	SD	26.80	41-64	18.57	Female	31.43	Hispanic	1.43
Range	18	Range	110	65-75	0.00			Asian	4.29
	54		232	>75	0.00			Others	0.00

For group 1 subjects (subjects #1 - #36):

Age, Years		Weight		Age Groups		Gender		Race	
				Range	N	Sex	N	Category	N
				<18	0.00			Caucasian	68.57
Mean	27.83	Mean	161.51	18-40	77.14	Male	74.29	Afr. Amer.	25.71
SD	11.60	SD	27.97	41-64	22.86	Female	25.71	Hispanic	0.00
Range	18	Range	115	65-75	0.00			Asian	5.71
	54		223	>75	0.00			Others	0.00

For group 2 subjects (subjects #37 - #72):

Age, Years		Weight		Age Groups		Gender		Race	
				Range	N	Sex	N	Category	N
				<18	0.00			Caucasian	57.14
Mean	26.66	Mean	158.11	18-40	85.71	Male	62.86	Afr. Amer.	37.14
SD	8.99	SD	25.87	41-64	14.29	Female	37.14	Hispanic	2.86
Range	18	Range	110	65-75	0.00			Asian	2.86
	46		232	>75	0.00			Others	0.00

Table 2. Dropout Information

Subject No.	Reason	Period	Replacement
26	Voluntarily withdrew due to personal reasons	II	No
38	Withdrawn by the investigator due to adverse events (lightheadness)	I	No

Table 3 Study Adverse Events

Sub. No.	Sub. Init.	Drg*	Adverse Event	ONSET Date	ONSET Time	END Date	END Time	Sev[1]	Rel[2]	Res[3]	Comment
01	(b) (6)	A	Itchy throat	03/06/04	0830	03/06/04	0845	1	3	S	None
01		A	Tired	03/06/04	0940	03/06/04	1600	1	2	S	None
02		A	Headache	03/13/04	1015	03/13/04	1131	1	3	S	None
04		A	Light headed	03/06/04	0830	03/06/04	0920	1	3	S	None
07		A	Light headed	03/06/04	0915	03/06/04	1001	1	3	S	Examined by medical Investigator.
23		A	Decreased blood pressure	03/12/04	1611	03/13/04	0955	1	1	S	Pre-dose Period II.
27		A	Decreased blood pressure	03/12/04	1701	13/13/04	0957	1	1	S	Pre-dose Period II.
30		A	Elevated blood pressure	03/12/04	1654	03/12/04	1709	1	1	S	Pre-dose Period II.
33		B	Headache	03/06/04	1200	03/07/04	0700	1	3	S	None
34		B	Elevated eosinophils, absolute	03/14/04	0816	Unknown	Unknown	1	2	NR	Subject referred to personal physician. Subject lost to follow up.

	(b) (6)										
36		B	Headache	03/13/04	1230	03/14/04	0150	1	3	S	None
38		A	Light headed	03/20/04	0842	03/20/04	0925	1	1	S	Examined by medical Investigator. Subject dropped from study.
38		A	Bruising, bilateral antecubital space	03/20/04	0842	Unknown	Unknown	1	1	NR	Subject lost to follow up.
38		A	Soreness, bilateral antecubital space	03/20/04	0842	Unknown	Unknown	1	1	NR	See above.
38		A	Headache	03/20/04	0900	03/21/04	0645	1	3	T	Administered 1000 mg acetaminophen on 03/20/04.
42		A	Elevated bilirubin, total	04/05/04	1355	Unknown	Unknown	1	1	NR	Subject lost to follow up.
46		B	Cut, small, right index finger	03/27/04	1707	03/30/04	1330	1	1	S	None
48		A	Pain, jaw, right side	03/26/04	1800	04/01/04	1700	1	1	S	Pre-dose Period II.
51		A	Decreased blood pressure	03/20/04	0951	03/20/04	1022	1	2	S	None
60		B	Nausea	03/28/04	0330	03/28/04	1700	1	2	S	None
61		B	Decreased pulse	03/20/04	0956	03/20/04	1002	1	2	S	None
63		B	Nausea	03/27/04	0900	03/27/04	0930	1	2	S	None
65		B	Dizzy	03/20/04	0955	03/20/04	1455	1	2	S	None
65		A	Dizzy	03/27/04	0827	03/27/04	0954	1	2	S	None
65		A	Headache	03/27/04	0904	03/27/04	1016	1	3	S	None
66		A	Light headed	03/20/04	0830	03/20/04	0950	1	2	S	None
66		A	Nausea	03/20/04	0934	03/20/04	0943	1	2	S	None
66		A	Light headed	03/20/04	1314	03/20/04	1334	1	2	S	None
66		A	Headache	03/20/04	1150	03/20/04	1652	1	3	S	None
70		B	Abdominal bloating	03/21/04	0645	03/21/04	1430	1	2	S	None

* Study Drug Last Administered: A- Test; B- Reference.
[1] Severity of Adverse Event: 1-Mild; 2-Moderate; 3-Severe.
[2] Relationship to Drug: 1-Unrelated; 2-Remote; 3-Possible; 4-Probable; 5-Definite.
[3] Resolution: S-Spontaneous, T-With Drug Treatment, NR-Not Resolved.

Table 4 Protocol Deviations

One subject received a concomitant medication for an adverse event during study (acetaminophen).

Comments on Dropouts/Adverse Events/Protocol Deviations: Acceptable.

c) Bioanalytical Results

Table 5 Assay Validation: Within-Study (Inter-Day)

	Fluticasone Propionate
QC Conc. (pg/mL)	3.00, 12.00, 24.00
Inter-day Precision (%CV)	6.4-13.8
Inter-day Accuracy (%)	103.3-105.8

Cal. Standards Conc. (pg/mL)	1.00, 2.00, 3.00, 5.00, 10.0, 15.0, 20.0, 27.0, 30.0
Inter-day Precision (%CV)	4.8-9.9
Inter-day Accuracy (%)	98.7-101.5
Range of r Values	0.9864-0.9982

Comments on Within-Study Assay: Acceptable.

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

Comments on Chromatograms: Acceptable.

Table 6 SOP's dealing with analytical repeats of study samples

Not submitted.

Reviewer's Comment:
The firm did not submit SOP dealing with reassays for the biostudy analysis. The firm should submit this information.

Summary/Conclusions, Study Assays: Incomplete.

d) Pharmacokinetic Results

Since the Group-by-Treatment interaction was statistically significant ($p<0.1$) for LCmax, the reviewer analyzed the two groups separately. The reviewer also analyzed all subjects together and reports the results.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Group 1 (n=35)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	pg.hr/mL	96.37	48.36	91.99	61.94	1.05
AUC0-t	pg.hr/mL	65.55	58.72	65.85	66.09	1.00
Cmax	pg/mL	9.25	48.43	8.98	55.41	1.03
Kel	1/hr	0.06	63.09	0.08	62.33	0.76
T1/2	hr	16.07	58.28	12.07	93.00	1.33
Tmax	hr	1.81	42.17	2.01	59.76	0.90

Group 2 (n=33)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	pg.hr/mL	76.20	61.83	71.75	68.69	1.06
AUC0-t	pg.hr/mL	62.19	61.22	51.92	56.37	1.20
Cmax	pg/mL	10.36	46.39	8.32	39.19	1.24
Kel	1/hr	0.11	60.17	0.12	61.88	0.90
T1/2	hr	9.74	93.28	9.02	90.88	1.08
Tmax	hr	1.49	32.63	1.51	43.83	0.99

All subjects (n-=68):

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	pg.hr/mL	86.82	54.51	84.84	64.25	1.02
AUC0-t	pg.hr/mL	63.92	59.51	59.09	63.76	1.08
Cmax	pg/mL	9.78	47.40	8.66	48.66	1.13
Kel	1/hr	0.09	68.54	0.10	65.34	0.88
T1/2	hr	13.07	73.87	11.00	93.11	1.19
Tmax	hr	1.65	39.85	1.77	56.75	0.93

Table 8. Least Square Geometric Means and 90% Confidence Intervals

Group 1 (n=35)

Parameter	Test	Reference	T/R	90% CI	
	Mean	Mean		Low	Upper
LAUC∞	81.66	76.65	1.07	91.96	123.43
LAUC0-t	55.88	53.91	1.04	92.49	116.15
LCmax	8.38	7.95	1.05	97.44	113.92

Group 2 (n=33)

Parameter	Test	Reference	T/R	90% CI	
	Mean	Mean		Low	Upper
LAUC∞	68.48	57.33	1.19	96.42	147.97
LAUC0-t	53.77	44.96	1.20	107.07	133.58
LCmax	9.57	7.81	1.22	111.33	134.69

All subjects (n-=68):

Parameter	Test	Reference	T/R	90% CI	
	Mean	Mean		Low	Upper
LAUC∞	75.21	67.96	1.11	98.88	123.88
LAUC0-t	54.71	49.20	1.11	102.77	120.34
LCmax	8.92	7.86	1.14	106.63	120.81

Table 9 Additional Study Information

Group 1:

Root mean square error, LAUC0-t	0.281454
Root mean square error, LAUC∞	0.193048
Root mean square error, LCmax	0.240179
Kel and AUC∞ determined for how many subjects?	21
Do you agree or disagree with firm's decision?	Do not agree. Firm analyzed the data as one group, the reviewer analyzed data as two separate groups
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	Yes

Group 2:

Root mean square error, LAUC0-t	0.263927
Root mean square error, LAUC∞	0.227270
Root mean square error, LCmax	0.198092
Kel and AUC∞ determined for how many subjects?	25
Do you agree or disagree with firm's decision?	Do not agree. Firm analyzed the data as one group, the reviewer analyzed data as two separate groups
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	Yes

Combined group 1 and group 2 (n=68):

Root mean square error, $LAUC_{0-t}$	0.275338
Root mean square error, $LAUC_{\infty}$	0.221617
Root mean square error, LC_{max}	0.217775
K_{el} and AUC_{∞} determined for how many subjects?	21
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

Comments on Pharmacokinetic and Statistical Analysis:

1. The reviewer analyzed data in two separate groups. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{\infty}$ and lnC_{max} are within the acceptable limits of 80-125% for group 1, but not for group 2, based on the reviewer's calculation
2. The reviewer also analyzed the data taking all subjects as one group. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{\infty}$ and lnC_{max} are within the acceptable limits of 80-125% and the results agrees with the firm's calculation.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Incomplete for the reasons given in the deficiency comments on the Single-Dose Bioequivalence Study (PK Study) section.

Table 11 Mean Plasma Concentrations of Fluticasone Propionate

Group 1:

Time	Test (n=35)		Reference (n=35)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.33	2.88	82.76	2.37	89.68	1.22
0.67	6.09	54.59	4.98	46.67	1.22
1	7.33	46.39	6.26	38.82	1.17
1.33	7.64	39.43	7.22	41.18	1.06
1.67	8.04	42.68	7.43	44.28	1.08
2	7.95	44.42	7.66	50.07	1.04
2.5	7.44	51.30	7.53	67.52	0.99
3	6.78	61.40	6.98	69.01	0.97
4	5.76	75.50	5.93	77.35	0.97
5	4.39	69.07	4.99	76.91	0.88
6	3.63	63.01	4.02	71.54	0.90
7	3.11	64.19	3.39	67.34	0.92
8	2.82	69.37	2.88	72.55	0.98
10	2.49	69.27	2.57	69.42	0.97
12	2.06	64.26	2.06	74.55	1.00
14	1.73	80.51	1.85	90.04	0.94
18	1.27	98.61	1.20	104.47	1.05
24	0.96	109.95	0.79	149.58	1.21

Group 2:

Time	Test (n=33)		Reference (n=33)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.33	3.61	59.55	2.73	69.40	1.32
0.67	7.06	41.30	5.39	50.18	1.31
1	8.48	38.18	6.97	38.43	1.22
1.33	9.21	43.68	7.34	40.85	1.25
1.67	9.46	51.41	7.62	38.31	1.24
2	9.17	52.37	7.21	43.23	1.27
2.5	8.37	59.05	6.83	46.93	1.23
3	7.31	67.28	6.14	46.71	1.19

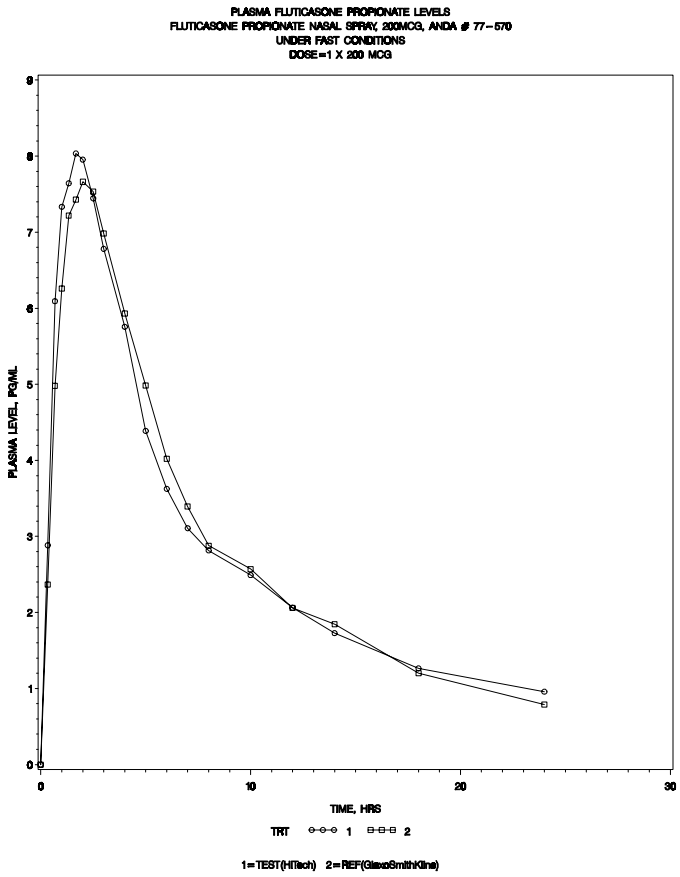
4	5.63	66.49	4.96	57.66	1.13
5	4.14	54.99	3.77	46.71	1.10
6	3.40	54.01	2.90	52.87	1.17
7	2.96	56.85	2.65	53.22	1.12
8	2.45	58.00	2.28	52.93	1.07
10	2.19	65.53	1.92	66.44	1.14
12	1.91	81.48	1.52	81.48	1.26
14	1.37	96.77	1.29	86.00	1.07
18	0.81	140.50	0.70	125.76	1.17
24	0.66	176.62	0.54	161.77	1.21

Combined (n=68):

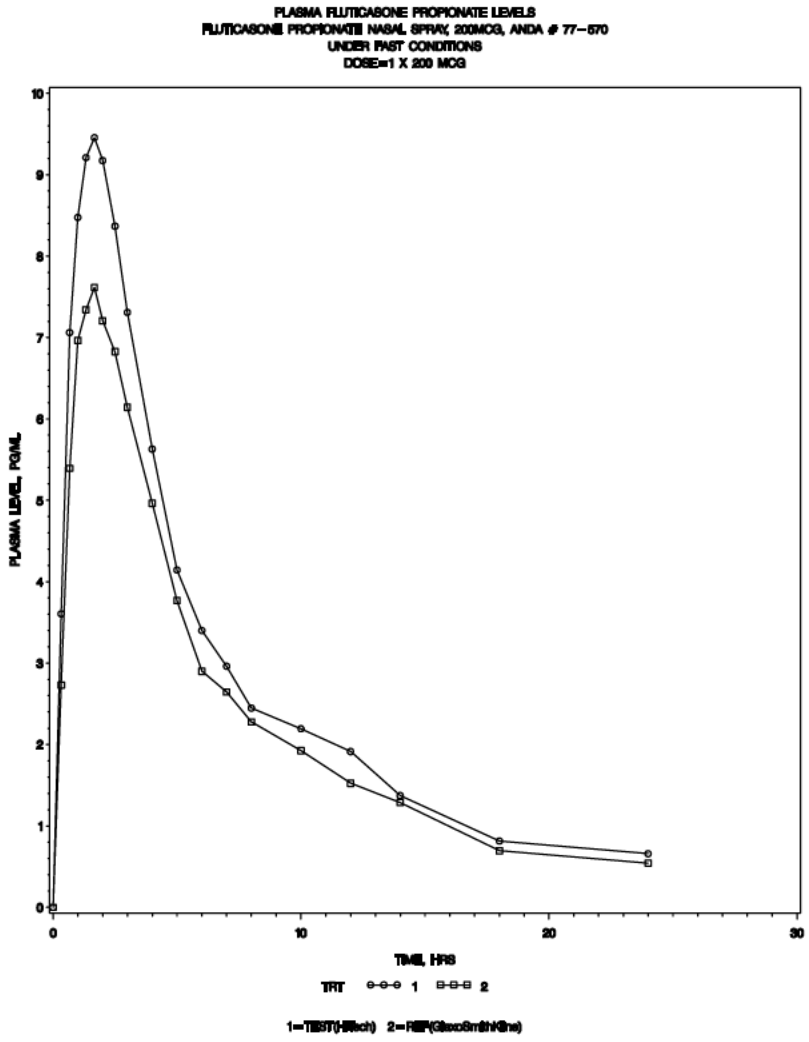
Time	Test (n=68)		Reference (n=68)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.33	3.23	70.68	2.54	78.98	1.27
0.67	6.56	47.98	5.18	48.38	1.27
1	7.89	42.44	6.60	38.75	1.19
1.33	8.40	42.84	7.28	40.72	1.15
1.67	8.72	48.32	7.52	41.13	1.16
2	8.55	49.28	7.44	46.86	1.15
2.5	7.89	55.63	7.19	59.27	1.10
3	7.04	64.21	6.57	60.63	1.07
4	5.69	70.86	5.46	70.51	1.04
5	4.27	62.65	4.39	69.46	0.97
6	3.52	58.78	3.48	68.31	1.01
7	3.04	60.53	3.03	63.81	1.00
8	2.64	64.95	2.59	66.94	1.02
10	2.35	67.65	2.26	70.10	1.04
12	1.99	72.08	1.80	78.70	1.11
14	1.56	87.60	1.57	91.28	0.99
18	1.05	115.74	0.96	116.02	1.10
24	0.81	136.57	0.67	155.98	1.21

Figure 1 Mean Plasma Concentrations, Single-Dose Bioequivalence Study

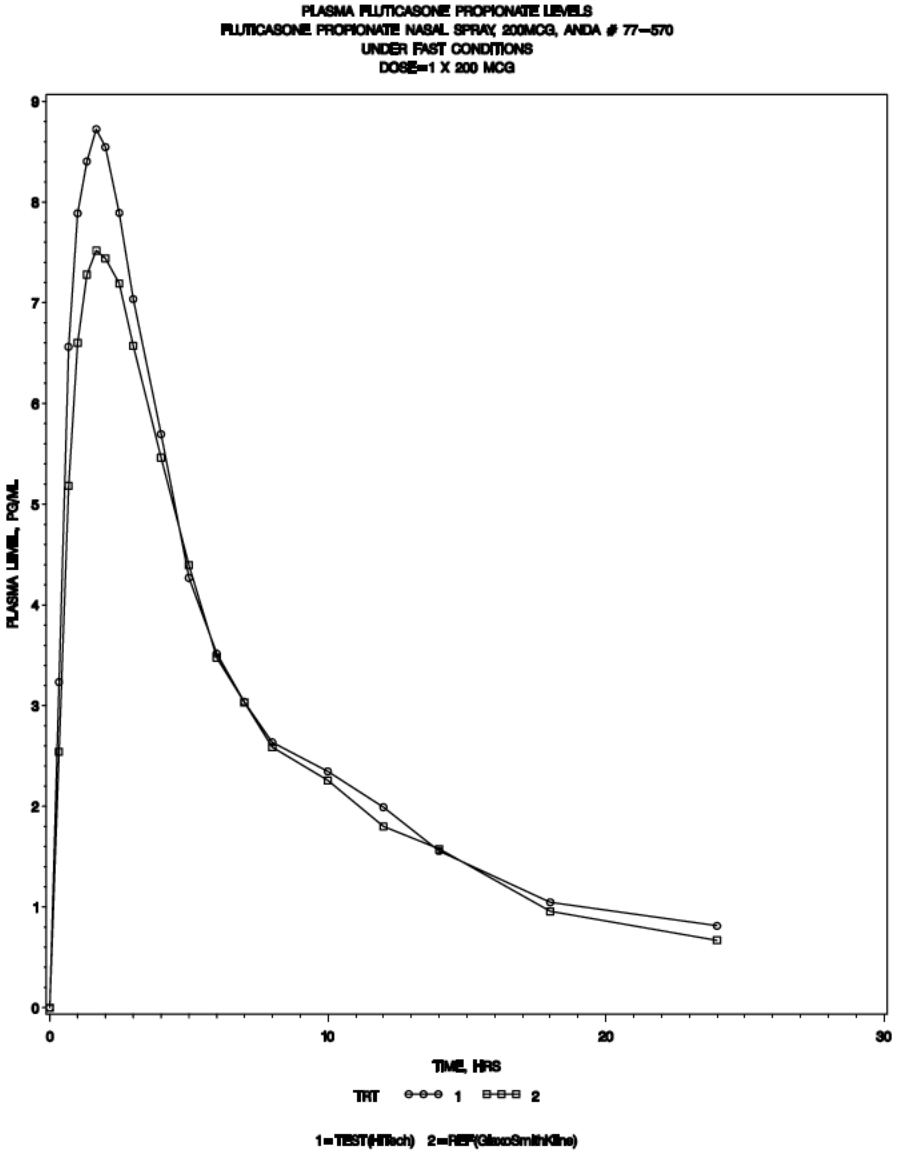
Group 1:



Group 2:



Combined group 1 and group 2:


PLASMA FLUTICASONE PROPIONATE LEVELS
FLUTICASONE PROPIONATE NASAL SPRAY, 200MCG, ANDA # 77-570
UNDER FAST CONDITIONS
DOSE=1 X 200 MCG
PLASMA LEVEL, PG/ML
0
1
2
3
4
5
6
7
8
9
0
10
20
30
TIME, HRS
TRT 1 2
1=TEST(HITech) 2=REF(GlaxoSmithKline)

B. Comparison of the Test and RLD Products:

B.1 Formulation (NOT TO BE RELEASED UNDER FOI)

Page 096, orange jacket V 1.1

Test Product		**RLD Product***	
Ingredient	mg per spray	Ingredient	mg per spray
Fluticasone Propionate	0.05	Fluticasone Propionate	0.05
Polysorbate 80, NF	(b) (4)	Polysorbate 80, NF	(b) (4)
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF		Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	
Dextrose (b) (4)		**Dextrose** (b) (4)	
Benzalkonium Chloride, USP	0. 02	Benzalkonium Chloride	0. 02
Phenylethyl Alcohol, USP	0.25	Phenylethyl Alcohol, USP	0.25
Purified Water, USP	q.s.to100 mg	Purified Water, USP	q.s.to100 mg
Total	100 mg Suspension	Total	100 mg Suspension

*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).

Reviewer's Comment on Formulation:

1. On May 13, 2003, the firm has submitted a request to OGD to comment on its formulation. OGD has found the formulation acceptable. (OGD Control # 03-402, see the attachment for details). In this document, the firm indicated that the (b) (4) was used in its formulation.
2. However, in the current application, the firm stated that (b) (4) was used in the formulation (Page 096, orange jacket V 1.1). The firm needs to clarify which (b) (4) was used in the formulation. If it is a (b) (4). Please notice that this issue has been addressed to the firm on Dec. 22, 2006 by the Division of Chemistry. The firm's response to this issue will be addressed in a separate amendment review.

B.2 Device

The firm did not provide the information about the device.

C. In-Vitro Equivalence Study Samples

Samples tested in the study were 10 bottles 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 given in a table below:

Table Lots used in the In-Vivo and In-Vitro studies

Study Types	RLD Product Lot No.	Date of Expiration	Test Product Lot No.	Date of Expiration
Single-dose bioequivalence study (PK study)	C089739*	08/05	302700*	11/05
In-Vitro equivalence studies	C089155	Not reported	301700	Not reported
	C089150	Not reported	302700*	11/05
	C089739*	08/05	303700	Not reported

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

Reviewer's Comment:

The firm did not provide the information about the expiration date of the two RLD lots used in the in-vitro study (lot C089155 and lot C089150). The firm did not provide the information of the manufacture date and/or expiration date for the test product lots (lot 301700 and lot 303700). The firm should provide this information.

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

A validated HPLC assay method was used for the assay of the finished product, the content of fluticasone propionate in bottle and assay per dose (Blue jacket, Vol. 1.16, p 5153).

Analyte	Fluticasone Propionate
Method	HPLC Detection
Standard Curve Range	25% -150% (2.5 µg/ml – 15 µg/ml)
Limit of Quantitation	Not included in the report
Linearity of Standard Curve	R^2=0.9998
Precision (repeatability of the finished product)	0.41
Intermediate Precision (2nd Chemist)	0.43
Accuracy	98%
QC concentration	Not included in the report
Intraday Precision of QC concentration*	Not Specified
Intraday Accuracy of QC concentrations*	Not Specified
Interday Precision of QC concentration*	Not Specified
Interday Accuracy of QC concentrations*	Not Specified
Recovery of Analyte	98.95-99.36%
Specificity	No Interfering Peaks
Stability of working standard	3 days

Experiment *(Orange Jacket Vol 1.9, p2910)**:***

The pump was primed by using 6 actuations (the Flonase® label recommends "wasting" of the first six actuations for priming). Testing was performed at the beginning of life stage, actuation # 7 (firm referred as #1) and at the end of bottle life actuation #126 (firm referred as #120). Each single actuation was collected into a 5 mL volumetric flask, and was assayed by HPLC.

Method validation report was submitted *(Orange Jacket Vol 1.9, p2962)*

Results *(Orange Jacket Vol 1.9, p2847):*

Continuation of Table 1: Single Actuation Content Through Container Life

	Lot 301700 (µg/dose)	Lot 302700 (µg/dose)	Lot 303700 (µg/dose)	Lot C089155 (µg/dose)	Lot C089150 (µg/dose)	Lot C089739 (µg/dose)
End Sprays						
Bottle 1	(b) (4)					
Bottle 2						
Bottle 3						
Bottle 4						
Bottle 5						
Bottle 6						
Bottle 7						
Bottle 8						
Bottle 9						
Bottle 10						
Mean	48 (96% LC)	48 (97% LC)	49 (99% LC)	49 (97% LC)	50 (99% LC)	47 (94% LC)
SD	0.63	1.65	3.23	0.48	0.71	0.88
RSD	1.31	3.40	6.56	0.99	1.43	1.86

LC - Label Claim

Reviewer's Comments:

Please refer to "Deficiency Comments Applicable to All In-Vitro Equivalence Studies"

2. **Spray Pattern:**

Methods: The firm employed two methods for the spray pattern analysis for Fluticasone Propionate Aqueous Nasal Spray.

Method 1. Nonimpaction automated analysis method using the (b) (4) (orange jacket Vol. 1.9, Page 2915). The spray patterns were visualized using a system based on a laser light sheet and high speed digital camera. Three lots of test and three reference products were analyzed. The bottles from each lot were tested at two distances (3 cm and 6 cm) from the nasal applicator tip at the beginning of the life stage of the bottle. The images were analyzed by the automated pattern recognition measurement.

Results:

Laser images and the (b) (4) actuation text report were submitted as electronic files and they are located in EDR.

The widest diameter (Dmax) and Ovality Ratio (Dmax/Dmin) from the Spray Patterns were reported.

Table 2: Spray Pattern results at a distance of 3 cm and 6 cm

Distance of 3 cm				Distance of 6 cm			
Lot 301700	Ovality	Area	Shape	Lot 301700	Ovality	Area	Shape
Sample 1		(b) (4)	OVAL	Sample 1		(b) (4)	OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			OVAL
Mean	**1.499**	**118.7**	**OVAL**	**Mean**	**1.404**	**479.5**	**OVAL**
Std	**0.14**	**50.2**	**OVAL**	**Std**	**0.07**	**167.2**	**OVAL**
RSD	**9.08**	**42.3**	**OVAL**	**RSD**	**5.21**	**34.9**	**OVAL**

Continuation of Table 2: Spray Pattern results at a distance of 3 cm and 6 cm

Distance of 3 cm				Distance of 6 cm			
Lot 302700	Ovality	Area	Shape	Lot 302700	Ovality	Area	Shape
Sample 1		(b) (4)	OVAL	Sample 1		(b) (4)	OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			OVAL
Mean	**1.512**	**148.75**	**OVAL**	**Mean**	**1.441**	**470.1**	**OVAL**
Std	**0.21**	**49.7**	**OVAL**	**Std**	**0.14**	**128.4**	**OVAL**
RSD	**13.94**	**33.4**	**OVAL**	**RSD**	**9.45**	**27.3**	**OVAL**
Distance of 3 cm				**Distance of 6 cm**			
Lot 303700	Ovality	Area	Shape	Lot 303700	Ovality	Area	Shape
Sample 1		(b) (4)	OVAL	Sample 1		(b) (4)	OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			OVAL
Mean	**1.384**	**135.4**	**OVAL**	**Mean**	**1.379**	**540.9**	**OVAL**
Std	**0.14**	**38.7**	**OVAL**	**Std**	**0.14**	**142.3**	**OVAL**
RSD	**9.99**	**28.6**	**OVAL**	**RSD**	**10.44**	**26.3**	**OVAL**

Continuation of Table 2: Spray Pattern results at a distance of 3 cm and 6 cm

Distance of 3 cm				Distance of 6 cm			
Lot C089155	Ovality	Area	Shape	Lot C089155	Ovality	Area	Shape
Sample 1		(b) (4)	OVAL	Sample 1		(b) (4)	OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			OVAL
Mean	**1.559**	**89.1**	**OVAL**	**Mean**	**1.448**	**351.6**	**OVAL**
Std	**0.18**	**33.9**	**OVAL**	**Std**	**0.15**	**138.9**	**OVAL**
RSD	**11.54**	**38.1**	**OVAL**	**RSD**	**10.16**	**39.5**	**OVAL**
Distance of 3 cm				**Distance of 6 cm**			
Lot C089150	**Ovality**	**Area**	**Shape**	**Lot C089150**	**Ovality**	**Area**	**Shape**
Sample 1		(b) (4)	OVAL	Sample 1		(b) (4)	OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			OVAL
Mean	**1.580**	**61.5**	**OVAL**	**Mean**	**1.449**	**299.4**	**OVAL**
Std	**0.14**	**17.6**	**OVAL**	**Std**	**0.19**	**101.9**	**OVAL**
RSD	**8.73**	**28.6**	**OVAL**	**RSD**	**12.85**	**34.0**	**OVAL**

Continuation of Table 2: Spray Pattern results at a distance of 3 cm and 6 cm

Distance of 3 cm				Distance of 6 cm			
Lot C089739	Ovality	Area	Shape	Lot C089739	Ovality	Area	Shape
Sample 1		(b) (4)	OVAL	Sample 1		(b) (4)	OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			OVAL
Mean	**1.545**	**106.6**	**OVAL**	**Mean**	**1.426**	**369.5**	**OVAL**
Std	**0.16**	**48.6**	**OVAL**	**Std**	**0.14**	**109.1**	**OVAL**
RSD	**10.26**	**45.6**	**OVAL**	**RSD**	**9.45**	**29.5**	**OVAL**

Reviewer's Comments on Method 1:

Please refer to "Deficiency Comments Applicable to All In-Vitro Equivalence Studies"

Method 2. The spray pattern determination was also performed using Thin-Layer Chromatograph (TLC) method (Vol. 1.9, Page 2957). Spray pattern was collected at two distances, 3 cm and 6 cm, at the beginning sprays of the unit.

Actuations were performed using manual hand actuations. The sprays were viewed under an ultra violet light at 254 nm. The images were evaluated by taking the outermost circle of the dark spray pattern. Dmax and Dmin were measured for each spray pattern at 3 cm and 6 cm.

Results:

Table 3: Spray pattern results at distance of 3 cm and 6 cm

Distance of 3 cm				Distance of 6 cm			
Lot 301700	**Dmax (mm)**	**Ovality Ratio**	**Shape**	**Lot 301700**	**Dmax (mm)**	**Ovality Ratio**	**Shape**
Sample 1		(b) (4)	SLIGHTLY OVAL	Sample 1		(b) (4)	OVAL
Sample 2			OVAL	Sample 2			SLIGHTLY OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			SLIGHTLY OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			SLIGHTLY OVAL
Sample 8			SLIGHTLY OVAL	Sample 8			SLIGHTLY OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			SLIGHTLY OVAL	Sample 10			SLIGHTLY OVAL
Mean	**28**	**1.1**		**Mean**	**38**	**1.2**	
Std	**1.29**	**0.08**		**Std**	**1.55**	**0.09**	
RSD	**4.58**	**7.29**		**RSD**	**4.10**	**7.39**	

Distance of 3 cm				Distance of 6 cm			
Lot 302700	**Dmax (mm)**	**Ovality Ratio**	**Shape**	**Lot 302700**	**Dmax (mm)**	**Ovality Ratio**	**Shape**
Sample 1		(b) (4)	SLIGHTLY OVAL	Sample 1		(b) (4)	SLIGHTLY OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			SLIGHTLY OVAL
Sample 4			OVAL	Sample 4			SLIGHTLY OVAL
Sample 5			OVAL	Sample 5			SLIGHTLY OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			SLIGHTLY OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			SLIGHTLY OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			OVAL
Mean	**28**	**1.2**		**Mean**	**38**	**1.1**	
Std	**1.03**	**0.05**		**Std**	**1.63**	**0.05**	
RSD	**3.72**	**4.45**		**RSD**	**4.30**	**4.29**	

Continuation of Table 3: Spray pattern results at a distance of 3 cm and 6 cm

Distance of 3 cm				Distance of 6 cm			
Lot 303700	**Dmax (mm)**	**Ovality Ratio**	**Shape**	**Lot 303700**	**Dmax (mm)**	**Ovality Ratio**	**Shape**
Sample 1	[redacted] (b) (4)		SLIGHTLY OVAL	Sample 1	[redacted] (b) (4)		SLIGHTLY OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			OVAL
Mean	**27**	**1.2**		**Mean**	**39**	**1.2**	
Std	**1.14**	**0.08**		**Std**	**1.29**	**0.09**	
RSD	**4.17**	**7.39**		**RSD**	**3.31**	**8.11**	
Distance of 3 cm				**Distance of 6 cm**			
Lot C089155	**Dmax (mm)**	**Ovality Ratio**	**Shape**	**Lot C089155**	**Dmax (mm)**	**Ovality Ratio**	**Shape**
Sample 1	[redacted] (b) (4)		OVAL	Sample 1	[redacted] (b) (4)		SLIGHTLY OVAL
Sample 2			OVAL	Sample 2			SLIGHTLY OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			SLIGHTLY OVAL
Sample 5			SLIGHTLY OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			SLIGHTLY OVAL	Sample 7			SLIGHTLY OVAL
Sample 8			OVAL	Sample 8			SLIGHTLY OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			OVAL	Sample 10			SLIGHTLY OVAL
Mean	**28**	**1.2**		**Mean**	**38**	**1.1**	
Std	**1.52**	**0.08**		**Std**	**1.89**	**0.00**	
RSD	**5.46**	**7.04**		**RSD**	**4.96**	**0.00**	

Continuation of Table 3: Spray pattern results at a distance of 3 cm and 6 cm

Distance of 3 cm				Distance of 6 cm			
Lot C089150	Dmax (mm)	Ovality Ratio	Shape	Lot C089150	Dmax (mm)	Ovality Ratio	Shape
Sample 1	(b) (4)		OVAL	Sample 1	(b) (4)		OVAL
Sample 2			OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			SLIGHTLY OVAL
Sample 8			OVAL	Sample 8			OVAL
Sample 9			SLIGHTLY OVAL	Sample 9			OVAL
Sample 10			SLIGHTLY OVAL	Sample 10			SLIGHTLY OVAL
Mean	**28**	**1.2**		**Mean**	**39**	**1.2**	
Std	**1.34**	**0.07**		**Std**	**1.40**	**0.05**	
RSD	**4.83**	**5.77**		**RSD**	**3.60**	**4.45**	
Distance of 3 cm				**Distance of 6 cm**			
Lot C089739	**Dmax (mm)**	**Ovality Ratio**	**Shape**	**Lot C089739**	**Dmax (mm)**	**Ovality Ratio**	**Shape**
Sample 1	(b) (4)		SLIGHTLY OVAL	Sample 1	(b) (4)		OVAL
Sample 2			SLIGHTLY OVAL	Sample 2			OVAL
Sample 3			OVAL	Sample 3			SLIGHTLY OVAL
Sample 4			OVAL	Sample 4			OVAL
Sample 5			OVAL	Sample 5			OVAL
Sample 6			OVAL	Sample 6			OVAL
Sample 7			OVAL	Sample 7			OVAL
Sample 8			OVAL	Sample 8			SLIGHTLY OVAL
Sample 9			OVAL	Sample 9			OVAL
Sample 10			SLIGHTLY OVAL	Sample 10			OVAL
Mean	**27**	**1.1**		**Mean**	**38**	**1.1**	
Std	**1.35**	**0.05**		**Std**	**1.73**	**0.05**	
RSD	**4.93**	**4.27**		**RSD**	**4.56**	**4.27**	

Reviewer's Comments on Method 2:

Please refer to "Deficiency Comments Applicable to All In-Vitro Equivalence Studies"

3. **Droplet Size Distribution by Laser Diffraction**

Experiment:

The droplet size distribution was analyzed using the (b) (4) The study was performed on actuations representing the Beginning (spray #1 after priming) and End (spray #120 after priming) of each unit at two distances, 3.0 and 6.0 cm (from nasal applicator tip to the laser beam). The method is located in Volume 1.9, p2930. The method validation report is located in the same Volume p3021.

Results:

Table 5: Droplet Size Distribution at 3.0 cm

	% T	Dv (10)µm	Dv (50)µm	Dv (90)µm	Span
Lot 301700: Beginning sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	77.50	21.42	63.24	141.32	1.90
SD	4.58	3.61	12.33	29.70	0.22
RSD	5.92	16.83	19.49	21.01	11.54

Continuation of Table 5: Droplet Size Distribution at 3.0 cm

	% T	Dv (10)µm	Dv (50)µm	Dv (90)µm	Span
Lot 301700: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	78.68	24.78	74.06	160.19	1.84
SD	5.08	6.36	17.59	36.83	0.10
RSD	6.46	25.68	23.76	22.99	5.23
Lot 302700 Beginning Sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	78.27	24.07	72.04	158.16	1.87
SD	3.36	3.22	12.91	25.14	0.16
RSD	4.29	13.38	17.91	15.90	8.50
Lot 302700: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	75.84	25.10	76.57	171.72	1.94
SD	2.34	3.28	12.00	25.20	0.35
RSD	3.08	13.08	15.68	14.67	18.08

Continuation of Table 5: Droplet Size Distribution at 3.0 cm

	% T	Dv (10)µm	Dv (50)µm	Dv (90)µm	Span
Lot 303700: Beginning sprays					
Bottle 1					(b) (4)
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	74.34	23.66	72.21	156.19	1.84
SD	2.92	2.72	10.86	19.54	0.07
RSD	3.93	11.52	15.05	12.51	3.72
Lot 303700: End sprays					
Bottle 1					(b) (4)
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	74.07	22.53	70.64	151.98	1.84
SD	2.22	2.67	9.67	16.36	0.13
RSD	3.00	11.85	13.69	10.77	7.10
Lot C089155: Beginning sprays					
Bottle 1					(b) (4)
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	73.90	26.27	78.71	160.42	1.74
SD	3.18	5.84	20.96	31.33	0.14
RSD	4.30	22.24	26.63	19.53	7.82

Continuation of Table 5: Droplet Size Distribution at 3.0 cm

	% T	Dv (10)µm	Dv (50)µm	Dv (90)µm	Span
Lot C089155: End sprays					
Bottle 1					(b) (4)
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	72.30	25.13	76.87	158.03	1.76
SD	3.09	5.66	20.59	31.51	0.12
RSD	4.28	22.52	26.79	19.94	6.96
Lot C089150: Beginning sprays					
Bottle 1					(b) (4)
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	75.21	27.23	81.66	165.95	1.73
SD	2.10	5.56	20.55	29.90	0.15
RSD	2.79	20.43	25.17	18.02	8.61
Lot C089150: End sprays					
Bottle 1					(b) (4)
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	74.51	27.25	81.71	166.41	1.74
SD	2.63	6.41	22.06	33.53	0.14
RSD	3.53	23.52	27.00	20.15	8.17

Continuation of Table 5: Droplet Size Distribution at 3.0 cm

	% T	Dv (10)µm	Dv (50)µm	Dv (90)µm	Span
Lot C089739: Beginning sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	77.21	25.71	75.22	154.68	1.75
SD	5.14	6.03	22.43	35.02	0.15
RSD	6.66	23.47	29.82	22.64	8.29
Lot C089739: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	78.32	27.37	86.10	173.69	1.72
SD	4.57	5.26	20.11	32.19	0.12
RSD	5.83	19.20	23.36	18.53	6.95

Table 6: Droplet Size Distribution at 6.0 cm

	% T	Dv (10)µm	Dv (50)µm	Dv (90) µm	Span
Lot 301700: Beginning sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	79.39	27.09	61.75	148.75	1.97
SD	3.11	2.04	6.00	15.03	0.10
RSD	3.91	7.52	9.72	10.10	5.13
Lot 301700: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	78.66	25.55	56.70	137.60	1.98
SD	2.41	2.26	6.62	16.90	0.12
RSD	3.06	8.84	11.67	12.28	6.19
Lot 302700: Beginning sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	79.30	27.46	62.16	142.85	1.86
SD	3.42	3.30	13.19	26.35	0.07
RSD	4.31	12.01	21.22	18.44	3.90

Continuation of Table 6: Droplet Size Distribution at 6.0 cm

	% T	Dv (10)µm	Dv(50)µm	Dv (90)µm	Span
Lot 302700: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	78.66	27.65	62.49	145.18	1.88
SD	3.31	3.04	11.68	23.96	0.08
RSD	4.21	11.00	18.69	16.50	4.12
Lot 303700: Beginning sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	78.20	25.88	56.95	139.85	2.00
SD	3.11	1.98	4.62	15.95	0.13
RSD	3.98	7.67	8.12	11.40	6.42
Lot 303700: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	79.24	25.88	57.18	142.47	2.04
SD	2.37	2.18	7.10	14.75	0.12
RSD	2.99	8.41	12.41	10.35	5.95

Continuation of Table 6: Droplet Size Distribution at 6.0 cm

	% T	Dv (10)µm	Dv (50)µm	Dv (90)µm	Span
Lot C089155: Beginning sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	77.73	29.47	71.77	157.65	1.79
SD	2.81	3.07	15.64	28.48	0.08
RSD	3.62	10.43	21.80	18.06	4.53
Lot C089155: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	77.91	28.95	69.80	156.20	1.83
SD	2.79	2.86	12.89	23.06	0.08
RSD	3.58	9.89	18.46	14.76	4.23
Lot C089150: Beginning sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	78.17	31.16	78.97	171.59	1.80
SD	2.63	3.84	17.58	27.03	0.10
RSD	3.37	12.31	22.26	15.75	5.56

Continuation of Table 6: Droplet Size Distribution at 6.0 cm

	% T	Dv (10)µm	Dv (50)µm	Dv (90)µm	Span
Lot C089150: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	76.71	29.59	72.30	157.23	1.78
SD	2.47	3.09	15.42	24.41	0.09
RSD	3.22	10.45	21.33	15.53	5.30
Lot C089739: Beginning sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	76.76	30.01	74.89	163.30	1.79
SD	2.45	3.53	15.23	25.80	0.09
RSD	3.19	11.76	20.34	15.80	4.90
Lot C089739: End sprays					
Bottle 1	(b) (4)				
Bottle 2					
Bottle 3					
Bottle 4					
Bottle 5					
Bottle 6					
Bottle 7					
Bottle 8					
Bottle 9					
Bottle 10					
Mean	76.75	30.87	75.70	163.92	1.78
SD	3.69	4.62	20.29	33.44	0.09
RSD	4.80	14.97	26.81	20.40	5.14

Reviewer's Comments:

Please refer to "Deficiency Comments Applicable to All In-Vitro Equivalence Studies"

4. Particle Size Distribution by Cascade Impactor

Experiment *(Vol 1.9, p2947):*
Particle Size Distribution determination was performed using a (b) (4) Cascade Impactor. A total of 10 actuations (#13-23) at the beginning of the life stage of each bottle were used in each experiment. The amount of fluticasone was determined by HPLC method.

Validation Report: (Vol 1.9, p3078). Three different standard concentrations are used to represent the different concentration of samples in the various stages of the cascade impactor: 0.01 mg/ml (100%) represents the preseparator stage (particle size ≥ 10 um); 0.002 mg/ml (20%) represents valve stem + actuator, and 0.0003 mg/ml (3%) represents Stage 0 (particle size = 9-10 um), as well as Stage 1 to Filter (particle size = 0.43-9 um). Standard concentration of 0.01 mg/ml was validated in the HPLC method TM-0122.

Standard concentrations of 0.002 mg/ml and 0.0003 mg/ml are validated in HPLC method TM-0169.

Particle Size Range Groups:

Drug deposited in the cascade impactor was grouped as follows:

Component	Size of Particles
Preseparator	>10.0 microns
Valvestem and actuator	NA
Stage 0	9.0-10.0 microns
Stage 1-filter	< 9.0 microns

Results:

Table 9: Particle Size Testing by Cascade Impaction

	Size Range (µm)	Bottle 1	Bottle 2	Bottle 3	Bottle 4	Bottle 5	Bottle 6	Bottle 7	Bottle 8	Bottle 9	Bottle 10	Mean
Lot 301700												
Preseparator(%)	10.0 & above										(b) (4)	94.76
Valvestem & actuator (%)	NA											1.44
Stage 0 (%)	9.0 – 10.0											0.27
Stage 1-filter (%)	< 9.0											0.31
Total Mass balance (%)	NA											96.79
Lot 302700												
Preseparator (%)	10.0 & above										(b) (4)	94.77
Valvestem & actuator (%)	NA											1.00
Stage 0 (%)	9.0 – 10.0											0.29
Stage 1-filter (%)	< 9.0											0.29
Total Mass balance (%)	NA											96.35
Lot 303700												
Preseparator (%)	10.0 & above										(b) (4)	91.29
Valvestem & actuator (%)	NA											0.65
Stage 0 (%)	9.0 – 10.0											0.28
Stage 1-filter (%)	< 9.0											0.29
Total Mass balance (%)	NA											92.51

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Continuation of Table 9: Particle Size Testing by Cascade Impaction

Lot C089155												
	Size Range (µm)	Bottle 1	Bottle 2	Bottle 3	Bottle 4	Bottle 5	Bottle 6	Bottle 7	Bottle 8	Bottle 9	Bottle 10	Mean
Preseparator (%)	10.0 & above										(b) (4)	93.38
Valvestem & actuator (%)	NA											0.74
Stage 0 (%)	9.0 – 10.0											0.31
Stage 1-filter (%)	< 9.0											0.32
Total Mass balance (%)	NA											94.74
Lot C089739												
	Size Range (µm)	Bottle 1	Bottle 2	Bottle 3	Bottle 4	Bottle 5	Bottle 6	Bottle 7	Bottle 8	Bottle 9	Bottle 10	Mean
Preseparator (%)	10.0 & above										(b) (4)	96.16
Valvestem & actuator (%)	NA											0.86
Stage 0 (%)	9.0 – 10.0											0.27
Stage 1-filter (%)	< 9.0											0.35
Total Mass balance (%)	NA											97.64
Lot C089150												
	Size Range (µm)	Bottle 1	Bottle 2	Bottle 3	Bottle 4	Bottle 5	Bottle 6	Bottle 7	Bottle 8	Bottle 9	Bottle 10	Mean
Preseparator (%)	10.0 & above										(b) (4)	93.29
Valvestem & actuator (%)	NA											1.08
Stage 0 (%)	9.0 – 10.0											0.28
Stage 1-filter (%)	< 9.0											0.28
Total Mass balance (%)	NA											94.92

Reviewer's Comments:
Please refer to "Deficiency Comments Applicable to All In-Vitro Equivalence Studies"

5. Plume Geometry by Laser Imaging:

Experimental method (Volume 1.9, p.2935). The plume geometry was analyzed using the (b) (4) The plume geometry data was measured at the beginning of unit life at a single view. The method validation report is located in Volume 1.9, p. 3064.

Results:

Table 7: Plume Geometry

Lot 301700	Plume Angle (°)	Width (mm)	Vertex-Intersect Distance (mm)
Bottle 1			(b) (4)
Bottle 2			
Bottle 3			
Bottle 4			
Bottle 5			
Bottle 6			
Bottle 7			
Bottle 8			
Bottle 9			
Bottle 10			
Mean	**47.5**	**53.1**	**60.0**
SD	**1.14**	**1.38**	**0.00**
RSD	**2.40**	**2.60**	**0.00**

Continuation of Table 7: Plume Geometry

Lot C089150	Plume Angle (°)	Width (mm)	Vertex-Intersect Distance (mm)
Bottle 1	(b) (4)		
Bottle 2			
Bottle 3			
Bottle 4			
Bottle 5			
Bottle 6			
Bottle 7			
Bottle 8			
Bottle 9			
Bottle 10			
Mean	**45.9**	**51.0**	**60.0**
SD	**0.92**	**1.12**	**0.00**
RSD	**2.00**	**2.20**	**0.00**
Lot C089739	**Plume Angle (°)**	**Width (mm)**	**Vertex-Intersect Distance (mm)**
Bottle 1	(b) (4)		
Bottle 2			
Bottle 3			
Bottle 4			
Bottle 5			
Bottle 6			
Bottle 7			
Bottle 8			
Bottle 9			
Bottle 10			
Mean	**46.9**	**52.3**	**60.0**
SD	**1.51**	**1.86**	**0.00**
RSD	**3.22**	**3.55**	**0.00**

Reviewer's Comments:

Please refer to "Deficiency Comments Applicable to All In-Vitro Equivalence Studies"

6. Priming and Repriming

Experimental method (Volume 1.9, p.2940)**.** The priming and repriming were conducted on 10 bottle of the test product and 10 bottles of the RLD product for each lot. The samples were analyzed using an HPLC method.

Part A: The samples were collected at the following spray numbers:

1). Assay spray No. 1 (after prime for 6 sprays)
2). Discharge spray No. 2-4. Samples were stored for 48 hours. Assay for spray No. 5 (unprimed spray)
3). Discharge spray No. 6-59, samples were stored for 96 hours. Assay for spray No. 60 (unprimed spray)
4). Discharge spray No. 61-100, samples were stored for 168 hours. Assay for spray No. 101 (unprimed spray)

Part B: The experiment was conducted according to the following procedures: discharge spray No. 1-110. Store the sample for 168 hours. After 168 hours, prime the pump by pressing down until a fine mist comes out of the nozzle. Collect the next spray.

Results:

Table 8: Priming and Repriming

	Lot 301700 (µg/dose)	Lot 302700 (µg/dose)	Lot 303700 (µg/dose)	Lot C089155 (µg/dose)	Lot C089150 (µg/dose)	Lot C089739 (µg/dose)
The bottles are primed using 6 actuations						
Assay/dose for Spray No. 1 (Primed Spray is Collected):						
Bottle 1	(b) (4)					
Bottle 2						
Bottle 3						
Bottle 4						
Bottle 5						
Bottle 6						
Bottle 7						
Bottle 8						
Bottle 9						
Bottle 10						
Mean	**48 (96% LC)**	**48 (96% LC)**	**47 (94% LC)**	**47 (93% LC)**	**47 (94% LC)**	**47 (95% LC)**
SD	**1.56**	**1.55**	**2.98**	**1.06**	**1.14**	**1.83**
RSD	**3.26**	**3.21**	**6.34**	**2.27**	**2.41**	**3.87**

Continuation of Table 8: Priming and Repriming

	Lot 301700 (µg/dose)	Lot 302700 (µg/dose)	Lot 303700 (µg/dose)	Lot C089155 (µg/dose)	Lot C089150 (µg/dose)	Lot C089739 (µg/dose)
Discharge sprays no. 2 – 4. The samples are stored for 48 h (2 days) in the vertical position.						
Assay/dose for Spray No. 5 (Unprimed Spray is Collected):						
Bottle 1	(b) (4)					
Bottle 2						
Bottle 3						
Bottle 4						
Bottle 5						
Bottle 6						
Bottle 7						
Bottle 8						
Bottle 9						
Bottle 10						
Mean	**48 (95% LC)**	**48 (95% LC)**	**47 (93% LC)**	**47 (94% LC)**	**48 (95% LC)**	**46 (92% LC)**
SD	**1.27**	**2.11**	**1.43**	**0.63**	**1.17**	**0.57**
RSD	**2.67**	**4.43**	**3.08**	**1.34**	**2.47**	**1.24**

Continuation of Table 8: Priming and Repriming

	Lot 301700 (µg/dose)	Lot 302700 (µg/dose)	Lot 303700 (µg/dose)	Lot C089155 (µg/dose)	Lot C089150 (µg/dose)	Lot C089739 (µg/dose)
Discharge sprays no. 6 – 59. The samples are stored for 96 h (4 days) in the vertical position.						
Assay/dose for Spray No. 60 (Unprimed Spray is Collected):						
Bottle 1	(b) (4)					
Bottle 2						
Bottle 3						
Bottle 4						
Bottle 5						
Bottle 6						
Bottle 7						
Bottle 8						
Bottle 9						
Bottle 10						
Mean	46 (93% LC)	48 (96% LC)	47 (93% LC)	48 (96% LC)	49 (99% LC)	49 (97% LC)
SD	0.82	1.66	1.78	0.57	1.77	0.85
RSD	1.78	3.47	3.81	1.19	3.58	1.75

Continuation of Table 8: Priming and Repriming

	Lot 301700 (µg/dose)	Lot 302700 (µg/dose)	Lot 303700 (µg/dose)	Lot C089155 (µg/dose)	Lot C089150 (µg/dose)	Lot C089739 (µg/dose)
Discharge sprays no. 61-100. The samples are stored for 168 h (7 days) in the vertical position.						
Assay/dose for Spray No. 101 (Unprimed Spray is Collected):						
Bottle 1	(b) (4)					
Bottle 2						
Bottle 3						
Bottle 4						
Bottle 5						
Bottle 6						
Bottle 7						
Bottle 8						
Bottle 9						
Bottle 10						
Mean	47 (93% LC)	46 (92% LC)	47 (94% LC)	46 (92% LC)	48 (96% LC)	47 (94% LC)
SD	1.07	1.93	2.33	1.41	2.38	1.15
RSD	2.31	4.18	4.95	3.07	4.96	2.46
Discharge sprays no. 102-110. The samples are stored for 168 h (7days) in the vertical position. The samples are then primed until a fine mist comes out of the nozzle.						

Continuation of Table 8: Priming and Repriming

	Lot 301700 (µg/dose)	Lot 302700 (µg/dose)	Lot 303700 (µg/dose)	Lot C089155 (µg/dose)	Lot C089150 (µg/dose)	Lot C089739 (µg/dose)
Assay/dose for the next spray (Primed Spray is Collected):						
Bottle 1	(b) (4)					
Bottle 2						
Bottle 3						
Bottle 4						
Bottle 5						
Bottle 6						
Bottle 7						
Bottle 8						
Bottle 9						
Bottle 10						
Mean	47 (94% LC)	47 (95% LC)	46 (92% LC)	48 (96% LC)	48 (96% LC)	47 (94% LC)
SD	1.37	2.46	1.93	1.10	0.92	0.79
RSD	2.91	5.19	4.18	2.29	1.92	1.67
Discharge sprays up to 119.						

LC - Label Claim

Reviewer's Comments:

Please refer to "Deficiency Comments Applicable to All In-Vitro Equivalence Studies"

E. SAS Output:

(b) (4)

Following this page, 55 pages withheld in full (b)(4)-SAS Output

F. Additional Attachment(s):

1. SAS Data Definition Tables for in Vitro Nasal Spray Data

Data in these tables should be arranged in columns as shown in examples. Data sets should be submitted as SAS Transport files.

Table 1. Single Actuation Content Through Container Life

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
ACTUATION	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number corresponding to B or E lifestages.*
AMOUNT	Actual delivered amount of drug mass	Numeric	Numeric values	Drug mass per single actuation
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Example

PRODUCT	SECTOR	LOT	CONTAINER	ACTUATION	AMOUNT	PCTLABEL
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 2. Priming and Repriming

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning. Lifestage not specified for repriming data.
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
ACTUATION	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number*
AMOUNT	Actual delivered amount of drug mass	Numeric	Numeric values	Drug mass per single actuation
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Example

PRODUCT	SECTOR	LOT	CONTAINER	ACTUATION	AMOUNT	PCTLABEL
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 3. Droplet Size Distribution by Laser Diffraction

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
DISTANCE	Distance	Numeric	Numeric values	Distance from the actuator tip to the laser beam (cm)
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref at each distance).
ACTUATION	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number corresponding to B or E lifestages.*
D10	D10	Numeric	Numeric values	D10
D50	D50	Numeric	Numeric values	D50
D90	D90	Numeric	Numeric values	D90
SPAN	SPAN	Numeric	Numeric values	SPAN calculated as ((D90-D10)/D50)

Example

PRODUCT	SECTOR	LOT	DISTANCE	CONTAINER	ACTUATION	D10	D50	D90	SPAN
TEST	B	1234		1					
				2					
				3					
				4					
				5					
				6					
				7					
				8					
				9					
				10					

Table 4. Plume Geometry

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
HEIGHT	Height	Numeric	Numeric values	Plume height
WIDTH	Width	Numeric	Numeric values	Plume width
ANGLE	Angle	Numeric	Numeric values	Cone angle of one side view at one delay time

Example

PRODUCT	SECTOR	LOT	CONTAINER	HEIGHT	WIDTH	ANGLE
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 5. Spray Pattern

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
DISTANCE	Distance	Numeric	Numeric values	Distance from the actuator tip to the laser beam (cm)
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref at each distance).
ACTUATION	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number corresponding to B or E lifestages.*
DMAX	Dmax	Numeric	Numeric values	Dmax
DMIN	Dmin	Numeric	Numeric values	Dmin
OVALITY	Ovality	Numeric	Numeric values	Ovality ratio (Dmax divided by Dmin)
AREA	Pattern Area	Numeric	Numeric values	Pattern area

Example

PRODUCT	SECTOR	LOT	DISTANCE	CONTAINER	ACTUATION	DMAX	DMIN	OVALITY	AREA
TEST	B	1234		1					
				2					
				3					
				4					
				5					
				6					
				7					
				8					
				9					
				10					

Table 6. Drug in Small Particles/Droplets by Cascade Impactor

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
AMT_STAGE1	Amount Stage 1	Numeric	Numeric values	Drug mass collected on stage 1
AMT_STAGE2	Amount Stage 2	Numeric	Numeric values	Drug mass collected on stage 2
AMT_STAGE3	Amount Stage 3	Numeric	Numeric values	Drug mass collected on stage 3
AMT_STAGE23	Amount Stage 2 and 3	Numeric	Numeric values	Drug mass collected on all lower stages (2 and 3 combined)
PCTLABEL	Percent of label claim	Numeric	Numeric value	Percentage of total drug mass collected on all stages and accessories per single actuation
MB_STAGE1	Mass Balance Stage 1	Numeric	Numeric value	Mass balance on stage 1
MB_STAGE2	Mass Balance Stage 2	Numeric	Numeric value	Mass balance on stage 2
MB_STAGE3	Mass Balance Stage 3	Numeric	Numeric value	Mass balance on stage 3

Example
See next page

PRODUCT	SECTOR	LOT	CONTAINER	AMT_STAGE1	AMT_STAGE2	AMT_STAGE3	AMT_STAGE23	PCTLABEL	MB_STAGE1	MB_STAGE2	MB_STAGE3
TEST	B	1234	1								
			2								
			3								
			4								
			5								
			6								
			7								
			8								
			9								
			10								

2. Control document #98-392 regarding the Group-by-Treatment interaction discussion.

(b) (4)

SEP 10 1999

Reference Number: OGD 98-392

Dear Dr. (b) (4)

This letter is in response to your correspondence dated October 30, 1998. We apologize for the delay in our response.

(b) (4) is requesting that the Office of Generic Drugs (OGD) provide comments regarding the appropriateness of the following dosing schemes to be used when bioequivalence study subjects are not recruited as a single group. The dosing schemes that you propose are shown below, for a drug with a one week washout period:

Dosing Scheme	11/1	11/8	11/15	11/22
1	Group 1 Period 1	Group 1 Period 2	Group 2 Period 1	Group 2 Period 2
2	Group 1 Period 1	Group 1 Period 2 Group 2 Period 1	Group 2 Period 2	

(b) (4) is also requesting comment on the appropriate statistical model to be used in data analysis for the above bioequivalence study designs.

OGD provides the following Comments:

1. Both Dosing Schemes are acceptable to the Division of Bioequivalence.

2. The following statistical model can be applied to both Dosing Schemes.

Group
Sequence
Treatment
Subject (nested within Group*Sequence)
Period (nested within Group)
Group-by-Sequence Interaction
Group-by-Treatment Interaction

3. Subject (nested within Group*Sequence) is a random effect and all other factors are fixed effects. If (b) (4) or equivalent software is used to analyze the study, including or not including this interaction will not change the confidence intervals. If (b) (4) is used, including this interaction might change the confidence intervals. By nesting the Period effect within Group, the model allows for the possibility that the effects of Period 1 and Period 2 in Group 1 may not be the same as the effects of Period 1 and Period 2 in Group 2.

4. An alternate model for Dosing Scheme 2 would include the following factors:

   Group
   Sequence
   Treatment
   Subject (nested within Group*Sequence)
   Week
   Group-by-Sequence Interaction
   Group-by-Treatment Interaction

5. The factor Week in the statistical model for Dosing Scheme 2 reflects which of the three weeks the observations came from. If (b) (4) or equivalent software is used to analyze the study, this model should produce the same confidence intervals as the model with Period (nested within Group).

6. If the Group-by-Treatment interaction test is not statistically significant ($p \geq 0.1$), only the Group-by-Treatment term can be dropped from the statistical model.

7. If the Group-by-Treatment interaction is statistically significant ($p < 0.1$), DBE requests that equivalence be demonstrated in one of the groups, provided that the group meets minimum requirements for a complete bioequivalence study.

8. DBE cautions the firm that statistical analysis for bioequivalence studies dosed in more than one group should commence only after all subjects have been dosed and all pharmacokinetic parameters have been calculated. Statistical analysis to determine bioequivalence within each dosing group should never be initiated prior to dosing the next group; otherwise the study becomes one of sequential design.

9. If ALL of the following criteria are met, it may not be necessary to include Group-by-Treatment in the statistical model:

- the clinical study takes place at one site;
- all study subjects have been recruited from the same enrollment pool;
- all of the subjects have similar demographics;
- all enrolled subjects are randomly assigned to treatment groups at study outset.

In this latter case, the appropriate statistical model need include only the factors Sequence, Period, Treatment, and Subject (nested within Sequence).

Please be advised that the above comments are subject to revision by the Division of Bioequivalence.

If you have any questions, please call Ms. Cecelia Parise, R.Ph., Special Assistant to the Director at (301) 827-5845. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

3. Control document #03-402 indicating that the firm proposed formulation is acceptable.

JUN 2 0 2003

Hi-Tech Pharmacal Co. Inc.
Attention: Elan Bar
369 Bayview Avenue
Amityville, NY 11701

Reference Number: OGD # 03-402

Dear Mr. Bar:

This letter is in response to your correspondence dated May 13, 2003. You request that the Office of Generic Drugs (OGD) provide comments regarding your proposed formulation for Fluticasone Propionate Nasal Spray, 50 mcg. OGD provides the following comments:

Your proposed formulation for Fluticasone Propionate Nasal Spray, 50 mcg, is acceptable for receipt as an Abbreviated New Drug Application (ANDA).

If you have any questions, please call Steven Mazzella, R.Ph., Project Manager, Division of Bioequivalence, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

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

Table 3: Fluticasone Formula (Current)

Item	Each 100 mg spray contains	Revised mg
1		
2	Fluticasone Propionate	0.05
3	Dextrose (b) (4)	(b) (4)
4	Polysorbate 80, NF	
5	**Microcrystalline Cellulose & Carboxymethylcellulose Sodium, NF** (b) (4)	
6	Phenyl Ethanol, USP	0.25 (0.25%)
7	Benzalkonium Chloride, NF	0.02 (0.02%)
8	Purified Water, USP	q.s. 100

(b) (4)

4. EDR's documents indicating that the firm's files were unacceptable and removed from EDR:

From the CDER Electronic Document Room Staff
As a Service for
Office of Generic Drugs (OGD) - HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, Room 150
Rockville, MD 20855 - 2773

To Contact:	Elan Bar	**Fax:**	631-841-4166	**Phone:**	631-789-8228 x4108
Firm:	Hi-Tech Pharm.	**Application**	N77570	**Letter Date**	2/23/05
Product Name	Fluticasone Propionate				

RESUBMISSION REQUIRED if any of following are checked	
✓	Document(s) submitted in non archival format (MS Word, etc.) – documents other than draft labeling text, should only be submitted in PDF format described in the guidance(s).
	Labeling was submitted in MS Word format as described in the guidance, but without a corresponding PDF rendition - labeling should be submitted in PDF format. Draft labeling text may also be submitted in MS Word format, but all labeling submitted in word processing format should be accompanied in the submission by a PDF rendition.
✓	Data set(s) submitted in non archival format(s) – SAS transport V5 as per SAS TS-140 (XPORT) is the format specified by the guidance.
✓	Other .xls, .png, and .html formatted files are not acceptable. Please resubmit.

RESUBMISSION NOT REQUIRED AT THIS TIME **Your electronic records may have been delayed for the following reasons, but no further action is necessary at this time. Please address these issues in future Submissions**	
	Electronic Submission submitted to wrong address – If electronic components are included, submit entire submission (paper and electronic components) only to the OGD Document Room (see address above).
	Duplicate copies of electronic media submitted - Submit only 1 set of electronic media, submitting a duplicate copy of electronic media may delay review and is unnecessary
✓	Electronic Table of Contents, e356h form and/or eCover Letter) not submitted -Including electronic PDF renditions of these paper documents, will help speed up the document room process.
	Other

For assistance or questions contact:
Office of Information Management – Russ Livermore
Email (preferred) EDRRESUB@CDER.FDA.GOV **Phone: 301-827-3909**
For Electronic Submission Guidance documents see:
http://www.fda.gov/cder/regulatory/ersr/default.htm

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-570 APPLICANT: Hi Tech Pharmacal Co. Inc.

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

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

Deficiency Comments for the *in vivo* Bioequivalence Study (PK Study):

- Please submit the Pre-Study Bioanalytical Method Validation report for the *in vivo* bioequivalence study in a summary table as shown below:

Analyte name	
Internal Standard	
Method description	
QC range	
Standard curve range	
Limit of quantitation	
Average recovery of Drug (%)	
Average Recovery of Int. Std (%)	
QC between-run precision range (CV%)	
QC between-run accuracy range (%)	
QC within-run precision range (CV %)	
QC within-run accuracy range (%)	
Bench-top stability (hrs)	
Stock stability (hours)	
Processed stability (hrs)	
Freeze-thaw stability (cycles)	
Long-term storage stability (days)	
Dilution integrity	
Specificity	
SOP (s)	

- Please submit SOP dealing with reanalysis of study samples.

Deficiency Comments Applicable to All In-Vitro Equivalence Studies:

- Please provide the information about: a) the expiration date for the RLD lot Nos. lot C089155 and lot C089150 and b) the manufacture date and/or expiration date for the test product lot Nos. 301700 and 303700.

- Please submit the information about the device components (container, pump, actuator, protection cap, and protective packages) of the test product. If possible, please provide a side-by-side comparison of the test and reference products of the components of the container and closure system, listing brand, model, dimensions of critical components, and engineering drawings.

- Please provide the information about the study site, study director and the analytical director for the in-vitro studies.

- Please provide the limit of quantitation and QC concentrations used in the method #TM-0122 for "Quantitation of Fluticasone Propionate in Fluticasone Propionate Aqueous Nasal Spray (Assay and Assay per Dose) and in Fluticasone Propionate Raw material (Assay)".

- Your electronic in vitro bioequivalence data were submitted in unacceptable format. The Division of Bioequivalence (DBE) has recently issued a standard data format for the in vitro studies for Nasal spray products. Please resubmit your electronic data based on the following DBE's recommended format as shown in Attachment I.

Deficiency Comments for Single Actuation Content through Container Life:

- Please provide a summary table for the Single Actuation Content through Container Life study results of both the test and reference products as shown below:

		Mean			Variability (%CV)		Ratio of Means TEST/RLD		P Value
Product TEST OR RLD	Sector BEG OR END	Arith.	Geo.	Within-Lot	Between-Lot	Total	Arith.	Geo.	
		(N=30)	(N=30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

Deficiency Comments for Spray Pattern Analysis using Laser Image:

- You used automated pattern recognition measurement for the image analysis. The description about the automated pattern recognition system in your method is not clear. Please clarify that using this system, the perimeter of the TRUE shape of the spray pattern was determined, the center of mass (COM) or center of gravity (COG) was identified, and the Dmin and Dmax that passed through COG were measured based on the TRUE shape of the images.

- Please provide a summary table for the Spray Pattern by Laser Image study results of both the test and reference products as shown below:

					Variability (%CV)			TEST/REF		
Products (test or reference)	Sector (B or E)	Distance	Parameter (Dmin, Dmax, Ovality)	Mean	Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
				(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

Deficiency Comments for Spray Pattern using Thin Layer Chromatography (TLC) impaction manual analysis:

- Please clarify whether the D_{max} and D_{min} measurements were taken from the TRUE perimeters of the patterns or from the ellipses fitted to the pattern. If the data were based on the latter, please provide data based on the TRUE shape of the patterns.

- You did not use an automated actuator for spray pattern study using TLC. Please explain why an automated actuator was not used for this test.

- please provide a summary table for the Spray Pattern by TLC study results of both the test and reference products as shown below:

					Variability (%CV)			TEST/REF		
PROD (T or R)	Sector (B or E)	Distance	Parameter (Dmin, Dmax, Ovality)	Mean	Within -Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
				(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

Deficiency Comments for Droplet Size Distribution by Laser Diffraction

- Please verify that the instrument was operated within the manufacturer's recommended obscuration or percent transmission (%T) range.

- Please submit your protocol or SOP which states the criterion of selecting the plateau region at which droplet size data was determined. This criterion should be established prior to the study and implemented consistently during the study.

- Please provide a summary table for the droplet size distribution study results (D50 and Span) of both the test and reference products as shown below:

				Variability (%CV)			TEST/REF		
PROD (T or R)	Sector (BEG or END)	Distance	Mean	Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
			(N = 30)	(N=10)	(N=3)	(N=30)	N=30	N=30	
		Dist. 1							
		Dist. 2							

Deficiency comments for Particle Size Distribution by Cascade Impactor

- Please provide the apparatus' flow rate (liters/min).

- Please note that the Cascade Impaction Studies on the nasal sprays are conducted to determine the relative amount of small droplets (< 9 µm, below the top stage) in the test and reference products. Since the amount of drug deposited below the top stage is of primary interest, the drug deposition should be categorized in two

groups. Group 1 should include all drug deposited below the top stage which are < 9 µm in size (stage 1 through F, according to the Cascade Impactor schematic shown in Vol. 1.9, p 2949). Group 2 should include the total mass of drug collected on all stages and accessories. Please resubmit the results for particle size distribution by Cascade Impactor in the DBE's recommended format (refer to Attachment I). It should be noted that Table 6 in Attachment I can be modified according to the different type of Cascade Impactor used in the study. Therefore, please include the data of particle size less than 9 µm and the total mass data in the submission.

- Please provide a summary table for particle size distribution by cascade Impaction study results in mass and % of label claim of both the test and reference products as shown below:

PROD. (T or R)	SECTOR (B or E)	Mean	Variability (%CV)			TEST/REF		
			Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
		(N=30)	(N=10)	(N=3)	(N=30)	N=30	N=30	
		Group 1						
		Group 2						

Deficiency Comments for Plume Geometry by Laser Imaging:

- Please provide documentation showing that the plume is fully developed at the selected delay time.

- Please provide a summary table for the plume geometry study results, including the plume length, width and angle of both the test and reference products as shown below:

			Variability (%CV)			TEST/REF		
PROD. (T or R)	Plume Stage (B or E)	Mean	Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
		(N=30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

Deficiency Comments for Priming and Repriming Study

- In the testing method for priming and repriming study experiment part B (Vol. 1.9, p 2944), you stated that "*prime the pump by pressing down until a fine mist comes out of the nozzle*". Please specify the number of sprays required for achieving such fine mist.

- Please provide a summary table for the prime and reprime study results of both the test and reference products as shown below:

			Variability (%CV)			TEST/REF		
PROD. (T or R)	Spray #	Mean	Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P Value
		(N =30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	

Sincerely yours,

{See appended electronic signature page}

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

Attachment I:

SAS Data Definition Tables for in Vitro Nasal Spray Data

Data in these tables should be arranged in columns as shown in examples. Data sets should be submitted as SAS Transport files.

Table 1. Single Actuation Content Through Container Life

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric /Numeric	Alphanumeric /Numeric	Identifier for product lot
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
ACTUATION	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number corresponding to B or E lifestages.*
AMOUNT	Actual delivered amount of drug mass	Numeric	Numeric values	Drug mass per single actuation
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Example

PRODUCT	SECTOR	LOT	CONTAINER	ACTUATION	AMOUNT	PCTLABEL
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 2. Priming and Repriming

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning. Lifestage not specified for repriming data.
LOT	Lot number	Alphanumeric /Numeric	Alphanumeric /Numeric	Identifier for product lot
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
ACTUATION	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number*
AMOUNT	Actual delivered amount of drug mass	Numeric	Numeric values	Drug mass per single actuation
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Example

PRODUCT	SECTOR	LOT	CONTAINER	ACTUATION	AMOUNT	PCTLABEL
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 3. Droplet Size Distribution by Laser Diffraction

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
DISTANCE	Distance	Numeric	Numeric values	Distance from the actuator tip to the laser beam (cm)
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref at each distance).
ACTUATION	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number corresponding to B or E lifestages.*
D10	D10	Numeric	Numeric values	D10
D50	D50	Numeric	Numeric values	D50
D90	D90	Numeric	Numeric values	D90
SPAN	SPAN	Numeric	Numeric values	SPAN calculated as ((D90-D10)/D50)

Example

PRODUCT	SECTOR	LOT	DISTANCE	CONTAINER	ACTUATION	D10	D50	D90	SPAN
TEST	B	1234		1					
				2					
				3					
				4					
				5					
				6					
				7					
				8					
				9					
				10					

Table 4. Plume Geometry

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning
LOT	Lot number	Alphanumeric /Numeric	Alphanumeric /Numeric	Identifier for product lot
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
HEIGHT	Height	Numeric	Numeric values	Plume height
WIDTH	Width	Numeric	Numeric values	Plume width
ANGLE	Angle	Numeric	Numeric values	Cone angle of one side view at one delay time

Example

PRODUCT	SECTOR	LOT	CONTAINER	HEIGHT	WIDTH	ANGLE
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 5. Spray Pattern

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric /Numeric	Alphanumeric /Numeric	Identifier for product lot
DISTANCE	Distance	Numeric	Numeric values	Distance from the actuator tip to the laser beam (cm)
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref at each distance).
ACTUATION	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number corresponding to B or E lifestages.*
DMAX	Dmax	Numeric	Numeric values	Dmax
DMIN	Dmin	Numeric	Numeric values	Dmin
OVALITY	Ovality	Numeric	Numeric values	Ovality ratio (Dmax divided by Dmin)
AREA	Pattern Area	Numeric	Numeric values	Pattern area

Example

PRODUCT	SECTOR	LOT	DISTANCE	CONTAINER	ACTUATION	DMAX	DMIN	OVALITY	AREA
TEST	B	1234		1					
				2					
				3					
				4					
				5					
				6					
				7					
				8					
				9					
				10					

Table 6. Drug in Small Particles/Droplets by Cascade Impactor

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
CONTAINER	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
AMT_STAGE1	Amount Stage 1	Numeric	Numeric values	Drug mass collected on stage 1
AMT_STAGE2	Amount Stage 2	Numeric	Numeric values	Drug mass collected on stage 2
AMT_STAGE3	Amount Stage 3	Numeric	Numeric values	Drug mass collected on stage 3
AMT_STAGE23	Amount Stage 2 and 3	Numeric	Numeric values	Drug mass collected on all lower stages (2 and 3 combined)
PCTLABEL	Percent of label claim	Numeric	Numeric value	Percentage of total drug mass collected on all stages and accessories per single actuation
MB_STAGE1	Mass Balance Stage 1	Numeric	Numeric value	Mass balance on stage 1
MB_STAGE2	Mass Balance Stage 2	Numeric	Numeric value	Mass balance on stage 2
MB_STAGE3	Mass Balance Stage 3	Numeric	Numeric value	Mass balance on stage 3

Example
See next page

PRODUCT	SECTOR	LOT	CONTAINER	AMT_STAGE1	AMT_STAGE2	AMT_STAGE3	AMT_STAGE23	PCTLABEL	MB_STAGE1	MB_STAGE2	MB_STAGE3
TEST	B	1234	1								
			2								
			3								
			4								
			5								
			6								
			7								
			8								
			9								
			10								

ANDA 77-570

BIOEQUIVALENCE - DEFICIENCIES Submission Date: 02/07/2005

1. Fasting Study — Strength: 50 µg per Spray
   Clinical: Novum Pharmaceutical Research Services. — Outcome: IC
   Analytical: (b) (4)

2. In Vitro study — Strength: 50 µg per Spray
   Single Actuation Content through Container Life — Outcome: IC

3. In Vitro study — Strength: 50 µg per Spray
   Spray Pattern non impaction automated analysis — Outcome: IC

4. In Vitro study — Strength: 50 µg per Spray
   Spray Pattern impaction manual analysis — Outcome: IC

5. In Vitro study — Strength: 50 µg per Spray
   Particle Size Distribution by Cascade Impactor — Outcome: IC

6. In Vitro study — Strength: 50 µg per Spray
   Droplet Size Distribution by Laser Diffraction — Outcome: IC

7. In Vitro study — Strength: 50 µg per Spray
   Plume Geometry — Outcome: IC

8. In Vitro study — Strength: 50 µg per Spray
   Priming and repriming — Outcome: IC

Outcome Decisions:
IC-incomplete

January 25, 2007

This review contains some errors in table B.1 Formulation on page 25. However, these errors would not affect the corresponding action letter. A corrected review was finalized on January 24, 2007.

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

/s/

Bing Li
1/23/2007 10:30:29 AM
BIOPHARMACEUTICS

Moheb H. Makary
1/23/2007 11:32:55 AM
BIOPHARMACEUTICS

Barbara Davit
1/24/2007 03:37:28 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-570
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 mcg per Spray
Applicant Name	Hi Tech Pharmacal Co. Inc.
Address	369 Bayview Avenue Amityville, NY 11701 Contact: Elan Bar 631-789-8228 ext. 4108 (phone) 631-789-8229 631-789-8429 (fax)
Submission Date(s)	June 5, 2006
Amendment Date(S)	NA
Reviewer	Bing V. Li, Ph.D.
First Generic	No

I. Executive Summary

This report reviews Hi Tech's response to a deficiency comment made by the Division of Chemistry in a letter of Dec. 22, 2005. The response is acceptable from the viewpoint of chemistry. However, the Division of Chemistry requested that "the response and supporting data be considered by the Division of Bioequivalence (DBE)".

The firm's formulation is not Q2 the same as the RLD for one of the inactive ingredients (b) (4). However, the firm submitted an in vivo pharmacokinetic (PK) study to demonstrate bioequivalence to the reference listed drug (RLD). In addition, the firm also submitted in vitro data to demonstrate equivalent performance of its test product to the RLD product. The firm's in vivo PK study and in vitro testing have been reviewed by the DBE and found incomplete (deficiency letter dated Dec. 12, 2006). Therefore, the DBE concludes that the firm's response to this deficiency is acceptable; however, the acceptance of the firm's formulation is pending the firm's acceptable results of its in vivo and in vitro studies. Therefore, the application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant History

See the DBE review of the original submission (April 14, 2005) located in DFS and the Chemistry review located at V:\FIRMSAM\HITECH\LTRS&REV\77570N00R02.doc

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

C. Review of Submission

Deficiency #1b identified by Division of Chemistry:

Regarding the revised "Composition of the Drug Product" in the amendment of April 14, 2005:

Your correspondence dated May 13, 2003 that was found acceptable by the Division of Bioequivalence on June 20, 2003 before submission of this ANDA stated that you would use (b) (4) *This discrepancy may affect the approvability of your ANDA for Fluticasone Propionate Nasal Spray. Please comment.*

Firm's Response: Hi-Tech acknowledges the (b) (4)

(b) (4)

Chemistry Reviewer's Comments: The response is acceptable from the viewpoint of chemistry. However, the response and supporting data should be considered by the DBE.

DBE Reviewer's Comments: Although the firm's formulation is not Q2 the same as the RLD for its inactive ingredient (b) (4) (refer to attachment #2 for formulation details), the firm has submitted an in vivo pharmacokinetic study to demonstrate bioequivalence to the reference listed drug (RLD). In addition, the firm also submitted in vitro data to demonstrate equivalent performance of its test product to the RLD product. The firm's in vivo PK study and in vitro testing have been reviewed by the DBE and found incomplete (deficiency letter dated Dec. 12, 2006). Therefore, the DBE concludes that the firm's response to this deficiency #1b is acceptable; however, the acceptance of the firm's formulation is pending the firm's acceptable results of its in vivo and in vitro studies.

D. Deficiency Comments

The acceptance of the firm's formulation is pending the firm's acceptable results of its in vivo and in vitro studies.

E. Recommendations

The firm's response to this deficiency is acceptable. However, the acceptance of the firm's formulation is pending the firm's acceptable results of its in vivo and in vitro studies.

The firm should be informed with the above deficiency.

Following this page, 2 pages withheld in full (b)(4)

2. Comparison of the components of the test and reference products:

Test Product		RLD Product	
Ingredient	mg per 100 mg	Ingredient	mg per 100 mg
Fluticasone Propionate	0.05	Fluticasone Propionate	0.05
Polysorbate 80, NF	(b) (4)	Polysorbate 80, NF	(b) (4)
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF		Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	
Dextrose (b) (4) **USP**		**Dextrose** (b) (4) **USP**	
Benzalkonium Chloride, USP	0. 02	Benzalkonium Chloride	0. 02
Phenylethyl Alcohol, USP	0.25	Phenylethyl Alcohol, USP	0.25
Purified Water, USP	q.s.to100 mg	Purified Water, USP	q.s.to100 mg
Total	100 mg Suspension	Total	100 mg Suspension

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-570 APPLICANT: Hi Tech Pharmacal Co. Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg per Spray

The Division of Bioequivalence (DBE) has completed the review of your submission acknowledged on the cover letter, and has the following comments about your responses to deficiency #1b in OGD's deficiency letter dated Dec. 22, 2005:

Your in vivo PK study and in vitro testing have been reviewed by the DBE and found incomplete (deficiency letter dated Dec. 12, 2006). The acceptance of your formulation is pending the acceptable results of your in vivo and in vitro studies.

Sincerely yours,

{See appended electronic signature page}

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

CC: ANDA 77-570

BIOEQUIVALENCE - DEFICIENCY Submission Date: 06/05/06

1. STUDY AMENDMENT (STA)

Strengths: 50 mcg per Spray
Outcome: IC

Outcome Decisions: IC-incomplete

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

/s/

Bing Li
1/19/2007 01:30:10 PM
BIOPHARMACEUTICS

Moheb H. Makary
1/19/2007 01:46:17 PM
BIOPHARMACEUTICS

Barbara Davit
1/19/2007 03:04:49 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-570
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 mcg per Spray
Applicant Name	Hi Tech Pharmacal Co. Inc.
Address	369 Bayview Avenue Amityville, NY 11701 Contact: Joanne Curri 631-789-8228 ext. 4127 631-789-8429 (fax)
Submission Date(s)	Jan. 11, 2007
Amendment Date(S)	NA
Reviewer	Bing V. Li, Ph.D.
First Generic	No

I. Executive Summary

Hi Tech Pharmacal Co. Inc. has submitted its response to the deficiency comments made by the Division of Bioequivalence (DBE) in its letter of December 12, 2006. The firm's responses to the in vivo bioequivalence study are acceptable. However, the firm's responses to the in vitro bioequivalence studies are incomplete. The application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

See the review of the original submission of the study located in DFS.

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

C. Background

On April 14, 2005, the firm submitted an in vivo fasted study and in vitro bioequivalence studies on its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per Spray. The in vivo and in vitro bioequivalence studies were found incomplete.

D. Review of Submission

Deficiency 1: *Deficiency Comments for the in vivo Bioequivalence Study (PK Study): Please submit the Pre-Study Bioanalytical Method Validation report for the in vivo bioequivalence study in a summary table.*

Firm's Response: The firm submitted the method validation report for the in vivo BE study.

Information Requested	Data
Analyte	Fluticasone Propionate
Internal Standard (IS)	(b) (4)
Method Description	Liquid-liquid extraction (b) (4) LC-MS-MS, (b) (4)
Limit of Quantitation (pg/mL)	1.00
Average Recovery of Drug (%)	68.5
Average Recovery of IS (%)	68.9
Standard Curve Concentrations (pg/mL)	1.00, 2.00, 3.00, 5.00, 10.0, 15.0, 20.0, 27.0, 30.0
QC Concentrations (pg/mL)	3.00, 12.0, 24.0
QC Intrarun Precision (% CV)	3.4 to 6.2
QC Intrarun Accuracy (% Bias)	3.3 to 4.0
QC Inter-run Precision (% CV)	4.2 to 7.2
QC Inter-run Accuracy (% Bias)	-1.7 to 1.3
Bench-top Stability (hrs)	25 @ room temperature
Stock Stability (Reference Standard)	98 days @ 4 °C and 15 hrs @ room temperature
Stock Stability (Intermediate)	Pending @ 4 °C and pending @ room temperature
Processed (Extract) Stability (hrs)	43 @ room temperature
Freeze-thaw Stability (cycles)	6
Long-term Storage Stability (days)	373 @ -20 °C
Dilution Integrity	90.0 pg/mL diluted 5-fold
Selectivity	No significant interfering peaks noted in blank plasma samples

Reviewer's Comments: The firm's response to deficiency #1 is acceptable.

Deficiency 2: *Deficiency Comments for the in vivo Bioequivalence Study (PK Study): Please submit SOP dealing with reanalysis of study samples.*

Firm's Response: The firm submitted the SOP entitled "Biological Fluid Assay – Study Sample Analysis" (PS-076, effective date 12/05/03). There is no PK repeat in the in vivo study.

Reviewer's Comment: The firm's response to deficiency #2 is acceptable.

Deficiency 3: *Deficiency Comments Applicable to All In-Vitro Equivalence Studies: Please provide the information about: a) the expiration date for the RLD lot Nos. lot C089155 and lot C089150 and b) the manufacture date and/or expiration date for the test product lot Nos. 301700 and 303700.*

Firm's Response: The firm provided the information as follows:

Study Types	RLD Product Lot No.	Date of Expiration	Test Product Lot No.	Date of Expiration
Single-dose bioequivalence study (PK study)	C089739*	08/05	302700*	11/05
In-Vitro equivalence studies	C089155	09/05	301700	10/05
	C089150	09/05	302700*	11/05
	C089739*	08/05	303700	11/05

Reviewer's Comment: The firm's response to deficiency #3 is acceptable.

Deficiency 4: *Please submit the information about the device components (container, pump, actuator, protection cap, and protective packages) of the test product. If possible, please provide a side-by-side comparison of the test and reference products of the components of the container and closure system, listing brand, model, dimensions of critical components, and engineering drawings.*

Firm's Response: The firm provided a report (RP-0074) and included the following information:

1. Pump Measurement:

Pump component measurements were performed on 10 samples of test product and 10 samples of reference product. Test method TM-0335 was followed.

The following test product sample was tested: - Pump (b) (4) component, (b) (4) Lot No.: P712RD06 ((b) (4) is the vitro test site per the firm's response for deficiency #5), manufacturer: (b) (4) manufacturer Lot No.: (b) (4)

The following reference sample was tested: - Pump component from Flonase Fluticasone Propionate Aqueous Nasal Spray, Lot No.: C089155.

Pump Component Measurements Summary:

Pump Component	Test	Test Product	Reference Product
Body	Weight (g)	(b) (4)	
	Height (mm)		
	Diameter (mm)		
Turet	Weight (g)		
	Height (mm)		
	Diameter (mm)		
Stem	Weight (g)		
	Length (mm)		
	Diameter (mm)		
Dip Tube	Weight (g)		
	Length (mm)		
	Diameter (mm)		
Floating Gasket	Weight (g)		
	Diameter (mm)		
Stem Gasket	Weight (g)		
	Diameter (mm)		
Sealing Gasket	Weight (g)		
	Diameter (mm)		
Spring Cap	Weight (g)		
	Diameter (mm)		
	Length (mm)		

Pump Component	Test	Test Product	Reference Product
Spring Support	Weight (g)	(b) (4)	
	Diameter (mm)		
	Length (mm)		
Piston	Weight (g)		
	Diameter (mm)		
	Length (mm)		
Stem Spring	Weight (g)		
Return Spring	Weight (g)		

2. Bottle Measurement:

Bottle measurements were performed on 10 samples of test product and 10 samples of reference product. Test method TM-0336 was followed.

The following test product sample was tested: - Amber glass bottle 15 mL, (b) (4) Lot No.: P709RD06, manufacturer: (b) (4) Manufacturer No.: (b) (4).

The following reference product sample was tested: - Bottle from Flonase Fluticasone Propionate Aqueous Nasal Spray Lot No: C089155.

Bottle Measurement Results:

Test		Test Product	Reference Product
Weight (g)	Sample 1	(b) (4)	
	Sample 2		
	Sample 3		
	Sample 4		
	Sample 5		
	Sample 6		
	Sample 7		
	Sample 8		
	Sample 9		
	Sample 10		
	Avg.:		
	Range:		
Overall Height (mm)	Sample 1		
	Sample 2		
	Sample 3		
	Sample 4		
	Sample 5		
	Sample 6		
	Sample 7		
	Sample 8		
	Sample 9		
	Sample 10		
	Avg.:		
	Range:		
Outer Diameter (mm) for round bottle and (Longest Side) for Moulded Bottle.	Sample 1		
	Sample 2		
	Sample 3		
	Sample 4		
	Sample 5		
	Sample 6		
	Sample 7		
	Sample 8		
	Sample 9		
	Sample 10		
	Avg.:		
	Range:		

	Test		Test Product	Reference Product
Outer Diameter (mm) (Short side) for Moulded Bottle		Sample 1	Not available because test bottle is round.	(b) (4)
		Sample 2		
		Sample 3		
		Sample 4		
		Sample 5		
		Sample 6		
		Sample 7		
		Sample 8		
		Sample 9		
		Sample 10		
		Avg.:		
		Range:		
Outer Neck Diameter (mm)		Sample 1		(b) (4)
		Sample 2		
		Sample 3		
		Sample 4		
		Sample 5		
		Sample 6		
		Sample 7		
		Sample 8		
		Sample 9		
		Sample 10		
		Avg.:		
		Range:		
Capacity (mL)		Sample 1		
		Sample 2		
		Sample 3		
		Sample 4		
		Sample 5		
		Sample 6		
		Sample 7		
		Sample 8		
		Sample 9		
		Sample 10		
		Avg.:		
		Range:		

3. Actuator Measurement:

Actuator measurement testing was performed on 10 samples of test product and 10 samples of reference product. Test method TM-0337 was followed.

The following test product sample was tested - Actuator (b) (4) Manufacturer: (b) (4) Manufacturer Lot No.: (b) (4), (b) (4) Lot No.: P711RD06.

The following reference product sample was tested: - Actuator from Flonase Fluticasone Propionate Aqueous Nasal Spray, Lot C089151.

Actuator Measurement Results:

Pump Component	Test		Test Product	Reference Product
Actuator	Weight (g)	Sample 1	(b) (4)	
		Sample 2		
		Sample 3		
		Sample 4		
		Sample 5		
		Sample 6		
		Sample 7		
		Sample 8		
		Sample 9		
		Sample 10		
		Avg.:		
		Range:		
	Diameter (mm)	Sample 1		
		Sample 2		
		Sample 3		
		Sample 4		
		Sample 5		
		Sample 6		
		Sample 7		
		Sample 8		
		Sample 9		
		Sample 10		
		Avg.:		
		Range:		
	Height (mm)	Sample 1		
		Sample 2		
		Sample 3		
		Sample 4		
		Sample 5		
		Sample 6		
		Sample 7		
		Sample 8		
		Sample 9		
		Sample 10		
		Avg.:		
		Range:		

The firm also submitted the schematic drawings of these components for the test product.

Reviewer's Comment: The firm submitted the comparative data for three device components: pump, bottle and actuator. For the pump, there are differences in the dip tube length, dip tube weight, sealing gasket weight, sealing gasket diameter, turret diameter, pump body weight between the test and reference product. These differences are due to the differences in the shape of the body of the pump and in the materials used to make the pump. For the bottle, there are differences in the bottle weight, outer diameter and outer neck diameter of the bottle between the test and reference product. This is because the test product bottle is cylindrical while the reference product bottle is oval in shape. For the actuator, there are differences in weight, diameter and height between the test and reference product. This is due to the difference in the shape of the actuators. The reference product actuator is custom molded and unique to the reference product.

Regarding the "container and closure system", the "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" (April 2003) states the followings:

"*For nasal aerosols and nasal sprays approved under an ANDA, we recommend BE be documented on the basis of validated in vitro and vivo tests, or, in the case of solutions, validated in vitro tests alone may be appropriate. Assurance of equivalence on the basis of in vitro tests is greatest when the test product uses the same brand and model of devices (particularly the metering valve or pump and the actuator) as used in the reference product. If this is infeasible, we recommend that valve, pump, and actuator designs be as close as possible in all critical dimensions to those of the reference product. We recommend that metering chamber volumes and actuator orifice diameters be the same. For a nasal spray, spray characteristics can be affected by features of the pump design, including the precompression mechanism, actuator design, including specific geometry of the orifice (Kublic and Vidgren 1998), and the design of the swirl chamber. The external dimensions of the test actuator are expected to ensure comparable depth of nasal insertion to the reference actuator. A test product is expected to attain prime within the labeled number of actuations for the reference product. We recommend you consider the volume of components of the device that must be filled to deliver an actuation, including the internal diameter and length of the diptube because this volume can influence the number of actuations required to prime a spray pump*".

The design of the actuator used for the RLD Flonase® is proprietary to Glaxo. The pump and actuator for the RLD is manufactured from proprietary molds, according to (b) (4). The oblong amber glass bottle used for Flonase® is proprietary (V:\firmsnz\Roxane\ltrs&rev\76504n1002.doc). It would be difficult for the generic to have the same design of the product.

The reviewer considers the firm's response acceptable because of the following reasons:

1. The pump model used in this application is (b) (4). This is the same model of pump as the ones used by (b) (4) and (b) (4) (b) (4) (b) (4) product has already been approved and (b) (4) bioequivalence review is evaluated as "acceptable".
2. The actuator model used in this application is (b) (4). This is the same model of actuator as the one used by (b) (4).
3. The firm's comparative data on the device components demonstrated similarities for most aspects. The minor differences should be permissible if (1) comparative in vitro and in vivo performances are equivalent (2) the deviation in design does not significantly increase the complexity of product substitution for the patient and does not require extensive retraining of the patient for effective product use.

The firm's response to deficiency #4 is acceptable.

Deficiency 5: *Please provide the information about the study site, study director and the analytical director for the in-vitro studies.*

Firm's Response:

The in vitro study site is:

Reviewer's Comment: The firm's response to deficiency #5 is acceptable.

Deficiency 6: *Please provide the limit of quantitation and QC concentrations used in the method #TM-0122 for "Quantitation of Fluticasone Propionate in Fluticasone Propionate Aqueous Nasal Spray (Assay and Assay per Dose) and in Fluticasone Propionate Raw material (Assay)".*

Firm's Response: The limit of quantitation for the test method is 0.0001 mg/ml. The firm also attached two validation reports. One validation is "High Pressure Liquid Chromatographic Method for Assay of Fluticasone Propionate in Raw Material and in Fluticasone Propionate Aqueous Nasal Spray Finished Product" and the other one is "Particle Size by Cascade Impaction for Fluticasone Propionate Nasal Spray". The linearity, accuracy of the method, method precision, intermediate precision, limit of quantitation and limit of detection were reported.

Reviewer's Comment: The firm's response to deficiency #6 is acceptable.

Deficiency 7: *Your electronic in vitro bioequivalence data were submitted in unacceptable format. The Division of Bioequivalence (DBE) has recently issued a standard data format for the in vitro studies for Nasal spray products. Please resubmit your electronic data based on the DBE's recommended format.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR). This report is an update which contains the tables formatted as DBE requested. However, the data is not in SAS transport format.

Reviewer's Comment: The firm's response to deficiency #7 is acceptable. However, in the future, the firm should submit its in vitro data in the SAS transport format.

Deficiency 8: *Deficiency Comments for Single Actuation Content through Container Life: Please provide a summary table for the Single Actuation Content through Container Life study results of both the test and reference products.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR) which included the raw data.

Reviewer's Comment: The firm's response to deficiency #8 is acceptable. The reviewer summarized the data and conducted the PBE analysis. Please refer to "In Vitro Study Results" section for details.

Deficiency 9: *Deficiency Comments for Spray Pattern Analysis using Laser Image: You used automated pattern recognition measurement for the image analysis. The description about the automated pattern recognition system in your method is not clear. Please clarify that using this system, the perimeter of the TRUE shape of the spray pattern was determined, the center of mass (COM) or center of gravity (COG) was identified, and the Dmin and Dmax that passed through COG were measured based on the TRUE shape of the images.*

Firm's Response: Using automated Spray Pattern recognition measurements, the perimeter of the TRUE shape of the Spray Pattern was determined, the center of mass (COM) was identified and is based on the shape of the true pattern. The Dmin and Dmax that passed through COG were measured based on the intensity of the true shape of the images.

Reviewer's Comment: The firm's response to deficiency #9 is acceptable.

Deficiency 10: *Please provide a summary table for the Spray Pattern by Laser Image study results of both the test and reference products.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR) which included the raw data.

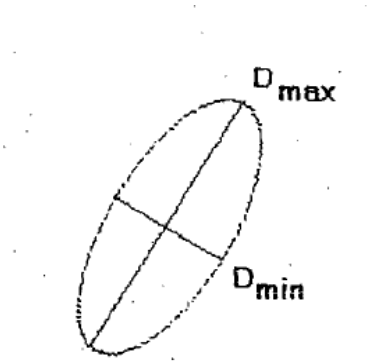
Reviewer's Comment: The firm's response to deficiency #10 is acceptable. The reviewer summarized the data and conducted the PBE analysis. Please refer to "In Vitro Study Results" section for details.

Deficiency 11: *Deficiency Comments for Spray Pattern using Thin Layer Chromatography (TLC) impaction manual analysis: Please clarify whether the D_{max} and D_{min} measurements were taken from the TRUE perimeters of the patterns or from the ellipses fitted to the pattern. If the data were based on the latter, please provide data based on the TRUE shape of the patterns.*

Firm's Response: The firm claimed that "*Dmax and Dmin measurements were taken from the true perimeters of the pattern*". The firm also attached the test method TM-0232 Issue Number 2 dated 1/3/07, "Test method for Spray Pattern for Fluticasone Propionate Nasal Spray Product In-Vitro Bioequivalence Study". The method related to evaluation of the shape of the spray is as follows:

"*Evaluate the shape of the spray by taking the outer most circle of the dark spray pattern. Measure the widest (Dmax) and shortest (Dmin) diameters for each spray pattern at 3.0 cm*

and at 6.0 cm Figure 2 should be used as a guide in determining the measurement of Dmax and Dmin". Figure 2:



Reviewer's Comment: The firm's response to deficiency #11 is NOT acceptable. The actual way used to measure the Dmax and Dmin described in the firm's method TM-0232 is not clear. The firm should submit few representative examples, for both test and reference products, of the its spray pattern by TLC measurement, clearly indicating schematic drawings of the true shape of the images, as well as the drawings of Dmax and Dmin based on the true shape of the image (e.g., each figure should be marked with the contour of the true shape, the estimated Center of Mass (COM), Dmax and Dmin).

Nasal BA/BE Guidance (April 2003) stating that "*Equivalence of spray patterns between test and reference products can be established based on a combination of qualitative and quantitative measures such as the perimeter of true shape and ovality ratio, where Dmax and Dmin are computed from the fitted geometric shapes (e.g. ellipse)".* It should be noted that this statement of the nasal BA/BE guidance pertains only to irregular shaped (e.g. horseshoe-shaped) patterns whose COM/COG falls outside the perimeter. Data based on the fitted ellipse are not acceptable for regular shaped spray patterns (V:\firmsnz (b) (4) ltrs&rev\ (b) (4) N0504.doc).

Deficiency 12: *Deficiency Comments for Spray Pattern using Thin Layer Chromatography (TLC) impaction manual analysis: You did not use an automated actuator for spray pattern study using TLC. Please explain why an automated actuator was not used for this test.*

Firm's Response: The automated actuation was not used for this study because the method was developed and validated using manual actuation. At the time the laboratory did not have access to an automated actuation device for Spray Pattern analysis using TLC impaction. The study was performed using samples which were blinded.

Reviewer's Comment: The firm also submitted the spray pattern test data using the automated Laser imaging technology. The firm's response to deficiency #12 is acceptable.

Deficiency 13: *Please provide a summary table for the Spray Pattern by TLC study results of both the test and reference products.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR) which included the raw data.

Reviewer's Comment: The firm's response to deficiency #13 is acceptable. The reviewer summarized the data and conducted the PBE analysis. Please refer to "In Vitro Study Results" section for details.

Deficiency 14: *Deficiency Comments for Droplet Size Distribution by Laser Diffraction: Please verify that the instrument was operated within the manufacturer's recommended obscuration or percent transmission (%T) range.*

Firm's Response: The manufacturer's recommended percent transmission (%T) is (b) (4). The instrument was operated within this range. The results for in-vitro bioequivalence study show range of 67.86-91.75%T which is within the manufacturer's recommended %T.

Reviewer's Comment: The firm's response to deficiency #14 is acceptable.

Deficiency 15: *Deficiency Comments for Droplet Size Distribution by Laser Diffraction: Please submit your protocol or SOP which states the criterion of selecting the plateau region at which droplet size data was determined. This criterion should be established prior to the study and implemented consistently during the study.*

Firm's Response: The firm submitted a report entitled "Determination of the Portion of the Spray Event Where the Plume is fully developed during the Droplet Size Testing of Fluticasone Propionate Aqueous Nasal Spray" (Report No.: RP-0119, Issue #1, effective date Jan 2, 07). The firm also mentioned that "*this criterion was established prior to the study and implemented consistently throughout the study*".

Reviewer's Comment: The firm's response to deficiency #15 is NOT acceptable. The effective date for report "Determination of the Portion of the Spray Event Where the Plume is fully developed during the Droplet Size Testing of Fluticasone Propionate Aqueous Nasal Spray" (Report No.: RP-0119, Issue #1) is Jan 2, 2007. The firm's Droplet Size Distribution by Laser Diffraction data were submitted on Feb. 7, 2005. The firm should provide a clear explanation on how this criterion could have been established prior to the study and implemented consistently during the study. If there was an early version of this report or SOP, the firm should submit and indicate its effective date.

Deficiency 16: *Deficiency Comments for Droplet Size Distribution by Laser Diffraction: Please provide a summary table for the droplet size distribution study results (D50 and Span) of both the test and reference products.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR) which included the raw data.

Reviewer's Comment: The firm's response to deficiency #16 is acceptable. The reviewer summarized the data and conducted the PBE analysis. Please refer to "In Vitro Study Results" section for details.

Deficiency 17: *Deficiency Comments for Particle Size Distribution by Cascade Impactor: Please provide the apparatus' flow rate (liters/min).*

Firm's Response: The apparatus flow rate is 28.3 L/min.

Reviewer's Comment: The firm's response to deficiency #17 is acceptable.

Deficiency 18: *Deficiency Comments for Particle Size Distribution by Cascade Impactor: Please note that the Cascade Impaction Studies on the nasal sprays are conducted to determine the relative amount of small droplets (< 9 µm, below the top stage) in the test and reference products. Since the amount of drug deposited below the top stage is of primary interest, the drug deposition should be categorized in two groups. Group 1 should include all drug deposited below the top stage which is < 9 µm in size (stage 1 through F, according to the Cascade Impactor schematic shown in Vol. 1.9, p 2949). Group 2 should include the total mass of drug collected on all stages and accessories. Please resubmit the results for particle size distribution by Cascade Impactor in the DBE's recommended format (refer to Attachment I). It should be noted that Table 6 in Attachment I can be modified according to the different type of Cascade Impactor used in the study. Therefore, please include the data of particle size less than 9 µm and the total mass data in the submission.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR) which included the raw data.

Reviewer's Comment: The firm's response to deficiency #18 is acceptable. The reviewer summarized the data and conducted the PBE analysis. Please refer to "In Vitro Study Results" section for details.

Deficiency 19: *Deficiency Comments for Particle Size Distribution by Cascade Impactor: Please provide a summary table for particle size distribution by Cascade Impaction study results in mass and % of label claim of both the test and reference products.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR) which included the raw data.

Reviewer's Comment: The firm's response to deficiency #19 is acceptable. The reviewer summarized the data and conducted the PBE analysis. Please refer to "In Vitro Study Results" section for details.

Deficiency 20: *Deficiency Comments for Plume Geometry by Laser Imaging: Please provide documentation showing that the plume is fully developed at the selected delay time.*

Firm's Response: The firm submitted a report entitled "Report for Determination that the Plume is Fully Developed at the Selected Delay Time for Plume Geometry Testing of Fluticasone Propionate Aqueous Nasal Spray" (Report No.: RP-0073). By comparing the delay time used to determine the plume geometry with the spray event for the droplet size testing, it was determined that the plume was fully developed at the selected delay time.

Reviewer's Comment: The firm's response to deficiency #20 is acceptable.

Deficiency 21: *Deficiency Comments for Plume Geometry by Laser Imaging: Please provide a summary table for the plume geometry study results, including the plume length, width and angle of both the test and reference products.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR) which included the raw data.

Reviewer's Comment: The firm's response to deficiency #21 is acceptable. The reviewer summarized the data and conducted the PBE analysis. Please refer to "In Vitro Study Results" section for details.

Deficiency 22: *Deficiency Comments for Priming and Repriming Study: In the testing method for priming and repriming study experiment part B (Vol. 1.9, p 2944), you stated that "prime the pump by pressing down until a fine mist comes out of the nozzle". Please specify the number of sprays required for achieving such fine mist.*

Firm's Response: According to the label claim for the reference product, the first time the pump is used it must be primed using 6 actuations. The reference product also states that if the pump is not used for greater than 7 days, then prime the pump until a fine mist appears. During the study, the number of sprays required for achieving such a fine mist was not more than 6 sprays.

Reviewer's Comment: The firm's response to deficiency #22 is acceptable.

Deficiency 23: *Deficiency Comments for Priming and Repriming Study: Please provide a summary table for the prime and reprime study results of both the test and reference products.*

Firm's Response: The firm submitted an "In-Vitro Bioequivalence Report for Fluticasone Propionate Nasal Spray" report (Report No.: RP-0072, located in EDR) which included the raw data.

Reviewer's Comment: The firm's response to deficiency #23 is acceptable. The reviewer summarized the data. Please refer to "In Vitro Study Results" section for details.

E. In Vitro Study Results

1. Single Actuation Content Through Container Life (SAC):

1.1. Method for Single Actuation Content Through Container Life:

Single actuation content through container life was performed on 3 batches of test product and 3 batches of reference product. The study was performed on 10 samples per each batch. Test method TM-0173 was followed.

The SAC testing method was validated for precision and intermediate precision. In addition, the analytical method (HPLC, method TM-0122) was also validated. The method validation report was provided in Vol. 1.9, p2963.

1.2. Summary Table for the SAC test:

SAC Amount:

Sector	Product	Mean		Variability (%CV)				TEST/REF		p
				Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
		Arith (N=30)	Geo (N=30)	Min (N=10)	Max (N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	Test	49.13	49.05	3.18	8.56	0.92	5.90	1.04	1.04	0.00
	Ref	47.03	47.02	2.19	3.88	0.44	2.82			
END	Test	48.67	48.62	1.31	6.56	1.17	4.33	1.00	1.00	0.62
	Ref	48.43	48.42	0.99	1.86	2.52	2.52			

SAC (% Label Claim):

Sector	Product	Mean		Variability (%CV)				TEST/REF		p
				Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
		Arith (N=30)	Geo (N=30)	Min (N=10)	Max (N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	Test	98.27	98.10	3.18	8.56	0.92	5.90	1.04	1.04	0.00
	Ref	94.07	94.03	2.19	3.88	0.44	2.82			
END	Test	97.33	97.25	1.31	6.56	1.17	4.33	1.00	1.00	0.76
	Ref	96.87	96.84	0.99	1.86	2.52	2.52			

1.3. In Vitro PBE Analysis for Single Actuation Content Through Container Life:

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1.4. Reviewer's Comments on SAC:

1. The ratio of the test/reference geometric means for the beginning and end of the unit life are with the limits of 0.90-1.11.
2. The test product passed PBE criteria for the SAC test.
3. The firm's SAC test is acceptable. However, it should be noted that the variability of the test product is higher than that of the reference product.

2. **Spray Pattern by Laser Image**:

2.1. Method for Spray Pattern by Laser Image:

Non Impaction Automated Analysis

Spray pattern was performed on 3 batches of test product and 3 batches of reference product by non impaction automated analysis. The study was performed on 10 samples per each batch at distances of 3 cm and 6 cm. Test method TM-0172 was followed.

The testing method was validated for precision, intermediate precision and robustness. The method validation report was provided in Vol. 1.9, p2974.

2.2. Summary Table for Spray Pattern by Laser Image:

Spray Pattern by Area:

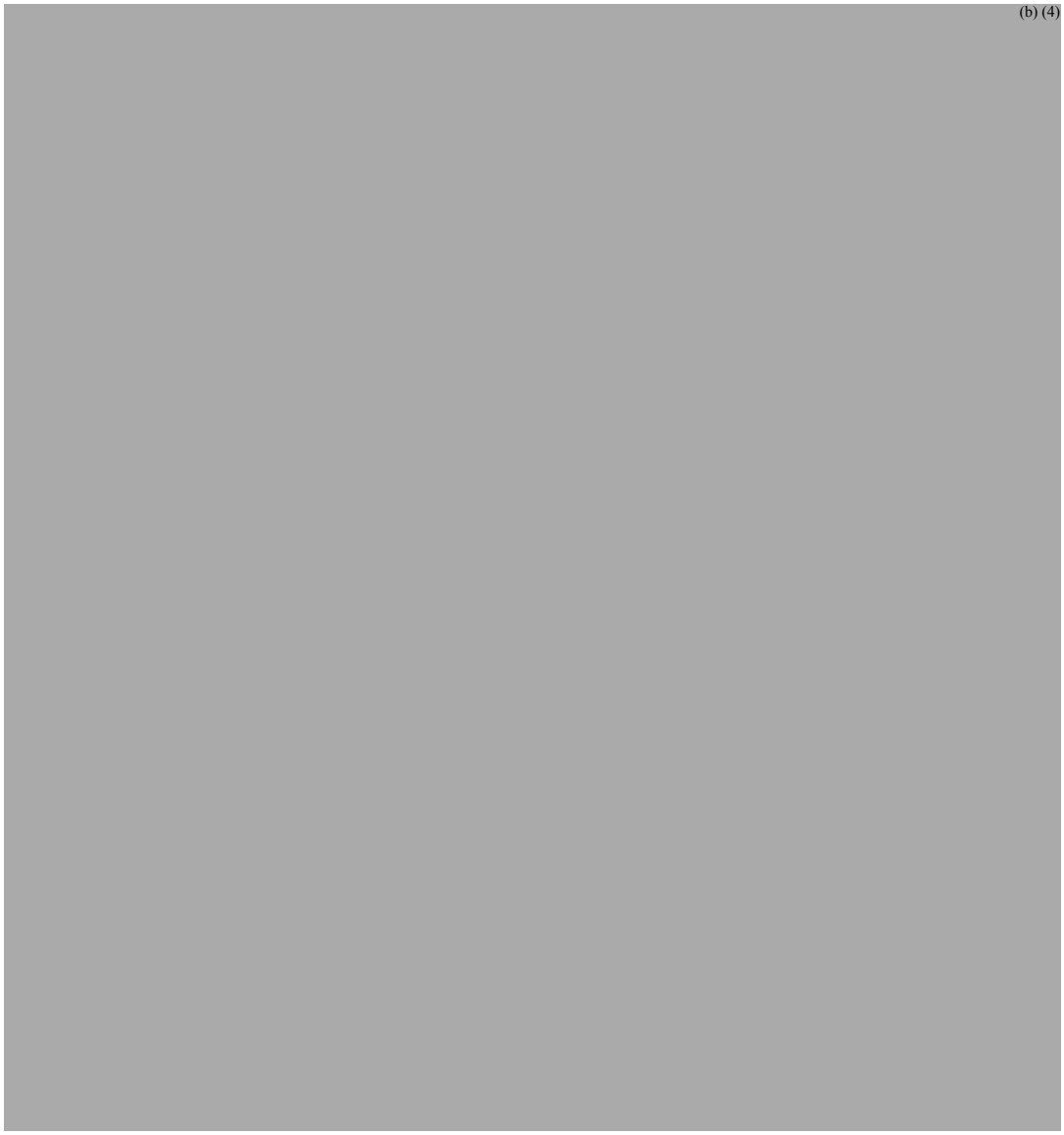
Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**3**	Test	134.28	127.00	28.60	42.32	11.20	34.71	1.57	1.61	0.00
		Ref	85.72	78.79	28.56	45.60	26.52	45.81			
BEG	**6**	Test	496.83	475.65	26.31	34.87	7.73	29.23	1.46	1.48	0.00
		Ref	340.16	322.17	29.51	39.50	10.72	34.55			

Spray Pattern by Ovality:

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**3**	Test	1.46	1.46	1.38	1.51	4.83	11.61	0.94	0.94	0.04
		Ref	1.56	1.55	8.73	11.54	1.15	9.92			
BEG	**6**	Test	1.41	1.40	5.21	10.44	2.21	8.56	0.98	0.98	0.00
		Ref	1.44	1.43	9.45	12.85	0.89	10.58			

2.3. In Vitro PBE Analysis for Spray Pattern by Laser Image:

(b) (4)



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2.4. Reviewer's Comments on Spray Pattern by Laser Image:

1. The test product passed the PBE criteria for the ovality ratio at both distances. However, the test product did not pass the PBE criteria for the area at both distances. For the non-impaction system, the guidance requires that "statistical analysis at each distance would be based on equivalence of area within the perimeter and ovality ratio".
2. The reviewers also run the PBE analysis for Dmax and Dmin at two distances. These two parameters did not pass the PBE criteria for bioequivalence.
3. The firm's spray pattern testing by laser image is not acceptable.

3. Spray Pattern by Thin Layer Chromatograph:

3.1. Methods for Spray Pattern by Thin Layer Chromatograph:

Impaction Manual Analysis

Spray pattern was performed on 3 batches of test product and 3 batches of reference product by impaction manual analysis. The study was performed on 10 samples per each batch at distances of 3 cm and 6cm. Test method TM-0232 was followed.

The testing method was validated for method precision (repeatability and intermediate precision), limit of detection, limit of quantitation and robustness. The method validation report was provided in Vol. 1.9, p2974.

3.2. Summary Table for Spray Pattern by Thin Layer Chromatograph:

Dmax:

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith (N=30)	Geo (N=30)	Min (N=10)	Max (N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**3**	Test	27.70	27.68	3.72	4.58	1.65	4.26	1.00	1.00	0.92
		Ref	27.67	27.63	4.83	5.46	0.91	4.96			
BEG	**6**	Test	38.23	38.20	3.31	4.30	1.53	3.99	1.00	1.00	1.00
		Ref	38.23	38.20	3.60	4.96	1.29	4.38			

Ovality:

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**3**	Test	1.15	1.14	1.13	1.16	1.33	6.37	0.99	0.99	0.72
		Ref	1.16	1.15	4.27	7.04	2.00	5.87			
BEG	**6**	Test	1.14	1.14	4.29	8.11	3.16	7.14	1.01	1.01	0.08
		Ref	1.13	1.13	0.00	4.45	2.65	4.12			

3.3. PBE Analysis for Spray Pattern by Thin Layer Chromatograph:

(b) (4)

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3.4. Reviewer's Comments on Spray Pattern by Thin Layer Chromatograph:

1. The firm claimed that the Dmax and Dmin measurements were taken from the true perimeters of the pattern and enclosed a Test Method TM-0232. However, the actual way used to measure the Dmax and Dmin described in the firm's method TM-0232 is not clear. The firm should submit few representative examples, for both test and reference products, of the its spray pattern by TLC measurement, clearly indicating schematic drawings of the true shape of the images, as well as the drawings of Dmax and Dmin based on the true shape of the image (e.g., each figure marked with the contour of the true shape, the estimated Center of Mass (COM), Dmax and Dmin).
2. Based on the firm's data, the test product passed the PBE criteria for Dmax and Ovality in spray pattern by TLC test.

4. Droplet Size Distribution by Laser Diffraction:

4.1. Methods for Droplet Size Distribution by Laser Diffraction:

Droplet size distribution by laser diffraction was performed on 3 batches of test product and 3 batches of reference product. The study was performed on 10 samples per each batch testing beginning and end sprays at a distance of 3 cm and 6 cm. Test method TM-0162 was followed.

The testing method was validated for precision, intermediate precision and robustness. The method validation report was provided in Vol. 1.9, p3022.

4.2. Summary Table for Droplet Size Distribution by Laser Diffraction:

D50:

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith (N=30)	Geo (N=30)	(min) (N=10)	(max) (N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**3**	Test	69.17	68.07	15.05	19.49	7.42	17.92	0.88	0.90	0.03
		Ref	78.53	75.83	25.17	29.82	4.11	26.43			
BEG	**6**	Test	60.29	59.73	8.12	21.22	4.80	14.61	0.80	0.81	0.00
		Ref	75.21	73.66	20.34	22.26	4.80	21.14			
END	**3**	Test	73.76	72.70	13.69	23.76	4.03	17.98	0.90	0.92	0.09
		Ref	81.56	79.01	23.36	27.00	5.66	25.21			
END	**6**	Test	58.79	58.19	11.67	18.69	5.46	15.09	0.81	0.82	0.00
		Ref	72.60	71.02	18.46	26.81	4.08	22.17			

Span:

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith (N=30)	Geo (N=30)	(min) (N=10)	max) (N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**3**	Test	1.87	1.86	1.84	1.90	1.58	8.42	1.08	1.08	0.03
		Ref	1.74	1.73	7.82	8.61	0.59	7.97			
BEG	**6**	Test	1.94	1.94	3.90	6.42	3.70	5.97	1.08	1.08	0.00
		Ref	1.79	1.79	4.53	5.56	0.12	4.84			
END	**3**	Test	1.87	1.86	5.23	18.08	3.17	11.80	1.08	1.07	0.07
		Ref	1.74	1.73	6.95	8.17	1.01	7.17			

END	**6**	Test	1.97	1.96	4.12	6.19	4.06	6.33	1.10	1.09	0.00
		Ref	1.80	1.79	4.23	5.30	1.66	4.93			

4.3. In Vitro PBE Analysis for Droplet Size Distribution by Laser Diffraction:

(b) (4)

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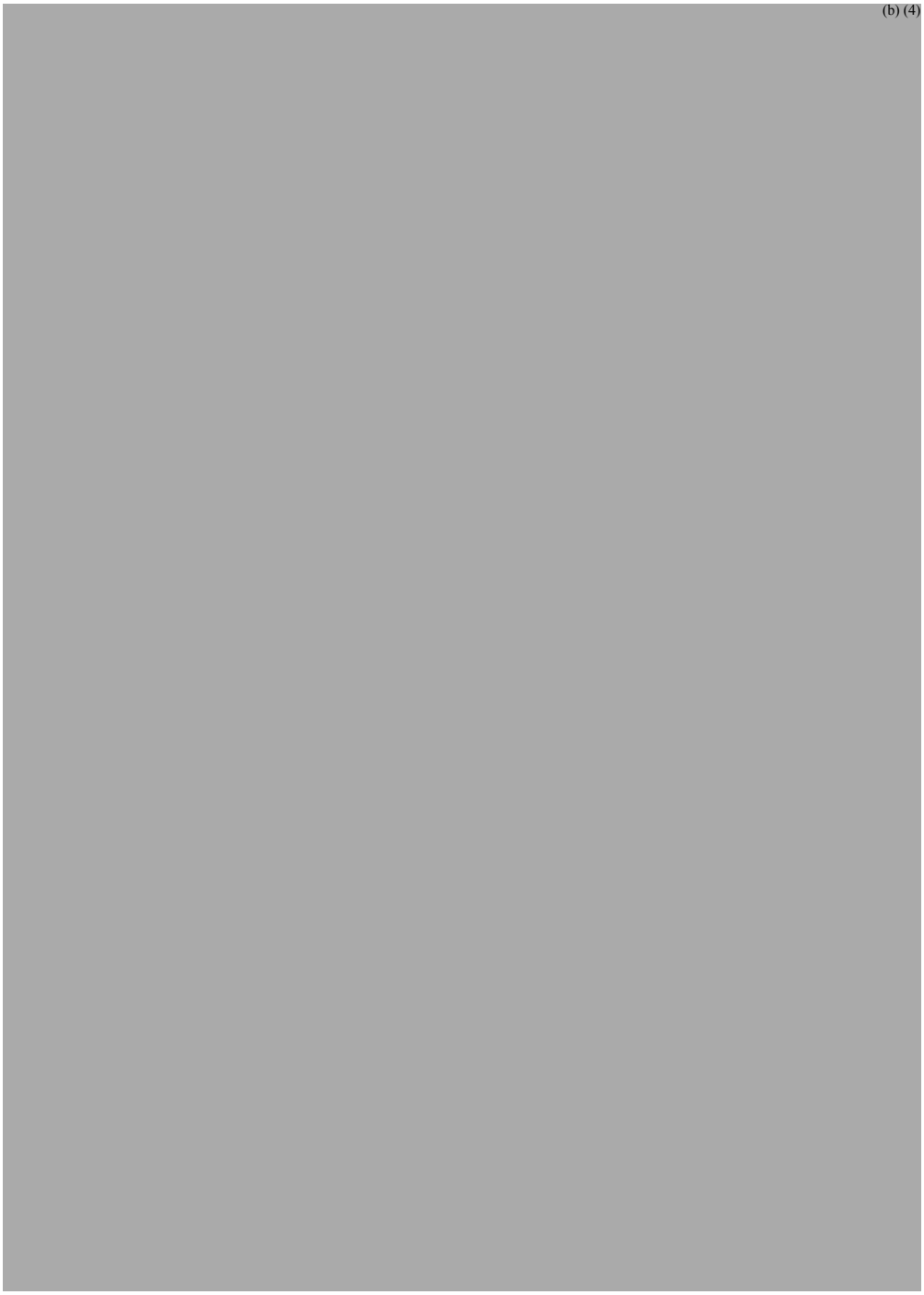


3.4. Reviewer's Comments on Droplet Size Distribution by Laser Diffraction:

1. The test product passed PBE criteria for D50 and Span at both distances of the Droplet Size Distribution by Laser Diffraction test.
2. The firm's Droplet Size Distribution by Laser Diffraction test is acceptable.

5. **Plume Geometry:**

5.1. Methods for Plume Geometry:

Plume geometry was performed on 3 batches of test product and 3 batches of reference product. The study was performed on 10 samples per each batch using beginning spray. Test method TM-0171 was followed.

The testing method was validated for precision, intermediate precision and robustness. The method validation report was provided in Vol. 1.9, p2974.

5.2. Summary Table for Plume Geometry:

Plume Angle:

Sector	Distance (cm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total			
			Arith	Geo	Min	Max			Arith Mean	Geo Mean	
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**6**	Test	49.89	49.82	2.40	5.67	4.49	5.66	1.07	1.07	0.00
		Ref	46.64	46.62	2.00	3.22	1.48	2.91			

Plume Width:

Sector	Distance (cm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total			
			Arith	Geo					Arith Mean	Geo Mean	
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**6**	Test	56.10	55.99	53.09	58.76	5.08	6.47	1.08	1.08	0.05
		Ref	51.94	51.92	2.20	3.55	1.54	3.21			

Geometric Mean of Log Transformed Data Summary:

	Geometric Mean (Test)	Geometric Mean (Ref)	Ratio (T/R)	Within 90-111%?
Ln Angle	49.80	46.61	**1.07**	Yes
Ln Width	55.96	51.91	**1.08**	Yes

5.3. In Vitro PBE Analysis for Plume Geometry:

Not applicable.

5.4. Reviewer's Comments on Plume Geometry:

1. The ratio of the geometric mean of the test product to that of the reference product, based on log transformed data, fall within 90-111% for plume angle and width.
2. The firm's plume geometry test is acceptable.

6. Particle Size Distribution by Cascade Impactor:

6.1. Methods for Particle Size Distribution by Cascade Impactor:

Particle size distribution by Cascade Impaction was performed on 3 batches of test product and 3 batches of reference product. The study was performed on 10 samples per each batch using beginning spray and bulk sample. Test method TM-0169 was followed.

The testing method was validated for linearity, accuracy of method, method precision, intermediate precision, limit of quantitation and limit of detection. This validation report is part of and in addition to the validation performed for test method TM-0122 titled "High pressure liquid chromatographic (HPLC) method for assay of fluticasone propionate in raw material and in fluticasone propionate aqueous nasal spray finished product". The method validation report was provided in Vol. 1.9, p3079.

6.2. Summary Table for Particle Size Distribution by Cascade Impactor:

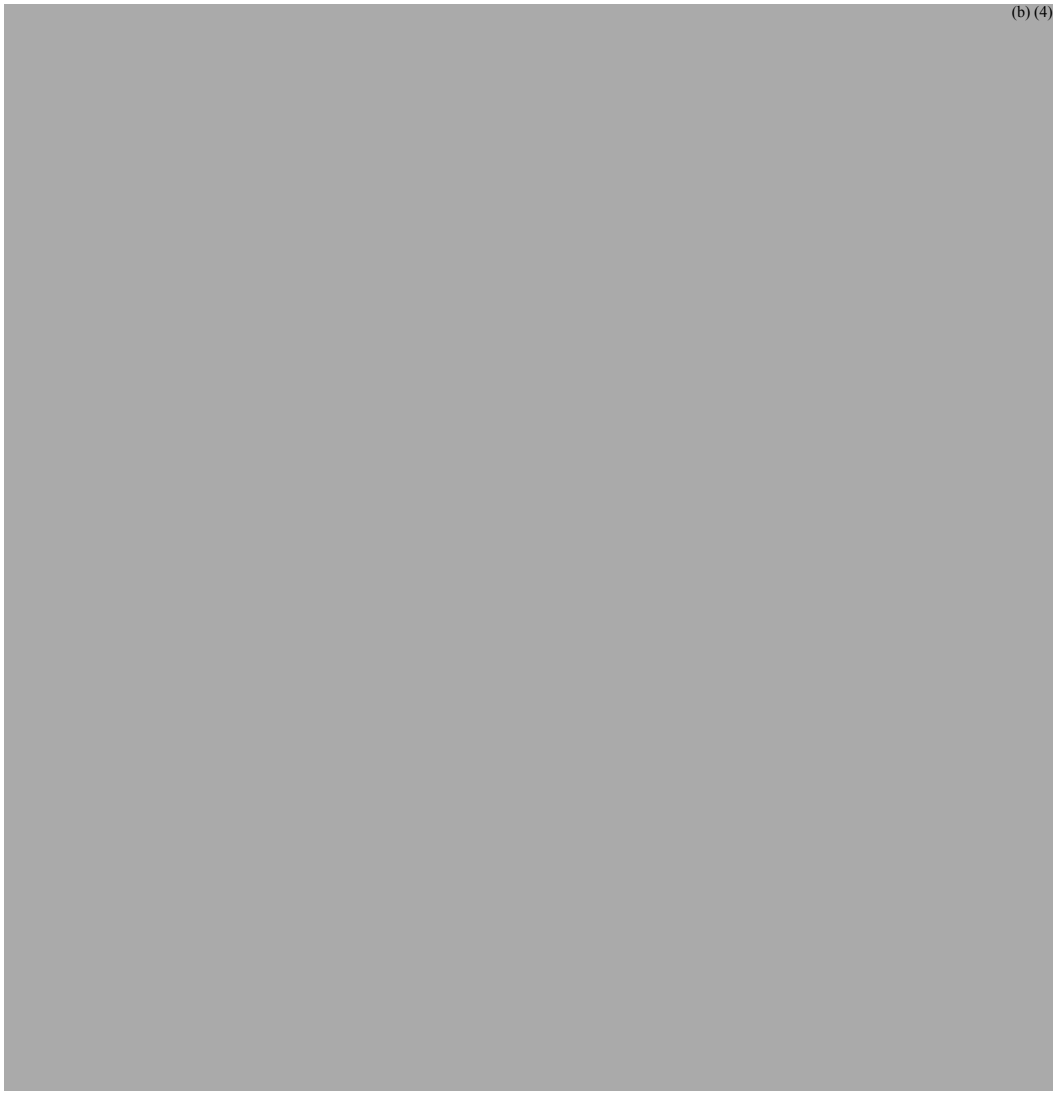
For particle size less than 9 mm:

Sector	Group (<9 μm)	Product	Mean		Variability (%CV)				TEST/REF		p-Value
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)	(N=10)	(N=3)	(N=30)	N=30	N=30	
BEG	**Stage 1-F**	Test	0.15	0.14	16.64	34.60	4.79	25.85	**0.96**	**0.98**	0.63
BEG	**Stage 1-F**	Ref	0.15	0.15	26.78	40.64	9.79	33.30			

6.3. In Vitro PBE Analysis for Particle Size Distribution by Cascade Impactor:

(b) (4)

Following this page, 4 pages withheld in full (b)(4)



6.4. Reviewer's Comments on Particle Size Distribution by Cascade Impactor:

1. The Nasal Guidance 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 **0.96**, and the T/R geometric mean ratio was **0.98**, 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.
2. The test product passed the PBE criteria for the total amount of drug collected at all stages and accessories and the total mass balance.

3. The total mass of the test product collected on all stages and accessories are ranging from 89.19 - 104.40%, within the acceptable limits of [85.0-115.0] specified by the current draft Nasal Guidance.
4. The firm's cascade impactor test is acceptable.

7. Priming and Repriming:

7.1. Methods for Priming and Repriming:

Priming and repriming was performed on 3 batches of test product and 3 batches of reference product. The study was performed on 10 samples per each batch. Test method TM-0174 was followed.

7.2. Summary Table for Priming and Repriming:

7.2.1. Priming:

The samples were collected at the following spray numbers: Assay spray No. 1 (after prime for 6 sprays), the data is analyzed and shown below.

Amount (mcg/dose):

Sector	Spray #	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**1**	Test	47.73	47.69	3.21	6.34	1.35	4.47	1.01	1.01	0.23
		Ref	47.07	47.05	2.27	3.87	0.68	2.90			

% of Labeled claim:

Sector	Spray	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo							
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**1**	Test	95.47	**95.37**	94.00	96.40	1.35	4.47	1.01	1.01	0.15
		Ref	94.13	**94.10**	2.27	3.87	0.68	2.90			

The firm also submitted the data for the following samples collections. These data are not analyzed.

1). Discharge spray No. 2-4. Samples were stored for 48 hours. Assay for spray No. 5 (unprimed spray)
2). Discharge spray No. 6-59, samples were stored for 96 hours. Assay for spray No. 60 (unprimed spray)
3). Discharge spray No. 61-100, samples were stored for 168 hours. Assay for spray No. 101 (unprimed spray)

7.2.2. Repriming:

The experiment was conducted according to the following procedures: Discharge spray No. 1-110. Store the sample for 168 hours. After 168 hours, prime the pump by pressing down until a fine mist comes out of the nozzle (less than 6 sprays according to the firm). Collect the next spray.

Amount (mcg/dose):

Sector	Spray	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**111**	Test	46.90	46.86	2.91	5.19	1.33	4.20	0.98	0.98	0.04
		Ref	47.70	47.69	1.67	2.29	0.96	2.07			

% of Label Claim:

Sector	Spray	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo							
			(N=30)	(N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	**111**	Test	93.80	**93.72**	2.91	5.19	1.33	4.20	0.98	0.98	0.01
		Ref	95.40	95.38	1.67	2.29	0.96	2.07			

7.3. In Vitro PBE Analysis for Priming and Repriming:

Not applicable.

7.4. Reviewer's Comments on Priming and Repriming:

1. 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)".*

2. The draft guidance states that "*For ANDAs, **priming** would be established providing that the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B life stage 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*".

3. The firm's priming data pass the 95-105% criterion (geometric mean of the test product emitted dose is **95.37%** of Labeled claim**)** but the repriming data did not pass it (geometric mean of the test product emitted dose is **93.72%** of Labeled claim**)**. However, it is noticed that the priming data for the reference product did not pass the 95-105% criterion either (geometric mean of the reference product emitted dose is **94.10%** of Labeled claim).

4. The firm's repriming test is NOT acceptable.

F. Waiver Request(s)

None.

G. Deficiency Comments

1. For Spray Pattern by Laser Image test: The test product passed the PBE criteria for the ovality ratio at both distances. However, the test product did not pass the PBE criteria for the area at both distances. For the non-impaction system, the guidance requires that "statistical analysis at each distance would be based on equivalence of area within the perimeter and ovality ratio". The firm's spray pattern testing by laser image is not acceptable.

2. For Spray Pattern test using Thin Layer Chromatography (TLC) impaction manual analysis, the firm submitted a test method TM-0232 entitled "Test method for Spray Pattern for Fluticasone Propionate Nasal Spray Product In-Vitro Bioequivalence Study". The actual way used to measure the Dmax and Dmin described in the firm's method TM-0232 is not clear. The firm should submit few representative examples, for both test and reference products, of the its spray pattern by TLC measurement, clearly indicating schematic drawings of the true shape of the images, as well as the drawings of Dmax and Dmin parameters on the true shape of the image (e.g., each figure marked

with the contour of the true shape, the estimated Center of Mass (COM), Dmax and Dmin).

3. For Droplet Size Distribution by Laser Diffraction, the DBE had previously requested the firm to submit a protocol or SOP which states the criterion of selecting the plateau region at which droplet size data was determined. This criterion should be established prior to the study and implemented consistently during the study. The firm submitted a report entitled "Determination of the Portion of the Spray Event Where the Plume is fully developed during the Droplet Size Testing of Fluticasone Propionate Aqueous Nasal Spray" (Report No.: RP-0119, Issue #1). The effective date for the report was **Jan 2, 2007**. The firm's Droplet Size Distribution by Laser Diffraction data was submitted on **Feb. 7, 2005**. The firm should provide a clear explanation on how this criterion could have been established prior to the study and implemented consistently during the study. If there is an early version of this report or SOP, the firm should submit and indicate its effective date.

4. The firm's repriming test is not acceptable. The geometric mean of the emitted dose of the test product, after repriming, was 93.72 according to the DBE's calculation. The geometric mean does not fall in the acceptable range of 95-105% Labeled Claim.

5. The firm's in vitro data is not in SAS transport format. In the future, the firm should submit its in vitro data in the SAS transport format.

H. Recommendations

1. The pharmacokinetic bioequivalence study # 10322808 submitted for Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per spray, by Hi Tech Pharmacal Co. Inc., comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 mcg per spray, manufactured by GlaxoSmithKline, is **acceptable**.

2. The in-vitro equivalence studies submitted for Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per spray, by Hi Tech Pharmacal Co. Inc. comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 mcg per spray, manufactured by GlaxoSmithKline, are **incomplete** due to deficiencies summarized under "Deficiency Comments".

   The firm should be informed of the deficiency comments and recommendations.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-570 APPLICANT: Hi Tech Pharmacal Co. Inc.

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

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

1. For Spray Pattern by Laser Image test: Your test product did not pass the Population Bioequivalence (PBE) criteria for the **area** at both distances. Your spray pattern by laser image test is not acceptable.

2. For Spray Pattern test using Thin Layer Chromatography (TLC) impaction manual analysis: The actual way used to measure the Dmax and Dmin described in your method TM-0232, "Test method for Spray Pattern for Fluticasone Propionate Nasal Spray Product In-Vitro Bioequivalence Study", is not clear. Please submit few representative examples, for both test and reference products, of the spray pattern by TLC measurement, clearly indicating schematic drawings of the **true shape** of the images, as well as the drawings of Dmax and Dmin parameters on the true shape of the image (e.g., each figure should be marked with the contour of the true shape, the estimated Center of Mass (COM), Dmax and Dmin).

3. For Droplet Size Distribution by Laser Diffraction: The DBE had previously requested you to submit a protocol or SOP which states the criterion of selecting the plateau region at which droplet size data were determined. This criterion should be established prior to the study and implemented consistently during the study. You submitted a report entitled "Determination of the Portion of the Spray Event Where the Plume is fully developed during the Droplet Size Testing of Fluticasone Propionate Aqueous Nasal Spray" (Report No. RP-0119, Issue #1). The effective date for this report was **Jan 2, 2007**. However, your Droplet Size Distribution by Laser Diffraction data were submitted on **Feb. 7, 2005**. Please provide a clear explanation on how this criterion could have been

established prior to the study and implemented consistently during the study. If there is an early version of this report, please submit it and indicate its effective date.

4. Your repriming test is not acceptable. The geometric mean of the emitted dose (as expressed in percent of the Labeled Claim) of the test product, after repriming (e.g., after stored for 168 hrs, spray #111), was 93.72% according to the DBE's calculation. The mean does not fall in the acceptable range of 95-105% Labeled Claim.

5. The firm's in vitro data were not submitted in SAS transport format. In the future, please submit your in vitro data in the SAS transport format.

Sincerely yours,

{See appended electronic signature page}

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

ANDA 77-570

BIOEQUIVALENCE - DEFICIENCIES

Submission Date: Jan. 11, 2007

1. STUDY AMENDMENT (STA)

Strengths: 50 mcg per Spray
Outcome: IC

Outcome Decisions: IC

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

/s/

Bing Li
2/22/2007 10:11:02 AM
BIOPHARMACEUTICS

Moheb H. Makary
2/22/2007 10:21:49 AM
BIOPHARMACEUTICS

Dale Conner
2/22/2007 12:26:24 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-570
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 mcg per Spray
Applicant Name	Hi Tech Pharmacal Co. Inc.
Address	369 Bayview Avenue Amityville, NY 11701 Contact: Joanne Curri 631-789-8228 ext. 4127 631-789-8429 (fax)
Submission Date(s)	March 14, 2007
Amendment Date(S)	NA
Reviewer	Bing V. Li, Ph.D.
First Generic	No

I. Executive Summary

Hi Tech Pharmacal Co. Inc. has submitted its responses to the deficiency comments made by the Division of Bioequivalence (DBE) in its letter of February 26, 2007. The deficiencies were related to the in vitro performance data for spray pattern and repriming. The firm's responses are acceptable. The application is now **acceptable**.

II. Table of Contents

III. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

See the reviews of the original submission and subsequent amendments of the study located in DFS.

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

C. Background

1. On April 14, 2005, the firm submitted an in vivo fasted study and in vitro bioequivalence studies on its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per Spray. The in vivo and in vitro bioequivalence studies were found incomplete.
2. On Jan. 11, 2007, the firm submitted its response to the deficiency comments made by the Division of Bioequivalence (DBE) in its letter of December 12, 2006. The firm's responses to the in vivo bioequivalence study were acceptable. However, the firm's responses to the in vitro bioequivalence studies were incomplete.
3. On March 14, 2007, the firm submitted the current submission, addressed deficiency comments made by the Division of Bioequivalence (DBE) in its letter of February 26, 2007.

D. Review of Submission

Deficiency 1: *For Spray Pattern by Laser Image test: Your test product did not pass the Population Bioequivalence (PBE) criteria for the **area** at both distances. Your spray pattern by laser image test is not acceptable.*

Firm's Response:

Please be advised Hi-Tech has quantitated the Spray Pattern Analysis by two (2) methods at distances of 30 mm and 60 mm.

a. Spray Pattern, Impaction, Manual Analysis
b. Spray Pattern, Non-impaction, Automated Image Analysis

Based on FDA Draft Guidance for Industry "Bioavailability and Bioequivalence for Nasal Aerosols and Nasal Sprays for Local Action" dated April 2003; Section V: IN VITRO STUDIES, Part B5 Spray Patterns, page 17. The guidance states: Spray pattern studies characterize the spray either during the spray prior to impaction (Automatic test method) or following impaction on an appropriate target such as Thin Layer Chromatography (Manual test method).

A review of Spray Pattern, Non-impaction, Automatic Analysis, and data from both Hi-Techs samples and the Reference Leader Drug revealed similar inconsistencies (large sample area variations). Similarly a review of the spray pattern by Impaction Manual Analysis show more uniform area results.

Based on this observation a decision was made to repeat Spray Pattern following Impaction, Manual Analysis.

Hi-Tech developed and validated the test method for spray by manual analysis based on impaction system studies, such as Thin Layer Chromatography (TLC) Plate Methodology (TM-0232) "Test Method for Spray Pattern For Fluticasone Propionate Nasal Spray Finished Product In-Vitro Bioequivalence Study".

The results of Spray Pattern, Impaction, Manual Analysis form original submission, section VI Bioavailability/Bioequivalence, pages 135F - 135M for both T-Test for Ovality and Dmax on pat30 mm and pat60 mm are as follows:

30 mm Dmax Test HN2 <O
30 mm Ovality Test HN2 <O
60 mm Dmax Test HN2 <O
60 mm Ovality Test HN2 <O

The area measurement were calculated for both R and T products found to be bioequivalent (HN2 <O)

30 mm Area Test HN2 <O
60 mm Area Test HN2 <O

Conclusions:

Manual In Vitro impaction studies more accurately simulate drugs which are administered intranasally for both local and systemic applications. Deposition within the nasal cavity by inertial impaction determines the likelihood of success. The impaction force, which is directly related to spray velocity, may provide a better way to evaluate in vitro equivalence as it more closely related to patient sensation. This is comparable to when a patient sprays

the product into the nasal passage and the spray is impacted onto the nasal mucosa. Automated analysis however is reliant only on the spray which is dispersed into the air prior to any impaction. Automated instrumentation captures the spray as it travels through the air prior to impacting on any surface. We would therefore surmise that impaction, since it simulates more closely the use in humans, would be a more accurate method of measurement for the analysis of BE.

When the spray pattern study was performed by manual actuation and impaction analysis, the in-vitro bioequivalence passes the acceptance criteria. Based on manual impaction results the Dmax, Ovality and Area the Population Bioequivalence (PBE) criteria have been met.

Reviewer's Comments:

The firm's response to deficiency #1 is acceptable for the following reasons:

1. The FDA Draft Guidance for Industry "Bioavailability and Bioequivalence for Nasal Aerosols and Nasal Sprays for Local Action" dated April 2003 states: *Spray pattern studies characterize the spray either during the spray prior to impaction (Automatic test method) or following impaction on an appropriate target such as Thin Layer Chromatography (Manual test method).*
2. For both test and RLD products, large variations were observed in the spray pattern area by laser image (% CV is 35% for the test and 46% for the RLD at distance 3cm, and % CV is 29 % for the test and 35% for the RLD at distance 6cm).

Therefore, the DBE considers it acceptable to the firm's spray pattern study based on its Thin Layer Chromatography (Manual test method) results.

Deficiency 2: *For Spray Pattern test using Thin Layer Chromatography (TLC) impaction manual analysis: The actual way used to measure the Dmax and Dmin described in your method TM-0232, "Test method for Spray Pattern for Fluticasone Propionate Nasal Spray Product In-Vitro Bioequivalence Study", is not clear. Please submit few representative examples, for both test and reference products, of the spray pattern by TLC measurement, clearly indicating schematic drawings of the **true shape** of the images, as well as the drawings of Dmax and Dmin parameters on the true shape of the image (e.g., each figure should be marked with the contour of the true shape, the estimated Center of Mass (COM), Dmax and Dmin).*

Firm's Response: Test Method TM-0232 "Test Method for Spray Pattern for Fluticasone Propionate Nasal Spray Product In Vitro Bioequivalence Study" has been revised to include the additional clarity for determining the true shape of the spray pattern, Dmax, Dmin and COM. Representative examples of test and reference products of the spray pattern by TLC measurements have been submitted. These examples show the true shape of the image and drawings of Dmax and Dmin and estimated center of mass (COM).

Reviewer's Comment: The firm's revised version of Test Method TM-0232 "Test Method for Spray Pattern for Fluticasone Propionate Nasal Spray Product In Vitro Bioequivalence Study" (Effective date 03/01/07) described the details of determining the true shape of the spray pattern, Dmax, Dmin and COM as follows:

Detection and Data Evaluation

(b) (4)

Perform the following on the photocopy of the TLC plate (true shape of spray pattern). Measure the longest $(D_{max})^{*}$ and shortest $(D_{min})^{**}$ distance for each spray pattern at 3.0 cm and at 6.0 cm. Refer to Figure 3

$^{*}D_{max}$ is the longest distance which crosses though COM (centre of mass) of the true shape of the spray pattern.

$^{**}D_{min}$ is the shortest distance which crosses through COM (centre of mass) of the true shape of the spray pattern.

Figure 2: Determination of COM (center of mass)

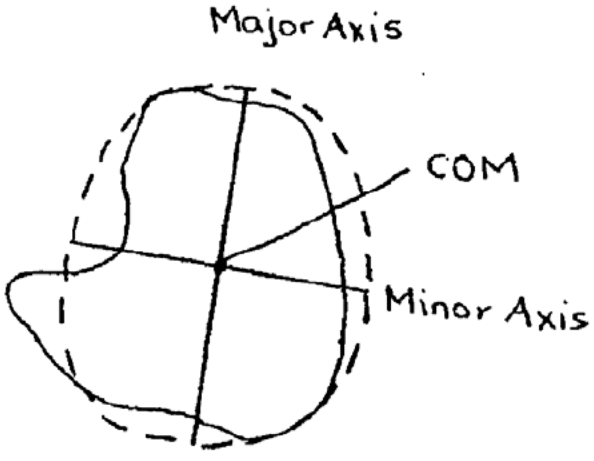
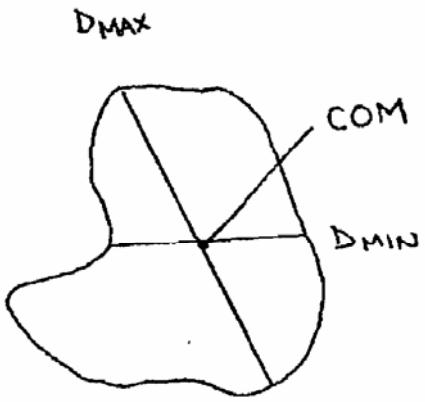


Figure 3: Determination of D_{max} and D_{min}



Calculate the ovality ratio for each spray pattern using the following formula:

Ovality ratio = D_{max}/D_{min}

The firm's revised Test Method is acceptable.

The firm also submitted some representative examples of test and reference products of the spray pattern by TLC measurements, showing the true shape of the image and drawings of Dmax and Dmin and estimated center of mass (COM).

The firm's response to deficiency #2 is acceptable.

Deficiency 3: *For Droplet Size Distribution by Laser Diffraction: The DBE had previously requested you to submit a protocol or SOP which states the criterion of selecting the plateau region at which droplet size data were determined. This criterion should be established prior to the study and implemented consistently during the study. You submitted a report entitled "Determination of the Portion of the Spray Event Where the Plume is fully developed during the Droplet Size Testing of Fluticasone Propionate Aqueous Nasal Spray" (Report No. RP-0119, Issue #1). The effective date for this report was **Jan 2, 2007**. However, your Droplet Size Distribution by Laser Diffraction data were submitted on **Feb. 7, 2005**. Please provide a clear explanation on how this criterion could have been established prior to the study and implemented consistently during the study. If there is an early version of this report, please submit it and indicate its effective date.*

Firm's Response: The report entitled "Determination of the Portion of the Spray Event Where the Plume is fully developed during the Droplet Size Testing of Fluticasone Propionate Aqueous Nasal Spray" (Protocol No. PR -01 19, Issue #I, Effective date: Jan. 2, 2007) states the criterion for selecting the plateau region at which the droplet size data were determined for Fluticasone Propionate Aqueous Nasal Spray. This protocol was prepared based on protocol "Determination of the Portion of the Spray Event Where the Plume is Fully Developed during the Droplet Size Testing for Nasal Sprays Using (b) (4) (b) (4)" (Protocol No. PR-0072, Issue #1, effective date: May 23, 2004). Protocol (PR-

0072) is a general protocol for nasal sprays and not specific to Fluticasone Propionate Aqueous Nasal Spray. This protocol was used by the chemists when they performed the droplet size testing for the In-Vitro Bioequivalence study for Fluticasone Propionate Aqueous Nasal Spray. This criterion was established prior to the study and implemented consistently during the study for the Droplet Size Distribution by Laser Diffraction for Fluticasone Propionate Aqueous Nasal Spray data which was started on May 25, 2004.

Reviewer's Comments: The firm's response to deficiency #3 is acceptable.

Deficiency 4: *Your repriming test is not acceptable. The geometric mean of the emitted dose (as expressed in percent of the Labeled Claim) of the test product, after repriming (e.g., after stored for 168 hrs, spray #111), was 93.72% according to the DBE's calculation. The mean does not fall in the acceptable range of 95-105% Labeled Claim.*

Firm's Response:

Hi-Tech agrees with the FDA, that the geometric mean of the emitted dose (as expressed in percent of the label claim) of the product after repriming (e.g. after stored for 168 hrs. spray 111) was 93.72% according to the DBE's calculation. These results were obtained from three (3) Test Product lots and three (3) lots of the Reference Listed Drug Product.

Hi-Tech would like to prove through scientific justification and supportive data that the repriming results met the geometric mean and fall within the acceptable range of 95 - 105% label claim according to the DBE calculation as follows:

1. Hi-Tech evaluated the data compiled from the "Characterization Study" Section 3.4 'Priming and Repriming in Various Orientations'. These studies were performed on the same three (3) Hi-Tech lots and one lot of the RLD. These samples were stored for the identical time 168 hrs in the inverted position. Hi-Tech calculated results obtained at the 111th spray identical to the data in question according to the DBE calculation.

   The geometric mean of the emitted dose of the three lots (301700, 302700, and 303700) of the test product and one lot (C089155) of the Reference product met the acceptable range of 95 - 105% Labeled Claim. Test Product and Reference Product are 98.0% and 99.9% respectfully. Enclosed is full data report.

2. Hi-Tech evaluated the data of the "Single Actuation Content Through Container Life" from the In Vitro Study for the end spray (spray 120) from both the same three (3) lot of the Test Product (lots 301700, 302700, 303700) and Reference Product (lots C089739, C089150, C089155). This test was performed on reprimed samples at the 120th spray in the upright position. The geometric mean of the emitted dose of the three lots of the test product and Reference product met the acceptable range of 95 - 105% Label Claim. Enclosed is full data report.

3. The data presented in the summary above demonstrate that all geometric mean calculated results are within the specification of 95 - 105% Label Claim for Repriming

and results above in conjunction with the in-vivo study are comparable to the RLD. Therefore the 93.72% results reported in observation #4 will not affect the efficacy or performance of the product.

4. Hi-Tech commits to repeat the Priming and Repriming study as part of the initial three (3) process validation batches in comparison with three (3) lots of the RLD.

5. Hi-Tech is confident that our existing formulation and container closure system will produce a finished product which is equivalent to the RLD.

Priming/ Repriming - Label Conetent
CHARACTERIZATION STUDY (INVERTED POSITION)
Test Product Lots 301700,302700,303700
Reference Product Lot: C091550

	Mean		_Variability (%CV)_		
Product TEST or REFERENCE	Arith. (N=30)	Geo. (N=30)	Within Lot (N=10)	Between Lot (N=3)	Total (N=30)
T	98.1	98.0	4.70	5.78	4.79
R	100	99.9	4.60	NA	4.60

Single Actuation Content Through Container Life - Label Conetent
In Vitro Bioequivalence study
Test Product Lots 301700,302700,303700
Reference Product Lot: C089739, C089155, C089150

		Mean		_Variability (%CV)_			Ratio of Means _TEST/REF_		
Product TEST or REFERENCE	Factor BEG or END	Arith. (N=30)	Geo. (N=30)	Within Lot (N=10)	Between Lot (N=3)	Total (N=30)	Arith.	Geo.	p-value
R	E	96.9	96.8	1.46	7.98	2.52	.	.	.
T	E	97.3	97.2	4.37	3.69	4.33	1.00	1.00	0.6018

Reviewer's Comments:

The ratios of the test geometric means to the reference geometric means for the priming and reprming are 1.01 and 0.98, respectively (see tables below). Based on submitted data, the test and reference products have same prime and reprime retention characteristics.

Prime:

Sector	Spray	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith (N=30)	Geo (N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	1	Test	95.47	95.37	94.00	96.40	1.35	4.47	1.01	**1.01**	0.15
		Ref	94.13	94.10	2.27	3.87	0.68	2.90			

Reprime:

Sector	Spray	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith (N=30)	Geo (N=30)	(N=10)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
BEG	111	Test	93.80	93.72	2.91	5.19	1.33	4.20	0.98	**0.98**	0.01
		Ref	95.40	95.38	1.67	2.29	0.96	2.07			

The firm responses to the comment are acceptable.

Deficiency 5: *The firm's in vitro data were not submitted in SAS transport format. In the future, please submit your in vitro data in the SAS transport format.*

Firm's Response: In the future, Hi-Tech's in vitro data will be submitted in the SAS transport format.

Reviewer's Comments: The firm's response to deficiency #5 is acceptable.

E. Deficiency Comments

None.

F. Recommendations

1. The pharmacokinetic bioequivalence study # 10322808 submitted for Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per spray, by Hi Tech Pharmacal Co. Inc., comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 mcg per spray, manufactured by GlaxoSmithKline, is **acceptable**.

2. The in-vitro equivalence studies submitted for Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 mcg per spray, by Hi Tech Pharmacal Co. Inc. comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 mcg per spray, manufactured by GlaxoSmithKline, are **acceptable.**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-570 APPLICANT: Hi Tech Pharmacal Co. Inc.

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

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,

{See appended electronic signature page}

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

G. Outcome Page

ANDA: 77-570

1.	**Study Amendment**	Strength(s):	50 mcg
	(STA)	Outcome:	**AC**
	Submission Date(s)	March 14, 2007	
	Clinical Site:	N/A	
	Analytical Site:	N/A	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable

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

/s/

Bing Li
4/4/2007 02:20:03 PM
BIOPHARMACEUTICS

Moheb H. Makary
4/4/2007 02:22:10 PM
BIOPHARMACEUTICS

Barbara Davit
4/4/2007 02:46:09 PM
BIOPHARMACEUTICS

Review of a Bioequivalence Study with a Clinical Endpoint

ANDA # 77-570
Hi-Tech Pharmacal, Co., Inc.

Fluticasone Propionate Nasal Spray, 50 mcg

Nicole Lee, Pharm. D
Clinical Review Team

Submission Date:
February 7, 2005
March 7, 2005;
April 14, 2005;
April 12, 2007 (updated electronic data)

Date of Review: November 26, 2007

Table of Contents

Clinical Review for ANDA 77-570

Executive Summary

A multi-center, three arm, placebo-controlled, parallel group, randomized clinical endpoint bioequivalence study in the treatment of seasonal allergic rhinitis (SAR) demonstrates that Hi-Tech Pharmacal Co., Inc's (Hi-Tech) Fluticasone Propionate Nasal Spray, 50 mcg/spray is bioequivalent to the Reference Listed Drug, (RLD) Flonase®, as measured by the change from baseline in the reflective Total Nasal Symptom Score (TNSS). The FDA's analysis shows the 90% Confidence Interval (CI) of the change from baseline in reflective TNSS (averaged over the 7 scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment score averaged over the remaining 27 scores obtained in the 14-day randomized treatment period to be (83.0%, 114.2%) which is within the bioequivalence limits of (80%, 125%). Seven hundred sixty-eight (768) patients who met the inclusion/exclusion criteria were enrolled into the seven day placebo lead-in period. A total of 501 patients were randomized to study drug; 497 (four hundred ninety-seven) patients were included in the Intent-To-Treat (ITT) population; 432 (four hundred thirty-two) were included in the Per Protocol (PP) population analyses.

I. Recommendation on Approval

The data submitted to ANDA 77-570, using the primary endpoint of change from baseline reflective TNSS (averaged over the 7 scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment score (averaged over the remaining 27 scores obtained in the 14 day treatment period) is adequate to demonstrate bioequivalence of Hi-Tech's Fluticasone Propionate Nasal Spray with the reference listed drug, GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg. Therefore, the test product is recommended for approval.

I. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The study #70322801 was a multi-center, three arm, placebo-controlled, parallel group, randomized clinical endpoint bioequivalence study of Hi-Tech's Fluticasone Propionate Nasal Spray, 50 mcg spray to GlaxoSmithKline's Flonase® Nasal Spray, in the treatment of seasonal allergic rhinitis (SAR) as measured by the Total Nasal Symptom Score. Following a 7-day baseline placebo lead-in period, 501 patients with SAR were randomized to receive one of 3 treatments, 2 sprays in each nostril once a day for 14 days (2 weeks).

Fluticasone Propionate is indicated for the management of the nasal symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and non-allergic rhinitis in adults and pediatric patients four years of age and older. Adult patients may be started on a 200-mcg once daily regimen (two 50-mcg sprays in each nostril once daily). An alternative 200-mcg/day

dosage regimen can be given as 100 mcg twice daily (one 50-mcg spray in each nostril twice daily). Maximum total daily doses should not exceed two sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

B. Comparative Efficacy

The FDA statistical review confirmed that the 90% Confidence Interval (CI) of the test/reference ratio of the change from baseline TNSS (averaged over the 7 scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment score averaged over the remaining 27 scores obtained in the 14 day treatment period is (.830, .1142), which is within the bioequivalence limits of (0.80, 1.25), and both active products were superior to placebo (p=0.0178 for reference vs. placebo and p=0.0217 for test vs. placebo). Therefore, this study is adequate to demonstrate bioequivalence of Hi Tech's Fluticasone Propionate Nasal Spray with the reference listed drug, GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg.

C. Comparative Safety

Adverse events were collected throughout the 7-day run-in period and the 14-day treatment period. The most frequently reported adverse events (reported by more than 2% of the patients) during the placebo lead-in period were headache (6.6% of patients reported at least once) and sinus headache (3.4%).

A total of one hundred seventy-three (173) adverse events were reported (66 in the test group, 78 in the reference group, and 29 in the placebo group.) The most frequently reported adverse event was headache reported by 6.31%, 8.95% and 6.67% of the patients in the test, reference and placebo groups, respectively. The only other adverse event reported by more than 2% of any one treatment group was sinus headache (4.37% in the test group, 3.68% in the reference group and 3.81% in the placebo group.)

All were consistent with the frequency of AEs reported in the reference product labeling and they were evenly distributed among the treatment arms. Therefore, the generic formulation is no worse than the reference product with regard to drug related AEs.

Clinical Review

I. Introduction and Background

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. Flonase® (fluticasone propionate) nasal spray is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. It is indicated for the management of the nasal symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and nonallergic rhinitis in adults and pediatric patients four years of age and older. Adult patients may be started on a 200-mcg once daily regimen (two 50-mcg sprays in each nostril once daily). An alternative 200-mcg/day dosage regimen can be given as 100 mcg twice daily (one 50-mcg spray in each nostril twice

daily). Maximum total daily doses should not exceed two sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

Fluticasone propionate delivered by the intranasal route has an absolute systemic bioavailability averaging less than 2%. Intranasal treatment of patients with allergic rhinitis results in low plasma concentrations of fluticasone propionate that are not always measurable by conventional techniques. However, there are now more sensitive analytical techniques that are adequate for evaluating pharmacokinetics of this product in the blood stream. Therefore, FDA has requested a pharmacokinetic study to ensure equivalent systemic exposure.

Currently, there is a draft guidance for Industry: *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* Issued on April 2003.

A. Drug Established Name, Drug Class

Drug Established Name: Fluticasone Propionate Nasal Spray, 50 mcg
Drug Class: Corticosteroid

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug: Flonase® Nasal Spray, 50 mcg, GlaxoSmithKline. (NDA 20-121)
Date of Approval: October 19, 1994
Approved Indications: Indicated for the management of the nasal symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and nonallergic rhinitis in adults and pediatric patients four years of age and older..
Dosing Regime: Adult patients may be started on a 200-mcg once daily regimen (two 50-mcg sprays in each nostril once daily). An alternative 200-mcg/day dosage regimen can be given as 100 mcg twice daily (one 50-mcg spray in each nostril twice daily). Maximum total daily doses should not exceed two sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

C. Regulatory Background

- INDs, Protocols, and/or Control Documents submitted by this sponsor

Submission	Submission Date
00-341	August 16, 2000
01-338	June 21, 2001
02-343	June 14, 2002
P03-035	June 13, 2003

- INDs, Protocols, and/or Control Documents submitted by other sponsors

  Numerous control documents, INDs and protocols have been submitted by other sponsors.

- Previous ANDA submissions for same or related product

  Currently, 2 ANDAs have been approved for this product (76-504/Roxane and 77-538/Apotex) and others are pending review.

II. Description of Clinical Data and Sources

CRO: Novum Pharmaceutical Research Services

Study Centers

Site #	#of patients (total=501)	Principal Investigator	Location
01	50	John J. Condemi, MD	Rochester, NY
02	53	Frank Hampel, MD	New Braunfels, Texas
03	9	John Winder, MD	Sylvania, OH
04	52	Paul Ratner, MD	San Antonio, TX
05	79	Nathan Segall, MD	Stockbridge, Georgia
06	16	Gregory M. Gottschlich, MD	Cincinnati, OH
07	20	Stephen Pollard, MD	Louisville, KY
08	31	Robert Anolik, MD	Blue Bell, PA
09	36	Judson Black, MD	Atlanta, Georgia
10	45	Andrew J. Pedinoff, MD	Skillman,NJ
11	3	David L. Fried, MD	Warwick, RI
12	75	Julius van Bavel, MD	Austin, TX
13	32	Shailen R. Shah, MD	Collegeville, PA

Study Period: August 18, 2004 through November 05, 2004

Enrollment: A total of 786 patients entered the 7-day placebo lead-in period, and 501 were randomized to study drug.

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: ANDA 77-570 Vol. 3.1-3.2 and electronic submission dated March 7, 2005.
Study Amendments : April 12, 2007

B. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI inspection : Not needed. The two largest sites have already been inspected for ANDA (b) (4) (b) (4) Fluticasone Proprionate Nasal Spray.

Statistical Analysis Consult:
A summary statistical analysis was conducted by the FDA statistician, concluding that the study met bioequivalence criteria on the following primary endpoint:

Primary endpoint:
Change from baseline reflective TNSS (averaged over the 7 scores obtained on the last 3 days of the run-in period and the morning of the first day of the randomized treatment period), to the treatment score averaged over the remaining 27 scores obtained in the 14 day treatment period.

Reviewer's comment:
The firm's primary endpoint was the mean reduction in "reflective" Total Nasal Symptom Score (rTNSS) at Day 14 (or at the time of early termination) compared to Baseline (Day 1). FDA's accepted primary endpoint is change from baseline TNSS (averaged over the 7 reflective scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment score averaged over the remaining 27 reflective scores obtained in the 14 day treatment period. Thus, the FDA statistician was consulted for analysis of the firm's data using the correct primary endpoint.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards?

The sponsor reported that the study was conducted in accordance with the provisions of the Declaration of Helsinki and International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) and the Code of Federal Regulations Guidelines for Good Clinical Practice.

D. Evaluation of Financial Disclosure

Each investigator was required to submit a financial disclosure statement to the sponsor prior to the initiation of the study stating whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b). No investigator disclosed such interests. In addition, the sponsor has certified that they have not entered into any financial arrangement with the listed clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Lastly, the sponsor certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

IV. Review of Bioequivalence

A. Brief Statement of Conclusions

The FDA's analysis supports that the 90% CI of change from baseline reflective TNSS (averaged over the 7 scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment score averaged over the remaining

27 scores obtained in the 14 day treatment period is (83.0%, 114.2%), which is within the bioequivalence limits of (80%, 125%). Both active products were superior to placebo (p=0.0178 for reference vs. placebo and p=0.0217 for test vs. placebo), demonstrating that the study is sufficiently sensitive to detect a difference between products. Therefore, this study is adequate to demonstrate bioequivalence of Hi-Tech Inc.'s Fluticasone Propionate Nasal Spray with the reference listed drug, GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (protocol # 70322801) was reviewed to determine bioequivalence of the test product and the reference product. The sponsor's primary efficacy endpoint for evaluation of this product is mean reduction in "reflective" Total Nasal Symptom Score (rTNSS) at Day 14 (or at the time of early termination) compared to Baseline (Day 1). FDA's accepted primary endpoint is the mean change from baseline (the average of the seven reflective TNSS scores collected on Day 5, 6, 7 of the run-in phase, and the morning of Day 1 of the randomization phase) to the reflective TNSS averaged over the entire randomization phase. An FDA statistical consult was requested for analysis of the data using the accepted primary endpoint.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoint

Sponsor's Protocol # 70322801

Title:
A Double-Blind, Randomized, Placebo Controlled, Parallel Group, Multi-Site Study to Compare the Clinical Equivalence of Fluticasone Nasal Spray (Hi-Tech Pharmacal, Co., Inc.) with Flonase® Nasal Spray (GlaxoSmith Kline) in the Relief of the Signs and Symptoms of Seasonal Allergic Rhinitis.

Objective:
1. To evaluate the clinical equivalence of the test formulation of fluticasone propionate 50 mcg/actuation nasal spray (Hi-Tech Pharmacal Co., Inc.) to the marketed formulation Flonase® (fluticasone propionate) Nasal Spray, 50 mcg (GlaxoSmith Kline) in patients with seasonal allergic rhinitis.
2. To evaluate the clinical efficacy of the test and reference nasal sprays compared to placebo and the comparative safety of all formulations.

Study Design:
The study #70322801 was a multi-center, double-blind, placebo-controlled, parallel group, randomized clinical equivalence study of Hi-Tech's Fluticasone Propionate Nasal Spray, 50 mcg/spray to GlaxoSmithKline's Flonase® Nasal Spray, in the treatment of seasonal allergic rhinitis (SAR) as measured by the Total Nasal Symptom Score. Following a seven-day placebo lead-in period, seven hundred nineteen (719) patients with SAR were randomized to receive one of 3 treatments, 2 sprays in each nostril once a day for 14 days (2 weeks):

1. Test Product Group: Fluticasone Propionate Nasal Spray, 50 mcg (Hi-Tech Pharmacal, Co.,Inc.) Lot # 302-700

2. Reference Group: Flonase® Nasal Spray, 50 mcg, (GlaxoSmithKline.) Lot # C089739
3. Placebo/Vehicle Group: Vehicle without active drug (Hi-Tech Pharmacal, Co., Inc.) Lot # 401-700P

Study Population:

Inclusion Criteria

1. Male or non-pregnant, non-lactating females 12 years of age or older
2. A signed informed consent form which met all criteria of the current FDA regulations. For patients under the age of 18 the parent or legal guardian signed the consent form and the child was required to sign a patient "assent" form that was written in such a way as to be understandable to a child.
3. If female and of child bearing potential, had a negative urine pregnancy test at the baseline visit and prepared to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g. condom, IUS, oral, injected, transdermal or implanted hormonal contraceptives.)
4. Documented positive allergic skin scratch test, performed within the previous 12 months, to one or more of the allergens in season at the time the study was being conducted.
5. A minimum of two years of previous history of seasonal allergic rhinitis to the pollen/allergen in season at the time the study was being conducted.
6. A score of at least 6 on the Total Nasal Symptom Score (TNSS) of which the score for "nasal congestion" and at least one other individual symptom was of moderate severity (score of 2 or greater).

Exclusion Criteria

1. Under 12 years of age.
2. Females who were pregnant lactating or likely to become pregnant during the study.
3. Negative or lack of documented skin allergen scratch test (performed within the previous 12 months) to at least one of the allergens in season at the time the study was conducted. The results of all positive skin allergen scratch test results were reported.
4. Patients who suffered from chronic perennial allergic rhinitis (PAR) were excluded from the study, unless they could avoid the perennial allergen during the study and the Investigator believed that the patient's current signs and symptoms were SAR rather than chronic PAR.
5. Patients who suffered only from perennial allergic rhinitis or seasonal allergic rhinitis to a different allergen than that in season at the time the study was conducted.
6. Previous history of less than 2 years of seasonal allergic rhinitis to the pollen/allergen in season at the time the study was being conducted.
7. A total score of less than 6 on the Total Nasal Symptom Score (TNSS) or a score less than 2 for "nasal congestion", or at least one of the remaining three symptoms is not at least of moderate (score 2 or more) severity. Any patient who met the minimum TNSS requirements at the start of the placebo lead-in period but no longer met the requirements prior to the randomized active treatment period of the study was not eligible to continue in the active treatment period.

8. History of asthma over the previous two years that required chronic therapy. Occasional acute or mild exercise induced asthma was allowable on the condition that the treatment of the attacks was restricted to beta-agonists only.
9. Clinically significant nasal deformity (e.g. significantly deformed septum, nasal polyps or ulcers) or any recent nasal surgery or trauma that has not completely healed.
10. Sinus infection within the previous 30 days or history or re-occurring sinus infection.
11. Patient had started immunotherapy for any reason (including topical) or changed their dose of immunotherapy within 30 days of starting the study, or was to start immunotherapy, or change their current dose during the study.
12. Treatment for oral Candidiasis within 30 days of starting the study or had a current oral Candidiasis infection.
13. Upper respiratory tract infection within the previous 30 days.
14. Conjunctivitis or other eye infection not related to the diagnosis of SAR, within previous 14 days.
15. Use of any ophthalmic steroids within 14 days or any inhaled nasal, oral or injected steroids within 30 days of the study start. Super or high potency topical steroids could not be used during the study. The use of low potency topical corticosteroids (e.g. OTC 1% hydrocortisone) was allowed.
16. Use of long acting anti-histamines (e.g. fexofenadine, loratadine, desloratadine, cetirizine) within 10 days, intranasal cromolyn within 14 days. Other intranasal or systemic anti-histamines, or other nasal decongestants within 3 days of the start of the study.
17. Use of any tricyclic anti-depressants within 28 days of the study start (e.g. amitriptyline, nortryptyline, doxepin).
18. Patients with attention-deficit disorder being treated with methylphenidate containing products that have not been on a stable dosing regimen for at least the 30 previous days and who could remain on the same dosing regimen throughout the study.
19. Desensitization therapy to the seasonal allergen that was causing the patients allergic rhinitis within the previous 6 months.
20. Previous SAR and/or PAR that had proven unresponsiveness to steroid therapy.
21. Any known hypersensitivity to fluticasone, other steroids or any of the components of the study nasal spray.
22. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that in the Investigator's opinion would have placed the study patient at undue risk by participating or could have jeopardized the integrity of the study evaluations.
23. Receipt of any drug as part of a research study within 30 days prior to the first placebo lead-in dose.
24. Planned travel outside of the local area for more than 2 consecutive days or 3 days in total, during the patient's participation in the study.

Concurrent Medications:
The following concomitant medications were restricted while enrolled in the study:

- Any inhaled or systemic steroid or corticosteroid therapy. Any high potency topical corticosteroid therapy. Low dose topical corticosteroid therapy (e.g. OTC 1% hydrocortisone) was permitted. HRT and hormonal contraceptives were allowed during

the study as long as the patients had been on a stable dose for the 3 months prior to entering the study and throughout the study.

- Any prescription or over-the-counter medications indicated for the treatment of allergic rhinitis. Examples included, but were not limited to : systemic antihistamines, fexofenadine, loratadine, desloratadine, cetirizine, intranasal cromolyn or intranasal (e.g. azelastine), injectable or ocular anti-histamines.

- Patients who required treatment during the study with a drug that was contraindicated when taken with steroids (e.g. ketoconazole or other P450 3A4 inhibitors)

- Any patient who developed chicken pox, shingles or measles during the study was to be dropped from the study and appropriate therapy initiated. Patients were advised to avoid exposure to these diseases while using steroids.

Procedures/Observations, and safety measures

Study participants who met the inclusion/exclusion criteria for the study were required to enter a seven day single blind, placebo lead-in period prior to entering the active treatment period of the study. Only those patients who continued to meet the inclusion/exclusion criteria at the end of the placebo lead-in period were randomized to the active treatment period. Subjects who qualified for the active treatment period were randomized in a 2:2:1 ratio (Test:Reference:Placebo) to one of the three treatment groups.

All patients were provided with verbal and written instructions on the dosing procedure for the study along with a patient diary in which to record the dates and times of each dose and to record both rTNSS and iTNSS.

The following Time and Events Schedule summarizes the frequency and timing of the safety and efficacy measurements.

Time and Events Schedule

	Visit 1	Visit 2	Visit 3
	Day -7	Day 1 ±1	Day 14±2
Informed Consent	X		
Demographics			
Medical/Allergy History	X		
Physical Examination	X		
Vital Examination	X		
Concomitant Medications	X	X	X
Pregnancy Test (all Females)	X		
Patient TNSS	X	X	X

Skin scratch test	X		
Patient diaries	X	X	X
Confirm eligibility	X	X	
Adverse Events		X	X
Concomitant Medications	X	X	X
Study discharge		X (if not eligible)	X

Endpoints Description of scales or instruments used:The clinical evaluation of Total Nasal Symptom Score (TNSS) will include the following common symptoms of Seasonal Allergic Rhinitis (SAR): nasal congestion, runny nose, sneezing and itchy nose.

Each symptom was rated by the patient using the following numerical rating scale:

Score	Severity	Description
0=	No symptom	
1=	Mild symptom	Sign/symptom present, minimal
2=	Moderate symptom	Definite awareness of sign/symptom, bothersome but tolerable
3=	Severe symptom	Sign/symptom hard to tolerate, causes interference with daily activities and/or sleeping

At each assessment time point patients were required to score each symptom two ways. For the "reflective" assessment (rTNSS) the patient was required to consider the overall severity of each symptom over the last twelve hour period. For the "instantaneous" assessment (iTNSS) the patient was required to consider the severity of each symptom as they perceived their severity at the time they were completing the assessment.

Statistical analysis plan

Primary Efficacy Parameter: Using the PP population, equivalence was to be concluded if the 90% confidence interval of the ratio of the difference between Day 14 and Baseline in mean rTNSS score for the test and reference products fell within the range interval 80-125%.

Using the ITT population, both the test and reference treatment groups would be considered superior to the placebo treatment group if the mean reduction in rTNSS and iTNSS between Day 14 and Baseline was statistically significantly greater compared to the placebo group using a pre-determined level of significance of $p<0.05$.

Study Conduct

Blinding

Because the test and placebo nasal spray bottles are slightly different in shape and size than the reference product, all three products were blinded by using a plastic "overlay-container" that covered the nasal spray bottle.

The cap that covered the upper nozzle of the test/placebo/reference product test spray bottles was removed and the bottle was placed into a molded five piece plastic overlay container that fitted together to completely cover the original bottle. The overlay container worked in the same fashion as the inner bottle. The top cap was removed from the overlay container so that only the nozzle of the inner bottle was exposed. By placing two fingers on the top lip of the container and the thumb at the bottom of the container and pressing downwards the spray bottle was discharged and single spray of the inner bottle was discharged through the nozzle.

All bottles were packaged in individual boxes that were identical in appearance and had tamper seals on the top and bottom of the box. Each box had identical labels that identified the subjects by a four digit number and had room for the patient's initials and dispensing date.

Storage/Retention samples

Prior to starting the study and at any time new drug supplies were shipped, one block of study drug was removed at random by the investigative site to be held as retention samples. Retained samples were retained at the study sites. No unused or retained study drug was returned to the Sponsor.

Discussion of ITT and PP populations:

ITT (intent-to-treat): All subjects in the PPP, plus subjects who met the following criteria were included: a patient who was randomized to the active treatment period of the study, took at least one dose of study medications and recorded at least one post randomization rating scale.

PP (per-protocol): Any individual that met the following criteria:

- met the inclusion/exclusion criteria as defined in this protocol
- did not take any prohibited medications during the study
- completed Visit 3 within 12 to 16 days inclusive from the first date of medication use in the randomized portion of the study
- were compliant with the dosing requirements of the study in that they did not miss two or more consecutive study doses or three or more total doses during the randomized period
- were compliant with the dosing requirements of the study in that they did not dose more than once per day on any occasion during the randomized period
- were compliant with filling out the TNSS diary and did not miss completing more than three assessments while in the study
- because of worsening severity of SAR the patient was dropped from the study because of lack of efficacy and/or was provided with alternative (rescue) therapy.

Discussion of compliance:

Compliance was determined if a patient did not miss two or more consecutive study doses or three or more total doses during the randomized period. In addition, the patient filled out the TNSS diary and did not miss completing more than three assessments while in the study.

Demographics

There were no statistically significant differences between the three treatment groups at baseline. Therefore all statistical procedures were conducted without need for treatment group baseline corrections.

Demographic and Baseline Characteristics of Randomized Patients by Treatment Group (per sponsor)

Characteristic	**Test**		**Reference**		**Placebo**	
	n	**%**	**n**	**%**	**n**	**%**
Gender						
Male	75	36	71	37	31	30
Female	131	64	119	63	74	70
Age in years (mean±SD)	36.2 ± 15.0		35.7 ± 14.4		37.1± 14.1	
Race						
African American	30	15	28	15	18	17
Asian	2	1	4	2	3	3
Caucasian	155	75	135	71	73	70
Hispanic	17	8	22	12	10	10
Other	2	1	0	0	1	1
American Indian	0	1	1	1	0	0
Tobacco Use						
Yes	14	7	21	11	7	7
No	192	93	169	89	98	93
Primary Allergen						
Weed	203	99	184	97	100	95
Mixed Allergens	3	1	4	2	5	5
Mold	0	0	2	1	0	0
Number of years with current allergy						
(mean ± SD)	19.4 ± 13.3		17.1 ± 12.0		19.3 ± 12.7	
Baseline (Day 1) Composite Signs and Symptoms Score (mean ± SD)						
rTNSS Score	8.9 ± 1.5		8.9 ± 1.6		8.9 ± 1.6	
iTNSS Score	8.4 ± 1.9		8.4 ± 1.9		8.3 ± 1.8	

Baseline disease severity
Baseline characteristics were similar among the three treatment groups. The mean baseline reflective scores were T 8.9, R 8.9, and P 8.9 and the mean baseline instantaneous scores were T 8.4, R 8.4 and P 8.3.

Results
A total of 501 patients were randomized; 206, 190, and 105 patients were randomized to the test, reference, and placebo treatment groups, respectively. Four hundred thirty two (432) patients were eligible for inclusion in the PPP, 175 in the test group, 160 in the reference group, and 97 in the placebo group. Four hundred ninety seven (497) patients were included in the ITT analysis, 204 in the test group, 188 in the reference product and 105 in the placebo group.

Analysis of Efficacy, Superiority to Placebo (ITT population)

	Mean difference between Day 14 (or last visit if terminated early) and Baseline for rTNSS	p-value
Test	2.33	0.026
Reference	2.35	0.015
Placebo	1.70	
	Mean difference between Day 14 (or last visit if terminated early) and Baseline for iTNSS	p-value
Test	2.04	0.022
Reference	2.13	0.007
Placebo	1.42	

Analysis for Efficacy, clinical equivalence (PP population)

	Mean difference between Day 14 (or last visit if terminated early) and Baseline for rTNSS	Test to reference ratio	90% confidence interval
Test	2.35	97.73	82.67-117.33
Reference	2.40		

	Mean difference between Day 14 (or last visit if terminated early) and Baseline for iTNSS	Test to reference ratio	90% confidence interval
Test	2.03	93.28	81.37-118.63
Reference	2.18		

Reviewer's comments: *As mentioned previously, due to the firm's incorrect primary endpoint, the FDA statistician was consulted to do an analysis of primary efficacy and bioequivalence based on the accepted FDA primary endpoint.*

Reasons for Exclusion of subjects from Per-Protocol (PP) Analysis

	Test		**Reference**		**Placebo**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Randomized	**206**	100	**190**	100	**105**	100	501	**100**
Randomized/ enrolled in error	9	4.4	6	3.2	3	2.9	18	3.6
Lost to follow-up	1	0.5	2	1.1	0	0	3	0.6
Outside visit window 3	7	3.4	5	2.6	1	0.95	13	2.6
Diary/dosing compliance	13	6.3	13	6.8	3	2.9	29	5.8
Restricted med	1	0.5	3	1.6	1	0.95	5	1
Other	0	0	1	0.5	0	0	1	0.2
Per Protocol Sample	**175**	85	**160**	84.2	**97**	92.4	**432**	86.2

***Reviewer's comments*:**
The following patients were incorrectly excluded from the evaluable population:

Patients 02-020 and 09-1161 missed 2 ratings. According to the protocol, the patient can miss up to 3 ratings without being excluded. Thus, these patient should be included in the PP population.

The following patients should be excluded from the PP population due to use of prohibited medications:

06-1061(pseudoephedrine,diphenhyramine)
10-1297 (started birth control one month before treatment)
12-1269 (fexofenadine)

Patient 10-1523 was on montelukast (leukotriene receptor antagonist) 8 days prior to the start of treatment. There was no protocol specified for this category of drugs. The half life of this medication is 3-7 hours. Thus, in this reviewer's opinion, it is ok to include this patient in the PP population.

D. Bioequivalence Conclusion

According to the sponsor's analysis, the data submitted to ANDA 77-750, using the primary endpoint of mean reduction in "reflective" Total Nasal Symptom Score (rTNSS) at Day 14 (or at the time of early termination) compared to Baseline (Day 1) are adequate to demonstrate bioequivalence of Hi-Tech's Fluticasone Propionate Nasal Spray with the reference listed drug, GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg. The FDA statistical review showed that the

90% Confidence Interval (CI) of the test/reference ratio of the change from baseline TNSS (averaged over the 7 scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment score averaged over the remaining 27 scores obtained in the 14 day treatment period is (.830, .1142), which is within the bioequivalence limits of (0.80, 1.25), and both active products were superior to placebo (p=0.0178 for reference vs. placebo and p=0.0217 for test vs. placebo).

V. Comparative Review of Safety

A. Brief Statement of Conclusions

This study showed no significant difference between the generic and reference products with regard to the adverse events reported.

B. Description of Adverse Events

Adverse events were collected throughout the 7-day run-in period and the 14-day treatment period. The most frequently reported adverse events (reported by more than 2% of the patients) during the placebo lead-in period were headache (6.6% of patients reported at least once) and sinus headache (3.4%).

A total of one hundred seventy-three (173) adverse events were reported (66 in the test group, 78 in the reference group, and 29 in the placebo group.) The most frequently reported adverse event was headache that was reported by 6.31%, 8.95% and 6.67% of the patients in the test, reference and placebo groups respectively. The only other adverse event reported by more than 2% of any one treatment group was sinus headache (4.37% in the test group, 3.68% in the reference group and 3.81% in the placebo group.)

All were consistent with the frequency of AEs reported in the reference product labeling and they were evenly distributed among the treatment arms. Therefore, the generic formulation is no worse than the reference product with regard to drug related AEs.

No serious adverse events were reported during the study.

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Division of Scientific Investigations

A DSI inspection was not needed for this ANDA due to a previous inspection of 2 sites from ANDA [redacted] (b) (4). The study that is the subject of this review was completed in November 2004. Therefore, the DSI recommendations for ANDA [redacted] (b) (4) could not have been implemented prior to the conduct of this study.

The sites were [redacted] (b) (4) and [redacted] (b) (4). Both sites were issued FDA Forms 483 for failure to follow the protocol. The firms understood

the observations and agreed to make the efforts to prevent such occurrences in the future. Their final classifications were both VAI. Although there were only two sites with previous inspection history within the past three years, these two sites had the greatest amount of patients of all the sites. In addition, because these sites were inspected for studies of the same exact medication, this reviewer feels it is acceptable not to require further inspections for this ANDA.

B. Statistical Consultation

The following comments were sent to the Statistician:
1. The following patients were incorrectly excluded from the evaluable population:

Patients 02-020 and 09-1161 missed 2 ratings. According to the protocol, the patient can miss up to 3 ratings without being excluded. Thus, these patient should be included in the PP population.

Patients 08-1081, 6-1053 and 13-1498 were not on any restricted medications that would affect the outcome of this study. Thus, they should be included in the PP population.

2. The following patients should be excluded from the PP population due to use of prohibited medications:

06-1061(pseudoephedrine,diphenhyramine)
10-1297 (started birth control one month before treatment)
12-1269 (fexofenadine)

3. Patient 10-1523 was on montelukast (leukotriene receptor antagonist) 8 days prior to the start of treatment. There was no protocol-specified exclusion for this category of drugs. The half life of this medication is 3-7 hours. Thus, in this reviewer's opinion, it is ok to include this patient in the PP population.

4. A summary statistical analysis by the FDA statistician is requested on the following primary endpoint to verify for bioequivalence and efficacy (due to sponsor using an incorrect primary endpoint for their evaluation):

Change from baseline TNSS (averaged over the 7 scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment score averaged over the remaining 27 scores obtained in the 14 day treatment period.

Per the FDA Statistical analysis:

Table 1.1: Efficacy analysis for the mean change from baseline of TNSS (ANCOVA model)

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value of difference	Ref. Drug LS Mean	Placebo LS Mean	p-value of difference
Reflective	**2.6160**	**1.9592**	**0.0217**	**2.3227**	**1.7101**	**0.0178**
Instantaneous	2.2355	1.6030	0.0212	2.0666	1.4158	0.0109

The test and reference treatments were statistically significantly better than placebo for the mean change from baseline of TNSS (reflective and instantaneous) for the ITT population.

Table 1.2: Equivalence analysis for the mean change from baseline of TNSS (ANCOVA model)

			Sample mean response			Sample median response			Baseline value to pass equivalence	
Variable	Test LS mean	Ref. LS mean	Mean*	90% Confidence Interval (%) for the ratio of means	Pass /Fail	Median*	90% Confidence Interval (%) for the ratio of means	Pass /Fail	Baseline value	90% Confidence Interval (%) for the ratio of means
Reflective	**2.5784**	**2.6479**	**9.0141**	**83.0, 114.1**	**Pass**	**9.000**	**83.0, 114.2**	**Pass**	**7.43**	**80.0, 117.2**
Instantaneous	2.1531	2.2984	8.4300	*77.8, 112.3*	*Fail*	8.4286	*77.8, 112.3*	*Fail*	9.63	80.0, 110.8

Primary endpoint: Mean change from baseline of TNSS (reflective): The equivalence test passed at the sample baseline mean and baseline median of the FPP population. Table 1.2 also provides the minimum value of baseline (7.43) for which the products passed the usual equivalence test.

Secondary endpoint: Mean change from baseline of TNSS (instantaneous): The equivalence test failed at the sample baseline mean and baseline median of the FPP population (90% CI of (77.8%, 112.3%) for iTNSS at both sample mean and median). Table 1.2 also provides the minimum value of baseline (9.63) for which the products passed the usual equivalence test.

VII. Formulation

Ingredients	**Test Product**	**Flonase®**
Fluticasone Propionate	0.05 mg	0.05 mg
Benzalkonium Chloride, NF	(b) (4)	
(b) (4)		
Dextrose (b) (4)		
Polysorbate 80, NF		
Phenylethyl Alcohol, USP	0.25 mg	0.25 mg
Water, Purified, USP	Q.S.	Q.S.

*From chemistry review

***Reviewer's comments*:** *The test formulation is qualitatively and quantitatively **identical** to the reference formulation.*

VIII. Conclusion and Recommendation

A. Conclusion

The data submitted to ANDA 77-570, using the primary endpoint of change from baseline reflective TNSS (averaged over the 7 scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment

score (averaged over the remaining 27 scores obtained in the 14 day treatment period) is adequate to demonstrate bioequivalence of Hi-Tech's Fluticasone Propionate Nasal Spray, 50 mcg, with the reference listed drug, GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg.

Although the secondary endpoint, change from baseline instantaneous TNSS, fails to meet bioequivalence limits, the efficacy trend is similar. Given that the primary endpoint meets the bioequivalence limits and that the product is qualitatively and quantitatively the same as the RLD, these study results support approval of this ANDA as long as the pharmacokinetic and in vitro data are acceptable.

B. Recommendation

The results of this clinical endpoint bioequivalence study are adequate to support approval of this application provided that the pharmacokinetic and in vitro studies are also acceptable.

_____ _____
Nicole Lee, Pharm.D. Date
Clinical Reviewer
Office of Generic Drugs

_____ _____
Dena R. Hixon, M.D. Date
Associate Director for Medical Affairs
Office of Generic Drugs

_____ _____
Dale P. Conner, Pharm.D. Date
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:77-570 APPLICANT: Hi-Tech Pharmacal Co., Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg/spray

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

The data submitted to ANDA 77-570 demonstrate clinical bioequivalence of Hi-Tech Pharmacal Co., Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg/spray with the reference listed drug, Flonase Nasal Spray, using the preferred primary endpoint of change from baseline TNSS (averaged over the 7 scores obtained on the last 3 days of the placebo-run-in period and the morning of the first day of the randomized treatment period), to the treatment score averaged over the remaining 27 scores obtained in the 14 day treatment period.

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

Sincerely yours,

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

ANDA 77-570
Representative: Elan Bar
Phone: 631-789-8228 ext. 4108
Fax: 631-789-8429

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BIOEQUIVALENCY - ACCEPTABLE

submission dates:
February 7, 2005
March 7, 2005;
April 14, 2005
April 12, 2007

1. Bioequivalence Study (STU); February 7, 2005
   Strengths: 50 mcg/spray
   Outcome: **AC**
2. Bioequivalence Study Ammendment (STA); March 7, 2005
   April 14, 2005
   April 12, 2007

Please note: This review should close the BCE and BST assignments.

Outcome Decisions: AC - Acceptable
WC – Without charge
IC – Incomplete
UC - Unacceptable

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

/s/

Nicole Lee
12/4/2007 07:01:17 PM
BIOEQUIVALENCE CLINICAL END POIN

Dena Hixon
12/5/2007 02:18:01 PM
MEDICAL OFFICER

Dale Conner
12/5/2007 03:45:38 PM
BIOPHARMACEUTICS