CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076979

BIOEQUIVALENCE REVIEWS

Calcitonin Salmon
Nasal Spray, 200 IU/0.09 mL
ANDA # 76-979
Reviewer: Moheb H. Makary
W. 76979N1203

Nastech Pharmaceutical Co. Inc.
Hauppauge, NY
Submission Date:
December 23, 2003

REVIEW OF IN VITRO AND IN VIVO BIOEQUIVALENCE STUDY DATA

Executive Summary

This submission consisted of an *in vivo* bioequivalence (BE) study and *in vitro* studies.

The BE study design was a single-dose, open-label, two-way crossover study of two formulations of calcitonin-salmon administered via intranasal (IN) spray (Nastech and Novartis' Miacalcin^R) at 200 IU in normal healthy male and female subjects (N=123). The study was found unacceptable due to the deficiencies stated below.

The *in vitro* bioequivalence studies were conducted for the following tests: spray actuation content through container life, droplet size distribution by laser diffraction, drug in small particles/droplets by cascade impactor, spray pattern, plume geometry and priming and repriming. The *in vitro* data was submitted in a format that could not be reviewed. See deficiencies stated below.

Background

Miacalcin^R Nasal Spray was approved in 1995 (NDA 20-313). It is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years post-menopause with low bone mass. The recommended dose is 200 I.U. per day administered intranasally, alternating nostrils daily. The pump is designed to deliver 200 I.U. per actuation. The active ingredient calcitonin is a polypeptide hormone. Miacalcin^R is absorbed rapidly by the nasal mucosa. In healthy subjects, peak plasma calcitonin concentrations occurred 31-39 minutes after dosing. Approximately 3% of a nasally-administered dose is bioavailable compared to the same dose given by intramuscular injection. Adverse reactions seen in clinical trials and in patients include allergic reactions, alterations of the nasal mucosa, and back pain.

Relevant DBE History

Several firms have written to the Office of Generic Drugs (OGD) asking about requirements for marketing approval of a generic calcitonin salmon nasal spray product. In addition, ANDA 76-396, for Calcitonin-Salmon Nasal Spray, 200 I.U./Spray was submitted by Novex on 7/17/02 and is currently under review in the OGD.

Nastech Pharmaceutical Co. submitted a control document (02-531 dated 9/13/2002) seeking approval for a generic form of Miacalcin^{R} (calcitonin salmon) Nasal Spray. The proposed product will be labeled and used in the same way as the RLD. However, Nastech proposes to use chlorobutanol (b) (4), whereas the RLD contains benzalkonium chloride. The table below compares Nastech's formulation with that of Miacalcin^{R} Nasal Spray.

Component	RLD, amount per mL	Nastech, amount per mL
calcitonin salmon	2200 I.U.	2200 I.U.
sodium chloride	(b) (4)	(b) (4)
benzalkonium chloride		0
chlorobutanol	0	(b) (4)
nitrogen	(b) (4)	
hydrochloric acid	p.r.n.	p.r.n.
purified water	q.s.	q.s.

(b) (4)

The two products are neither Q1 nor Q2 the same. The Agency's current practice for establishing bioequivalence of generic nasal spray solution drug products is outlined in a new draft guidance for industry, *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (Nasal Spray Guidance), posted in April, 2003. The recommended approach relies on (1) Q1 and Q2 sameness of formulation of test and reference products; (2) comparability in container and closure systems; and (3) *in vitro* methods that demonstrate equivalent performance. These three criteria must be met to ensure that drug delivery to the nasal mucosa and respiratory and gastrointestinal tracts is comparable for the generic and reference product.

The firm was informed to submit its application under Section 505(j). However, it was advised that to be considered therapeutically equivalent and approvable DBE recommended that the submission should contain in addition to the *in vitro* studies, an *in vivo* bioequivalence study based on pharmacokinetic measures showing that its product is bioequivalent to the RLD. This is because (1) its product is not Q1 and Q2 the same as Miacalcin^{R}; and (2) the product is intended to act systemically. The applicant should also submit safety data on chlorobutanol.

Formulation:

Test Product

Components	Function	Formulation per 0.09 mL dose (% w/w)	ANDA Batch (b) (4)	Commercial Batch (b) (4)
Calcitonin Salmon, EP	Active	200 IU (0.033 mg)	(b) (4)	
Sodium Chloride, USP	(b) (4)			
Chlorobutanol (b) (4) NF				
Nitrogen, NF				
(b) (4) Hydrochloric Acid, NF	pH adjuster	TAP*		
Purified Water USP	(b) (4)	q.s. (q.s. to 100.00%)		
Total		**0.09 mL**		

*TAP = To adjust pH

(b) (4)

Notes:

1. Applicant provided a comparison table of the proposed levels of inactive ingredients in their formulation and those found in a previously approved drug application for the nasal route of administration. The levels of each inactive ingredient are at, or below, those found in a previously approved drug applications.

2. Applicant provided justification of safety (pp. 19-21, Vol.1.1) for the use of chlorobutanol (b) (4), NF in the place of benzalkonium chloride (used in RLD) (b) (4). A table of approved drug products with chlorobutanol (b) (4) intended for nasal administration as well as pulmonary inhalation, and ophthalmic administration is provided. An approved intranasal product (listed as "nasal spray", and "nasal spray, metered") at "maximum potencies" of 0.5% is included. A comparison table of total daily exposure to the chlorobutanol of an approved Nasal Spray (Desmopressin Acetate) and proposed Nastech's Calcitonin Salmon Nasal Spray is provided. The total daily exposure to the chlorobutanol for

Nastech's Calcitonin Salmon Nasal Spray was calculated to be less than that of an approved Nasal Spray [redacted] (b) (4).

In Vivo Study Section

Single-dose Bioequivalence Study (Failed Study)

Study Summary	
Study No.	C03-002
Study Design	Two-period, two-treatment crossover bioequivalence study
No. of subjects enrolled	123 Subjects, the study population was divided into 4 groups (Groups I, II, III and IV).
No. of subjects completing	119 (all periods)
No. of subjects analyzed	121 (all subjects who had a post-dose measurement for at least one study period were included in the Intent-To-Treat analysis)
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 56 Female: 65
Test product	Calcitonon-Salmon (Nastech) Intranasal (IN) Spray, 200 IU per activation (0.09 mL/spray)
Reference product	Miacalcin® Nasal Spray (calcitonin-salmon Novartis), 200 IU per activation (0.09 mL/spray)
Strength tested	200 IU/Spray
Dose	One IN spray administration of 200 IU calcitonin-salmon
Blood Sampling Times	Prior to dosing and at 2, 5, 10, 15, 20, 30, 35, 40, 45, 50, 60, 70, 80, 90, 120, 180 and 240 minutes postdose.
Bioanalytical Method	Plasma calcitonin-salmon levels were measured by a standard ELISA assay with LLOQ of 24 uIU/mL

The firm indicated that all Group I subjects (subject Nos. 001 to 045) were observed to have positive pre-dose levels of calcitonin for both treatments. This group also had increased values of Cmax, AUCt and AUCinf for both treatments relative to the other groups. A quality control (QC) analysis of the data indicated that the anomalous results in Group I were traceable to a single lot of aprotinin, a calcitonin protease inhibitor, used by the sponsor to prepare the blood collection tubes before sample collection. One lot of aprotinin from commercial vendor was

used for tubes for the first 45 subjects, while another lot of aprotinin from the same commercial vendor was used for blood tubes for the other subjects and for the method development and method validation work.

Statistical analyses on PK data were based on the Intent-To-Treat (ITT) population. Subjects who were included in the statistical analysis of the ITT population were all subjects who had a post-dose measurement for at least one study period. In addition, statistical analyses of PK data were also performed on the population that include all except the first 45 subjects [is referred to as the Per-Protocol (PP) subjects]. Subject Nos. 075, 084, 113 and 117 received a dose outside of the $\pm$ 20% criterion specified in the Report and Analysis Plan for one of the two treatments. The above subjects were excluded from all descriptive statistics calculations for the plasma concentration and PK parameters data in the PP population for both treatments.

Average bioequivalence was assessed by examining the 90% confidence intervals of the ln-transformed Cmax, AUCt and AUCinf for the ratio of the test group mean relative to the reference group mean. Population bioequivalence was also examined. Population bioequivalence was achieved if the ratio of the test group mean relative to the reference group mean of the ln-transformed Cmax, AUCt and AUCinf were contained within the interval 80% to 125% and the upper bound of the 95% confidence intervals of the linearized criteria (referenced -scaled or constant-scaled) of the ln-transformed Cmax, AUCt and AUCinf were strictly less than zero.

Pharmacokinetic parameters results for ITT Population:

Pharmacokinetic Parameters	Test Mean (SD) Nastech, Trt A	Reference Mean (SD) Miacalcin[R], Trt B
Cmax (UIU/mL)	211 (157.4)	228 (145.4)
AUCt (uIU.hr/mL)	280 (245.7)	275 (242.1)
AUCinf (uIU.hr/mL)	1822 (6899.2)	823 (1352.5)
T1/2 (hr)	8.16	3.34
Tmax (hr)*	0.25	0.25

*Median (min, max) shown for Tmax

Parameters	N[a]	Test Mean[b]	Reference Mean[b]	Point Estimate[c]	90% CI[d]	Upper Bound[e]
lnCmax (UIU/mL)	121	163	183	89.4	(80.6, 99.1)	-0.626
lnAUCt (uIU.hr/mL)	121	128	139	92.2	(81.1, 105)	-2.37
lnAUCinf (uIU.hr/mL)	171	284	291	97.5	(84.9, 112)	-0.164

[a] Total number of subjects used in the statistical analysis

[b] Least squares mean from ANOVA. Natural log parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means)

[c] Ratio of parameter mean for ln-transformed parameters (expressed as a percent). Ln-transformed ratios transformed back to linear scale.

[d] 90% confidence interval for ratio of parameter means of ln-transformed parameters (expressed as percent). Ln-transformed confidence limits transformed back to linear scale.

[e] Upper bound based on mixed scaling approach recommended in the FDA Guidance (Guidance for Industry *"Statistical Approaches to Establishing Bioequivalence"* January 2001)

Based on the above results, the firm stated that the 90% confidence intervals for natural log transformed PK parameters are all contained within the (80-125) average bioequivalence range. The point estimate for the test to reference geometric mean ratio was between 80 and 125% and the upper bound for the population bioequivalence criterion was below zero for all parameters, suggesting population bioequivalence for calcitonin. However, given the potential for bias in PK parameters for all Group I subjects, these ITT results should be interpreted with caution and may not be appropriate for drawing bioequivalence conclusions from this study.

Pharmacokinetic Parameter Results for PP Population:

Pharmacokinetic Parameters	Test Mean (SD) Nastech, Trt A	Reference Mean (SD) Miacalcin[R], Trt B
Cmax (UIU/mL)	185 (184.7)	204 (159.1)
AUCt (uIU.hr/mL)	91.1 (101.8)	97.7 (85.3)
AUCinf (uIU.hr/mL)	110 (103.1)	120 (85.0)
T1/2 (hr)	0.282	0.267
Tmax (hr)*	0.167	0.167

*Median (min, max) shown for Tmax

Parameters	N[a]	Test Mean[b]	Reference Mean[b]	Point Estimate[c]	90% CI[d]	Upper Bound[e]
lnCmax (UIU/mL)	72	131	151	87.0	(73.4, 103)	-0.78
lnAUCt (uIU.hr/mL)	72	54.2	61.3	88.4	(71.1, 110)	-1.62
lnAUCinf (uIU.hr/mL)	69	81.1	91.6	88.6	(75.8, 104)	-0.133

[a] Total number of subjects used in the statistical analysis

[b] Least squares mean from ANOVA. Natural log parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means)

[c] Ratio of parameter mean for ln-transformed parameters (expressed as a percent). Ln-transformed ratios transformed back to linear scale.

[d] 90% confidence interval for ratio of parameter means of ln-transformed parameters (expressed as percent). Ln-transformed confidence limits transformed back to linear scale, based on average bioequivalence.

[e] Upper bound based on mixed scaling approach recommended in the FDA Guidance(Guidance for Industry *"Statistical Approaches to Establishing Bioequivalence"* January 2001)

Based on the above results, the firm indicated that using the population bioequivalence approach, the point estimate for the test to reference geometric mean ratio was between 80 and 125% and the upper bound for the population bioequivalence criterion was below zero for all parameters. These data meet the criteria for demonstrating population bioequivalence for test and reference products for the PP population.

The Per Protocol (PP) population (72 subjects) was also evaluated by average bioequivalence criteria. The firm stated that as expected for a reduced data set size for a highly variable product, the log-transformed PK parameters are not contained within the (80, 125) average bioequivalence range for the PP population (72 subjects).

The firm concluded that for the PP population (72 subjects), the results from this study indicate bioequivalence of the test and reference calcitonin-salmon nasal spray based on population bioequivalence criterion.

In Vitro Section

Drug Products:

The test product, Nastech Pharmaceutical Company Inc. Calcitonin Nasal spray, consisted of one lot of bulk drug product (lot #03008) which was sublotted into three sublots with actuators from three different lots of pump/actuators units to the primary container. The reference product consisted of four (4) lots of Miacalcin^{R} Nasal Spray. The specific lot numbers used for each test are listed in Table 1.

Test	Lot Numbers	
	Nastech Calcitonin	Miacalcin^{R}
Single actuation content through container life	2054N-00929-1 2054N-00930-1 2054N-00978-1	009H8661 012H8664 042G7921
Droplet size distribution by laser diffraction	2054N-00929-1 2054N-00930-1 2054N-00978-1	001H9917 009H8861 042G7921
Droplet size by cascade impaction	2054N-00929-1 2054N-00930-1 2054N-00978-1	001H9917 009H8861 042G7921
Spray pattern	2054N-00929-1 2054N-00930-1 2054N-00978-1	001H9917 009H8861 042G7921
Plume geometry	2054N-00929-1 2054N-00930-1 2054N-00978-1	001H9917 009H8861 042G7921
Priming and repriming	2054N-00929-1 2054N-00930-1 2054N-00978-1	001H9917 009H8861 042G7921

The *in vitro* bioequivalence data were submitted on compact disks in PDF format. The *in vitro* data could not be reviewed in such format. The firm is advised to submit all *in vitro* bioequivalence data on CDs or floppy diskettes in SAS transport and xls formats.

Deficiency Comments

1. Subjects Nos. 001 to 045 (Group I subjects) were observed to have positive pre-dose levels of calcitonin for both treatments. The predose value for each

subject was more than 5 percent of his Cmax. In addition, these subjects also had increased values of Cmax, AUCt and AUCinf for both treatments relative to the other non-Group I subjects. For subjects with predose plasma concentrations, the CDER Guidance *"Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations"* (3/2003), recommends that if the predose value is more than 5 percent of Cmax, the subject be dropped from all BE study evaluations. Also, since the firm presented evidence suggesting that the sampling tubes from subjects #001 to 045 may have been contaminated, it is not possible to determine what the true caltinonin plasma concentrations were in this group of subjects. Therefore, subject Nos. 001 to 045 should be excluded from the statistical analysis of the study. Based on average bioequivalence criteria, after excluding these subjects from the study the 90% confidence intervals for log-transformed AUCt, AUCinf and Cmax do not fall within the acceptable 80-125% range. Therefore, the bioequivalence study #C03-002 is unacceptable.

2. For pharmacokinetic studies, the CEDR Guidance *"Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations"* (3/2003), recommends use of an average bioequivalence criterion to compare bioavailability measures for replicate and nonreplicate bioequivalence studies of both immediate- and modified-release products. In addition, the Agency has not implemented the use of population bioequivalence approach for pharmacokinetic-bioequivalence studies. Therefore, using population bioequivalence criteria for drawing bioequivalence conclusions for this study is unacceptable.

3. The *in vitro* bioequivalence data were submitted on compact disks in PDF format. The *in vitro* data could not be reviewed in such format. The firm is advised to submit all *in vitro* bioequivalence data on CDs or floppy diskettes in SAS transport and xls formats.

4. The firm did not provide the expiration dates for the 4 lots of the reference product used in the *in vitro* bioequivalence studies.

Recommendations

1. The *in vivo* bioequivalence study conducted by Nastech Pharmaceutical Co. Inc., on its Calcitonin Salmon Nasal Spray, 200 IU/0.09 mL, lot # 03008 , comparing it to Novartis' Miacalcin^{R} Nasal Spray, 200 IU/Spray, lot # H3001, is unacceptable for the reasons given in deficiency comments 1&2.

2. The *in vitro* performance data submitted by Nastech Pharmaceutical Co. Inc. on its Calcitonin Salmon Nasal Spray, 200 IU/0.09 mL, is incomplete due to the deficiency comments 3 and 4.

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

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch IV

Kuldeep R. Dhariwal, Ph.D. Date 11/18/04
Team Leader, Branch IV

Concur: Date: 11/18/04
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

MMakary/11-2-04, 76979N1203.doc
cc: ANDA #76-979, original, HFD-658 (Makary), Drug File, Division File.

V:\FIRMSNZ\NASTECH\LTRS&REV\76979N1203.doc

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-979 APPLICANT: Nastech Pharmaceutical Co. Inc.

DRUG PRODUCT: Calcitonin Salmon Nasal Spray, 200 IU/0.09 mL

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

In Vivo Study Section

1. Group I subjects (#001 to 045) in study #C03-002 had measurable levels of calcitonin in predose samples of period 1 as well as period 2. These predose values for each subject were more than 5 percent of their Cmax. In addition, these subjects also had higher Cmax, AUCt and AUCinf values for both treatments compared to the other non-Group I subjects. The CDER Guidance *"Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations"* (3/2003), recommends that if the predose value is more than 5 percent of Cmax, the subject be dropped from all bioequivalence (BE) study evaluations. Also, since you present evidence suggesting that the sampling tubes from subjects #001 to 045 may have been contaminated, it is not possible to determine what the true caltinonin plasma concentrations were in this group of subjects. Therefore, subject Nos. 001 to 045 should be excluded from the statistical analysis of the study. Based on average bioequivalence criteria, the 90% confidence intervals for log-transformed AUCt, AUCinf and Cmax do not fall within the acceptable 80-125% range after excluding these subjects from the study. Therefore, the bioequivalence study #C03-002 is unacceptable.

2. For pharmacokinetic studies, the CDER Guidance *"Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations"* (3/2003), recommends use of an average bioequivalence criterion to compare bioavailability measures for replicate and nonreplicate bioequivalence studies of both immediate- and modified-release products. In addition, the Agency has not implemented the use of population bioequivalence approach for pharmacokinetic-bioequivalence studies. Therefore, the use of population bioequivalence criterion

for drawing bioequivalence conclusions for this study is unacceptable.

In Vitro Study Section

1. The *in vitro* bioequivalence data were submitted on compact disks in PDF format. The *in vitro* data could not be reviewed in such format. Please submit all *in vitro* bioequivalence data on CDs or floppy diskettes in SAS transport and xls formats.

2. Please provide the expiration dates for the 4 lots of the reference product used in the in vitro bioequivalence studies.

Sincerely yours,

Barbara M Davit

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

CC: ANDA #76-979
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

V:\FIRMSNZ\NASTECH\LTRS&REV\76979N1203.doc
Printed in final on 11/18/04

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MMM
HFD-658/ Bio team Leader K. Dhariwal 11/18/04
HFD-652/ Bio GJP Singh 11/18/04
HFD-650/ D. Conner BW 11/18/04

BIOEQUIVALENCE - DEFICIENCIES

Submission Date: 12/23/2003

✓1.	Study (STA)	Strength: 200 IU/0.09 mL Outcome: IC
✓2.	Study (STA)	Strength: 200 IU/0.09 mL Outcome: IC
✓3.	Study (STA)	Strength: 200 IU/0.09 mL Outcome: IC
✓4.	Study (STA)	Strength: 200 IU/0.09 mL Outcome: IC
✓5.	Bioequivalence Study	Strength: 200 IU/0.09 mL Outcome: ~~IC~~ UN

Outcome Decisions:
IC - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-979
Drug Product Name	Calcitonin Salmon Nasal Spray
Strength	200 IU/0.09 mL
Applicant Name	Nastech Pharmaceutical Company Inc.
Address	3450 Monte Villa Parkway, Bothell, WA 98021
Submission Date(s)	12/10/2004
Amendment Date(s)	4/26/2005, 8/29/2005
Reviewer	Devvrat Patel
First Generic	No
File Location	V:\firmsnz\nastech\ltrs&rev\76979A1204.doc

Review of an Amendment

I. Executive Summary

The firm submitted several amendments in response to the following deficiency comments communicated earlier by the Division of Bioequivalence (DBE): Unacceptable in vivo bioequivalence study; in vitro test data in an unacceptable electronic format; and the expiration dates for the four lots of the reference product used in the in vitro studies (Review file: 76979N1203.doc) were not provided.

The fill size for the reference listed drug (RLD) was changed on 8/22/2003. The RLD is now marketed as 30 dose product instead of the previously approved 14 dose product (NDA 20-313, SCS-023).

Nastech submitted amendments to propose addition of 30 day product. The firm provided the requested electronic data files for all in vitro tests conducted on 14 day and 30 day products. Additionally, the firm conducted two in vivo bioequivalence studies (C04-002 and C04-006).

The C04-002 bioequivalence study design was not a standard design, and therefore, the reviewer did not analyze the data. The DBE requested a statistical consult on 7/11/2005 for analyzing bioequivalence data. As per statistical consult (attached under in Section E), the 90% confidence intervals for AUCt are outside the acceptable limits of 80-125%. Therefore, the study is not acceptable. However, since the study enrolled only 22 subjects, it is likely that this study did not have adequate statistical power to demonstrate bioequivalence.

The C04-006 bioequivalence study was a randomized, replicate design study in 192 (199 enrolled) healthy male (69) and female (123) subjects given a dose of 200 IU/0.09 mL actuation in the right nostril. Subjects were dosed in two groups. Since the treatment*group interaction

was statistically significant for log-transformed Cmax, the reviewer analyzed the two groups separately. The results (point estimate, 90% CI) of Group 1 are $LAUC_{0-t}$ 0.93, 80.54-107.84%; $LAUC_{0-\infty}$ 1.02, 90.78-113.84%; LC_{max} 0.92, 83.60-101.59%; and the results of Group 2 are $LAUC_{0-t}$ 1.06, 91.79-122.90%; $LAUC_{0-\infty}$ 1.09, 97.52-121.50%; LC_{max} 1.03, 94-01-113.79%. The 90% confidence intervals remain within the acceptable limits if the two groups are combined.

Additionally, the reviewer reanalyzed data and included only the subjects having at least four consecutive non-zero plasma concentration values. The results of Group 1 are $LAUC_{0-t}$ 1.02, 90.03-115.72%; $LAUC_{0-\infty}$ 1.00, 89.11-112.23%; LC_{max} 0.98, 88.26-108.11%. The results of Group 2 are $LAUC_{0-t}$ 1.00, 88.18-112.95%; $LAUC_{0-\infty}$ 1.09, 97.80-122.02%; LC_{max} 0.99, 90.01-109.83%. The in vivo bioequivalence study is incomplete due to deficiencies noted in Section F. The bioequivalence conclusions in this ANDA are based on this study for the reasons given on page 59.

Consistent with the recommendations made in the revised Draft Nasal BA/BE Guidance issued on 4/3/2003, the in vitro bioequivalence studies were conducted on the following tests for both 14 dose and 30 dose products: Single Actuation Content Through Container Life, Droplet Size Distribution by Laser Diffraction, Drugs in Small Particles/Droplets by Cascade Impactor (for 14 dose product only), Spray Pattern, Plume Geometry, and Priming. The in vitro studies were reviewed, but will not be used to document bioequivalence for the reasons given on page 10.

The application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Calcitonin Salmon Nasal Spray, 200 IU/0.09 mL
Reference Product	Miacalcin® Nasal Spray, 200 IU/0.09 mL
RLD Manufacturer	Novartis
NDA No.	20-313
RLD Approval Date	August 17, 1995
Indication	Indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years post-menopause with low bone mass.

B. PK/PD Information

Bioavailability	The data on bioavailability using different methods show great variability. Miacalcin nasal spray is absorbed rapidly by the nasal mucosa. In normal volunteers approximately 3% (range 0.3%-30.6%) of a nasally administered dose is bioavailable compared to the same dose administered by intramuscular injection.
Food Effect	Not applicable
Tmax	Peak plasma concentrations of drug appear 31-39 minutes after nasal administration.
Excretion	There is no accumulation of the drug on repeated nasal administration at 10 hour intervals for up to 15 days.
Half-life	The half-life of elimination is approximately 43 minutes.
Relevant OGD or DBE History	The DBE reviewed ANDA 76-396 for calcitonin salmon nasal spray (Novex Pharma, Submission Date: 4/5/2002). Additionally the DBE has reviewed the following control documents: 98-217 ((b) (4) 6/4/1998); 01-455 ((b) (4) 9/4/2001); 02-590 ((b) (4) 11/13/2002); 02-531 (Nastech, 9/13/2002).
Agency Guidance	None
Drug Specific Issues	N/A

C. Contents of Submission

Studies	Y/N	How Many
Single Actuation Content Through Container Life	Y	2
Priming and Re-priming	Y	2

Droplet Size Distribution by Laser Diffraction	Y	2
Drug in Small Particles / Droplets by Cascade Impactor	Y	1
Particle / Droplet Size Distribution by Cascade Impactor (aerosol only)	N	--
Drug Particle Size Distribution by Microscopy (suspension only)	N	--
Spray Pattern	Y	2
Plume Geometry	Y	2
In Vivo Bioequivalence Studies (PK Studies)	Y	2

Initial submission dated 12/23/2003 was incomplete because of the following reasons: In vivo bioequivalence study was not acceptable, the firm did not submit in vitro bioequivalence data in acceptable electronic format, and the firm did not provide the expiration dates for the four lots of the reference product used in the in vitro studies (Review file: 76979N1203.doc).

The firm submitted the following amendments in response to the deficiencies noted above:

Amendment Date	**Description**
10/14/2004	The firm submitted an amendment for the addition of 3.8 mL fill for 30 day use.
12/10/2004	The firm provided the requested electronic data files in SAS transport file format. The firm submitted datasets for in vitro studies conducted on (b) (4) mL fill size (14 days product) and 3.8 mL fill size (30 days product).
4/26/2005	The firm provided data for additional in vivo bioequivalence study (C04-002).
8/29/2005	The firm submitted new in vivo bioequivalence study (C04-006) on 30 dose products.
11/29/2005	The firm provided in vivo bioequivalence study (C04-006) datasets in proper format and structure.

Initial submission was for calcitonin nasal spray containing 200 IU per 0.09 mL actuation. Each bottle was filled with 1.6 mL of solution designed to provide 14 doses, one spray per daily administration. The actuator is metered multiple dose nasal actuator from (b) (4) delivering 0.09 mL per spray. It is noted that the RLD 14 day presentation contains 2.0 mL of solution, whereas, the proposed test product contains 1.6 mL of solution.

The innovator submitted supplemental NDA (20-313, SCS-023, 4/21/2003) and proposed a larger 7 mL vial containing 3.7 mL of solution to deliver 30 doses instead of the previously approved 14 doses (2 mL). As per the NDA Chemist's Review, no changes were planned concerning the glass vial quality and supplier, the drug solution (composition and manufacturing), the rubber stopper, the flip tear-off cap and the nasal pump. The supplemental application was approved on 8/22/2003.

Therefore, Nastech submitted an amendment for the addition of 3.8 mL fill for 30 day use. The firm provided 30 day product in vitro bridging studies to support a change in fill size. The 30 day package uses [redacted] (b) (4) Clear Glass Bottle [redacted] (b) (4) or [redacted] (b) (4) Clear Glass Bottle with identical screw cap used for the 14 dose product. It also uses identical actuator that is packaged with the 14 dose product.

As per the labeling review, based on the in vitro spray actuation content through container life study, the firm proposes a fill of 3.8 mL to ensure 30 doses plus priming sprays. It is noted in the labeling review that when the ANDA was originally submitted, the RLD only had the 14 day presentation. The 30 day presentation was later approved for the RLD. Ultimately, Nastech will only market the 30 day presentation although the firm is requesting an approval for the 14 day presentation as well (Review file: 76979.ap.L.doc).

D. Pre-Study Bioanalytical Method Validation

	Parcnt
Analyte name	Calcitonin
Internal Standard	N/A
Method description	Enzyme Linked Immunosorbent Assay (ELISA)*
QC range	4 pg/mL to 64.0 pg/mL
Standard curve range	4.00 pg/mL to 64.0 pg/mL
Limit of quantitation	4.00 pg/mL
Average recovery of Drug (%)	N/A
Average Recovery of Int. Std (%)	N/A
QC Intraday precision range (%)	3.88% to 16.5%
QC Intraday accuracy range (%)	83.2% to 101.3%
QC Interday precision range (%)	5.45% to 11.3%
QC Interday accuracy range (%)	96.6% to 116.6%
Bench-top stability (hrs)	24 hours at 0-5°C
Stock stability (days)	N/A
Processed stability (hrs)	N/A
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	594 days at -80 °C
Dilution integrity	1:10
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

* The method involved isolation and purification of salmon calcitonin from human EDTA plasma by protein precipitation. Subsequently, salmon calcitonin was quantified by an ELISA. [redacted] (b) (4)

[redacted] (b) (4) Data were generated using endpoint analysis.

E. In Vivo Studies

1. Single-dose Bioequivalence Study

Study Summary, Bioequivalence Study	
Study No.	C04-002
Study Design	Randomized, single-dose, 8-period crossover
No. of subjects enrolled	22
No. of subjects completing	21
No. of subjects analyzed	21
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 10 Female: 11
Test product	Calcitonin salmon nasal spray
Reference product	Miacalcin® Nasal Spray
Strength tested	200 IU/0.09 mL actuation
Dose	1 x 200 IU/dose

Summary of Statistical Analysis, Fasting Bioequivalence Study
Since the bioequivalence study design was not standard, the DBE requested statistical consult for analyzing bioequivalence data for this study (Consult was requested on 7/11/2005). As per statistical consult (attached in Section E), the 90% confidence intervals for AUCt are outside the acceptable limits of 80-125%. Therefore, the study is not acceptable. Additionally, the firm submitted another in vivo bioequivalence study (C04-006) conducted in 199 subjects. The study #C04-006 was reviewed in detail.

Reanalysis of Study Samples, Fasting Bioequivalence Study				
Reason why assay was repeated	**Number of samples reanalyzed**		**Number of recalculated values used after reanalysis**	
	Actual number	**% of total assays**	**Actual number**	**% of total assays**
Analytical repeats	201	13.0	201	13.0
Pharmacokinetic repeats	0	0	0	0
Total	**201**	**13.0**	**201**	**13.0**

Number of samples analyzed: 1548

Did use of recalculated plasma concentration data change study outcome? No. There were no pharmacokinetic repeats.

2. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	C04-006
Study Design	Randomized, Replicate, Four periods, Two sequences
No. of subjects enrolled	199
No. of subjects completing	192
No. of subjects analyzed	192
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 69 Female: 123
Test product	Calcitonin salmon nasal spray
Reference product	Miacalcin® Nasal Spray
Strength tested	200 IU/0.09 mL actuation
Dose	1 x 200 IU/dose

Subjects were dosed in two groups. Since the treatment*group interaction was statistically significant for log-transformed Cmax ($p<0.1$), the two groups were analyzed separately by the reviewer. Summary of statistical analysis of two individual groups are provided below:

Group 1 (N=98)

Summary of Statistical Analysis, Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_{0-t}$	0.93	80.54 – 107.84
$LAUC_{0-\infty}$	1.02	90.78 – 113.84
LCmax	0.92	83.60 – 101.59

Group 2 (n=91)

Summary of Statistical Analysis, Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_{0-t}$	1.06	91.79 – 122.90
$LAUC_{0-\infty}$	1.09	97.52 – 121.50
LCmax	1.03	94.01 – 113.79

The reviewer reanalyzed data and included only the subjects having at least four consecutive non-zero plasma concentration values for determination of pharmacokinetic parameters and statistical analysis. The results are provided below:

Group 1 (n=78)

Summary of Statistical Analysis, Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_{0-t}$	1.02	90.03 – 115.72
$LAUC_{0-\infty}$	1.00	89.11 – 112.23
LCmax	0.98	88.26 – 108.11

Group 2 (n=81)

Summary of Statistical Analysis, Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_{0-t}$	1.00	88.18 – 112.95
$LAUC_{0-\infty}$	1.09	97.80 – 122.02
LCmax	0.99	90.01 – 109.83

Reanalysis of Study Samples, Fasting Bioequivalence Study				
Reason why assay was repeated	**Number of samples reanalyzed**		**Number of recalculated values used after reanalysis**	
	Actual number	**% of total assays**	**Actual number**	**% of total assays**
Analytical repeats*	1327	13.1	1327	13.1
Pharmacokinetic repeats	0	0	0	0
Total	**1327**	**13.1**	**1327**	**13.1**

Number of samples analyzed: 10122

* Samples were re-assayed due to following possible analytical abnormalities: unacceptable quality control results, quantifying below a raised lower limit of quantification, quantifying above the calibration range, unacceptable calibration curve, unacceptable %CV between replicates, unacceptable dilution QC results, unacceptable high matrix blank.

Did use of recalculated plasma concentration data change study outcome? No. There were no pharmacokinetic repeats.

Comments on In Vitro Tests:

For this product, the DBE requests that firms document bioequivalence by in vitro testing only if the test and RLD products are qualitatively and quantitatively the same. Because this product does not have the same inactive ingredients as the RLD, the DBE asked the firm to conduct an in vivo study. In addition, because this drug is active systemically, in vivo bioequivalence can support a determination that this product is therapeutically equivalent to the RLD. Therefore, only an in vivo study is necessary to document bioequivalence. The in vitro studies were reviewed, but findings from the in vitro studies will not be used to document bioequivalence for this product.

F. Deficiency Comments

In Vivo Bioequivalence Studies:

1. The in vivo bioequivalence study (C04-002) is not acceptable because the 90% confidence intervals for LAUCt are outside the acceptable limits of 80-125%.

2. The following comments and requests for information pertain only to bioequivalence study C04-006:

   - The firm should provide content uniformity data for the test product used in the study.

   - In the Clinical Study Report, pages 49, and 52, the firm reported 11 adverse events following administration of Miacalcin®. According to Table 12.2.2-1, Summary of Distinct Subjects with Adverse Events by Treatment and Preferred Term, 10 adverse events were reported following administration of Miacalcin®. The firm should clarify the discrepancy.

   - The subjects in group 2, periods 2, 3 and 4 were dosed on 4/1/2005, 4/2/2005 and 4/3/2005 respectively. Sample analysis began on 4/1/2005. 2005). The firm should note that analysis of blood samples should be initiated after the completion of clinical portion of the in vivo bioequivalence study.

   - The firm should provide a summary table stating the dates the individual subject samples were analyzed.

G. Recommendations

1. The in vivo bioequivalence study (C04-002) conducted by Nastech on its calcitonin salmon nasal spray, 200 IU/0.09 mL, comparing it to the reference product, Miacalcin® Nasal Spray, 200 IU/0.09 mL, is not acceptable.

2. The *in vivo* bioequivalence study (C04-006) conducted by Nastech on its calcitonin salmon nasal spray, 200 IU/0.09 mL (30 dose product), comparing it to the reference product Miacalcin® Nasal Spray, 200 IU/0.09 mL (30 dose product), is incomplete due to deficiencies noted above.

3. In vitro tests are incomplete due to deficiencies noted above.

Devvrat Patel 8/3/2006

Devvrat Patel, Pharm.D. Date Signed
Division of Bioequivalence, Branch V

Dhariwal 8/3/2006

Kuldeep R. Dhariwal, Ph.D. Date Signed
Team Leader
Division of Bioequivalence, Branch V

for Barbara Davit 8/3/06

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

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

A. Study Design

Study Information	
Study Number	C04-002
Study Title	A phase 1, 8-period crossover, pharmacokinetic study of two formulations of salmon calcitonin administered via intranasal spray (Nastech and Miacalcin®) in normal healthy male and female subjects
Clinical Site	Diabetes and Glandular Diseases Research, 5107 Medical Drive, San Antonio, TX 78229
Principal Investigator	Sherwyn Schwartz, MD
Study/Dosing Dates	3/22/2004 – 4/19/2004
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	4/19/2004 to 5/5/2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	44 days

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Calcitonin salmon nasal spray	Miacalcin®
Manufacturer	Nastech	Novartis
Batch/Lot No.	03012	045H2472
Manufacture Date	8/6/2003	N/A
Expiration Date	N/A	Not provided
Strength	200 IU/dose (14 doses per bottle)	200 IU/dose (28 doses per bottle)
Dosage Form	Nasal spray	Nasal spray
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.3%	102.1%
Content Uniformity (mean, %CV)	Not provided	Not provided
Formulation	See Appendix	N/A
Dose Administered	200 IU/dose	200 IU/dose
Route of Administration	Nasal	

No. of Sequences	2
No. of Periods	8
No. of Treatments	2
No. of Groups	1
Washout Period	20 hours
Randomization Scheme	Sequence A: 1, 3, 5, 8, 10, 12, 14, 15, 18, 19, 22, 23, 26, 27 Sequence B: 2, 4, 6, 7, 9, 11, 13, 16, 17, 20, 21, 24, 25, 28 Sequence A: Test-right, Ref-left, Ref-right, Test-left, Test-right, Ref-left, Ref-right, Test-left Sequence B: Ref-right, Test-left, Test-right, Ref-left, Ref-right, Test-left, Test-right, Ref-left
Blood Sampling Times	0, 5, 10, 15, 20, 25, 30, 45 and 60 minutes post-dose.
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	The blood samples were collected in EDTA coated Vacutainers.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Not applicable
Length of Confinement	Approximately 2 hours prior to treatment period 1, subjects reported to the clinic and remained in the clinic for 2 hours post-dose. For treatment periods 2-8, subjects reported to the clinic 1 hour prior to dosing and remained in the clinic for 2 hours post-dose.
Safety Monitoring	Clinical laboratory evaluations, physical examination, nasal examinations, 12-lead ECGs, and vital signs were performed at screening. Subjects were monitored throughout the confinement for adverse reactions.

b) Clinical Results

Table 1 Demographics of Study Subjects

Age (years)		Weight (kg)		Age Groups		Gender		Race*	
				Range	%	Sex	N (%)	Category	%
N	21	N	21	<18	0			Caucasian	27.3
Mean	40.0	Mean	85.3	18-40	52.4	Male	10 (47.6)	Afr. Amer.	18.2
SD		SD		41-64	47.6	Female	11 (52.4)	Hispanic	54.5
Min	19.1	Min	57.7	65-75	0			Asian	0.0
Max	64.2	Max	120.3	>75	0			Others	0.0

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
21	Subject used concomitant medications during treatment period	5	N

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Ear pain	0	2
Nausea	1	2
Vomiting	0	1
Asthenia	0	1
Dizziness	0	2
Headache	1	1
Pharyngitis	2	1
Total:	**4**	**10**

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
None	--	--

Comments on Dropouts/Adverse Events/Protocol Deviations:

No serious adverse events occurred during the conduct of the study.

There were no other protocol deviations in this study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent						Metabolite			
QC Conc. (pg/mL)		12.0		24.0	36.0		N/A			
Inter day Precision (%CV)		10.2		9.69	10.5					
Inter day Accuracy (%)		101.8		95.9	94.3					
Cal. Standards Conc (pg/mL)	1.00	2.00	4.00	8.00	10.0	16.0	20.0	32.0	48.0	64.0
Inter day Precision (%CV)	78.8	22.9	7.19	7.83	6.20	5.44	2.98	3.65	3.32	1.29
Inter day Accuracy (%)	57.1	101.5	111.9	96.7	101.1	98.1	102.0	99.7	100.1	99.9
Linearity Range (range of R^2 values)	0.9917 to 1.000									

Any interfering peaks in chromatograms?	N/A (ELISA method was used.)
Were 20% of chromatograms included?	N/A
Were chromatograms serially or randomly selected?	Serial

Comments on Chromatograms:

Chromatograms were not applicable.

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

SOP No.	Date of SOP	SOP Title
LP-BA-002	12/15/2002	Guidelines for Excluding Data from Bioanalytical Assays
LP-BA-012	4/1/2004	Conduct of an Analytical Method
LP-PAL-1013	3/1/2003	Preparation of Quality Control Pools for Immunoassays
LP-PAL-1017	3/1/2003	Calibration Standards: Preparation and Acceptance Criteria for Immunoassays

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

The firm provided SOPs for the repeat assays and analytical method. Samples were reassayed as per the SOPs.

d) Pharmacokinetic Results

Comments on Pharmacokinetic and Statistical Analysis:

The firm conducted statistical analysis using two methods and the firm's results are provided below:

1. The 90% confidence intervals when the results for each parameter within each preparation and subject were averaged before the analysis in terms of the ratio of test to reference are as follows: Cmax: 85.5-109.2%; AUCt: 82.3-111.8%; AUCi: 90.4-123.6%.

2. The 90% confidence intervals based on antilog of the results for the difference in log means taking all data pairs obtained as separate pairs for each individuals are as follow: Cmax: 84.2-113.3%; AUCt: 79.3-114.6%; AUCi: 91.2-127.2%.

The Division of Bioequivalence requested statistical consult for analyzing bioequivalence data for this study.

As per the statistical consult (attached under attachment section), the 90% confidence intervals for AUCt are outside the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

As per the statistical consult report, the 90% confidence intervals for AUCt are outside the acceptable limits of 80-125%. Therefore, Study C04-002 is not acceptable.

The firm submitted another bioequivalence study (C04-006) which is reviewed in detail (see below).

2. Single-dose Bioequivalence Study (C04-006)

A. Study Design

Study Information	
Study Number	C04-006
Study Title	A 2 x 2 Replicate Bioequivalence Study of Two Formulations of Salmon Calcitonin Administered via Intranasal Spray (Nastech and Miacalcin®) in Normal Healthy Male and Female Subjects
Clinical Site	SFBC International, 11190 Biscayne Blvd, Miami, FL 33181
Principal Investigator	Kenneth C. Lasseter, MD
Study/Dosing Dates	Group 1 (Subjects 1-100) Period 1: 3/24/2005 Period 2: 3/25/2005 Period 3: 3/26/2005 Period 4: 3/27/2005 Group 2 (Subjects 101-199) Period 1: 3/31/2005 Period 2: 4/1/2005 Period 3: 4/2/2005 Period 4: 4/3/2005
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	4/1/2005 to 6/7/2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	76 days

Comment on Study Design:

The firm started analysis of blood samples on April 1, 2005, which was before the completion of dosing in the in vivo bioequivalence study (April 3, 2005). The firm should note that analysis of blood samples should be initiated after the completion of clinical portion of the in vivo bioequivalence study.

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Calcitonin salmon nasal spray	Miacalcin® nasal spray
Manufacturer	Nastech	Novartis
Batch/Lot No.	R05002	H4043
Manufacture Date	1/5/2005	N/A
Expiration Date	N/A	9/2007
Strength	200 IU/dose (0.09 mL) (30 doses per 3.8 mL bottle)	200 IU/dose (0.09 mL) (30 doses per 3.7 mL bottle)
Dosage Form	Nasal spray	Nasal spray
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	104.7%	102.3%
Content Uniformity (mean, %CV)	Not provided	Not provided
Formulation	See Appendix	N/A
Dose Administered	200 IU/dose (1 spray)	200 IU/dose (1 spray)
Route of Administration	Nasal	

No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	2
Washout Period	20 hours
Randomization Scheme	ABAB: 1, 4, 5, 6, 7, 12, 15, 16, 18, 20, 21, 24, 26, 27, 29, 33, 34, 35, 38, 40, 41, 42, 43, 45, 50, 52, 53, 55, 56, 58, 62, 63, 67, 68, 70, 71, 73, 74, 75, 77, 82, 83, 84, 85, 88, 91, 92, 93, 97, 99, 102, 103, 104, 107, 108, 112, 114, 115, 118, 120, 121, 122, 127, 128, 130, 131, 134, 135, 137, 139, 142, 143, 144, 145, 147, 151, 153, 155, 157, 159, 163, 164, 165, 168, 170, 171, 172, 173, 176, 177, 182, 185, 187, 188, 190, 192, 193, 196, 198, 199 BABA: 2, 3, 8, 9, 10, 11, 13, 14, 17, 19, 22, 23, 25, 28, 30, 31, 32, 36, 37, 39, 44, 46, 47, 48, 49, 51, 54, 57, 59, 60, 61, 64, 65, 66, 69, 72, 76, 78, 79, 80, 81, 86, 87, 89, 90, 94, 95, 96, 98, 100, 101, 105, 106, 109, 110, 111, 113, 116, 117, 119, 123, 124, 125, 126, 129, 132, 133, 136, 138, 140, 141, 146, 148, 149, 150, 152, 154, 156, 158, 160, 161, 162, 166, 167, 169, 174, 175, 178, 179, 180, 181, 183, 184, 186, 189, 191, 194, 195, 197
Blood Sampling Times	0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, and 120 minutes post-dose.
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Blood samples were collected in pre-chilled EDTA coated Vacutainer evacuated blood collection tubes. 100 µL of aprotinin was added to each Vacutainer tube and placed on ice until centrifuged. Plasma was transferred into two labeled polypropylene storage tubes and stored at or below -70 °C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Subjects were not required to fast prior to dosing.
Length of Confinement	Overnight and until all study activities were completed on Day 4.

Safety Monitoring	Clinical laboratory evaluations, 12-lead ECG measurements, nasal and physical examination were performed at screening. Subjects were monitored throughout the confinement for adverse reactions.

Comments on Study Design:

The study design is appropriate.

Initially 200 subjects were planned for the study. However, 199 subjects were enrolled and dosed in the study.

Test and reference products were alternated for 4 doses, per the randomization sequence. Subjects received both treatments from a single vial. Prior to dose administration, subjects were instructed to gently blow his or her nose. The nostrils were gently examined to ensure that the nasal passage was clear of mucous and there was no evidence of bleeding. The subjects remained in a seated position and all doses were administered in the right nostril, when possible, using the primed applicator. Both the pre-dose and post-dose weights of containers were recorded.

If a subject was not administered the correct dose weight ±20% (correct dose was 0.091 mg), the data for that subject were excluded from analysis. If a subject had sneezed within 20 minutes following dose administration, the data for that subject were excluded. Subjects with evaluable PK parameters for at least 2 study periods during which the subject received the test and reference treatments were included in the statistical analysis.

According to RLD labeling, the recommended dose of Miacalcin® is one spray (200 IU) per day administered intranasally, alternating nostrils daily.

b) Clinical Results

Table 8 Demographics of Study Subjects*

Age (years)		Weight (kg)		Age		Gender		Race*	
						Sex	N (%)	Category	%
N	199	N	199	N	199			Caucasian	5
Mean	45	Mean	77.9	Mean	45	Male	72 (36)	Afr. Amer.	11
SD	13.7	SD	18.1	SD	13.7	Female	127 (64)	Hispanic	84
Min	18	Min	44.5	Min	18			Asian	0
Max	70	Max	154.5	Max	70			Others	0

* The firm provided summary of demographics for all subjects enrolled in the study.

Demographics of Subjects in Two Groups

Group	Gender		Race		
	Male	Female	Black	Caucasian	Hispanic
1	42	58	13	5	82
2	30	69	9	5	85

Table 9 Dropout Information

Subject No	Reason	Period	Replaced?
25	Subject was withdrawn on day 3 because of upper abdominal pain and nausea.	3	N
52	Consent withdrawn (Day 3)	3	N
101	Consent withdrawn (Day 3)	3	N
116	Subject was withdrawn on day 3 because of elevated blood pressure.	3	N
144	Consent withdrawn (Day 2)	2	N
156	Subject was withdrawn on day 3 because of hypertension, anxiety, and catheter site pain.	3	N
178	Consent withdrawn (Day 3)	3	N

Table 10 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Abdominal pain upper	1	0
Anxiety	0	1
Blood pressure increased	0	1
Catheter site pain	0	1
Dizziness	0	1
Headache	3	3
Hepatic enzyme increased	1	0
Hordeolum	0	1
Hypertension	0	1
Nausea	1	0
Pain in extremity	1	0
Toothache	1	0
Venipuncture site pain	0	1
Vomiting	1	0
White blood cell count increased	1	0
Total:	**10**	**10**

Table 11 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Subject 19 used Premarin for menopause before and during the study.	19	19
Subject 25 used Maalox for stomachache on day 3.	--	25
Subject 53 used Ortho Evra to regulate menses before and during the study.	53	53
Subject 182 used Ortho Novum for contraception before and during the study.	182	182
The 30 min and 40 min blood samples were drawn together at the 40 min time point due to difficulty with the catheter.	150	--

Comments on Dropouts/Adverse Events/Protocol Deviations:

Fourteen of 199 subjects experienced at least 1 adverse event during the study period. Overall, 20 adverse events were reported, with 10 adverse events reported following administration of test product and 10 adverse events reported following administration of reference product. No serious adverse events occurred during the conduct of the study.

In Clinical Study Report, pages 49, and 52, the firm noted that 11 adverse events were reported following administration of Miacalcin®. According to Table 12.2.2-1, Summary of Distinct Subjects with Adverse Events by Treatment and Preferred Term, 10 adverse events were reported following administration of Miacalcin®. The firm should clarify the discrepancy.

The firm's calculated pharmacokinetic parameters were similar to the reviewer's calculated parameters (using the scheduled sample collection times).

There were no other protocol deviations in this study.

c) Bioanalytical Results

Table 12 Assay Quality Control – Within Study

	Parent					Metabolite				
QC Conc. (pg/mL)	12.0	24.0	36.0			N/A				
Inter day Precision (%CV)	9.65	6.53	6.69							
Inter day Accuracy (%)	100.3	102.0	101.8							
Cal. Standards Conc (pg/mL)	1.00*	2.00*	4.00	8.00	10.0	16.0	20.0	32.0	48.0	64.0
Inter day Precision (%CV)	66.4	26.9	9.24	6.49	6.95	4.79	3.97	2.79	3.17	1.18
Inter day Accuracy (%)	69.2	83.9	90.4	103.4	104.0	103.9	104.4	97.6	97.0	101.6
Linearity Range (range of R^2 values)	0.9928 to 1.00									

* Calibration standards of 1.00 and 2.00 pg/mL were anchor calibration standards.

The lower limit of quantitation was originally intended to be 2.00 pg/mL. However, during the course of the validation, neither pool quantified consistently within acceptable limits. Therefore, the lower limit of quantitation was raised to 4.00 pg/mL. Since the 1.00 and 2.00 pg/mL calibration standards were no longer within the calibration range, they were designated as anchor calibrators and have no acceptable criteria.

Any interfering peaks in chromatograms?	N/A
Were 20% of chromatograms included?	N/A
Were chromatograms serially or randomly selected?	N/A

Comments on Chromatograms: N/A

The samples were quantified by Enzyme Linked Immunosorbent Assay (ELISA).

Table 13 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
LP-BA-002	12/15/2002	Guidelines for Excluding Data from Bioanalytical Assays
LP-BA-012	4/1/2004	Conduct of an Analytical Study

Table 14 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

There were 1327 reassays in this study. All of the reassays were considered as analytical repeats. There were no pharmacokinetic repeats.

The firm provided SOPs for the repeat assays and analytical method. Samples were reassayed as per the SOPs.

d) Pharmacokinetic Results

Subjects with evaluable PK parameters for at least 2 study periods during which the subject received the test and reference treatments were included in the statistical analysis by the firm. Subjects were dosed in two groups and therefore the Group-by-Treatment interaction term was used in the model. A statistically significant ($p<0.1$) Group-by-Treatment interaction was observed for LCmax but the firm dropped this term from the model and analyzed the data keeping all subjects in one group. The firm reported the following results:

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCI	11.7	11.3	1.04	95.22	112.78
LAUCT	5.22	5.12	1.02	91.72	113.06
LCMAX	14.4	14.5	0.991	92.61	106.04

ANALYSIS 1:

Since the Group-by-Treatment interaction was statistically significant ($p<0.1$), the reviewer analyzed the two groups separately.

Note: The firm provided concentrations and pharmacokinetic parameters for subjects that were discontinued from the study. The reviewer excluded data of subjects that were withdrawn from the study, and the results below are from all subjects who completed the study.

Table 15 Arithmetic Mean Pharmacokinetic Parameters

Group 1 - Replicate 1 (n=98)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	13.84	66.33	15.54	75.84
Tmax	hour	0.26	46.67	0.25	48.30
AUCT	pg·hr/mL	5.85	95.31	6.47	108.35
AUCI	pg·hr/mL	10.40	50.33	12.15	57.60
Kel	$hour^{-1}$	2.63	35.39	2.86	45.49
THALF	hour	0.30	33.53	0.29	46.74

Group 1 - Replicate 2 (n=98)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	16.16	58.59	16.98	58.81
Tmax	hour	0.28	52.59	0.25	52.58
AUCT	pg·hr/mL	7.67	90.11	7.71	97.57
AUCI	pg·hr/mL	13.95	53.04	12.53	68.05
Kel	$hour^{-1}$	2.54	35.61	2.77	42.37
THALF	hour	0.32	42.18	0.30	45.61

Group 2 - Replicate 1 (n=91)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	19.33	74.79	18.41	65.84
Tmax	hour	0.23	41.73	0.24	37.28
AUCT	pg·hr/mL	8.68	108.93	8.51	103.43
AUCI	pg·hr/mL	14.81	75.09	13.39	83.05
Kel	$hour^{-1}$	2.54	47.88	2.99	37.85
THALF	hour	0.34	52.96	0.27	38.10

Group 2 - Replicate 2 (n=91)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	24.29	92.33	22.01	74.79
Tmax	hour	0.23	43.92	0.23	39.23
AUCT	pg·hr/mL	10.68	101.66	9.97	100.43
AUCI	pg·hr/mL	15.96	74.34	15.50	68.92
Kel	$hour^{-1}$	3.02	43.32	3.00	32.66
THALF	Hour	0.27	36.59	0.26	36.06

Table 16 Geometric Means and 90% Confidence Intervals

Group 1 (n=98)

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCI	9.8426192	9.6824114	1.02	90.776	113.836
LAUCT	3.8669208	4.1493611	0.93	80.536	107.840
LCMAX	11.965195	12.983928	0.92	83.598	101.586

Group 2 (n=91)

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCI	11.85317	10.889351	1.09	97.517	121.502
LAUCT	5.4748159	5.1546801	1.06	91.785	122.904
LCMAX	15.776414	15.25341	1.03	94.014	113.786

ANALYSIS 2:

There were many subjects who had very few non-zero plasma concentration values through the 120-minute plasma collection period following a single treatment. Therefore, the reviewer excluded all subjects having fewer than **four** consecutive non-zero plasma concentration value through 120-minute collection period following a single treatment as per current DBE practice (see attachment in section F). Following results were obtained:

Note: Only the periods where subjects having fewer than four consecutive non-zero concentrations were excluded from analysis.Table 17 Arithmetic Mean Pharmacokinetic Parameters

Group 1 - Replicate 1 (n=78)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	16.33	55.96	17.73	68.98
Tmax	hour	0.26	49.19	0.26	46.17
AUCT	pg·hr/mL	7.33	76.25	7.81	93.16
AUCI	pg·hr/mL	10.40	50.33	12.45	56.68
Kel	$hour^{-1}$	2.63	35.39	2.87	45.75
THALF	hour	0.30	33.53	0.29	47.19

Group 1 - Replicate 2 (n=78)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	18.04	51.83	18.36	54.44
Tmax	hour	0.27	43.40	0.27	50.77
AUCT	pg·hr/mL	9.03	77.00	8.71	87.72
AUCI	pg·hr/mL	14.09	52.90	12.66	67.63
Kel	$hour^{-1}$	2.57	34.95	2.77	42.84
THALF	hour	0.31	42.45	0.30	45.82

Group 2 - Replicate 1 (n=81)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	22.06	67.70	20.06	60.21
Tmax	hour	0.24	39.89	0.24	37.37
AUCT	pg·hr/mL	10.40	94.86	9.55	93.66
AUCI	pg·hr/mL	15.03	75.66	13.39	83.05
Kel	$hour^{-1}$	2.56	48.16	2.99	37.85
THALF	hour	0.34	53.95	0.27	38.10

Group 2 - Replicate 2 (n=81)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	25.01	90.49	24.83	65.53
Tmax	hour	0.23	44.94	0.23	40.04
AUCT	pg·hr/mL	11.08	98.52	11.56	86.94
AUCI	pg·hr/mL	15.96	74.34	15.50	68.92
Kel	$hour^{-1}$	3.02	43.32	3.00	32.66
THALF	hour	0.27	36.59	0.26	36.06

As per the demographics table, the number of subjects dosed in groups 1 and 2 were similar with regards to race and gender. All subjects in groups 1 and 2 were dosed less than 10 days apart and therefore were probably screened and enrolled at the same time. Therefore, the reviewer combined the subjects in one group and results of the combined group are provided below:

Groups 1 and 2 Combined – Replicate 1 (n=159)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	19.11	65.77	18.93	64.21
Tmax	hour	0.25	45.40	0.25	42.28
AUCT	pg·hr/mL	8.82	91.43	8.71	94.08
AUCI	pg·hr/mL	12.78	71.77	12.96	72.88
Kel	$hour^{-1}$	2.59	42.00	2.93	41.23
THALF	hour	0.32	46.68	0.28	42.94

Groups 1 and 2 Combined – Replicate 2 (n=159)

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	pg/mL	21.83	83.01	21.60	64.06
Tmax	hour	0.25	45.04	0.25	47.01
AUCT	pg·hr/mL	10.15	92.09	10.13	88.86
AUCI	pg·hr/mL	15.14	67.04	14.02	69.09
Kel	$hour^{-1}$	2.82	41.18	2.88	37.94
THALF	hour	0.29	40.38	0.28	42.86

Table 18 Geometric Means and 90% Confidence Intervals

Group 1 (n=78)

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCI	9.9017136	9.9014954	1	89.107	112.229
LAUCT	5.8870101	5.7674675	1.02	90.032	115.724
LCMAX	14.638506	14.98641	0.98	88.256	108.107

Group 2 (n=81)

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCI	11.891336	10.885549	1.09	97.795	122.024
LAUCT	6.7538052	6.7674392	1	88.181	112.947
LCMAX	17.289241	17.388631	0.99	90.011	109.832

Groups 1 and 2 combined (n=159)

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCI	10.901535	10.412758	1.05	96.738	113.304
LAUCT	6.3408175	6.2775617	1.01	92.681	110.083
LCMAX	15.98186	16.206736	0.99	92.069	105.621

Table 19 Additional Study Information (From Analysis 1 above).

Group 1

K_{el} and $AUC_{0-\infty}$ determined for how many subjects?	Replicate 1	T= 38	R= 36
	Replicate 2	T= 38	R= 49
Do you agree or disagree with firm's decision?	Yes		
Indicate the number of subjects with the following:			
-measurable drug concentrations at 0 hr	None		
-first measurable drug concentration as C_{max}	None		
Were the subjects dosed as more than one group?	Yes		

	Treatment	LAUCt	LAUCi	LCmax
Within subject variability	T	0.571	0.162	0.234
	R	0.483	0.140	0.242
Between subject variability	T	0.448	0.109	0.115
	R	0.487	0.148	0.132

Group 2

Kel and $AUC_{0-\infty}$ determined for how many subjects?	Replicate 1	T= 40	R= 41
	Replicate 2	T= 47	R= 44
Do you agree or disagree with firm's decision?	Yes		
Indicate the number of subjects with the following:			
-measurable drug concentrations at 0 hr	3 (2 of 3 had first measurable drug concentration as Cmax)		
-first measurable drug concentration as Cmax	2 (See note below)		
Were the subjects dosed as more than one group?	Yes		

	Treatment	LAUCt	LAUCi	LCmax
Within subject variability	T	0.257	0.149	0.169
	R	0.432	0.156	0.169
Between subject variability	T	0.834	0.186	0.340
	R	0.638	0.169	0.263

Comments on Pharmacokinetic and Statistical Analysis:

- Subject #136 (Period 4) had pre-dose concentration level greater than 5% of Cmax. Subject #111 (Period 1) and subject #139 (Period 2) had first measurable drug concentration as Cmax. Therefore, these subjects were excluded from all statistical analysis of group 2 given above.

- As per protocol, if a subject had sneezed within 20 minutes following dose administration, the data for that subject were excluded. No subject sneezed within 20 minutes following dose administration.

- The firm started sample analysis on April 1, 2005 before completing dosing of group 2 subjects. Since Group 1 subjects completed the study prior to the start of blood sample analysis, and analysis of Group 1 data meet the bioequivalence criteria, the study may be acceptable.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

Since the Group-by-Treatment interaction was statistically significant ($p<0.1$), groups 1 and 2 were not combined together for statistical analysis. As per current DBE practice, if the Group-by-Treatment interaction is statistically significant, the equivalence can be demonstrated in one of the groups, provided that the group meets minimum requirements for a complete bioequivalence. See attachment regarding this DBE practice in Section F.

The reviewer calculated 90% confidence intervals for groups 1 and 2 for all pharmacokinetic parameters are within the acceptable limits. However, the in vivo bioequivalence study is incomplete.

Table 20 Mean Plasma Concentrations, Single-Dose Bioequivalence Study [Includes all subjects as reported by the firm (Analysis 1)]

Group 1 – Replicate 1

Time (min)	Test		Reference	
	Mean Conc. (pg/mL)	%CV	Mean Conc. (pg/mL)	%CV
0	.	.	.	.
5	10.96	66.28	11.70	71.65
10	12.77	64.37	14.27	77.87
15	12.76	67.92	13.53	79.77
20	11.57	64.85	13.32	75.08
25	10.61	63.76	10.93	76.34
30	10.16	57.18	11.32	71.40
40	8.49	53.34	9.60	55.49
50	8.14	46.18	8.64	48.05
60	6.53	28.36	8.02	32.56
75	5.27	28.62	7.72	40.16
90	8.89	.	5.99	11.08
120	.	.	.	.

Group 1 – Replicate 2

Time (min)	Test		Reference	
	Mean Conc. (pg/mL)	%CV	Mean Conc. (pg/mL)	%CV
0	.	.	.	.
5	12.87	62.36	12.21	55.40
10	13.15	70.92	14.57	55.95
15	14.34	59.82	13.72	57.11
20	12.96	59.68	13.70	58.23
25	12.82	53.22	12.29	65.14
30	11.92	57.81	11.44	80.58
40	10.64	56.90	9.50	81.86
50	9.83	47.85	8.90	93.84
60	8.23	40.32	9.13	74.51
75	6.57	52.23	7.80	62.49
90	5.85	46.39	6.61	25.56
120	4.48	.	.	.

Group 2 – Replicate 1

Time (min)	Test		Reference	
	Mean Conc. (pg/mL)	%CV	Mean Conc. (pg/mL)	%CV
0	.	.	.	.
5	14.22	98.36	12.31	65.82
10	17.18	84.70	15.94	66.32
15	16.63	80.52	16.70	71.19
20	15.92	71.58	15.07	76.80
25	14.10	78.36	13.70	77.04
30	13.10	72.84	12.54	73.87
40	10.30	76.72	10.27	75.95
50	8.08	60.68	7.82	67.30
60	7.49	50.97	7.08	56.35
75	8.69	75.59	8.77	57.46
90	8.23	59.63	8.81	39.91
120	.	.	.	.

Group 2 – Replicate 2

Time (min)	Test		Reference	
	Mean Conc. (pg/mL)	%CV	Mean Conc. (pg/mL)	%CV
0	.	.	.	.
5	18.84	82.28	16.83	84.69
10	22.52	101.92	19.83	78.34
15	21.60	94.39	19.84	71.91
20	17.52	84.26	17.59	75.22
25	15.52	92.00	16.86	64.40
30	13.94	75.58	13.81	58.66
40	10.74	61.84	11.03	60.64
50	7.95	63.14	9.92	63.51
60	7.60	50.66	9.15	61.66
75	5.30	27.42	8.08	39.21
90	4.97	14.10	6.29	37.20
120	.	.	5.14	.

Group 1 – Composite Plasma Values for Both Replicates

Time (min)	Test		Reference	
	Mean Conc. (pg/mL)	%CV	Mean Conc. (pg/mL)	%CV
0	.	.	.	.
5	11.95	64.29	11.97	62.96
10	12.97	67.78	14.42	67.06
15	13.54	63.72	13.63	68.90
20	12.27	62.12	13.51	66.65
25	11.68	58.69	11.60	70.48
30	11.08	57.99	11.39	76.35
40	9.60	56.69	9.55	71.39
50	9.07	47.81	8.80	79.07
60	7.61	38.80	8.68	62.91
75	6.18	48.56	7.77	52.28
90	6.36	42.88	6.38	21.37
120	4.48	.	.	.

Group 2 - Composite Plasma Values for Both Replicates

Time (min)	Test		Reference	
	Mean Conc. (pg/mL)	%CV	Mean Conc. (pg/mL)	%CV
0	.	.	.	.
5	16.79	89.07	14.57	80.71
10	20.06	97.95	17.91	74.90
15	19.28	91.23	18.28	72.14
20	16.82	79.44	16.36	76.21
25	14.90	86.78	15.25	70.66
30	13.57	74.18	13.17	66.06
40	10.54	68.41	10.64	67.97
50	8.01	61.48	8.91	65.84
60	7.54	49.97	8.06	60.60
75	6.36	61.98	8.37	46.75
90	6.60	51.94	7.30	40.80
120	.	.	5.14	.

Figure 1 Mean Plasma Concentrations for Test and Reference, Group 1 (Analysis 1)

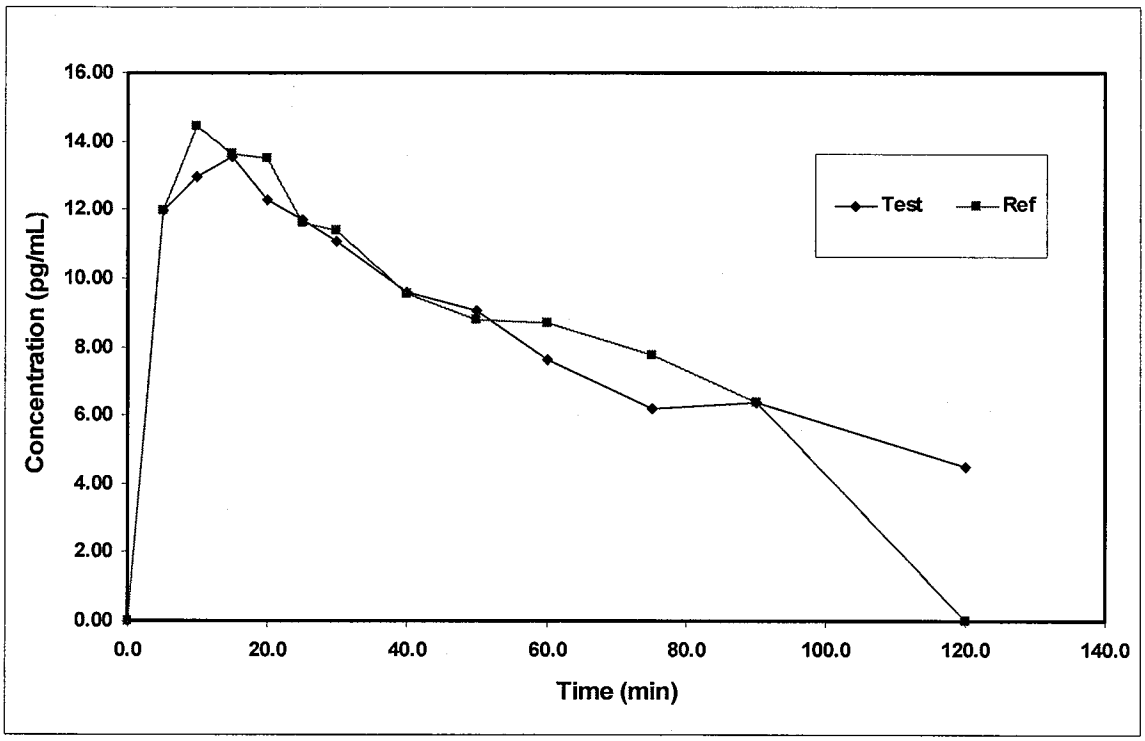
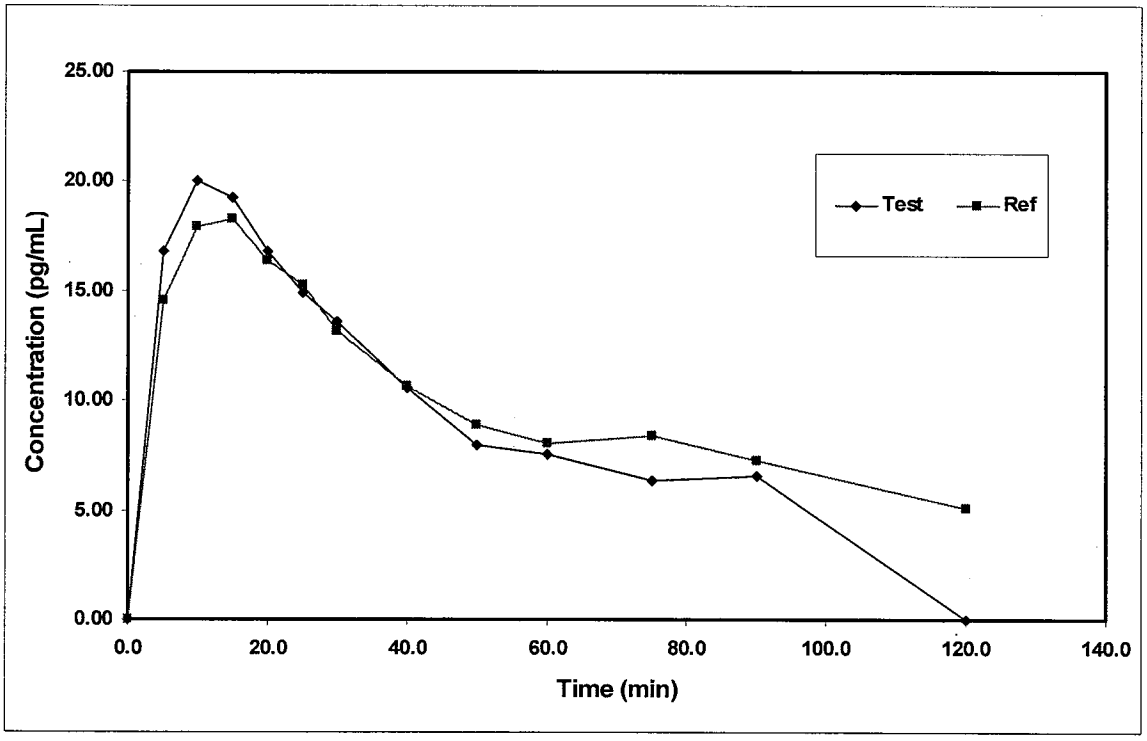


Figure 2 Mean Plasma Concentrations for Test and Reference, Group 2 (Analysis 1)



B. Formulation

The formulation provided in the original submission (14 day product) and the formulation of the 30 day product are identical. Formulation of the test product is provided below.

Components	Function	Formulation per 0.09 mL dose (% w/w)
Calcitonin Salmon, EP	Active	200 IU (0.033 mg)
Sodium Chloride, USP	[redacted]	[redacted]
Chlorobutanol [redacted] NF		
Nitrogen, NF		
[redacted] Hydrochloric Acid, NF	pH adjuster	TAP*
Purified Water USP	[redacted]	q.s. (q.s. to 100.00%)
Total		**0.09 mL**

*TAP = To adjust pH

The test product and the RLD formulations are provided below:*

Component	RLD, amount per mL	Nastech, amount per mL
Calcitonin salmon	2200 I.U.	2200 I.U.
Sodium chloride	[redacted]	[redacted]
Benzalkonium chloride		0
Chlorobutanol	0	[redacted]
Nitrogen	[redacted]	
Hydrochloric acid	p.r.n.	p.r.n.
Purified water	q.s.	q.s.

* Formulations from review file: 76979N1203.doc.

Comments

Formulation of the test product was previously reviewed by the DBE and was acceptable (Review file: 76979N1203.doc). The formulation comments from the original review are summarized below.

As per the original DBE review, the firm was advised that to be considered therapeutically equivalent and approvable DBE recommended that the submission should contain in addition to the in vitro studies, an in vivo bioequivalence study based on pharmacokinetic measures showing that its product is bioequivalent to the RLD. This is because (1) its product is not Q1 and Q2 the same as Miacalcin®; and (2) the product is intended to act systemically. The applicant was also advised to submit safety data on chlorobutanol.

The applicant provided a comparison table of the proposed levels of inactive ingredients in their formulation and those found in a previously approved drug application for the nasal route of administration. The levels of each inactive ingredient were at or below those found in a

previously approved drug applications. Applicant provided justification of safety for the use of chlorobutanol [redacted] NF in place of benzalkonium chloride (used in RLD) [redacted]. The total daily exposure to the chlorobutanol for Nastech's calcitonin salmon nasal spray was calculated to be less than that of an approved nasal spray [redacted].

The Office of Generic Drugs is currently evaluating the use of chlorobutanol in this formulation.

C. Procedures and Information Applicable to All In Vitro Tests

Summary	
Study Site(s)	Nastech Pharmaceutical Co. 3450 Monte Villa Pkwy Bothell, WA 98021 Cascade Impactor Test (b) (4) [redacted]
Study Dates	Not Applicable
Number of Units Tested / Lot	10
Strength Tested	200 IU/spray (14 and 30 dose bottles)

14 Day Product

Tests	Lot Numbers	
	Test	**Reference (Exp. Date)**
Single Actuation Content, Spray Pattern, Plume Geometry, Priming	2054N-00929-1 2054N-00930-1 2054N-00978-1	009H8661 (2/2006) 012H8664 (2/2006) 042G7921 (12/2005)
Droplet Size Distribution by Laser Diffraction, Cascade Impactor		001H9917 (1/2006) 009H8661 (2/2006) 042G7921 (12/2005)

30 Day Product [From Electronic Data Sets and Amendment (12/10/2004)]

Tests	Lot Numbers	
	Test	**Reference**
Single Actuation Content	2054N-01236-1 2054N-01237-1 2054N-01368-1	004J3171 (1/2007) 008J3546T (2/2007) 009J3172 (2/2007)
Droplet Size Distribution by Laser Diffraction, Priming	2054N-01236-1 2054N-01237-1 2054N-01238-1	
Spray Pattern, Plume Geometry[1]	2054N-00929-1 2054N-00930-1 2054N-00978-1	018J3927 (3/2007) 020J4390 (3/2007) 022J3928 (4/2007)

[1] The same lot numbers of product packaged into 14-day and 30-day bottles were used for spray pattern, and plume geometry.

30 Day Product [From Statistical Report for 30 Day Bottles (Vol. 3.5, Page. 983)]

Tests	Lot Numbers	
	Test	Reference
Single Actuation Content, Droplet Size Distribution by Laser Diffraction, and Priming	2054N-01236-1 2054N-01237-1 2054N-01238-1	044J3171 008J3546T 009J3172
Spray Pattern and Plume Geometry[1]	2054N-00929-1 2054N-00930-1 2054N-00978-1	

[1] The same lot numbers of product packaged into 14-day and 30-day bottles were used for spray pattern, and plume geometry.

The lot number (2054N-01238-1) for 30 day test product provided in Statistical Report (Vol 3.5, Page 983) does not match the lot number (2054N-01368-1) in electronic data set for Single Actuation Content Through Container Life test.

The lot numbers for 30 day reference product provided in Statistical Report (Vol 3.5, Page 983) do not match the lot numbers in electronic data set for spray pattern and plume geometry tests.

Actuation method	(b) (4) Actuation Station
Actuation force	(b) (4)
Force rise time	
Hold time	
Force fall time	
Spray delay	
Minimum travel distance	
Maximum travel time	
Trigger signal delay	

Vol 1.13, Page 8143

Population Bioequivalence Analyses of In Vitro Performance Data

On August 3, 2005, the DBE management made a decision to implement the draft Population Bioequivalence (PBE) method that was developed for evaluation of certain comparative in vitro performance studies on aerosols and nasal sprays. All comparative data submitted in this application were analyzed using the PBE method as outlined in the June 1999 draft Nasal BA/BE guidance. These analyses used a $sigma_{TO}$ of 0.1 and epsilon of 0.01.

The memorandums for development and application of PBE analyses method are attached in Section F. The memorandums provide an explanation of the timeline for using PBE analyses instead of the geometric mean analysis for in vitro data and they provide explanation of why PBE is superior to geometric mean for in vitro data analysis.

D. In-Vitro Studies

1. Single Actuation Content through Container Life

The single actuation content (SAC) through container life of both the test and reference products was performed on samples from each of three sub-lots of the test product and three batches of the reference product (14 day and 30 day bottles). The test product batches were manufactured from a single batch of solution and three sub-lots of product were created with the addition of three different batches of the same actuator ((b) (4) actuators). The products were unprimed prior to the conduct of the test.

For 14-day bottle, delivered drug mass from 10 primed units from each of three batches or sub-lots of test and reference product at the beginning (1st actuation) and end (14th actuation) of unit life was determined.

For 30-day bottle, delivered drug mass from 10 primed units from each of three batches or sub-lots of test and reference product at the beginning (1st actuation) and end (30th actuation) of unit life was determined.

The SAC through container life test was performed by collecting the emitted dose from the nasal spray, using an (b) (4) automated actuation station, in an inverted Erlenmeyer flask and measuring the mass of drug per actuation using HPLC.

Content uniformity summary results are provided below:

Table 21: Unit Dose Summary Data (Single Actuation Content)[1]

14 Day Bottle

Sector	Spray #[2]	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	1	Test	94.42	94.38	1.77	3.53	2.54	3.26	1.03	1.03	0.37
		Ref	91.92	91.76	4.06	6.26	4.29	6.00			
END	14	Test	97.11	97.04	1.76	4.88	1.39	3.76	0.96	0.96	0.00
		Ref	100.67	100.65	0.98	1.12	1.65	1.71			

[1] Data are expressed as the percentage of the label claim (LC).
[2] Spray #'s are the spray number after priming.

30 Days Bottle

Sector	Spray #[2]	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	1	Test	103.03	103.02	1.63	1.77	0.94	1.84	1.00	1.00	0.73
		Ref	103.25	103.23	1.69	2.29	0.65	2.03			
END	30	Test	103.91	103.88	1.56	3.11	1.31	2.48	1.00	1.00	0.75
		Ref	104.21	104.20	1.12	1.92	1.31	1.80			

[1] Data are expressed as the percentage of the label claim.
[2] Spray #'s are the spray number after priming.

Comments on SAC through container life:

14 Day Product
The test and reference products delivered 191.5 IU/dose (95.8% LC) and 192.5 IU/dose (96.3% LC), respectively, across all doses and all samples.

For beginning lifestage, the test product delivered 188.8 IU/dose or 94.4% of labeled claim and the reference product delivered 183.8 IU/dose or 91.9% of labeled claim. For end lifestage, the test product delivered 194.2 IU/dose or 97.1% of labeled claim and the reference product delivered 201.3 IU/dose or 100.7% of labeled claim.

The ratios of the test/reference geometric means for the beginning (spray #1) and end (spray #14) of the unit life are within the acceptable limits of 0.90-1.11.

The results of the PBE analyses also demonstrate equivalence between the test and reference product with regard to the single actuation content for the 14 day product.

30 Day Product
The test and reference drugs delivered 206.9 IU/dose (103% LC) and 207.5 IU/dose (104% LC), respectively, for all doses and all samples.

For beginning lifestage, the test product delivered 206 IU/dose (103.0% LC) and the reference product delivered 206 IU/dose (103.3% LC). For end lifestage, the test product delivered 208 IU/dose (103.9% LC) and the reference product delivered 208 IU/dose (104.2% LC).

The ratios of the test/reference geometric means for the beginning (spray #1) and end (spray #30) of the unit life are within the acceptable limits of 0.90-1.11.

The results of the PBE analyses also demonstrate equivalence between the test and reference product with regard to the single actuation content for the 30 day product.

2. Priming and Re-priming

Based on the RLD labeling, Miacalcin® nasal spray should be at room temperature before the first dose administration. To prime the pump, the bottle should be held upright and the two white side arms of the pump depressed toward the bottle until a full spray is produced. The pump is primed once the first full spray is emitted. The pump should not be primed before each daily dose. No further information regarding repriming is included in the labeling. The RLD labeling is attached in Section F.

The firm also conducted this study to determine the effect of storage in multiple orientations and after different periods of non-use of calcitonin nasal spray compared to Miacalcin® nasal spray. Spray weight and spray content uniformity parameters were evaluated.

An analysis of the spray weight and content uniformity of nasal spray was performed on samples from each of three sub-lots of both the test and three lots of the reference product. The test product samples were divided into three groups in order to determine the effect of actuation frequency on the need to re-prime the actuator. The test product actuation frequencies studied were daily, every three days and every seven days until container exhaustion. The reference product was studied daily as per the labeling instructions.

Group 1: Daily actuations were performed for calcitonin spray using three lots of nasal actuators. Two lots of actuators were analyzed in upright and sideways orientations (10 units/lot). A third lot was evaluated only in the upright orientation (10 units/lot). Upright samples were compared to Miacalcin® lots. Three lots of Miacalcin® nasal spray were tested side by side in the upright orientation for daily actuation (10 units/lot).

Group 2: Testing once every three days was performed only for calcitonin nasal spray using two lots of pumps (10 units/lot upright and 10 units/lot sideways).

Group 3: Testing every seven days was performed only for calcitonin nasal spray using two lots of pumps (10 units/lot upright and 10 units/lot sideways).

The spray content uniformity was characterized by HPLC. The samples were collected using a (b) (4) automated actuation station to actuate the spray. Spray weight was performed using an (b) (4) automated actuation station to actuate the spray sample. The product bottle was weighed before and after each spray to determine the actual weight delivered.

Initial Priming: The firm noted that the first two actuations generally do not drive out any amount of sprays. Actuations were continued until a spray weight of least 0.078 g was delivered. Priming may take four actuations. After one full spray is delivered (weight range of 0.78-0.105 g), the unit is considered primed.

For bioequivalence determination, the firm submitted data for upright daily-actuated calcitonin samples (Group 1) compared to Miacalcin® upright daily-actuated samples.

Table 22: Priming Data[1]

14 Days Bottle

Product	Mean		Variability (%CV)				TEST/REF		p
			Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
	Arith	Geo	Min	Max					
			(N=10)		(N=3)	(N=30)	N=30	N=30	
Test	96.26	96.20	0.92	3.63	2.97	3.47	0.95	0.95	0.00
Ref	101.76	101.73	1.74	2.12	1.79	2.37			

[1] Data are expressed as the percentage of the label claim.

30 Days Bottle

Product	Mean		Variability (%CV)				TEST/REF		p
			Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
	Arith	Geo	Min	Max					
			(N=10)		(N=3)	(N=30)	N=30	N=30	
Test	90.98	90.96	1.66	1.90	1.02	1.92	1.02	1.02	0.00
Ref	89.07	89.06	1.84	2.05	0.44	1.89			

[1] Data are expressed as the percentage of the label claim.

Comments on Priming Data:

No information regarding repriming is included in the RLD labeling. Therefore, repriming study is not necessary.

14 Day Bottle

As per the Nasal Guidance, priming would be established providing that the geometric mean of the test product falls within 95-105 percent of label claim (LC). For the 14 day bottle, the geometric mean of the test product is 96.20 % LC, which falls within the acceptable range. The geometric mean ratio, test to reference, is 0.95.

30 Day Bottle

As per Report SCR-0007, the test and reference products delivered a spray weight of 90.1 mg (2.2 %CV) and 89.3 mg (2.4 %CV), respectively.

For the 30 day bottle, the geometric mean of the test product is 90.96% LC, and therefore, does not fall within the acceptable range. However, the geometric mean ratio, test to reference, is 1.02.

The firm did not provide complete method validation results for HPLC method used for quantitation of calcitonin.

3. Droplet Size Distribution (DSD) by Laser Diffraction

Droplet size distribution by laser diffraction was assessed for the fully formed plume at two distances from the actuator orfice (2 and 5 cm) at the beginning and end of unit life. The droplet size distribution was characterized by laser diffraction using a [redacted] (b) (4) particle size analyzer and a [redacted] (b) (4) automated actuation station.

Prior to use for the first time, each container was primed manually by depressing the actuator until appearance of the first full spray. Sprays were counted after priming had occurred. For each of the products, 10 bottles from three lots were analyzed at each height (2 cm and 5 cm from the tip of the actuator). Droplet size was characterized during the fully developed phase of each actuation. Fully developed phase was determined automatically by the software and defined as maximum obscuration to 90% maximum obscuration.

For 14 day bottle, the products were analyzed at beginning (sprays 1-3 after priming) and end (sprays 12-14 after priming) lifestages. For 30 day bottle, the products were analyzed at beginning (sprays 1-3 after priming) lifestage. For both products, measurements were collected at two distances from the actuator orfice separated by 3 cm (2 cm and 5 cm).

Based on the revised draft Nasal BA/BE Guidance, bioequivalence evaluation is based only on D50 and SPAN data for the fully formed plume (intermediate). A summary of these data based on the reviewer's calculations is given below.

Table 23: Droplet Size Distribution (D50) -- 14 Day Bottle

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	(min)	(max)					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	2	Test	30.51	30.45	5.33	7.08	3.69	6.83	0.80	0.80	0.00
		Ref	38.04	37.83	6.53	13.05	6.60	10.73			
BEG	5	Test	33.45	33.39	4.35	6.64	3.65	6.20	0.93	0.94	0.00
		Ref	35.79	35.71	2.57	12.40	1.85	7.66			
END	2	Test	31.05	30.97	3.81	8.55	4.91	7.50	0.85	0.85	0.00
		Ref	36.44	36.29	6.12	8.78	6.66	9.18			
END	5	Test	34.10	33.90	3.78	19.54	4.79	12.59	0.97	0.97	0.18
		Ref	35.08	35.04	3.19	4.35	3.76	4.69			

Table 24: SPAN -- 14 Day Bottle

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	(min)	max)					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	**2**	Test	1.98	1.97	1.94	2.05	3.12	10.13	0.99	1.00	0.00
		Ref	2.00	1.98	9.60	19.75	7.72	15.49			
BEG	**5**	Test	1.42	1.40	8.56	19.13	8.59	17.32	0.82	0.90	0.03
		Ref	1.73	1.56	13.16	106.64	26.08	80.74			
END	**2**	Test	2.04	2.02	8.91	22.71	9.28	17.45	1.08	1.07	0.03
		Ref	1.89	1.88	5.91	14.28	0.77	11.34			
END	**5**	Test	1.45	1.42	7.39	33.43	12.47	24.29	1.03	1.02	0.02
		Ref	1.40	1.39	6.86	16.28	3.84	11.33			

Table 25: Droplet Size Distribution (D50) -- 30 Day Bottle

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	(min)	(max)					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	**2**	Test	30.76	30.69	4.68	7.00	4.50	6.88	0.75	0.75	0.00
		Ref	40.93	40.83	5.36	7.96	2.62	7.03			
BEG	**5**	Test	34.31	34.25	5.23	6.88	2.75	6.12	1.02	1.02	0.18
		Ref	33.74	33.72	1.96	4.19	1.39	3.14			

Table 26: SPAN -- 30 Day Bottle

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	(min)	max)					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	**2**	Test	1.93	1.93	1.86	2.00	3.54	5.31	1.07	1.07	0.00
		Ref	1.81	1.81	6.56	13.04	4.56	9.60			
BEG	**5**	Test	1.24	1.23	8.00	14.90	6.44	11.96	0.94	0.94	0.28
		Ref	1.32	1.31	7.27	14.39	2.32	11.40			

Comments on Droplet Size Distribution by Laser Diffraction:

Evaluation of the comparative droplet size distributions by laser diffraction is based on data pertaining to the fully formed plume, which is represented by the intermediate plume stage. The firm provided supporting graphical representation of data consisting of transmission, droplet size and obscuration plots including the time-history plots.

The firm noted that fully developed phase was determined automatically by the software and defined as maximum obscuration to 90% maximum obscuration. However, the firm did not provide the criteria for selecting the region of the plateau at which droplet size data were determined (e.g., the average of all scans over the entire plateau, the data of a single scan (sweep) only at the maximum obscuration, or the average of a specified range of scans around this obscuration). It is not clear if this criterion was established prior to the study for each of the two distances and implemented consistently during the study.

14 day product

Based on the geometric mean data for the intermediate portion of the plume, the T/R ratios for SPAN are within the 0.9-1.11. However, for D50, the T/R ratios are outside the acceptable limits.

The droplet size distribution data were also analyzed in the DBE using the PBE method stated above. Based on this analysis the test product's D50 and SPAN are equivalent to those of the reference product at both distances **except for D50 at distance of 2 cm.**

30 day product

It is noted that for the 30 day product, data were collected at the beginning lifestage only. If the firm intends to market both the 14 day and 30 day product, it is not necessary to conduct DSD test at end lifestage since the firm provided DSD data at both beginning and end lifestages for the

14 day product. However, if the firm only intends to market 30 day product, the firm should provide DSD data at end lifestage for the 30 day product.

Based on the geometric mean data for the intermediate portion of the plume, the T/R ratios for SPAN are within the 0.9-1.11. However, for D50, the T/R ratios are outside the acceptable limits.

The droplet size distribution data were also analyzed by the DBE using the PBE method. Based on this analysis the test product's D50 and SPAN are equivalent to those of the reference product at both distances **except for D50 at distance of 2 cm.**

Please see attachment in Section F for DBE recommendations regarding acceptance of in vitro test results.

4. Particle/Droplet Size Distribution by Cascade Impactor

Study Summary	
Cascade impactor	(b) (4)
Actuation Method	(b) (4) Nasal Spray Pump Actuation Station
Flow Rate	28.3 ±1.4 L/min

Method Validation (Vol 1.13, pp 8378-8417)	
Analyte	Calcitonin
Method	HPLC
Standard Curve Range	Range 1: 0.3 IU/mL to 10 IU /mL Range 2: 10 IU/mL to 50 IU /mL
Limit of Quantitation	0.3 IU/mL
Linearity of Standard Curve	Range 1: r=1.00 Range 2: r= 1.00
Precision (Instrument)	Range 1: Six replicates of calcitonin standard prepared at 0.3 IU/mL (%CV=8.0). Range 2: Six replicates of calcitonin standard prepared at 20 IU/mL (%CV=0.9).
Recovery	95.0% to 104.9%
Specificity	Yes
Stability	2 days at ambient conditions and at 4 °C

Drug deposited in the cascade impactor was grouped as follows:

Collection Stages		
Group #	Components	Aerodynamic Diameter (μm)
1	Pump nozzle, Globe, Preseparator, Plate 0	≥ 9.0 μm
2	Plate 1	≤ 9.0 and ≥ (b) (4) μm
3	Plate 2 to 7, plus filter (composite)	< (b) (4) μm

Data for the reference and test products are summarized below.

Table 27: Cascade Impaction - Material Recovered

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	Groups 2 & 3	Test	4.84	4.76	15.53	22.62	4.10	19.21	1.28	1.40	0.00
EG	Groups 2 & 3	Ref	3.78	3.41	34.87	45.78	9.33	38.62			

Comments on Drug in Small Particles / Droplets by Cascade Impaction:
The firm provided electronic data for the amount of drug in small droplets [<9 μm, (Groups 2 and 3 combined)]. The firm did not provide electronic data for amount of material deposited in droplets ≥9 μm. A comparison of the data for mass deposited in the impactor < 9 μm for each product shows that the test and reference products resulted in an average of 4.84 IU, and 3.78 IU, respectively.

According to Cascade Impactor Study Report (TTP-NZU-M0002.00, pages 8304-8326), less than 1% of the total dose of calcitonin was delivered to the impactor plates. This resulted in deposition levels at or below the limit of quantitation for calcitonin (0.3 IU/mL). The firm provided grouped summary data (group 1, groups 2 and 3 combined) for the test and reference products. Results were generated for the amount (mass) of calcitonin deposited on the various surfaces of the cascade impactor assembly.

According to the study report, a comparison of the data for mass deposited in the impactor < 9 μm for each product shows that the test and reference products resulted in an average of 4.9 IU, and 4.0 IU, respectively. The amount of drug collected in Group 1 for the test and reference products were 94.5%, and 99.9% of label claim, respectively. The amount of drug collected in Group 1 and Group 2 combined for the test and reference products were 94.9% and 100.2% of

label claim. Therefore, cascade impaction data met the requirement that the mass balance of recovered calcitonin was in the range of 85% to 115%.

It is noted that groups 2 and 3 combined data provided in the Study Report do not match the electronic data provided by the firm. The firm should clarify this discrepancy.

The PBE analysis conducted by the DBE with regard to cascade impactor data demonstrate equivalence between the test and reference products.

The firm did not conduct this test for the 30 day product. If the firm intends to market only the 30 day product, the firm should conduct drug in small particles/droplets by cascade impactor test for the 30 day product.

5. Spray Pattern

Method Validation:

The method validation is provided on pages 1593-2202.

Standard Testing Procedure:

Provided on pages 8433-8435.

Experiment:

The spray pattern was evaluated using (b) (4) (b) (4).

During the development of the method, it was found that at distances greater than 3 cm the plume began to dissipate and was affected by turbulence, leading to unreliable spray pattern measurement. Consequently, spray pattern was determined at 1.5 and 3.0 cm from the tip of the actuator. Ten bottles from three lots of the test and reference products were used. The first 3 sprays after priming were analyzed for each bottle. Data were collected at the fully developed phase of the spray at the beginning lifestage.

Study Summary	
Method Description	Captured images were analyzed using the [redacted] measuring tool, which allows the elliptical shape of the spray pattern to be calculated.
Visualization Apparatus	[redacted]
Actuation Apparatus	
Spray Pattern Distance 1	1.5 cm
Spray Pattern Distance 2	3 cm
Metrics Determined by Software?	Yes

Parameters

[redacted] **Automated Actuation Station**	
Velocity	[redacted]
Acceleration	
Initial Actuation Delay	
Actuation Hold Time	
Post Actuation Delay	

Table 28: Spray Pattern Data

Dmax (14 Day Bottle)

Sector	Distance (mm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	**15**	Test	19.81	19.68	18.30	20.77	6.68	11.78	1.19	1.18	0.02
		Ref	16.69	16.61	7.77	12.58	0.50	9.87			
BEG	**30**	Test	33.04	32.89	5.65	10.07	5.81	9.40	1.20	1.21	0.02
		Ref	27.43	27.25	8.61	15.85	3.75	11.60			

Dmin (14 Day Bottle)

Sector	Distance (mm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	15	Test	16.13	16.02	7.72	13.31	7.93	12.37	1.19	1.19	0.00
		Ref	13.59	13.50	8.94	15.00	1.63	11.82			
BEG	30	Test	26.08	25.95	5.63	14.43	4.41	9.88	1.16	1.16	0.00
		Ref	22.52	22.37	8.69	13.25	6.90	12.03			

Pattern Area (14 Day Bottle)

Sector	Distance (mm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	15	Test	253.88	246.89	14.68	25.39	15.11	23.89	1.40	1.39	0.00
		Ref	181.66	177.90	15.26	26.60	0.63	20.22			
BEG	30	Test	687.20	677.61	8.61	21.75	9.45	16.57	1.38	1.39	0.00
		Ref	498.75	485.93	16.30	30.13	9.89	22.92			

Ovality Ratio (14 Day Bottle)

Sector	Distance (mm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	15	Test	1.23	1.23	1.22	1.25	1.39	5.28	1.00	1.00	0.01
		Ref	1.23	1.23	3.81	6.62	1.22	5.37			
BEG	30	Test	1.27	1.27	6.07	8.68	1.54	7.06	1.04	1.04	0.03
		Ref	1.22	1.22	2.35	6.98	3.83	6.28			

Dmax (30 Day Bottle)

Sector	Distance (mm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	15	Test	18.17	17.83	12.60	21.79	9.22	18.95	0.85	0.83	0.00
		Ref	21.45	21.42	4.19	6.10	3.24	5.42			
BEG	30	Test	32.12	31.49	11.71	18.21	15.10	20.11	0.90	0.88	0.00
		Ref	35.76	35.70	4.10	7.47	1.33	6.04			

Dmin (30 Day Bottle)

Sector	Distance (mm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	15	Test	14.51	14.27	13.07	15.46	8.72	17.77	0.78	0.77	0.04
		Ref	18.54	18.51	3.63	6.18	2.98	5.16			
BEG	30	Test	24.58	24.17	9.51	20.45	12.65	18.90	0.94	0.92	0.16
		Ref	26.26	26.15	6.33	12.95	0.66	9.11			

Pattern Area (30 Day Bottle)

Sector	Distance (mm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	15	Test	215.05	201.18	22.57	38.10	18.07	34.55	0.68	0.64	0.00
		Ref	314.58	312.96	7.85	12.00	5.46	10.20			
BEG	30	Test	651.45	606.41	19.72	34.70	28.60	38.20	0.82	0.77	0.00
		Ref	791.95	786.10	10.45	15.22	1.10	12.40			

Ovality Ratio (30 Day Bottle)

Sector	Distance (mm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	15	Test	1.25	1.25	1.24	1.27	1.26	5.92	1.08	1.08	0.02
		Ref	1.16	1.16	1.89	2.88	1.24	2.63			
BEG	30	Test	1.31	1.30	4.16	10.57	2.88	7.62	0.96	0.95	0.15
		Ref	1.37	1.36	5.20	9.02	1.76	6.81			

Comments on Spray Pattern:

The spray pattern data are incomplete because the firm should clarify whether area, Dmax and Dmin 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 ellipses fitted to the pattern, the firm should provide data based on the true shape of the pattern.

Spray pattern was determined at 1.5 cm and 3.0 cm from the tip of the actuator. As per the draft Nasal BA/BE Guidance, these distances are recommended to be at least 3 cm apart within the range of 3 to 7 cm.

Based on the draft Nasal BA/BE Guidance, measures of spray pattern, using automated laser analyses, are area and ovality ratio. Measurement of Dmax and Dmin axes is not necessary for such analyses.

14 Day Bottle

The ratio of the geometric mean of test/reference for the ovality metric was within the 0.9-1.11 acceptance range at the beginning lifestage. It should be noted that the ratios of the geometric mean of test/reference for the Dmax, Dmin, and pattern area metrics were not within the 0.9-1.11 acceptance range at the beginning lifestage.

As per the draft Nasal Guidance, statistical evaluation is based on PBE analysis of area and ovality ratio for automated analysis.

Spray pattern data were also analyzed by the DBE using the PBE method. The results of ovality ratio at both distances but not of pattern area demonstrate bioequivalence between the test and reference products.

30 Day Bottle
The ratio of the geometric mean of test/reference for the ovality metric was within the 0.9-1.11 acceptance range at the beginning lifestage. It should be noted that the ratios of the geometric mean of test/reference for the Dmax, Dmin (except at 3 cm), and pattern area metrics were not within the 0.9-1.11 acceptance range at the beginning lifestage.

Spray pattern data were also analyzed by the DBE using the PBE method. The results of ovality ratio at both distances demonstrate bioequivalence between the test and reference products.

Please see attachment in Section F for DBE recommendations regarding acceptance of in vitro test results.

6. Plume Geometry

Study Summary	
Method Description	Digital image capture of laser illuminated side view of spray plume
Visualization Apparatus	(b) (4)
Actuation Apparatus	

Parameters

(b) (4) Automated Actuation Station	
Velocity	(b) (4)
Acceleration	
Initial Actuation Delay	
Actuation Hold Time	
Post Actuation Delay	

Plume geometry was characterized for a single frame during the intermediate stable phase of each actuation at the beginning lifestage. The plume was characterized at a height of 3 cm from the tip of the actuator. For the 14 day product, the plume was characterized for sprays 1-3. For the 30 day product, the plume was characterized for sprays 4-6.

Plume Geometry data are summarized below:

Table 29: Plume Angle Data (14 Day Bottle)

Sector	Distance (cm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	3	Test	66.64	66.48	4.25	6.88	5.87	7.21	1.01	1.00	0.68
		Ref	66.25	66.22	1.76	3.96	0.76	2.84			

Table 30: Plume Width Data (14 Day Bottle)

Sector	Distance (cm)	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo							
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG	3	Test	39.65	39.50	36.30	41.35	7.32	9.11	1.01	1.01	0.83
		Ref	39.21	39.19	2.12	4.93	0.92	3.54			

Table 31: Plume Angle Data (30 Day Bottle)

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo	Min	Max					
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG		Test	69.97	69.67	5.87	10.50	4.11	9.57	0.96	0.96	0.06
		Ref	72.64	72.57	2.91	4.14	3.02	4.35			

Table 32: Plume Width Data (30 Day Bottle)

Sector	Distance	Product	Mean		Variability (%CV)				TEST/REF		p
					Within-Lot		Between-lot	Total	Arith Mean	Geo Mean	
			Arith	Geo							
					(N=10)		(N=3)	(N=30)	N=30	N=30	
BEG		Test	42.40	42.08	40.30	44.93	5.53	12.74	0.96	0.95	0.28
		Ref	44.23	44.15	3.95	5.52	4.07	5.80			

Comments on Plume Geometry:

14 Day Product
The geometric mean ratio of plume angle, and width fall within the acceptable range of 90-111%. The PBE analysis for plume angle, and width demonstrates bioequivalence.

30 Day Product
The geometric mean ratio of plume angle, and width fall within the acceptable range of 90-111%. The 95% Upper Confidence Bound for Linearized Criteria for plume angle demonstrates bioequivalence. The PBE analysis for plume width demonstrate the lack of equivalence between the test and reference products. But as per Nasal guidance, statistical evaluation of plume geometry data for BE is based on point estimates, not PBE.

E. Consult Reviews

Statistical consult from Dr. Donald Schuirmann is attached below:


76979st.doc

F. Attachments

	In Vivo Study (C04-006)	
	Group 1	**Group 2**
SAS Program	 Repl_dp2_Group1.txt	 Repl_dp2_Group2.txt
Statistical Output	 Grp1_STAT.txt	 Grp2_STAT.txt
Plasma Concentration Data	 conc.txt	 conc.txt
PK Data	 pk.txt	 pk.txt

In Vitro Population Bioequivalence Analysis Results

In Vitro Tests	Result Output	
	14 Day Product	30 Day Product
Single Actuation Content Through Container Life	SAC_14Days_LC.doc Pass	SAC_30Days_LC.doc Pass
Droplet Size Distribution by Laser Diffraction	D50_DIST2..doc Fail D50_DIST5..doc Pass SPAN_DIST2..doc Pass SPAN_DIST5..doc Pass	D50_DIST2..doc Fail D50_DIST5..doc Pass SPAN_DIST2..doc Pass SPAN_DIST5..doc Pass
Drug in Small Particle/Droplets by Cascade Impactor	CI_.doc Pass	Test not performed
Spray Pattern	AREA_DIST3..doc Fail AREA_DIST15..doc Fail RATIO_DIST3..doc Pass RATIO_DIST15..doc Pass DMAX_DIST3..doc Fail	AREA_DIST3..doc Fail AREA_DIST15..doc Fail RATIO_DIST3..doc Pass RATIO_DIST15..doc Pass DMAX_DIST3..doc Fail

	DMAX_DIST15..doc Fail DMIN_DIST3..doc Fail DMIN_DIST15..doc Fail	DMAX_DIST15..doc Fail DMIN_DIST3..doc Fail DMIN_DIST15..doc Fail
Plume Geometry	ANGLE_DIST3..doc Pass WIDTH_DIST3..doc Pass	ANGLE_DIST3..doc Pass WIDTH_DIST3..doc Fail
Priming	PRIME.doc Pass	PRIME.doc Pass

Control document #98-392 regarding the Group-by-Treatment interaction discussion is attached below.


98-392.pdf

Control document #03-361 that provides justification for the DBE's recommended blood sampling scheme is attached below.


03-361 fluticasone NS PK sampling.pdf

Memorandums for development and application of PBE analysis method to compare in vitro performance data submitted to support approval of ANDAs for proposed fluticasone propionate nasal spray suspension drug products and for other nasal spray products are attached below.


76504bio_PBE_02-21-06.doc


76504bio_PBE_02-22-06.doc

RLD labeling is attached below.


MiacalcinLabeling.pdf

DBE recommendations for in vitro tests in this submission:

The firm has conducted an in vivo bioequivalence study in addition to in vitro tests. The in vitro tests are not critical for efficacy of the test product. In vitro tests are used as supportive information. Therefore, although some in vitro tests may not meet the equivalence criteria set forth in the draft BA/BE Nasal Guidance, these tests may be acceptable since the in vivo bioequivalence study demonstrate that the 90% confidence intervals for the test to reference ratios for the natural log transformed parameters, AUC_{0-t} $AUC_{0-\infty}$ and C_{max} are within acceptable limits of 80%-125%.

Summary of Bioequivalence Studies Conducted By the Firm:

The original submission dated 12/23/2003 contained an in vivo bioequivalence study (C03-002). This study was a two-way crossover study in 123 subjects. This study was unacceptable due to the following reasons:

1. Subjects Nos. 001 to 045 (Group I subjects) were observed to have positive pre-dose levels of calcitonin for both treatments. The predose value for each subject was more than 5 percent of his Cmax. In addition, these subjects also had increased values of Cmax, AUCt and AUCinf for both treatments relative to the other non-Group I subjects. For subjects with predose plasma concentrations, the CDER Guidance *"Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations"* (3/2003), recommends that if the predose value is more than 5 percent of Cmax, the subject be dropped from all BE study evaluations. Also, since the firm presented evidence suggesting that the sampling tubes from subjects #001 to 045 may have been contaminated, it was not possible to determine what the true caltinonin plasma concentrations were in this group of subjects. Therefore, subject Nos. 001 to 045 were excluded from the statistical analysis of the study. Based on average bioequivalence criteria, after excluding these subjects from the study the 90% confidence intervals for log-transformed AUCt, AUCinf and Cmax did not fall within the acceptable 80-125% range. Therefore, the bioequivalence study #C03-002 was unacceptable.

2. For pharmacokinetic studies, the CEDR Guidance *"Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations"* (3/2003), recommends use of an average bioequivalence criterion to compare bioavailability measures for replicate and nonreplicate bioequivalence studies of both immediate- and modified-release products. In addition, the Agency has not implemented the use of population bioequivalence approach for pharmacokinetic-bioequivalence studies. Therefore, firm's proposal to use population bioequivalence criteria for drawing bioequivalence conclusions for this study was unacceptable.

The firm submitted another study (C04-002) on 4/26/2005. This was an eight period crossover study in 22 subjects. As per the statistical consult, this study is unacceptable. Since the study was conducted in only 22 subjects, it is likely that it did not have sufficient power to show bioequivalence.

The study C04-006 was conducted using 199 subjects and is reviewed in detail in this document. The bioequivalence conclusions in this ANDA are based on the results submitted in this study.

ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Patel

Printed in final on 08/03/2006
V:\FIRMSNZ\NASTECH\LTRS&REV\76979A1204.DOC

Endorsements: (Final with Dates)
HFD-658/ Patel 8/3/06
HFD-658/ Dhariwal 8/3/06
HFD-658/ Thompson
HFD-650/ D. Conner 8/3/06

BIOEQUIVALENCE - INCOMPLETE
Submission dates: 12/10/2004, 4/26/2005, 8/29/2005

✓1. Other (STS) Strength: 200 IU/0.09 mL (14 doses)
Outcome: IC

✓2. Other (STS) Strength: 200 IU/0.09 mL (30 doses)
Outcome: IC

✓3. Bioequivalence Study (STF) Strength: 200 IU/0.09 mL (14 doses)
Clinical Site: Diabetes and Glandular Disease Research, San Antonio, TX
Analytical Site: (b) (4) Outcome: IC

✓4. Bioequivalence Study (STF) Strength: 200 IU/0.09 mL (30 doses)
Clinical Site: SFBC, Miami, FL
Analytical Site: (b) (4) Outcome: IC
8/29/05

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-979
Drug Product Name	Calcitonin Salmon Nasal Spray
Strength	200 IU/0.09 mL (30 doses product)
Applicant Name	Nastech Pharmaceutical Company Inc.
Address	3450 Monte Villa Parkway, Bothell, WA 98021
Submission Date(s)	August 18, 2006
Contact Information	Steven J. Phillips Phone: 425-415-3047; Fax: 425-908-3655
Amendment Date(s)	N/A
Reviewer	Devvrat Patel
First Generic	No

Review of an Amendment

I. Executive Summary

Previously, Nastech submitted in vivo bioequivalence (C04-006) study on its calcitonin salmon nasal spray, 200 IU/0.09 mL (30 doses product, Lot R05002), comparing it to the reference product, Miacalcin® Nasal Spray, 200 IU/0.09 mL (30 doses product, Lot H4043). The bioequivalence study was incomplete due to several deficiencies.

In the current amendment, the firm satisfactorily responded to all deficiencies.

From the DBE point of view, the application is complete with no deficiencies.

II. Table of Contents

III. Review of Submission

In the current amendment, the firm responded to the following deficiencies:

Deficiency 1: *The in vivo bioequivalence study (C04-002) is not acceptable because the 90% confidence intervals for LAUCt are outside the acceptable limits of 80-125%.*

Firm's Response: The firm acknowledged that the bioequivalence study C04-002 is not acceptable.

Reviewer's Comment: The firm's response is acceptable since the firm had conducted another bioequivalence study C04-006 previously.

The following comments and requests for information pertain only to bioequivalence study C04-006:

Deficiency 2: *Please provide content uniformity data for the test product used in the study.*

Firm's Response: The firm noted that the test product used in the study was from lot number R05002 which is the packaged lot number for lot number 05001. The spray content uniformity for packaged lot R05002 is provided below:

Mean: 104% Min: (b) (4) Max: (b) (4)

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

Deficiency 3: *In the Clinical Study Report, pages 49, and 52, you reported 11 adverse events following administration of Miacalcin®. According to Table 12.2.2-1, Summary of Distinct Subjects with Adverse Events by Treatment and Preferred Term, 10 adverse events were reported following administration of Miacalcin®. Please clarify the discrepancy.*

Firm's Response: The firm noted that a single subject (#111) had two adverse events (dizziness) coding to the same Preferred Term. Table 12.2.2-1 counts the distinct number of subjects who experienced the adverse events. If a subject has more than one adverse event that codes to the same preferred term, the subject should be counted only once for that preferred term. Therefore, in this table, for the MedDRA Preferred Term of "Dizziness" there is a count of 1. According to Listing 16.2.9-1, the subject experienced two separate events (classified as dizziness and lightheaded) that were both coded to the Preferred Term of Dizziness.

Reviewer's Response: The firm's response is acceptable.

Deficiency 4*: The subjects in group 2, periods 2, 3 and 4 were dosed on 4/1/2005, 4/2/2005 and 4/3/2005 respectively. Sample analysis began on 4/1/2005. 2005). Please note that analysis of blood samples should be initiated after the completion of clinical portion of the in vivo bioequivalence study.*

Firm's Response: The firm acknowledged that sample analysis began prior to completion of enrollment. However, no samples were analyzed for a particular subject prior to that subject's completion of all study treatment.

The firm noted that only samples from subjects 1-6 were analyzed prior to completion of the clinical portion of the entire study. Moreover, at no time were results from these analyses were available to the firm prior to completion of study treatments for either group.

Subjects in Group 1 were administered doses on March 24-27, 2005, and discharged from the clinic on March 27, 2005. Plasma samples from Group 1 were received by analytical site on March 31, 2005, and sample analysis were started on April 26, 2005.

Subjects in Group 2 were administered doses on March 31, and April 1-3, 2005, and discharged from the clinic on April 3, 2005. Plasma samples from Group 2 were received by analytical site on April 6, 2005. No samples from Group 2 were analyzed until April 26, 2005. The firm also provided a summary table stating the dates the individual subject samples were analyzed.

The firm noted that the analytical site provided the final assay results to pharmacokinetic staff for analysis on June 23, 2005.

Reviewer's Comment: The firm's response is satisfactory.

Deficiency 5*: Please provide a summary table stating the dates the individual subject samples were analyzed.*

Firm's Response: The firm provided a summary table stating the dates the individual subject samples were analyzed.

Reviewer's Comment: The firm's response is satisfactory. Group 1 subjects completed the study prior to the start of blood sample analysis, and analyses of group 1 data meet the bioequivalence criteria.

Comment about baseline calcitonin levels

It is noted that the firm did not measure baseline endogenous calcitonin concentrations because the firm demonstrated that ELISA assay was specific for salmon calcitonin. (b) (4) (b) (4) Salmon Calcitonin ELISA (b) (4) Kit by (b) (4) was used to measure salmon calcitonin. As per the assay kit package insert (attached in Section VI), the cross-reactivity of the salmon calcitonin antiserum was measured against the human calcitonin up to 500 pg/mL, and no cross-reactivity was detected.

E-mail correspondences are attached in Section VI.

IV. Deficiency Comments

None

V. Recommendations

1. The *in vivo* bioequivalence study (C04-06) conducted by Nastech on its calcitonin salmon nasal spray, 200 IU/0.09 mL (30 doses product, Lot R05002), comparing it to the reference product, Miacalcin® Nasal Spray, 200 IU/0.09 mL (30 doses product, Lot H4043), is acceptable. The study demonstrates that Nastech's calcitonin salmon nasal spray, 200 IU/0.09 mL (30 doses product) is bioequivalent to the reference product, Miacalcin® Nasal Spray, 200 IU/0.09 mL (30 doses product).

The application is complete.

VI. Attachments

Email correspondences discussing the baseline calcitonin levels are attached below:

From: Dhariwal, Kuldeep R
Sent: Monday, November 06, 2006 2:15 PM
To: Patel, Devvrat
Subject: FW: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

From: Davit, Barbara M
Sent: Monday, November 06, 2006 2:05 PM
To: Dhariwal, Kuldeep R
Cc: Conner, Dale P
Subject: RE: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

Kuldeep:

Thanks!

Barbara

From: Dhariwal, Kuldeep R
Sent: Monday, November 06, 2006 2:05 PM
To: Davit, Barbara M
Cc: Conner, Dale P; Dhariwal, Kuldeep R
Subject: RE: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

Barbara:

Ten different lots of human EDTA plasma were spiked with Salmon calcitonin at a concentration of 12 pg/mL. The following were the results: [redacted] (b) (4) (mean 11.4).

The firm concluded that the method was specific.

Kuldeep

From: Davit, Barbara M
Sent: Monday, November 06, 2006 1:59 PM
To: Dhariwal, Kuldeep R
Cc: Conner, Dale P
Subject: RE: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

Kuldeep:

What was the conclusion? Was the assay specific for salmon calcitonin?

Thanks,

Barbara

From: Dhariwal, Kuldeep R

Sent: Monday, November 06, 2006 1:57 PM
To: Davit, Barbara M
Cc: Conner, Dale P; Dhariwal, Kuldeep R
Subject: RE: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

Barbara

The firm used [redacted] (b) (4) Salmon Calcitonin ELISA kit. Salmon Calcitonin standard was used. Standard and unknown samples were incubated with [redacted] (b) (4) to salmon calcitonin.

Blank matrix specificity was demonstrated by the analysis of ten separate lots of unspiked human EDTA plasma. Spiked matrix specificity was demonstrated by analyzing ten different lots of human EDTA plasma that were spiked with salmon calcitonin.

Kuldeep

From: Davit, Barbara M
Sent: Friday, November 03, 2006 1:51 PM
To: Dhariwal, Kuldeep R; Conner, Dale P
Subject: RE: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

Kuldeep:

Are there data in the Method Validation report that show that the ELISA used by Nastech can distinguish between salmon and human calcitonin? You and I can discuss this issue later this afternoon.

Thanks,

Barbara

From: Dhariwal, Kuldeep R
Sent: Thursday, October 12, 2006 9:21 AM
To: Conner, Dale P; Davit, Barbara M
Cc: Dhariwal, Kuldeep R; Patel, Devvrat
Subject: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

Dale and Barbara:

Attached please find review of an amendment. Nastech has satisfactorily responded to our minor Bio deficiencies. Therefore, from our point of view, this application is complete.

Y-C had raised the issue of baseline calcitonin levels recently. Yi recently reviewed a protocol from [redacted] (b) (4) for this drug product. The firm proposed that it will measure baseline levels and will submit baseline corrected and uncorrected data. The firm plans to use RIA and a LOQ of 5 pg/mL. I do not think that the baseline levels will be detectable because in the Nastech study only 3 out of 192 subjects had measurable drug level at 0 h with LOQ of 4 pg/mL.

Our concern is Nastech application. Nastech did not measure baseline levels.

Observations from Nastech studies:

1. The first study was reviewed by Moheb and the DBE did not ask for such data. However, the firm indicated that all Group I subjects (subject Nos. 001 to 045) were observed to have positive pre-dose levels of calcitonin for both treatments. This group also had increased values of Cmax, AUCt and AUCinf for both treatments relative to the other groups. A quality control (QC) analysis of the data indicated that the anomalous results in Group I were traceable to a single lot of aprotinin, a calcitonin protease inhibitor, used by the sponsor to prepare the blood collection tubes before sample collection. One lot of aprotinin from commercial vendor was used for tubes for the first 45 subjects, while another lot of aprotinin from the same commercial vendor was used for blood tubes for the other subjects and for the method development and method validation work.

2. The study reviewed by Dev had 192 subjects and only 3 subjects had measurable calcitonin levels at 0 h. Therefore, the firm could not have submitted baseline levels even if we had asked. The firm used ELISA and LOQ was 4 pg/mL. The firm also states that the lower limit of quantitation was originally intended to be 2.00 pg/mL. However, during the course of the validation, neither pool quantified consistently within acceptable limits. Therefore, the lower limit of quantitation was raised to 4.00 pg/mL.

Thanks,

Kuldeep

<< File: 76979A0806.doc >> << File: 76979SignOff.doc >>

From: Dhariwal, Kuldeep R
Sent: Monday, November 06, 2006 2:14 PM
To: Patel, Devvrat
Subject: FW: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

From: Davit, Barbara M
Sent: Monday, November 06, 2006 2:14 PM
To: Dhariwal, Kuldeep R; Conner, Dale P
Subject: RE: REVIEW 76979 Nastech Calcitonin Nasal Spray Dev 8-18-06

Kuldeep:

Please make a note somewhere in the review that baseline concentrations were not measured because Nastech demonstrated the ELISA assay was specific for salmon calcitonin and that human calcitonin did not interfere with the assay. Please attach the emails regarding assay specificity.

Other than that, no changes. Please finalize.

Barbara

(b) (4) Salmon Calcitonin ELISA (b) (4) Kit by (b) (4) (b) (4) is attached below.

Following this page, 6 pages withheld in full (b)(4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-979 APPLICANT: Nastech Pharmaceutical Company Inc.

DRUG PRODUCT: Calcitonin Salmon Nasal Spray
200 IU/0.09 mL (30 doses product)

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,

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

BIOEQUIVALENCE – ACCEPTABLE Submission dates: 8/18/2006

1. **STUDY AMENDMENT** (STA) Strength: 200 IU/0.09 mL
Outcome: AC

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

/s/

Devvrat Patel
11/6/2006 03:17:11 PM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
11/6/2006 03:22:20 PM
BIOPHARMACEUTICS

Barbara Davit
11/7/2006 01:12:56 PM
BIOPHARMACEUTICS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	76-979 **SPONSOR:** Nastech Pharmaceutical Company Inc.
DRUG & DOSAGE FORM:	Calcitonin Salmon Nasal Spray
STRENGTH(S):	200 IU/0.09 mL (30 doses product)
TYPES OF STUDIES:	N/A
CLINICAL STUDY SITE(S):	SFBC, Miami, FL
ANALYTICAL SITE(S):	(b) (4)
STUDY SUMMARY:	In vivo bioequivalence study (C04-006) conducted on 30 days product is acceptable.
DISSOLUTION:	N/A

DSI INSPECTION STATUS

Inspection needed:	NO	**Inspection status:**	**Inspection results:**
First Generic	NO		
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable? N/A

Yes _____ No _____ (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes ____ No ____

AMENDMENT DATE: _____

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Devvrat Patel, Pharm.D. **BRANCH:** V
INITIAL: _____ DATE: _____

TEAM LEADER: Kuldeep R. Dhariwal, Ph.D. **BRANCH:** V
INITIAL: _____ DATE: _____

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: _____ DATE: _____

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

/s/

Barbara Davit
11/7/2006 03:07:03 PM
Signing for Dale P Conner