CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-800

Bioequivalence Review(s)

Cromolyn Sodium
Nasal Solution (26- & 13-mL Fill Sizes)
40 mg/mL (5.2 mg/Actuation)
ANDA #74-800
Reviewer: Gur J.P. Singh
File name: 74800A.401

ALPHARMA
Cassel Drive
Baltimore, MD
Submission Dates:
February 27, April 4, 10 & 23, and May 8, 2001

Review of Bioequivalency Amendments

Barre-National (ALPHARMA) initially submitted this application on December 1, 1995. The application contained a request for waiver of in vivo bioequivalence study requirements for its cromolyn sodium 5.2 mg/actuation nasal sprays (26- and 13-mL fill sizes), and in vitro data comparing performance of delivery devices of the test and reference (Nasalcrom®, Pharmacia and Upjohn, 5.2 mg/spray) products.

The Division of Bioequivalence (DBE) completed its review of this application on April 4, 1996. Based on that review, the firm was informed (letter date: April 16, 1996) that DBE had no further questions, and it was emphasized that the comments expressed in that letter were preliminary, which might be revised upon complete review of the application.

Though DBE completed its review previously, the "Office-Level" approval sheet was not prepared at that time. During preparation for the "Office-level" sign off, it was determined that the application was incomplete due to deficiencies in the Unit Dose (Uniformity of Dose), Priming and Repriming, and Droplet Size Distribution data. Therefore based on the November 21, 2000 amendment to the bioequivalency review, the firm was informed (letter date: November 29, 2000) of deficiencies in the in vitro data.

On December 11 and 22, 2000, the firm submitted its response to the deficiencies cited by DBE. Based the review of that response, the sponsor was informed (letter date: February 5, 2001) of the following:

1. *The prime retention (prime hold) data indicates that, after the 14-day storage period, the prime retention characteristics of the test product are not the same as that of the reference product. You are requested to repeat this test consistent with the reference product labeling. The primed units of the test and reference products should be stored for 14 days, and then reprimed by wasting 2 sprays. The amount of drug in the first spray after priming and the first spray after repriming should be determined for 10 units of each product.*

2. *The droplet size distribution of the test product spray based on D50 and SPAN is not the same as that of the reference product. The ratios of test/reference means are outside the . imit stipulated in the draft Guidance for industry:*

Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action.

You may repeat the test using 10 units of each product. For determination of droplet size distribution by ' ι please provide D10, D50, D90 and SPAN for individual units in an electronic spreadsheet. In addition please provide representative plots of percent transmission vs. time with D10, D50 and D90 vs. time on the same plot over the entire spray duration starting with the actuation trigger. These graphs should be labeled for the sampling time duration.

3. *The Division of Bioequivalence acknowledges lack of availability of certain information due to a proprietary agreement between the devise supplier and the reference product manufacturer. However, for both the 26- and 13-mL products (test and reference), please provide measurements for the metering chamber volume, dip tube internal diameter, actuator tip length and orifice diameter. In addition, you are requested to provide information regarding pre-compression mechanism and swirl chamber design of the test product. If the same information on the reference product is available, it should be submitted as evidence for comparability of pump design.*

On February 27, 2001, the firm submitted its response to above deficiencies. The following comments are based on the review of those data:

Prime Retention/Loss of Prime: The reference listed drug's package insert states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before use. Therefore, the sponsor was requested to provide data supporting the sameness of prime retention characteristics of the test and reference products.

To determine prime retention characteristics the firm primed the test and reference products with five actuations. Spray #6 was collected and analyzed. Each unit was stored upright for 14 days. After that period, each unit was reprimed by wasting 2 sprays and the 3rd (9th from the beginning of use) spray was analyzed for the amount of drug per spray in 10 units of the test (Lot #PP0852F) and reference(Lot #49DYC) products. The results of prime retention testing are summarized in the following table:

Spray #	Product	Mean	%CV	TEST/REF
6 (Initial)	Test	107.9	2.7	0.98
	Ref	110.1	3.1	
9 (14 days)	Test	105.3	3.4	0.97
	Ref	108.5	3.4	

Based on the above data, the prime retention properties of the test product are similar to those of the reference product. Consistent with the repriming instructions given in the

RLD patient package insert, the test product also delivers the labeled amount of drug per actuation after a storage period of 14 days.

Droplet Size Distribution: The droplet size distribution of the test and reference products was studied using Malvern/Insitec at Beginning (immediately after priming), Middle (actuations 97-105) and End (actuations 152-160) sectors of product life. The test was performed at three distances (3, 6 and 12 cm) from the actuator orifice. The test and reference lot used in this testing were PP0852F and 65FDM (Exp. 8/02), respectively.

Annova automated actuator was used to actuate the test and reference products. The actuation parameters included the following:

Actuation force:	4.5 kg,
Dose time:	15 msec
Hold time:	1 sec
Return time:	20 msec.

The following operating conditions were used for the Malvern/Insitec apparatus:

Test duration :	300 msec
Data acquisition rate:	1000 Hz
Acquisition duty cycle:	0%,
Experimental trigger:	95% transmission.

The firm provided the raw D10, D50 D90 and SPAN data. It also provided the requested plots of Time vs. D10, D50, D90 and % transmission and computer outputs of the laser diffraction analyses.

The droplet size distribution data were found to be unacceptable. In a teleconference on March March 13, 2001, the firm was requested to repeat the test.

On March 23, March 2001, the sponsor indicated that it wished to replace actuator on the test product. The firm was informed that it should repeat three in vitro tests including Unit Spray Content, Droplet Size distribution and Spray pattern.

The sponsor submitted data regarding above tests on April 4 and 10, 2001. A brief survey of that submission indicated that supporting data for unit dose and spray pattern were still not submitted. On April 13, 2001 the firm was requested to submit the required data. The firm's response was submitted on April 23, 2001, which was still deficient. On May 7, 2001, the firm was requested to address the Agency questions on spray pattern testing included in the April 23 submission. The firm submitted its response on May 8, 2000. The following review is based on the information submitted April 4, 10, 23 and May 8, 2001.

Unit Spray Content

The Unit Spray Content determinations were based o· ınalysis of single actuations of the primed units of test and reference products, at the beginning (actuations 6 & 7) and end (actuations 204 &205). The units were actuated using AnnovaSysytem's automated actuators operated at the following parameters:

Actuation force:	5 kg
Dose time:	25 msec
Return time:	20 msec
Hold time:	1 sec
Delay time:	1 sec

The following table provides a summary of the unit spray data:

Sector	Product	Arith. Mean	%CV	Geomean	Test/Ref		
					Arith. Mean	Geomean	*p*-value
Beg	Test	107.86	6.48	107.64	1.04	1.03	0.12
	Ref	104.18	2.69	104.14			
End	Test	111.98	3.74	111.91	1.05	1.05	0.01
	Ref	106.42	1.26	106.41			

Based on the above data, the unit spray content of the test product is within the acceptable range of 0.9-1.11 stipulated in the draft BA/BE guidance and used by the Division of Bioequivalence for evaluations of similar data on other solution nasal spray applications.

A review of the raw data indicated that the Unit Spray Content data also conformed to the following recommendations in the draft guidance regarding the 'first-tier' based on 10 units:

Not more than one unit should be outside ɔf the label claim, and none should be outside the ınd

Mean values should not outside 85-115%.

Droplet Size Distribution

The droplet size distribution was studied based on testing conditions mentioned above. Based on % transmission the plume was divided into three portions (initial middle, and dissipating). The middle portion represents the fully formed plume where obscuration of the laser beam highest and stable relative to that of the other two portions. In other applications currently under review, for determination of equivalence, the DBE is using the D50 and Span data for the fully formed plume. The following tables provide a summary of the D50 and SPAN data for the fully formed plume:

D50

Product	Distance	Sector	Arith. Mean	% CV	Geomean	Test/Ref		*p*-value
						Arith. Mean	Geomean	
		Beg	37.49	5.94	37.42	1.02	1.02	0.3446
TEST	3 Cm	Mid	35.82	6.98	35.74	1.00	1.00	0.8209
		End	36.67	5.57	36.61	1.01	1.01	0.4370
		Beg	36.90	6.41	36.83			
REF	3 Cm	Mid	35.99	7.27	35.90			
		End	36.22	6.27	36.15			
		Beg	38.27	2.02	38.26	1.02	1.02	0.0047
TEST	6 Cm	Mid	38.36	3.35	38.33	1.01	1.01	0.1430
		End	38.92	3.82	38.89	1.03	1.03	0.0026
		Beg	37.59	2.71	37.57			
REF	6 Cm	Mid	37.90	3.19	37.88			
		End	37.65	4.23	37.62			
		Beg	51.24	8.75	50.97	1.01	1.01	0.4694
TEST	12 Cm	Mid	51.67	4.78	51.61	1.04	1.04	0.0006
		End	51.76	3.76	51.73	1.04	1.04	0.0004
		Beg	50.59	3.72	50.56			
REF	12 Cm	Mid	49.50	5.28	49.43			
		End	49.77	4.22	49.73			

SPAN

Product	Distance	Sector	Arith. Mean	% CV	Geomean	Test/Ref		p-value
						Arith. Mean	Geomean	
		Beg	1.72	7.01	1.72	1.00	1.00	0.8394
TEST	3 Cm	Mid	1.76	5.69	1.75	0.99	0.99	0.4445
		End	1.76	5.36	1.75	0.98	0.98	0.2870
		Beg	1.73	8.28	1.72			
REF	3 Cm	Mid	1.78	8.39	1.78			
		End	1.79	9.02	1.78			
		Beg	1.13	9.31	1.13	0.94	0.94	0.0257
TEST	6 Cm	Mid	1.15	8.86	1.15	0.98	0.98	0.4875
		End	1.16	7.56	1.16	0.98	0.98	0.3279
		Beg	1.20	10.08	1.19			
REF	6 Cm	Mid	1.17	11.32	1.16			
		End	1.19	11.39	1.18			
		Beg	1.10	5.79	1.09	1.06	1.06	0.0008
TEST	12 Cm	Mid	1.02	5.16	1.02	0.98	0.98	0.1401
		End	1.02	5.57	1.02	0.99	0.99	0.6017
		Beg	1.03	6.27	1.03			
REF	12 Cm	Mid	1.05	6.61	1.04			
		End	1.03	7.55	1.03			

Based on the above data:

The test/reference geometric mean ratios for the D50 data are within the acceptable the limit of ipulated in the draft Nasal BA/BE guidance. The test and reference products exhibited approximately the same variability (%CV) in D50.

The test/reference geometric mean ratios for the SPAN data are within the acceptable the limit stipulated in the draft Nasal BA/BE guidance. The test and reference products exhibited approximately same variability (%CV) in SPAN.

Droplet size distribution conducted by the firm is acceptable.

In the March 13, 2001 teleconference the firm was also requested to provide data regarding duration of the test and reference product's fully formed plume as well as the entire spray. These data were requested for information only, *not to be used in determination of equivalence of in vitro performance*. Reviewer's summary of the plume duration data is as follows:

Distance	Sector	Product		Plume Duration (sec)		TEST/REF	
				Stable Portion	Entire Spray	Stable Portion	Entire Spray
3	Beginning	TEST	Mean	0.095	0.200	0.92	1.09
			%CV	10.291	12.071		
			Geomean	0.094	0.199	0.92	1.09
		REF	Mean	0.103	0.183		
			%CV	6.443	10.950		
			Geomean	0.102	0.182		
3	Middle	TEST	Mean	0.105	0.172	0.95	1.03
			%CV	5.523	3.721		
			Geomean	0.105	0.172	0.95	1.03
		REF	Mean	0.111	0.167		
			%CV	6.461	5.595		
			Geomean	0.111	0.167		
3	End	TEST	Mean	0.123	0.174	1.10	1.02
			%CV	5.693	3.877		
			Geomean	0.123	0.174	1.10	1.02
		REF	Mean	0.112	0.171		
			%CV	5.151	5.505		
			Geomean	0.112	0.171		
6	Beginning	TEST	Mean	0.097	0.194	0.92	1.01
			%CV	6.578	5.796		
			Geomean	0.097	0.194	0.92	1.01
		REF	Mean	0.106	0.192		
			%CV	6.185	5.461		
			Geomean	0.105	0.192		
6	Middle	TEST	Mean	0.103	0.197	0.91	1.03
			%CV	5.387	5.933		
			Geomean	0.103	0.196	0.91	1.03
		REF	Mean	0.114	0.191		
			%CV	8.347	5.110		
			Geomean	0.113	0.191		
6	End	TEST	Mean	0.107	0.200	1.00	1.05
			%CV	7.050	5.625		
			Geomean	0.107	0.200	1.01	1.05
		REF	Mean	0.107	0.191		
			%CV	11.429	5.587		

			Geomean	0.106	0.191		
12	Beginning	TEST	Mean	0.128	0.290	1.21	1.51
			%CV	12.587	4.922		
			Geomean	0.127	0.290	1.20	1.51
		REF	Mean	0.106	0.192		
			%CV	6.185	5.461		
			Geomean	0.105	0.192		
12	Middle	TEST	Mean	0.100	0.295	0.95	1.54
			%CV	3.074	2.564		
			Geomean	0.100	0.295	0.95	1.54
		REF	Mean	0.106	0.192		
			%CV	6.185	5.461		
			Geomean	0.105	0.192		
12	End	TEST	Mean	0.108	0.288	1.02	1.50
			%CV	7.088	5.913		
			Geomean	0.107	0.287	1.02	1.50
		REF	Mean	0.106	0.192		
			%CV	6.185	5.461		
			Geomean	0.105	0.192		

The above data are presented for information only, no comments are warranted.

Spray Pattern

The firm submitted spray pattern data for 10 units of the test and reference products. The units were actuated using Annova System's automated actuators operated at the following parameters:

Actuation force:	4.5 kg
Dose time:	30 msec
Return time:	20 msec
Hold time:	0.5 sec

The sprays were actuated on to chromatography paper at distances of 3, 5 and 7 cm from the orifice. The patterns of dried sprays were visualized using 2,3,5-triphenyltetrazolium chloride solution in methanol. The firm submitted color photocopies showing images of spray patterns with lines indicating Dmax and Dmin.

The patterns were manually quantitated in terms of longest diameter (Dmax), shortest diameter (Dmin) and Ovality ratio (Dmax/Dmin). The following table provides the reviewer's summary of the spray pattern data:

Distance	Parameter	Product	Sector	Arith. Mean	% CV	Geomean	Test/Ref Arith. Mean	Test/Ref Geomean	p
		TEST	Beg	5.03	8.94	5.01	0.99	0.99	0.835
	Dmax		End	4.55	8.17	4.54	1.01	1.01	0.778
		REF	Beg	5.07	5.50	5.06			
			End	4.50	6.54	4.49			
3		TEST	Beg	4.18	12.24	4.15	0.95	0.95	0.369
	Dmin		End	3.78	7.67	3.77	1.10	1.10	0.016
		REF	Beg	4.38	9.67	4.36			
			End	3.44	4.59	3.44			
		TEST	Beg	1.22	14.87	1.21	1.05	1.04	0.396
	Oval. Ratio		End	1.21	5.80	1.20	0.92	0.92	0.049
		REF	Beg	1.16	6.08	1.16			
			End	1.31	7.80	1.31			
		TEST	Beg	6.68	10.32	6.65	0.99	0.99	0.835
	Dmax		End	6.42	9.45	6.39	0.99	0.99	0.811
		REF	Beg	6.73	8.69	6.71			
			End	6.49	6.79	6.48			
5		TEST	Beg	5.71	9.06	5.69	1.01	1.01	0.828
	Dmin		End	5.46	8.11	5.44	1.04	1.04	0.404
		REF	Beg	5.68	10.62	5.65			
			End	5.27	12.90	5.23			
		TEST	Beg	1.17	9.87	1.17	0.99	0.98	0.751
	Oval. Ratio		End	1.18	7.02	1.17	0.95	0.95	0.196
		REF	Beg	1.19	8.77	1.19			
			End	1.24	9.81	1.24			
		TEST	Beg	8.37	7.70	8.35	1.05	1.05	0.302
	Dmax		End	7.95	5.97	7.94	1.00	1.00	1.000
		REF	Beg	7.96	8.52	7.94			
			End	7.95	6.31	7.94			
7		TEST	Beg	6.73	9.98	6.70	1.08	1.08	0.089
	Dmin		End	6.40	6.91	6.39	1.05	1.05	0.216
		REF	Beg	6.24	8.55	6.22			
			End	6.12	10.47	6.09			
		TEST	Beg	1.25	7.05	1.25	0.97	0.98	0.531
	Oval. Ratio		End	1.25	7.92	1.24	0.95	0.95	0.292

REF	Beg	1.28	10.12	1.28
	End	1.31	12.87	1.30

In the above data test/ref ratios based on geometric means were within the range stipulated in the draft Nasal BA/BE guidance. The variability of the test and reference products was comparable. These data are indicative of comparable spray patterns of test and reference products.

Device Comparability

The ALPHARMA product uses the Valois pump 5) and actuator . The innovator product uses similar pump and actuator manufactured by Valois. Comparability of the delivery devices used in the test and reference product is also evident from comparable performance based on the in vitro testing.

Overall Comments

1. The formulation of the test and reference products have been previously found to be qualitatively (Q_1) and quantitatively (Q_2) the same as that of the reference product (see the April 4, 1996 DBE review).

2. The Priming and Tail off data are acceptable. The Prime Retention (prime hold) data indicates that the prime retention characteristics of the test product after the 14-day storage period are the same.

3. Based on the Unit Spray Content data, Droplet Size Distribution data, and Spray pattern analyses reviewed herein, the in vitro performance of the test product is within range stipulated in the draft guidance. The plume geometry data were found to be acceptable previously.

4. This application was initially submitted several years before the issuance of the June 99 draft nasal BA/BE guidance. Therefore, it is based on in vitro data from single lots of the test and reference products. The criteria used for evaluation of the test are similar to those used for other nasal spray applications (ANDA 74-830 and 75-702) submitted before issuance of the draft guidance. Comparability of in vitro performance of the test and reference products was established based on ratios of geometric means and consideration of relative variability of these drug products.

Recommendation

The formulations of the test product is Q1 and Q2 the same as that of the reference product. The in vitro testing conducted by Barre-National (ALPHARMA) comparing its cromolyn sodium nasal sprays (5.2 mg/spray, 26- and 13-mL fill sizes) and the reference product (Nasalcrom®, Pharmacia and Upjohn, 5.2 mg/spray) has been found to be acceptable to the Division of Bioequivalence. In terms of dose delivered per actuation, the size shape and droplet size distribution of the spray, the test product's performance is similar to that of the reference product. Therefore the Division of Bioequivalence deems the test product to be equivalent to the reference product in dose delivery and performance of the delivery device.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ Date 5/10/2001

Concur: _____ Date 5/31/2001
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-800 APPLICANT: ALPHARMA

DRUG PRODUCT: Cromolyn Sodium Nasal Solution, 40 mg/mL
(26 and 13-mL fill sizes)

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

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

Sincerely yours,

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

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

BIOQUIVALENCY DEFICIENCIES

ANDA: 74-800 APPLICANT: ALPHARMA

DRUG PRODUCT: Cromolyn Sodium Nasal Solution, 40 mg/mL

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

1. The prime retention (prime hold) data indicates that, after the 14-day storage period, the prime retention characteristics of the test product are not the same as that of the reference product. You are requested to repeat this test consistent with the reference product labeling. The primed units of the test and reference products should be stored for 14 days, and then reprimed by *wasting 2 sprays*. The amount of drug in the first spray after priming and the first spray after repriming should be determined for 10 units of each product.

2. The droplet size distribution of the test product spray based on D50 and SPAN is not the same as that of the reference product. The ratios of test/reference means are outside the 90-111% limit stipulated in the draft *Guidance for industry: Bioavaialbility and bioequivalence studies for nasal aerosols and nasal sprays for local action*.

   You may repeat the test using 10 units of each product. For determination of droplet size distribution by laser diffraction please provide D10, D50, D90 and SPAN for individual units in an electronic spreadsheet. In addition please provide representative plots of percent transmission vs. time with D10, D50 and D90 vs. time on the same plot over the entire spray duration starting with the actuation trigger. These graphs should be labeled for the sampling time duration.

3. The Division of Bioequivalence acknowledges lack of availability of certain information due to a proprietary agreement between the devise supplier and the reference product manufacturer. However, for both the 26- and 13-mL products (test and reference), please provide measurements for the metering chamber volume, dip tube internal diameter,

actuator tip length and orifice diameter. In addition, you are requested to provide information regarding pre-compression mechanism and swirl chamber design of the test product. If the same information on the reference product is available, it should be submitted as evidence for comparability of pump design.

Sincerely yours,

Dale P. Conner

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

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Cassel Drive
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Submission Dates:
11 and 21 December 2000

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The Division of Bioequivalence (DBE) completed its review of this application on April 4, 1996. Based on that review, the firm was informed (letter date: April 16, 1996) that DBE had no further questions, and it was emphasized that the comments expressed in that letter were preliminary, which may be revised upon complete review of the application.

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1. *Unit Dose/Content Uniformity: The unit dose was based on weight measurements. The amount of drug per actuation should be based on a validated chromatographic/chemical assay. The test should be performed at Beginning and End life sectors using single actuations from ten units from one lot of the test and reference products.*

2. *Priming, loss of prime, and tail off: Please submit data (based on a validated chromatographic/chemical assay) to support comparative performance of the test and reference products with regard to priming, loss of prime, and tail off.*

   The reference listed drug's patient package insert states that for the first time use the pump should be primed by wasting 5 actuations. The package insert further states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before using again.

Comparative tail off data should be based on actuations representing the labeled end of product life to depletion.

3. *Droplet Size Distribution: You determined droplet size distribution by laser diffraction only at the Beginning sector of the product life. This test should be performed at all three sectors (Beginning, Middle and End). The test should be performed using 10 units of the test and reference products.*

The 26- and 13-mL fill sizes use the same pump and actuator. Therefore separate testing of the 13-mL test product is not warranted, with the exception of priming which may be influenced by the length of the dip tube and a change in the dead volume of the pump.

In addition to the above in vitro data, please submit evidence supporting comparability of the test and reference devices. The evidence should include manufacturer and model numbers of the pumps and actuators, technical drawings with legible dimension of the pump and the actuator (including the tip, orifice, and the actuator insert nominal angle).

The firm has submitted the requested Unit Dose and Priming (December 21 amendment) and Droplet size distribution (11 December amendment) data. The 11 December amendment also contains Unit Dose and Priming data based on gravimetric measurements. The firm has been previously informed that such data were not acceptable to support bioequivalence of test and reference products. Therefore the following evaluation of the Priming/Repriming and Unit Dose data utilizes information based on an analysis given in the 21 December amendment.

Priming: The test and reference product units were actuated using InnovaSystem's automated actuation device designed for nasal sprays, with the following parameters:

Actuation force:	5 kg
Dose time:	25 msec
Return time:	16 msec
Hold time:	1 sec
Delay time:	1 sec

Priming characteristics of the test products were determined in terms of the amount of cromolyn sodium per spray beginning with the first actuation. The amount of drug in each actuation was determined using a validated assay.

Priming data for the 13-mL and 26-mL products are summarized on pages 21 and 22, vol. 41. Based on these data, both fill sizes of the test product deliver the labeled amount of cromolyn sodium by the 5th spray. Therefore the test products meet priming characteristics of the reference product.

Prime Retention/Loss of Prime: The reference listed drug's package insert states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before use. Therefore, the sponsor was requested to provide data supporting the sameness of prime retention characteristics of the test and reference products.

To determine prime retention characteristics the firm primed the test and reference products with five actuations. Another 100 actuations were wasted and the amount of drug present in spray #106 was determined. The units were left unused for 7 and 14 days. At the end of these periods, spray #107 was analyzed to determine the amount of drug.

Prime retention testing was performed on the 26-mL product only. As indicated in the 30 November Agency letter, separate testing for the 13-mL product may not be warranted because the 26- and 13-mL fill sizes use the same pump and actuator. The data showing 14-day prime retention are presented on page 39, vol. 4.1. These data indicate that, after the 14-day storage period, the test product delivered 90.6% of the label claim compared with 107.7% on day 1, a drop of 17.1%. One of the 10 test product bottles yielded 71.2% of label claim, which is outside the 80-120% of the label claim. After the same storage period, the reference product delivered 105.8% of the label claim compared with 114.4% on day 1. These data indicate that the prime retention characteristics of the test and reference products are *not* similar.

It is notable that the sponsor's testing of prime retention was not consistent with the reference product labeling. After the 14-day hold period, the next actuation (#107) was assayed for drug content, instead of wasting two sprays (as indicated in the RLD labeling) and analyzing the third spray (#109). Based on the prime retention data submitted by the firm, it is difficult to deduce whether the test product would have demonstrated same prime retention as the reference product, if the test was conducted consistent with the RLD labeling.

Tail Off: The sponsor determined comparative tail off characteristics of the test and reference products. Based on the data presented in vol. 4.1, pages 25-28, the test product delivers greater number of full medication doses. It starts tailing off at actuation #218 and the reference product tails off at actuation#201. The test product's tail off is no more erratic than that of the reference product. The tail off data are acceptable.

Unit Dose/Content Uniformity: In the 30 November 2000 letter, the sponsor was informed that unit dose data were requested only for 26-mL product, and separate testing for the 13-mL product was not requested because the 26- and 13-mL fill sizes use the same pump and actuator. Nonetheless, the priming data for the 13-mL product indicates that at the beginning of the product use (6th actuation), the test product delivers 104.6% of the label claim with a test/reference ratio of 0.96.

For the 26-mL product, this test was performed at the Beginning (actuations 6 and 7) and End of sectors (actuations 203 and 204 for Test, 199 and 200 for RLD) of the primed products. A summary of the unit dose data, and raw unit dose data are given on pages 24 and 33-36 (vol. 4.1), respectively. Based on these data the test/reference ratios for unit spray content at the beginning and end sectors were in the range of 0.96-0.97. None of the units (n=10) was outside 80-120% of the label claim. Variability (CV) of the test and reference products was in the range of 1.1-6.4% and 1.8-15.0%.

The unit dose data submitted by the sponsor are acceptable.

Droplet Size Distribution: The droplet size distribution of the test and reference products was studied using Malvern Mastersizer at Beginning (immediately after priming), Middle (actuations 97-105) and End (actuations 152-160) sectors of product life. The test was performed at three distances (3, 6 and 12 cm) from the orifice.

Droplet size distribution was characterized by D50 (median diameter) and SPAN. A summary of the relevant data is provided on pages 68 and 70 (vol. 5.1). Based on these data the test/reference ratios for D50 and SPAN were in the range of 1.00-1.13 and 1.09-1.19 respectively.. For D50, variability (CV) of the test and reference products was in the range of 6.34-22.44% and 7.68- 20.44%, respectively. For SPAN, variability (CV) of the test and reference products was in the range of 8.02-18.03% and 7.63-17.17%, respectively. The sponsor did not provide raw data. Therefore, the reviewer could not determine statistical significance of the test-reference differences.

Based on the ratio of means, the test product's D50 and SPAN fall outside the 90-111% limits stipulated in the draft *Guidance for industry: Bioavailbility and bioequivalence studies for nasal aerosols and nasal sprays for local action.* Therefore, the droplet size distribution data *are not acceptable.*

Device Comparability: In the 29 November letter, the firm was requested to provide information to establish comparability of the test and reference product devices. The sponsor submitted a technical drawing of the test product, with a statement that such information is not available for the reference product because of proprietary agreement between the supplier and the RLD manufacturer.

DBE acknowledges lack of availability of certain information due to the proprietary agreement. However, for both the 26- and 13-mL products, the sponsor should be able to determine the metering chamber volume, dip tube internal diameter, actuator tip length and orifice diameter.

Comments

1. The priming and tail off data are acceptable.

2. The unit dose data are acceptable.

3. The prime retention (prime hold) data indicates that the prime retention characteristics of the test product after the 14-day storage period are not the same.

4. The droplet size distribution of the test product spray based on D50 and SPAN is not the same as that of the reference product.

5. For both the 26- and 13-mL products, the sponsor should provide information regarding the metering chamber volume, dip tube internal diameter, actuator tip length and orifice diameter. In addition the firm should be requested to provide information regarding pre-compression mechanism and swirl chamber design of the test product. If the same information on the reference product is available, it should be submitted as evidence for comparability of pump design.

Recommendation

The in vitro testing conducted by Barre-National (ALPHARMA) comparing its cromolyn sodium nasals sprays (5.2 mg/spray, 26- and 13-mL fill sizes) and the reference product (Nasalcrom®, Pharmacia and Upjohn, 5.2 mg/spray) is incomplete due to deficiencies indicated in comments 3 - 5.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence

Gurjarpal Singh 2/2/01

RD INITIALED S. NERURKAR
for FT INITIALED S. NERURKAR Moharowal Date 2/2/01

Concur: Dale P. Conner Date 2/2/01
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

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BIOQUIVALENCY DEFICIENCIES

ANDA: 74-800 APPLICANT: Barre-National (ALPHARMA)

DRUG PRODUCT: Cromolyn Sodium Nasal Solution, 40 mg/mL

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

1. ***Unit Dose/Content Uniformity:*** The unit dose was based on weight measurements. The amount of drug per actuation should be based on a validated chromatographic/chemical assay. The test should be performed at Beginning and End life sectors using single actuations from ten units from one lot of the test and reference products.

2. ***Priming, loss of prime, and tail off:*** Please submit data (based on a validated chromatographic/chemical assay) to support comparative performance of then test and reference products with regard to priming, loss of prime, and tail off.

   The reference listed drug's package insert states that for the first time use the pump should be primed by wasting 5 actuations. The package insert further states that if the product is not used for 14 days, it should be reprimed by wasting 2 sprays before using again.

   Comparative tail off data should be based on actuations representing the labeled end of product life to depletion.

3. ***Droplet Size Distribution:*** You determined droplet size distribution by laser diffraction only at the Beginning sector of the product life. This test should be performed at all three sector (Beginning, Middle and End) sectors. The test should be performed using 10 units of the test and reference products.

The 26- and 13-mL fill sizes use the same pump and actuator. Therefore separate testing of the 13-mL test product is not warranted, with the exception of priming which may be influenced

by the length of the dip tube and a change in the dead volume of the pump.

In addition to the above in vitro data, please submit evidence supporting comparability of the test and reference devices. The evidence should include manufacturer and model numbers of the pumps and actuators, technical drawings with legible dimension of the pump and the actuator (including the tip, orifice, and the actuator insert nominal angle).

Sincerely yours,

for Barbara M. Gavil

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

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The 26- and 13-mL fill sizes use the same pump and actuator. Therefore separate testing of the 13-mL test product is not warranted, with the exception of priming which may be influenced

by the length of the dip tube and a change in the dead volume of the pump.

In addition to the above in vitro data, please submit evidence supporting comparability of the test and reference devices. The evidence should include manufacturer and model numbers of the pumps and actuators, technical drawings with legible dimension of the pump and the actuator (including the tip, orifice, and the actuator insert nominal angle).

Sincerely yours,

Barbara M. Saint

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

APR 4 1996

Cromolyn Sodium Nasal Solution (Nasal Spray)	Barre-National
40 mg/mL, 13 mL and 26 mL nasal spray containers	Baltimore, MD
ANDA #74800	Submission Date:
Reviewer: Moo Park	December 1, 1995
Filename: 74800W.D95	

Review of two Waiver Requests

I. Objective

Review of Barre-National's waiver requests on two package sizes, 13 mL and 26 mL, of Cromolyn Sodium Nasal Solution, 40 mg/mL strength. Reference products are Fisons' Nasalcrom®, 40 mg/mL, packaged in 13 mL and 26 mL nasal spray containers.

II. Background

Chemically, cromolyn sodium is the disodium salt of 1,3-bis (2-carboxychromon-5-yloxy)-2-hydroxypropane. The empirical formula is $C_{23}H_{14}Na_2O_{11}$.

- Pharmacologic Category: Mast cell stabilizer/antiallergic
- Therapeutic Category: Antiallergic
- Absorption: Cromolyn sodium is poorly absorbed from the gastrointestinal tract. After instillation, less than 7% of the total dose administered is absorbed and is rapidly excreted unchanged in the bile and urine. The remainder of the dose is expelled from the nose, or swallowed and excreted via the alimentary tract.
- Dosing: After priming the delivery system, each actuation of the unit delivers a metered spray containing 5.2 mg of cromolyn sodium. The contents of one bottle delivers at least 100 sprays (13 mL bottle) or 200 sprays (26 mL bottle).

III. Requirements for waiver

In vitro data showing the test and reference products are same:

- Formulation
- Performance of the finger pump: Volume per actuation, plume

geometry, spray pattern, droplet size, number of doses deliverable, etc.

IV. Formulation

Formulations for the test and reference products are identical. The test formulation is shown in Table 1.

Table 1. Test Formulation

Ingredient	Amount
Cromolyn sodium	
Benzalkonium chloride	
Edetate sodium	
Purified water	
Total	

V. *In Vitro* Evaluation of finger pump

1. VOLUME (OR DOSE) DELIVERED

The average volume delivered for both the Nasalcrom® and Barre product in single and multiple actuation testing was 138 µl per spray. The prescribed dose is one spray per nostril hence two sprays. Thus the volume of a typical dose based on this test would be 276 µl. In the dose delivered through use life study, the average volumes delivered per dose were determined as 272 µl for the 13 ml Nasalcrom®, 271 µl for the 26 ml Nasalcrom®, 271 µl for the 13 ml Barre product and 274 µl for the 26 ml Barre product. These data indicate that the delivery from the device used on Barre product is equivalent to the Nasalcrom®.

TABLE 2. VOLUME DELIVERED PER SINGLE ACTUATION

SAMPLE	AVERAGE Target 130 µL N=30	RSD
Nasalcrom®		
BARRE FORMULATION		

TABLE 3. VOLUME DELIVERED PER MULTIPLE ACTUATION

SAMPLE	AVERAGE Target 130 µL N=20	RSD
Nasalcrom®	138 µL	1.54%
BARRE FORMULATION	138 µL	1.35%

TABLE 4. CROMOLYN SODIUM DELIVERED PER SINGLE ACTUATION

SAMPLE	AVERAGE Target = 5.2 mg N = 30	RSD
Nasalcrom®	5.45 mg	2.71%
BARRE Product	5.56 mg	1.89%

TABLE 5. CROMOLYN SODIUM DELIVERED PER MULTIPLE ACTUATION

SAMPLE	AVERAGE Target = 5.2 mg N = 20	RSD
Nasalcrom®	5.46 mg	2.31%
BARRE FORMULATION	5.58 mg	1.28%

2. DOSE DELIVERED THROUGH THE USE LIFE OF THE UNIT

Ten samples for both bottle sizes of the Cromolyn Sodium Nasal Solution, USP (Barre formulation lot# PH5546) utilizing three lots of Valois VP3/140F pumps (lot#'s: 13 ml - 018828, 018328, 018007 & 26 ml - 018829, 018329, 018008) were evaluated. In addition, ten samples for both bottle sizes of the Nasalcrom® using three separate lots (lot#'s: 13 ml - ALF5E, ALF503E, ALF504E & 26 ml - AKE507E, AKE503G, AKE48D) were evaluated in this study.

Each set of two sprays represents one dose - 1 spray per nostril. For the 13 ml bottle size, the claimed use life is 100 sprays (or 50 doses) for the 26 ml the claim is 200 sprays (100 doses). From the measured spray weights, the quantity of Cromolyn Sodium

delivered was calculated in the same fashion as outlined for the Volume (or dose) Delivered. A suitable dose of two sprays was considered 10.4 mg Cromolyn Sodium ± 33%. Therefore, it was expected that the product would deliver 50 (13 ml size) or 100 (26 ml size) consecutive doses after priming within the range of 10.4 mg Cromolyn Sodium ± 33% (limits 7.0 mg to 13.8 mg).

From Figures 1 through 4, it is apparent that neither bottle size for both the Nasalcrom® and Barre product met the criteria of delivering 10.4 mg ± 33% Cromolyn Sodium per dose during the expected life of the product.

13 ml Bottle Size

Figure 1. Dose Delivered Through Use Life of Nasalcrom®
Target = 10.4 mg (*limits 7.0 to 13.8 mg*)

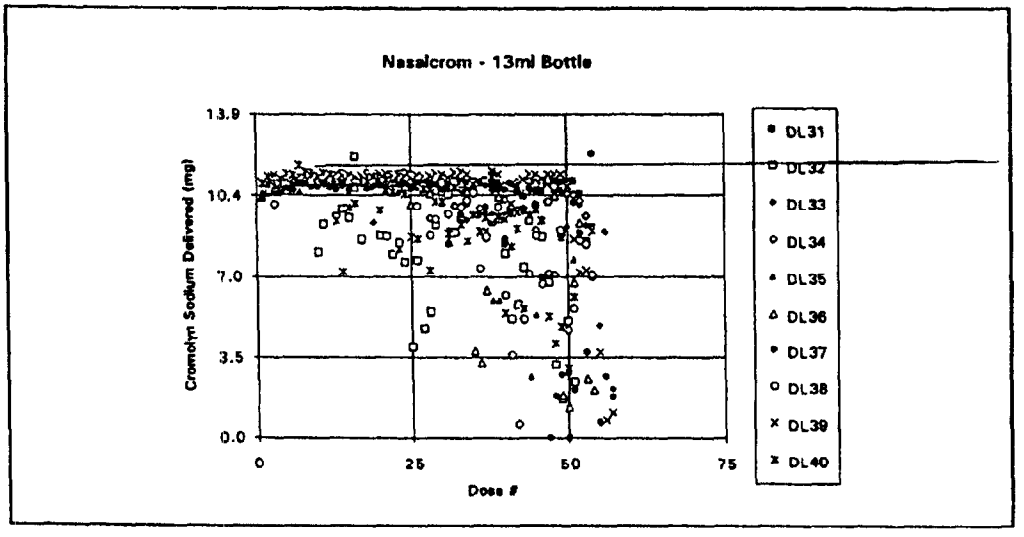
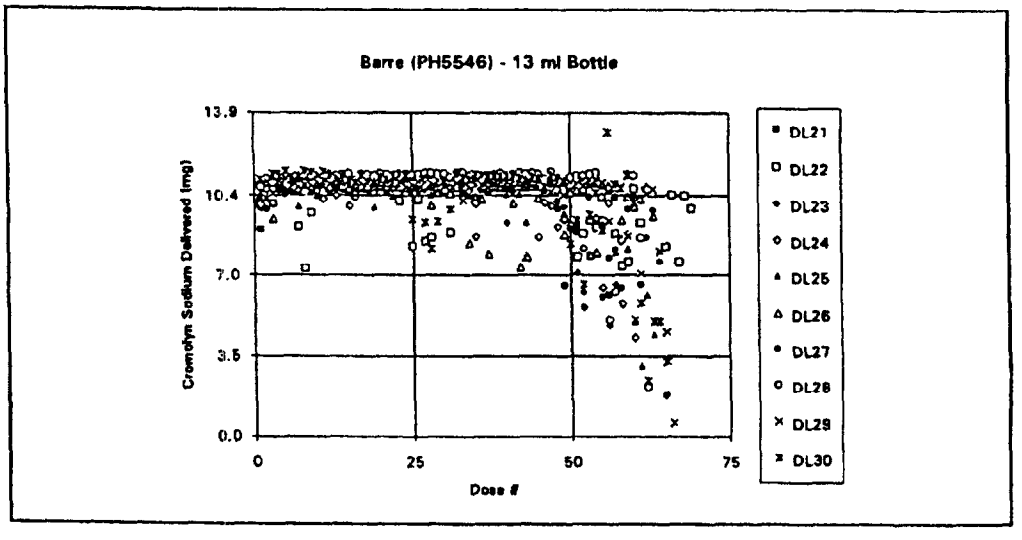


Figure 2. Dose Delivered Through Use Life of Barre Product
Target = 10.4 mg (limits 7.0 to 13.8 mg)



26 ml Bottle Size

Figure 3. Dose Delivered Through Use Life of Nasalcrom®
Target = 10.4 mg (*limits 7.0 to 13.8 mg*)

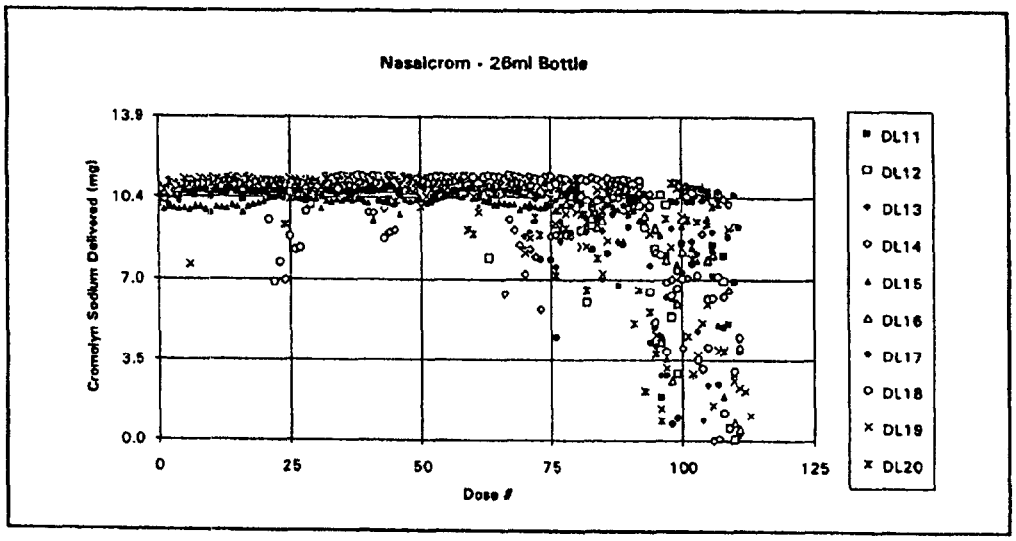
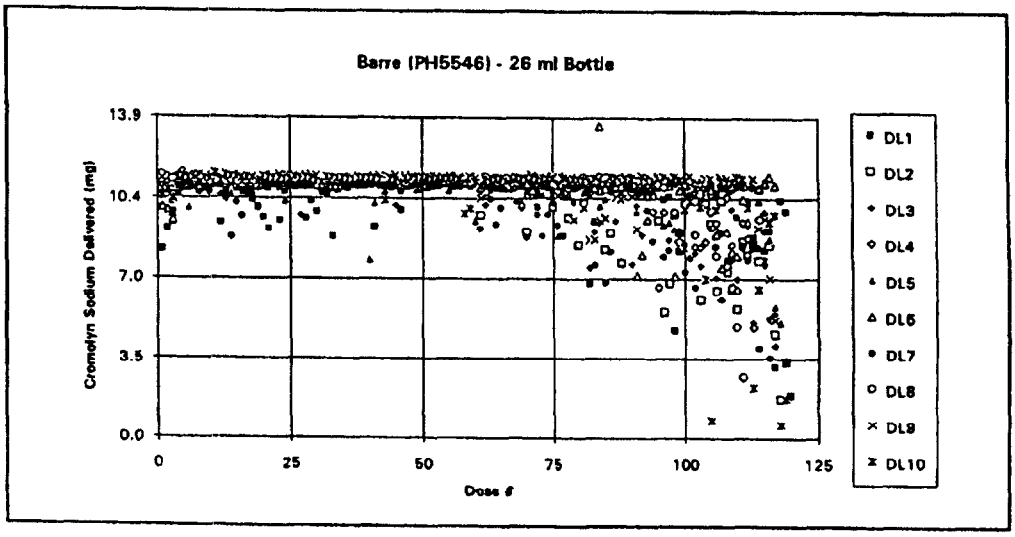


Figure 4. Dose Delivered Through Use Life of Barre Product
Target = 10.4 mg (*limits 7.0 to 13.8 mg*)



A comparison of the mean volume of spray delivered from each bottle size per dose is shown in Table 6. The mean volume was calculated using only the first 25 doses in the 13 ml size and the first 65 doses in the 26 ml size.

Table 6. Cumulative Mean Volume Delivered per Dose

	Nasalcrom®		Barre Product	
	13 ml	26 ml	13 ml	26 ml
Mean Volume/dose	272 µl	271 µl	271 µl	274 µl
%RSD	3.90%	1.74%	2.50%	2.03%

The mean volume delivered per dose by the Barre product in the 13 ml bottle size was 0.4% lower than the Nasalcrom®. The 26 ml bottle size of the Barre product delivered 1.1% more volume per dose than the Nasalcrom®.

The delivery of the Barre product in both bottle sizes is equivalent to the Nasalcrom® for approximately the first half of the use life. Beyond that point, the Barre product consistently delivers the expected dose while the Nasalcrom® starts to exhibit an increase in the number of low doses. The performance of the pumps used on both bottle sizes of the Barre product is equivalent to those of the reference product.

3. DROPLET SIZE DISTRIBUTION

The light scattering device was used to measure the droplet size of this fine mist. The measured median diameter, d(0.5), the % less than 9.48 µm and the computed span, were used to characterize the droplet size distribution produced by the nasal spray pumps. The span is a measure of the width of the distribution calculated from the data at the 10th, 50th and 90th percentiles of the volume distribution. The equation is shown below:

$$SPAN = [d(0.9)-d(0.1)] / d(0.5)$$

Ten samples of the Barre formulation with three lots of the pump and ten samples of Nasalcrom® from three separate lots were evaluated in this study. The test heights employed were 3, 6 and 12 cm.

The average median droplet size distribution of the Barre product was found to be slightly smaller than the Nasalcrom® as measured by the light scattering instrument. These differences

were not significant. The reference and Barre products are equivalent. Since the droplets will only travel a short distance before impaction, median droplet size is not a critical parameter. The fraction below approximately 9 microns is of greater interest since this represents the portion of the dose which could potentially become entrained in the airstream and not be available for nasal administration. The results showed both the Nasalcrom® and Barre product only produce about 1 to 1.5% of the dose below 9.48 microns. The Impactor (without preseparator) selectively admits particles less than 9 microns based on their mass median aerodynamic diameter (MMAD).

The median diameter of the droplets generated by a nasal spray actuator is much larger than the size appropriate for the Therefore, only a very small portion of the sample will actually be evaluated in the test. The majority of the Cromolyn Sodium, approximately 99%, for both products was recovered in Fraction A. Fraction A has a cutoff diameter of greater than 9 microns. Thus these results indicate that the majority of the spray droplets are larger than 9 microns in diameter and that the drug will be deposited in the desired location, the nasal cavity. These results agreed closely with the Impactor results in which approximately 1% of the dose was found to be below 9 microns. Thus the Barre product and the Nasalcrom® are equivalent in terms of the droplet size distribution.

TABLE 7. SUMMARY OF DROPLET SIZE RESULTS BY MALVERN

DETERMINATION OF DROPLET SIZE BY MALVERN							
SAMPLE	Test Height cm	d(0.5) - (μm)		Span		%< 9.48μm	
		Avg	%RSD	Avg	%RSD	Avg	%RSD
Nasalcrom®	3	56.1	9.57	1.96	12.34	1.33	13.4
Barre Product		51.8	9.66	2.08	16.8	1.56	21.5
Nasalcrom®	6	50.2	7.62	1.90	47.4	1.52	10.4
Barre Product		48.8	5.74	1.32	9.03	1.62	13.6
Nasalcrom®	12	62.3	3.84	1.12	6.93	1.04	15.8
Barre Product		60.2	5.33	1.05	12.1	1.06	25.6

4. SHAPE OF THE SPRAY PLUME

The actuations were captured on high speed video film. The film was then edited to slow motion and frames of the spray plumes at their apex were selected. Photographs of the selected frames were developed and used to make measurements of the spray plume. Two measurements, the longest vertical distance (LVD) and the widest horizontal distance (WHD), were taken from the photographs. A measurement of the grid was also performed and used to correct the height and width for the reduction of size that occurred during videotaping and photograph production.

In both the spray pattern testing and plume geometry testing, negligible differences were noted. In general the Barre product did not produce as wide of a plume as the brand. These differences were not significant especially in light of the narrow confines of the nasal cavity. Thus the Barre product and the Nasalcrom® are equivalent in terms of the shape of the spray plume.

Table 8 represents the Nasalcrom® and Barre product averages and relative standard deviations (RSD) for the shortest and longest diameters at the three test heights. The limit represents a +/- 25% range around the mean diameters of the Nasalcrom® product.

Equivalency between the Nasalcrom® and the Barre product can be established if the averages for the shortest and longest diameter for the Barre product are within this range.

TABLE 8. Spray Pattern Analysis

SPRAY PATTERN ANALYSIS							
SAMPLE	Test Ht. cm	S_D (mm)			L_D (mm)		
		Limit	Avg	RSD	Limit	Avg	RSD
Nasalcrom®	2.5	41-68	55	5%	50-83	66	8%
Barre Product			49	11%		58	8%
Nasalcrom®	5.0	56-94	75	6%	67-112	90	4%
Barre Product			72	6%		85	4%
Nasalcrom®	7.5	53-88	70	11%	68-113	90	10%
Barre Product			81	13%		101	10%

The average results for the Longest Vertical Distance (LVD) and Widest Horizontal Distance (WHD) in millimeters are presented in Table 9.

Table 9. Analysis Of Plume Geometry

	Nasalcrom®		Barre Product	
	LVD	WHD	LVD	WHD
Average (mm)	444	196	487	180
%RSD	4.30%	9.23%	3.22%	8.98%

VI. Comments

1. Volume (or dose) delivered: The average volume delivered for both the Nasalcrom® and Barre product in single and multiple actuation testing was 138 μl per spray (equivalent to 5.5 mg cromolyn sodium). The delivery from the device used on Barre product is equivalent to the Nasalcrom®.

2. Droplet size distribution: Median diameters ranged form 49 to 62 micrometer with comparable distributions for the test and reference products.

3. Spray pattern and flume geometry are comparable for the test and reference products.

4. The formulations for the test and reference products are identical.

5. Waiver of *in vivo* bioequivalence study requirements is granted for the test product.

VII. Deficiency

None.

VIII. Recommendation

The Division of Bioequivalence agrees that the information submitted by Barre-National demonstrate that Cromolyn Sodium Nasal Solution, 40 mg/mL, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Fisons' Nasalcrom® Nasal Solution, 40 mg/mL.

The firm should be informed of the recommendation.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE Ramakant M. Mhatre 3/26/96

Concur: _____ Date: 4/4/96

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

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File history: