CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-702

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75702 APPLICANT: Bausch and Lomb

DRUG PRODUCT: Cromolyn Sodium Nasal Solution
40 mg/mL (5.2 mg/spray)
26 mL fill-size

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,

Dale P. Conner

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

4.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75702 APPLICANT: Bausch and Lomb

DRUG PRODUCT: Cromolyn Sodium Nasal Solution
40 mg/mL (5.2 mg/spray)
13 mL fill size

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,

Dale P. Conner

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

Cromolyn Sodium
Nasal Solution, USP
40 mg/mL, 5.2 mg/spray
13 mL fill size
ANDA #75-702
Reviewer: Kuldeep R. Dhariwal
File name: 75702W.600

Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637

Submission Date:
June 19, 2000

Review of an Amendment

Submission History:

October 1995:	The firm submitted for cromolyn sodium nasal solution, 40 mg/mL on October 11, 1995 and requested its withdrawal on October 16, 1998. The ANDA was withdrawn on December 1, 1998.
Sep. 13, 1999:	Original submission, ANDA 75-702 (26 mL and 13 mL fill sizes).
March 3, 2000:	The submission was reviewed, the deficiencies were communicated to the firm on March 16, 2000.
April 28, 2000:	Response to the deficiencies.
June 1, 2000:	The review of waiver of *in vivo* bioequivalence study requirements for the 26 mL fill size was completed.
This submission:	Amendment containing *in vitro* testing data for the 13 mL fill size.

RLD: Nasalcrom® (Pharmacia and Upjohn), 5.2 mg/spray. It is available over-the-counter.

The demonstration of bioequivalence of aqueous solution nasal sprays may be accomplished based on: a) Q1 and Q2 sameness of the generic and innovator formulations, and b) equivalent performance of the test product to the reference product.

The comparative performance of the drug delivery devices of the test and reference products may be based on the following tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least 2 methods
4. Spray pattern
5. Plume geometry

Review of application:

Formulation:
Composition of the test product is quantitatively and qualitatively the same as the reference listed drug (see earlier review dated March 3, 2000, file name

Comparability of Spray Devices:

-- - . developed and provided to Bausch and Lomb a nasal spray pump exhibiting performance properties comparable to those of the innovator product. Both the pumps are made by the same manufacturer, use the same operating principles and same material of construction (with the exception of a different colorant for the safety clip which makes no contact with the product).

The actuators are the same for the Bausch and Lomb and reference listed drug product. The spray insert is the same for both the innovator as well as the test product (see attachment 1).

The test product contains thermoplastic neck gasket comprised of the ethylvinyl acetate resin. The firm states that the stability data have been acquired for the test product, which demonstrate no product quality compromise.

A comparison of test and reference product's spray devices is provided as attachment 1. The spray devices are same for 13 mL fill size and 26 mL fill size.

Drug Products:

Test: Cromolyn sodium nasal solution USP, 4%; Lot #125884 (13 mL fill size); Lot #12588 (lot size: was filled into 4 sub-lots, 125881,125882,125883, and 125884 corresponding to different packaging configurations; Manufacturing date: 12/16/98; pH: 5.7; Assay: 101.3%

Reference: Nasalcrom® nasal spray, 4%; Pharmacia and Upjohn; Lot #34CHW (13 mL fill size); Expiry Date: 3/2000; pH: 5.5; Assay: 101.4%

Unit Dose and Uniformity of Unit Dose

Testing was performed for 10 units each of reference and test product for all sprays in the bottle, including beginning

(actuations 11-20), middle (actuations 46-55), and end (actuations 91-100) of use life. The test was not blinded. One dose equals one actuation (5.2 mg). The amount actuated per spray was measured by a validated HPLC analysis with measurement by weight recorded as supportive data.

The reference product is labeled to provide 100 sprays. The firm has used the mean of 10 sprays at beginning (#11-20), middle (#46-55), and end (#91-100) of unit life for dose delivery. However, consistent with the priming instructions given in the RLD labeling, the reviewer used the mean of 6^{th} and 7^{th} actuation as beginning, mean of 49^{th} and 50^{th} as middle, and mean of 99^{th} and 100^{th} sprays as the end of unit life. The following data are based on reviewer's calculations:

Phase	Test mean delivery, mg/spray (%CV)	Ref	T/R	*p*
Beginning	5.50 (1.81)	5.47 (1.7)	1.00	0.137
Middle	5.57 (0.81)	5.61 (1.0)	0.99	0.004
End	5.59 (0.72)	5.60 (1.1)	1.00	0.360

Comments:

1. The differences in the test and reference products at beginning and end of unit life are not statistically significant. The differences at middle of unit life are statistically significant, even though the ratio of means is 0.99.

2. The Division of Pulmonary Drug Products standards for content uniformity of aerosol products (draft guidance: Chemistry, Manufacturing, and Controls Documentation for Inhalation Drug Products: MDIs and DPIs) recommend that the mean dose at the beginning of the product use life be within 85-115% of the label claim. In addition, the draft guidance recommends that based on the 'first tier' of testing (10 units), not more than one unit be outside 80-120% of the label claim, and none should be outside the 75-125%. When these criteria for content uniformity were applied to the test product data, the following observations were made:

   At the beginning of the product use (spray #6 and 7 based on innovator labeling), the test product mean dose was 5.50 mg/actuation, which is within the 85-

115% of the label claim as the product is labeled to deliver 5.2 mg/actuation.

At the 6th and 7th actuations, none of the bottles tested in this study delivered doses outside the range of 80-120%

3. The data given above are based on averages of two actuations at each stage. The reviewer has also compared the test and reference product unit doses based on single actuation data. These comparisons show that the test product performance is the same as that of the reference product with regard to dose delivery and spray content uniformity.

Priming

The reference listed drug's insert states: "If this is the first time you are using the pump, spray 5 times into the air or until you get a fine mist." Based on the unit dose data (Table 1), a labeled dose is delivered by 6th actuation for the 10 bottles of the test and reference products. At the 6th actuation, there was almost no difference in the amount of drug delivered by the test and reference products. The 6th actuation data also meet the content uniformity criteria mentioned above.

Prime retention

The reference listed drug insert states: "If you have not used the pump for 14 days, spray 2 times into the air before using again." A study was therefore conducted to test the ability of the test pump system to ensure that after a period of non-use of 14 days or more the pump can be re-primed after two sprays. Eighteen bottles of each test and reference product were included in the study. On day 0, the pump was primed 5 times and the 6th spray was collected and analyzed by HPLC (this was done on all 18 bottles). On days 14-16, the 3 initial sprays were collected (after priming 2 times as stated in the labeling) and analyzed. Three bottles (#1,2 and 3) were used to represent day 14, three bottles (#4,5 and 6) were used on day 15, and three bottles (#7,8 and 9) were used on day 16. The results given in volumes 14-15 (orange jackets 1.10,1.11,1.12) demonstrate that test and reference products deliver the labeled dose after sitting for a period of 14-16 days from the last use, after they were primed 2 times as stated in the product insert.

Note: The firm also collected sprays on days 17 and 18 but the data were not used because the pipette used for collecting the samples was found to be out of specification.

Tail off

The reference listed drug is labeled to deliver 100 sprays. Based on the data given in Table 1, the reference product begins to tail off at 109^{th} actuation, compared to test product, which does not tail off up to 124^{th} actuation. Based on the labeled product use life, the tail off characteristics of the test product are same as those of the reference product.

Droplet size distribution

Testing was performed on the Malvern Mastersizer Model S, with one spray per test per distance (duplicate testing per interval). Testing was performed for 10 units each of the reference and test products at beginning (spray #11-16), middle (spray #46-51), and end (spray #91-96) of use life. Distances from the laser beam were 3, 5 and 7 cm. The testing method was same as used for 26 mL fill size.

The Malvern light scattering device measures the droplet size distribution of the spray. The droplet size is characterized by the median diameter (d_{50}) based on volume distribution and SPAN $[(d_{90}-d_{10})/d_{50}]$ which is a measure of the dispersity of the volume distribution relative to the median diameter. SPAN is the value that represents width of the histogram relative to the median. With the exception of d_{10} at beginning stage (3 cm), there were no statistically significant differences for d_{10}, d_{90}, and mean diameter (d_{50}) at the beginning, middle, and end stages of product use between test and reference products. At this time, the DBE requests comparison of only two indicators of droplet size and its distribution for determining bioequivalence: d_{50} and SPAN. A summary of these two indicators based on reviewer's calculations is given in Table 2. For d_{50}, differences between test and reference products were not statistically significant. With regard to SPAN, differences between test and reference products were not statistically significant with the exception of SPAN value at 3 cm (end), even though the ratio of means was 0.953.

Comments: The Malvern laser diffraction data demonstrate that the distribution of droplets in the test product spray is similar to that of the reference product spray.

Cascade Impaction

The Anderson cascade impactor selectively segregates particles less than about 10 microns in diameter. Cascade impaction assures that there is not an excess mass of fines in the test product relative to the RLD. The firm states that its method enables droplet evaporation to occur and therefore the data collected in this test overestimates the fraction of fine droplets that would be seen in the real patient scenario.

Testing was performed on 10 units each of the test and reference drug products at beginning (spray #11-12) and end (spray #91-92) of the product use life. Setup of the Anderson cascade impactor instrument included stages 0-7 and the terminal filter. The drug deposited on the throat (the pre-separator was counted as part of the throat) and stages 0,1,2,3 and filter were determined separately by the validated HPLC method. For the HPLC method, the limit of detection was 0.1 microgram/mL and the limit of quantification was 0.2 microgram/mL.

Testing was performed in a blinded manner to hide the identity of test and RLD products from the analyst. The units were manually actuated (2 actuations per test) for all testing for the test and reference products.

The mean recovery amounts for the test and reference products at beginning as well as at end were almost the same (96.94% to 98.31%). Almost the entire drug was recovered from the throat (Table 3).

Spray Pattern

Spray pattern testing was done on 10 units each of test and reference products at 3, 5, and 10 cm distances from nozzle to plate and tested at beginning (11^{th} actuation) and end (86^{th} actuation) of the use life. The 86^{th} actuation was selected to insure that the spray pattern testing did not over lap with tail off. Duplicate testing was conducted for each distance, 1 spray at 3 cm, 2 sprays at 5 cm, 4 sprays at 10 cm. For visualization of the spray pattern on the plate, UV light at 254 nm was used to illuminate the plate light green, leaving a black pattern wherever the drug substance rests on the plate. Color images were then digitized and analyzed by the LECO IA32 Image Analysis System. This system automatically determines the longest and shortest radii and calculates the corresponding spray angles,

the elliptical ratio (longest/shortest angle), and the ovality ratio (longest/shortest diameter).

The test was not blinded as all units were mechanically actuated with no analyst mechanical intervention on the results.

Results of spray pattern testing are presented in Table 4. With regard to Dmin, differences between mean values of test and reference products were in the range of 2-7% and the observed differences were statistically not significant.

With the exception of Dmax measured at 10 cm distance (beginning of unit life), the observed differences between test and reference products were less than 9%.

With regard to the ovality ratio, differences between test and reference products were less than 2%.

Plume Geometry

Freeze-frame photographs for 10 units each of the test and reference products were captured photographically at the beginning of the product use life. Testing was performed in a blinded manner so as to hide the identity of test and reference products from the analyst. The units were manually actuated (10 times to assure prime, 11^{th} spray test) for all testing for the test and reference products. The plume angle was measured using LECO IA32 Image Analysis System. The program has a function built into it that allows an analyst to draw over a digitized image a varied number of shapes and lines from which various figures can be obtained such as length, area, and angle. Two lines can be drawn over the photographed image along the edge of the plume down to the tip. The program automatically gives the angle of the two lines in relation to each other. Plume height and width were measured by drawing a line over the photograph from the nozzle tip to the top of the plume. Width was measured at the plume height and represented the plume's maximum width at that time frame.

The plume height, width, and angle data are summarized in tables 5,6, and 7. Individual photographs per bottle are provided in volume 4.10 and 4.11.

Based on individual delay times the test/reference ratios for plume height ranged from 1.04 to 1.12 and for plume width ranged from 0.95 to 1.45. For plume height the differences between test

and reference products were statistically insignificant with the exception of ratios at 0.0501 seconds. With regard to plume width the differences between test and reference products were statistically insignificant at all time frames. Overall (average of all delay times) differences between test and reference means were <7%.

Based on individual delay times the test/reference ratios for plume angle ranged from 0.60 to 1.02. Overall (average of all delay times) differences between test and reference means were less than 14%.

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General Comments: **NOT TO BE RELEASED UNDER FOI**

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data for cromolyn sodium nasal solution, 40 mg/mL, 13 mL fill

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Recommendation:

Data submitted by Bausch and Lomb on its Cromolyn Sodium nasal solution (40 mg/mL, 5.2 mg/spray, 13 mL fill size) indicate that the formulation of the test product is same as that of the reference product Nasalcrom® (40 mg/mL, 5.2 mg/spray, 13 mL fill size) manufactured by Pharmacia. In addition, the *in vitro* performance of nasal spray devices of these products is comparable. Therefore, in terms of dose delivered per actuation, and size, shape and droplet size distribution of the spray, the test product is equivalent to the reference product. Therefore, the Division of Bioequivalence deems the test product to be equivalent in dose delivery and performance of the device to the reference product, Nasalcrom® manufactured by Pharmacia.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ Date 7/3/2000

Concur: _____ Date 7/12/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75702 APPLICANT: Bausch and Lomb

DRUG PRODUCT: Cromolyn Sodium Nasal Solution
40 mg/mL (5.2 mg/spray)
26 mL fill-size

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,

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

Cromolyn Sodium
Nasal Solution, USP
40 mg/mL, 5.2 mg/spray
ANDA #75-702
Reviewer: Kuldeep R. Dhariwal
File name: 75702W.400

Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637
Submission Date:
April 28, 2000
~~May 26, 2000~~

Review of Waiver Request Amendments

Submission History:

Sep. 13, 1999:	Original submission.
Sep. 14, 1999:	Additional information. The firm submitted original photographs used for plume geometry evaluations.
Sep. 14, 1999:	Methods validation package.
Oct. 13, 1999:	Electronic submission (the reviewer was informed that the bio section was not included in electronic submission).
Oct. 14, 1999:	Amendment containing: correction of data submitted earlier in the original application, correction of quantitative composition of the drug, correction of description of components, and correction of product regulatory specifications.
Oct. 21, 1999:	Packaged product accountability.
Oct. 25, 1999:	Amendment: Waiver request not submitted earlier, revised form 356h, explanation for the disposition of cromolyn sodium nasal solution.
March 3, 2000:	The submission was reviewed, the deficiencies were communicated to the firm on March 16, 2000.
April 28, 2000:	Response to the deficiencies.
May 26, 2000:	RLD corrected on form 356h.

Response:

Comment 1: **For the unit dose testing you state that the test was not blinded because of mechanical actuation of the bottle, mechanical weighing of the bottle, and the fact that the scintillation vial is also weighed. The assay result is checked against the 2 spray weights, so the chances for bias are**

essentially eliminated. Please submit the standard operating procedure (SOP) describing that blinding was not necessary.

Response: The procedures that describe the testing are contained in the submitted SOPs and C-spec in the original ANDA filing.

product release testing.

Reviewer's comments: The Agency has previously accepted such justification for testing on another solution nasal spray (ANDA #74830). The response is satisfactory.

Comment 2a: **Cascade Impaction: Please provide the SOP for this method including the flow rate and nature of throat.**

Response: Nasal instrument Procedure
"Determination of Droplet Size from Nasal Sprays by
8 stages)" is provided in volume 3.1 as attachment C. All information regarding the test procedure is contained in this document.

Reviewer's comments: The flow rate was The atomization chamber (throat) was a circular cylinder (see the attached diagram, Attachment 1). The Agency has previously accepted the use of similar atomization chamber for studies on another nasal spray (ANDA# 74830). The response is satisfactory.

Comment 2b: **Cascade Impaction: Was the drug deposited on stages 2-7 measured? If so, please provide the data.**

Response: Table 3(b) of the ANDA original submission contained data for only the throat, stage 0, stage 1, and the filter. Stages 2 and 3 were analyzed by testing, but the numbers were so small that they were not itemized in the submitted table. The firm has provided the stages 2 and 3 data in this amendment. Although the testing was performed with all 8 stages included in the Cascade Impactor setup, stages 4

through 7 were not analyzed by . because experimental testing showed recoveries for stages 4-7 to be below the limit of quantitation of the method used for analysis.

Reviewer's comments: In the original submission, the firm did not report the amount of drug deposited on stages 2 and 3, though the amount was included in the overall recovery. The firm has now itemized the amount of the drug deposited on stages 0, 1, 2, and 3. The amount of the drug recovered from stages 0-4 was less than Almost all of the recovered drug was from the atomization chamber (Table 1). Based on reviewer's calculations, the ratios of means for test and reference products for beginning and end intervals were 1.01 and 1.01.

Comment 3a: **Spray Pattern: It is not clear if the same threshold was used for the test and reference products. How many samples were analyzed with a given threshold? What was the level of fluctuation between the various threshold levels? Please furnish the records to support the statement.**

Response: The threshold was set at for all testing. This threshold value is listed at the top of the printout page.

Reviewer's comments: The firm used the same threshold for the test and reference products and the response is satisfactory.

Comment 3b: **Spray Pattern: Please provide a complete SOP for the method used for spray pattern testing. The method described in volume 3, page 986 does not include is System.**

Response: The firm has submitted the Nasal Instrument Procedure . "Measurement of Spray Pattern of Cromolyn Sodium Nasal Solution USP (40 mg/mL) 26 ml fill size Using .s System in Conjunction with the ". All information regarding the test procedure is contained in this document.

Reviewer's comments: The response is satisfactory.

Comment 3c: **Spray Pattern: By definition, diameters should pass through the centers of spray patterns. Markings on photocopies of spray pattern for smallest and largest diameter do not go through the center of the spray patterns. Please recalculate the data making markings going through the center of the spray pattern rather than center of the plate.**

Response: The firm has recalculated the spray pattern data with diameters passing through the center of the spray pattern. The spray patterns, tables of the data, and the statistical analysis of the data are included in Volume 3.1.

Reviewer's comments: Results of the spray pattern testing are presented in Table 2. Based on mean values the test/reference ratios for Dmin, Dmax, and ovality ratio ranged from 0.94 to 1.04. With regard to Dmin and Dmax, differences between test and reference products were statistically insignificant. With regard to the ovality ratio, differences between test and reference products were statistically insignificant with the exception of ratios at 3 cm distance (end of unit life) and 10 cm distance (beginning and end of unit life). A sample of spray pattern analysis is attached (Attachment 2).

Comment 3d: **Spray pattern. Please submit color photographs representing placebo and active drug spray patterns.**

Response: Enclosed are digital color prints of the plate sitting inside the , and images representing placebo and active drug spray patterns (Volume 3.1, attachment G).

Reviewer's comments: The firm has submitted desired photos (Volume 3.1, page 365). For visualization of the spray pattern on the plate, at a wavelength of nm was used to illuminate the plate light green, leaving a black pattern wherever the drug substance rests on the plate. Color images were then analysis system. The placebo spray does not produce detectable spray pattern on the plate. The response is satisfactory.

Comment 4a: **Plume geometry data: What are the units on used to calculate height and width? Were these parameters calculated based on the shown in color photos or marking on photocopies?**

Response: The units of the the photographs are square inches. The firm has submitted SOP, Nasal Instrument Procedure . "Measurement of photographs of Cromolyn Sodium Nasal Solution USP (40 mg/mL) 26 mL fill size to Determine Plume Geometry Using System in Conjunction with the '. The test procedure (part 4.8) describes how the system computes the plume height and width. All results are a to adjust for magnification to

approximate numbers representing "actual" measurements. The conversion factor was determined by

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Reviewer's comments: The firm has submitted photographs of all frames for test and reference products with markings showing dimension of plume width and plume height.

Comment 4b: **Plume geometry data: Quantitation of plume angle based on lines drawn on photocopies is inappropriate because on many patterns lines go through the plume images, rather than representing the periphery of these plumes. Please revise the plume geometry data based on plumes shown in color photographs.**

Response: SOP ontains a detailed description of the method for measuring the plume angles with the .

gravity. This

Reviewer's comments: The firm's argument is acceptable.

Comment 4c: **Plume geometry data: For some bottles plume height and width are not reported at all time delays. Please provide complete data sets.**

Response: The firm has submitted the printouts of the plumes calculating the height and width, tables of the data, and the statistical analysis (Volume 3.2). The data represent revised values for the previously submitted photographs. For a few delay times, the plume tip went beyond the scale of the photograph. Plume height data were not reported for such images.

Reviewer's comments: The recalculated plume height and width are summarized in Tables 3 and 4. Based on individual delay times the test/reference ratios for plume height ranged from

and for plume width ranged from [redacted] For plume height the differences between test and reference products were statistically insignificant with the exception of ratios at 0.1503 seconds. With regard to plume width the differences were statistically insignificant with the exception of ratios at 0.1503 and 0.167 seconds. Overall (average of all delay times) differences between test and reference means were <5%.

Comment 5: **The innovator product is marketed in two fill-sizes: 13 mL and 26 mL. Your correspondences dated October 14, 1999 and October 25, 1999 mention packaging configurations of [redacted] and 26 mL fill size. The correspondence dated October 21, 1999 mentions packaging configurations of [redacted] and 26 mL fill size. In the original submission, you provided primimg retention data for [redacted] and 26 mL fill sizes with a note that information regarding the [redacted] mL fill size may be ignored since this packaging configuration is not included in the application. Please explain these discrepancies.**

Response: The firm states that the data for [redacted] fill size will be submitted in a separate bioequivalence amendment. The initial intention was to file for both fill sizes, however, the firm was not able to accomplish this goal. The [redacted] fill size will now be amended to the application. The [redacted] fill size uses a 15 mL container.

Reviewer's comments: This submission is for the 26 mL fill size only. The [redacted] fill size data were not submitted.

Comment 6: **The procedure for blinding test and reference product bottles given on page 1113, volume 3 is for desmopressin acetate nasal spray. Please provide the blinding procedure for cromolyn sodium nasal solution, which is the subject of this application.**

Response: The firm has submitted the blinding procedure for cromolyn sodium nasal solution (Volume 3.2, Attachment J).

Reviewer's comments: The response is satisfactory.

General Comments: NOT TO BE RELEASED UNDER FOI

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Information and are not

releasable.

4/28/00

Recommendations:

Data submitted by Bausch and Lomb comparing its Cromolyn Sodium nasal solution (40 mg/mL, 5.2 mg/spray) with the reference listed drug, Nasalcrom® manufactured by Pharmacia indicate that the formulation of the test product is same as that of the reference product. In addition, the *in vitro* performance of nasal spray devices of these products is comparable. Therefore, in terms of dose delivered per actuation, and size, shape and droplets distribution of the spray, the test product is equivalent to the reference product. Therefore the Division of Bioequivalence deems the test product to be equivalent in dose delivery and performance of the device to the reference product, Nasalcrom® manufactured by Pharmacia.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

Date 5/31/2000

Concur: Date 6/1/00

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

2.1 V2.1

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-702 APPLICANT: Bausch and Lomb

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. For the unit dose testing you state that the test was not blinded because of mechanical actuation of the bottle, mechanical weighing of the bottle, and the fact that the scintillation vial is also weighed. The assay result is checked against the 2 spray weights, so the chances for bias are essentially eliminated. Please submit the standard operating procedure (SOP) describing that blinding was not necessary.

2. Cascade Impaction:
   a. Please provide the SOP for this method including the flow rate and nature of throat.
   b. Was the drug deposited on stages 2-7 measured? If so, please provide the data.

3. Spray Pattern:
   a. It is not clear if the same threshold was used for the test and reference products. How many samples were analyzed with a given threshold? What was the level of fluctuation between the various threshold levels? Please furnish the records to support the statement.
   b. Please provide a complete SOP for the method used for spray pattern testing. The method described in volume 3, page 986 does not include
      System.
   c. By definition, diameters should pass through the centers of spray patterns. Markings on photocopies of spray pattern for smallest and largest diameter do not go through the center of the spray patterns. Please recalculate the data making markings going through the center of the spray pattern rather than center of the plate.
   d. Please submit color photographs representing placebo and active drug spray patterns.

4. Plume geometry data:
   a. What are the units on grids used to calculate height and width? Were these parameters calculated based on the shown in color photos or marking on photocopies?
   b. Quantitation of plume angle based on lines drawn on photocopies is inappropriate because on many patterns lines go through the plume images, rather than representing the periphery of these plumes. Please revise the plume geometry data based on plumes shown in color photographs.
   c. For some bottles plume height and width are not reported at all time delays. Please provide complete data sets.

5. The innovator product is marketed in two fill-sizes: 13 mL and 26 mL. Your correspondences dated October 14, 1999 and October 25, 1999 mention packaging configurations of 15 mL and 26 mL fill size. The correspondence dated October 21, 1999 mentions packaging configurations of and 26 mL fill size. In the original submission, you provided priming retention data for nd 26 mL fill sizes with a note that information regarding the , fill size may be ignored since this packaging configuration is not included in the application. Please explain these discrepancies.

6. The procedure for blinding test and reference product bottles given on page 1113, volume 3 is for desmopressin acetate nasal spray. Please provide the blinding procedure for cromolyn sodium nasal solution, which is the subject of this application.

Sincerely yours,

Dale P. Conner

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

MAR 16 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-702 APPLICANT: Bausch and Lomb

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. For the unit dose testing you state that the test was not blinded because of mechanical actuation of the bottle, mechanical weighing of the bottle, and the fact that the scintillation vial is also weighed. The assay result is checked against the 2 spray weights, so the chances for bias are essentially eliminated. Please submit the standard operating procedure (SOP) describing that blinding was not necessary.

2. Cascade Impaction:
   a. Please provide the SOP for this method including the flow rate and nature of throat.
   b. Was the drug deposited on stages 2-7 measured? If so, please provide the data.

3. Spray Pattern:
   a. It is not clear if the same threshold was used for the test and reference products. How many samples were analyzed with a given threshold? What was the level of fluctuation between the various threshold levels? Please furnish the records to support the statement.
   b. Please provide a complete SOP for the method used for spray pattern testing. The method described in volume 3, page 986 does not include
      System.
   c. By definition, diameters should pass through the centers of spray patterns. Markings on photocopies of spray pattern for smallest and largest diameter do not go through the center of the spray patterns. Please recalculate the data making markings going through the center of the spray pattern rather than center of the plate.
   d. Please submit color photographs representing placebo and active drug spray patterns.

4. Plume geometry data:
   a. What are the units on used to calculate height and width? Were these parameters calculated based on the shown in color photos or marking on photocopies?
   b. Quantitation of plume angle based on lines drawn on photocopies is inappropriate because on many patterns lines go through the plume images, rather than representing the periphery of these plumes. Please revise the plume geometry data based on plumes shown in color photographs.
   c. For some bottles plume height and width are not reported at all time delays. Please provide complete data sets.

5. The innovator product is marketed in two fill-sizes: 13 mL and 26 mL. Your correspondences dated October 14, 1999 and October 25, 1999 mention packaging configurations of 15 mL and 26 mL fill size. The correspondence dated October 21, 1999 mentions packaging configurations of and 26 mL fill size. In the original submission, you provided priming retention data for , and 26 mL fill sizes with a note that information regarding the , fill size may be ignored since this packaging configuration is not included in the application. Please explain these discrepancies.

6. The procedure for blinding test and reference product bottles given on page 1113, volume 3 is for desmopressin acetate nasal spray. Please provide the blinding procedure for cromolyn sodium nasal solution, which is the subject of this application.

Sincerely yours,

Dale P. Conner

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

Cromolyn Sodium
Nasal Solution, USP
40 mg/mL, 5.2 mg/spray
ANDA #75-702
Reviewer: Kuldeep R. Dhariwal
File name: 75702W.999

Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637
Submission Dates:
September 13, 1999
October 14, 1999
October 25, 1999

Review of a Waiver Request

Submission History:

Sep. 13, 1999:	Original submission.
Sep. 14, 1999:	Additional information. The firm submitted original photographs used for plume geometry evaluations.
Sep. 14, 1999:	Methods validation package.
Oct. 13, 1999:	Electronic submission (the reviewer was told that bio section was not included in electronic submission).
Oct. 14, 1999:	Amendment containing: correction of data submitted earlier in the original application, correction of quantitative composition of the drug, correction of description of components, and correction of product regulatory specifications.
Oct. 21, 1999:	Packaged product accountability.
Oct. 25, 1999:	Amendment: Waiver request not submitted earlier, revised form 356h, explanation for the disposition of cromolyn sodium nasal solution.

Previous submission: The firm submitted ANDA for cromolyn sodium nasal solution, 40 mg/mL on October 11, 1995 and requested its withdrawal on October 16, 1998. The ANDA was withdrawn on December 1, 1998.

RLD: Nasalcrom® (Pharmacia and Upjohn), 5.2 mg/spray. It is available over-the-counter.

Indication: Nasalcrom® is a mast cell stabilizer. It is indicated for the prevention and relief of nasal symptoms of hay fever and other nasal allergies.

Requirements for waiver:

The demonstration of bioequivalence of aqueous nasal sprays may be accomplished based on: a) Q1 and Q2 sameness of the generic and innovator formulations, and b) equivalent performance of the test product to the reference product.

The comparative performance of the drug delivery devices of the test and reference products may be based on the following tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least 2 methods
4. Spray pattern
5. Plume geometry

Review of application:

Formulation: NOT TO BE RELEASED UNDER FOI

Ingredient	Test	Reference
Cromolyn sodium	40 mg/mL	40 mg/mL
Benzalkonium chloride	0.01%	0.01%
Edetate disodium dihydrate	0.01%	
Edetate disodium*		0.01%
Purified water		

Comment: Composition of the test product is quantitatively and qualitatively the same as the reference listed drug.

Physicochemical properties:

Product	pH	Viscosity (Cps)	Sp. Gravity	Osmolality (mOsm/Kg)	Density (g/mL)
Nasalcrom					
Lot #AHQ382	5.4	1.07	1.02	78	1.02
Lot #AHQ377	5.4	1.06	1.02	77	1.02
Lot #55CHM	5.4	ND	1.02	ND	1.02
Lot #34CHW	5.4	ND	1.02	ND	1.02

Bausch & Lomb Product AAI-069	6.0	1.04	1.02	75	1.02
Lot #12588	5.7	ND	1.02	ND	1.02

ND = not done

Comment: Viscosity and osmolality tests were not done on lots of test and reference products used in *in vitro* testing.

Comparability of Spray Devices:

. developed and provided to Bausch and Lomb a nasal spray pump exhibiting performance properties comparable to those of the innovator product. Both the pumps are made by the same manufacturer, use the same operating principles and same material of construction (with the exception of a different colorant for the safety clip which makes no contact with the product).

The actuators are the same for the Bausch and Lomb and reference listed drug product. The spray insert is the same for both the innovator as well as the test product (see the attached table).

The test product contains thermoplastic neck gasket comprised of the ethylvinyl acetate resin. The firm states that the stability data have been acquired for the test product, which demonstrate no product quality compromise.

A comparison of test and reference product's spray devices is provided as attachment 1.

Drug Products:

Test: Cromolyn sodium nasal solution USP, 4%; Lot #125882; Lot #12588 (lot size: was filled into 4 sub-lots, 125881,125882,125883, and 125884 corresponding to different packaging configurations; Manufacturing date: 12/16/98; pH: 5.6; Assay: 101.7%

Reference: Nasalcrom® nasal spray, 4%; Pharmacia and Upjohn; Lot #55CHM; Expiry Date: 4/2000; pH: 5.5; Assay: 101.0%

Unit Dose and Uniformity of Unit Dose: 26 mL fill-size

Testing was performed for 10 units each of reference and test product for all sprays in the bottle, including beginning

(actuations 11-20), middle (actuations 96-105), and end (actuations 191-200) of use life. The test was not blinded. One dose equals one actuation (5.2 mg). The amount actuated per spray was measured by a validated analysis with measurement by weight recorded as supportive data. The assay was validated, a summary of the method validation is as follows:

The peak area was linear over a range of 0.0001 mg/mL to 0.4 mg/mL. The limit of detection was 0.0001 mg/mL. The LOQ was 0.0002 mg/mL. The method showed good specificity, accuracy and precision.

The reference product is labeled to provide 200 sprays. The firm has used the mean of 10 sprays at beginning (#11-20), middle (#96-105), and end (#191-200) of unit life for dose delivery. However, consistent with the priming instructions given in the RLD labeling, the reviewer used the mean of 6^{th} and 7^{th} actuation as beginning, mean of 99^{th} and 100^{th} as middle, and mean of 199^{th} and 200^{th} sprays as the end of unit life. The following data are based on reviewer's calculations:

Phase	Test mean delivery, mg/spray (%CV)	Ref mg/spray (%CV)	T/R	*p*
Beginning	5.55 (2.78)	5.45 (4.6)	1.02	0.052
Middle	5.59 (2.54)	5.49 (4.8)	1.02	0.134
End	5.52 (1.22)	5.36 (8.3)	1.03	0.075

Comments:

1. The differences in the test and reference products at beginning, middle, and end of unit life are not statistically significant.

2. The Division of Pulmonary Drug Products standards for content uniformity of aerosol products (draft guidance: Chemistry, Manufacturing, and Controls Documentation for Inhalation Drug Products: MDIs and DPIs) recommend that the mean dose at the beginning of the product use life be within 85-115% of the label claim. In addition, the draft guidance recommends that based on the 'first tier' of testing (10 units), not more than one unit be outside 80-120% of the label claim, and none should be outside the 75-125%. When these criteria for content uniformity were applied to the test product data, the following observations were made:

At the beginning of the product use (spray #6 and 7 based on innovator labeling), the test product mean dose was 5.55 mg/actuation, which is within the 85-115% of the label claim as the product is labeled to deliver 5.2 mg/actuation.

At the 6^{th} and 7^{th} actuations, none of the bottles tested in this study delivered doses outside the range of 80-120%

3. The data given above are based on averages of two actuations at each stage. The reviewer has also compared the test and reference product unit doses based on single actuation data. These comparisons show that the test product performance is the same as that of the reference product with regard to dose delivery and spray content uniformity.

4. The firm states that the test was not blinded because of mechanical (automated) actuation of the bottle, mechanical weighing of the bottle, and the fact that the scintillation vial is also weighed. The assay result is checked against the 2 spray weights, so the chances for bias are essentially eliminated.

   The Agency has earlier accepted Bausch and Lomb's above argument for not blinding this test for desmopressin acetate nasal solution. However, the Agency recommended that the SOP should provide the information described above to document that blinding is not necessary. The reviewer is unable to find such SOP in the submission.

Priming: 26 mL fill-size

The reference listed drug's insert states: "If this is the first time you are using the pump, spray 5 times into the air or until you get a fine mist." Based on the unit dose data (Table 1), a labeled dose is delivered by 6^{th} actuation for the 10 bottles of the test and reference products. At the 6^{th} actuation, the average difference in the amount of drug delivered by the test and reference product was 3%. The 6^{th} actuation data also meet the content uniformity criteria mentioned above.

Prime retention: 26 mL fill-size

The reference listed drug insert states: "If you have not used the pump for 14 days, spray 2 times into the air before using

again." A study was therefore conducted to test the ability of the test pump system to ensure that after a period of non-use of 14 days or more the pump can be re-primed after two sprays. Eighteen bottles of each test and reference product were included in the study. On day 0, the pump was primed 5 times and the 6th spray was collected and analyzed by (this was done on all 18 bottles). On days 14-16, the 3 initial sprays were collected (after priming 2 times as stated in the labeling) and analyzed. Three bottles (#1,2 and 3) were used to represent day 14, three bottles (#4,5 and 6) were used on day 15, and three bottles (#7,8 and 9) were used on day 16. The results given in volume 15 (orange jacket 1.11) demonstrate that test and reference products deliver the labeled dose after sitting for a period of 14-16 days from the last use, after they were primed 2 times as stated in the product insert.

Note: The firm also collected sprays on days 17 and 18 but the data were not used because the pipette used for collecting the samples was found to be out of specification.

The firm has submitted prime retention study data on fill size with a note that information regarding the fill size may be ignored since this packaging configuration is not included in the application (page 23 001A volume 14). The fill size data are therefore not reviewed.

Tail off: 26 mL fill-size

The reference listed drug is labeled to deliver 200 sprays. Based on data given in Table 1, the reference product begins to tail off at 203rd actuation, compared to test product which tailed off at 212th actuation. Based on the labeled product use life, the tail off characteristics of the test product are same as those of the reference product.

Droplet size distribution: 26 mL fill-size

Testing was performed on the with one spray per test per distance (duplicate testing per interval). Testing was performed for 10 units each of the reference and test products at beginning (spray #11-16), middle (spray #96-101), and end (spray #190-195) of use life. Distances from the laser beam were 3, 5 and 7 cm.

Two instruments were used in conjunction with each other to make the analysis completely automated. The ; Automated Spray Station is the device that mechanically actuates the nasal

spray into the fractor that reads the droplet size. This test was not blinded because the spray pumps for both the test and reference products were all mechanically actuated into the instrument, and all analyses were performed by the instrument. There was no human intervention. The automated mechanical actuation by definition involves the same dose time, return time, hold time and force for the test and reference products.

The scattering device measures the droplet size distribution of the spray. The droplet size is characterized by the median diameter (d_{50}) based on volume distribution and SPAN $[(d_{90}-d_{10})/d_{50}]$ which is a measure of the dispersity of the volume distribution relative to the median diameter. SPAN is the value that represents width of the histogram relative to the median. There were no statistically significant differences for d_{10}, d_{90}, and mean diameter (d_{50}) at the beginning, middle, and end stages of product use between test and reference products. At this time, DBE requires comparison of only two indicators of droplet size and its distribution for determining bioequivalence: d_{50} and SPAN. A summary of these two indicators based on reviewer's calculations is given in Table 2. For d_{50}, differences between test and reference products were not statistically significant. With regard to SPAN, differences between test and reference products were not statistically significant with the exception of SPAN value at 7 cm (end), even though the ratio of means was 0.94.

Comments: The data demonstrate that the distribution of droplets in the test product spray is similar to that of the reference product spray.

Cascade Impaction: 26 mL fill-size

The cascade impactor selectively segregates particles less than about 10 microns in diameter. Cascade impaction assures that there is not an excess mass of fines in the test product relative to the RLD. The firm states that its method enables droplet evaporation to occur and therefore the data collected in this test overestimates the % of fine droplets that would be seen in the real patient scenario.

Testing was performed on 10 units each of the test and reference drug products at beginning (spray #11-12) and end (spray #191-192) of the product use life. There were 2 actuations per test. Setup of the cascade impactor instrument included stages 0-7 and the terminal filter. The drug deposited on the

throat (the pre-separator was counted as part of the throat) and stages 0,1,2,3 and filter were determined separately by the validated method. For the method, the limit of detection was 0.1 microgram/mL and the limit of quantification was 0.2 microgram/mL.

Testing was performed in a blinded manner to hide the identity of test and RLD products from the analyst. The units were manually actuated (2 actuations per test) for all testing for the test and reference products.

The mean recovery amounts for the test and reference products at beginning as well as at end were almost the same (96.73% to 98.50%). All of the drug recovered was from the throat.

Comments:

1. The firm should provide SOP for this method including the flow rate and nature of throat.
2. Was the drug deposited on stages 2-7 measured? If so, the firm should provide the data.

Spray Pattern: 26 mL

Spray pattern testing was done on 10 units each of test and reference product at 3, 5, and 10 cm distances from nozzle to plate and tested at beginning (11^{th} actuation) and end (186^{th} actuation) of the use life. Duplicate testing was conducted for each distance, 1 spray at 3 cm, 2 sprays at 5 cm, 4 sprays at 10 cm. For visualization of the spray pattern on the plate, light at was used to illuminate the plate light green, leaving a black pattern wherever the drug substance rests on the plate. Color images were then and analyzed by the sis System. This system automatically determines the longest and shortest radii and calculates the corresponding spray angles, the elliptical ratio (longest/ shortest angle), and the ovality ratio (longest/shortest diameter).

Operation of System: Once the pattern is sprayed onto a plate and placed into position within the the camera and software digitize the pattern's image. The software recognizes the pattern by assigning a numerical gray scale value to each one of the millions of pixels comprising each image. Thus, contrast between bare (drug free) sections of the plate and the area occupied by the spray (drug) are critical. To ensure that no stray marks on the plate are considered to be part of the spray pattern, the analyst must

adjust the "threshold" of the image which essentially tells the computer, which gray scale values to consider as part of the pattern and which to exclude. Because the pattern boundaries are not sharply defined, the analyst must determine the boundary by setting an appropriate numerical threshold value. Once the appropriate threshold is set however, that value should not change over the series of samples to be compared and measured. By maintaining the same threshold value, each sample is measured with the same degree of sensitivity to the pattern boundary, thus eliminating sample to sample bias.
Calculations: The software measures the longest and shortest diameters through the geometric center of the plate since the spray nozzle was aligned to this mark on the plate before the pattern was created. Measuring from the plate's center takes into account any sprays that are off center.

The test was not blinded as all units were mechanically actuated with no analyst mechanical intervention on the results.

Results of spray pattern testing are presented in Tables 3 and 4. With regard to Dmin, differences between mean values of test and reference products were in the range of 2-7%. With the exception of Dmin measured at 3 cm distance (end of unit life), the observed differences were statistically not significant.

With regard to Dmax, the differences between test and reference products were statistically insignificant.

With regard to the ovality ratio, differences between test and reference products were statistically insignificant with the exception of ratios at 3 cm distance (end of unit life) and 10 cm distance (beginning and end of unit life).

For narrowest angle and widest angle, the differences between test and reference products were statistically insignificant. The differences between test and reference products for elliptical ratio were statistically significant at 3 cm distance (end of unit life) and at 10 cm distance (beginning and end of unit life).

Comments:

1. It is not clear if the same threshold was used for the test and reference products. How many samples were analyzed with a given threshold? What was the level of fluctuation between the various threshold levels? The firm should explain this and furnish the records to support the statement.

2. The firm should provide a complete SOP for the method used for spray pattern testing. The method described in volume 3, page 986 does not include System.
3. By definition, diameters should pass through the centers of the spray patterns. Markings on photocopies of spray pattern for smallest and largest diameter do not go through the center of the spray patterns. The firm should recalculate the data making markings going through the center of the spray pattern rather than center of the plate.
4. The firm should submit color photographs representing placebo and active drug spray patterns.

Plume Geometry: 26 mL

photographs for 10 units each of the test and reference products were captured photographically at the beginning of the product use life. At least, six time delays (0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds) were used. Testing was performed in a blinded manner so as to hide the identity of test and reference products from the analyst. The units were manually actuated (10 times to assure prime, 11th spray test) for all testing for the test and reference products. The plume angle was measured using System. The program has a function built into it that allows an analyst to draw over a image a varied number of shapes and lines from which various figures can be obtained such as length, area, and angle. Two lines can be drawn over the photographed image along the edge of the plume down to the tip. The program automatically gives the angle of the two lines in relation to each other. Plume height and width were measured by drawing a line over the photograph from the nozzle tip to the top of the plume. Width was measured at the plume height and represented the plume's maximum width at that time frame.

The plume height, width, and angle data are summarized in tables 5,6, and 7. Individual photographs per bottle are provided in volume 17.

Comments:

1. What are the units on used to calculate height and width? Were these parameters calculated based on the shown in color photos or marking on photocopies?
2. Quantitation of plume angle based on lines drawn on photocopies is inappropriate because on many patterns lines go through the plume images, rather than representing the

periphery of these plumes. The firm should revise the plume geometry data based on plumes shown in color photographs.

3. For some bottles plume height and width are not reported at all time delays. The firm should provide complete data sets.

General Comments:

1.

2.

Recommendations:

Data submitted by Bausch and Lomb comparing the *in vitro* performance of its cromolyn sodium (40 mg/mL) nasal spray device with that of the reference listed drug, Nasalcrom® (40 mg/mL) nasal spray manufactured by Pharmacia are incomplete due to above comments. The waiver of *in vivo* bioequivalence study requirements for the test product should be deferred till the sponsor has submitted satisfactory *in vitro* performance data.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

Date 2/24/2000

Concur: Dale P. Conner Date 3/3/00

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