CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-427

***Name*:** Cromolyn Sodium Nasal Solution USP

***Sponsor*:** L. Perrigo Company

***Approval Date*:** December 12, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-427

APPROVAL LETTER

ANDA 75-427

DEC 12 2001

L. Perrigo Company
Attention: Brian R. Schuster
515 Eastern Ave.
Allegan, MI 49010

Dear Sir:

This is in reference to your abbreviated new drug application dated July 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cromolyn Sodium Nasal Solution USP, 5.2 mg cromolyn sodium delivered/spray, (40 mg/mL), packaged in 13 mL (100 metered spray) and 26 mL (200 metered spray) bottles.

Reference is also made to your amendments dated November 20, 1998; November 30, 2000; and January 26, June 29, and October 17, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted Over-The-Counter (OTC) labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray, to be bioequivalent to the listed drug (NasalCrom® Nasal Spray, 5.2 mg cromolyn sodium/spray, of Pharmacia and Upjohn Consumer Healthcare).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

Robert Lumpkin / for
12/12/2001

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-427
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205/F.O.I.

Endorsements:
HFD-625/E.Schaefer/ ES 12/3/01
HFD-625/M.Smela/ M Smela 12/3/01
HFD-617/M.Dillahunt/11/28/01 M Dillahunt 12/3/01
HFD-613/A.Payne/ A Payne 11/28/01
HFD-613/J.Grace/ J Grace 11/29/2001

F/T by: gp/11/28/01

V:\FIRMSNZ\PERRIGO\LTRS&REV\75427.ap.doc
APPROVAL

Robert L. West
12/12/2001

RLWest 12/13/01

APPEARS THIS WAY
ON ORIGINAL

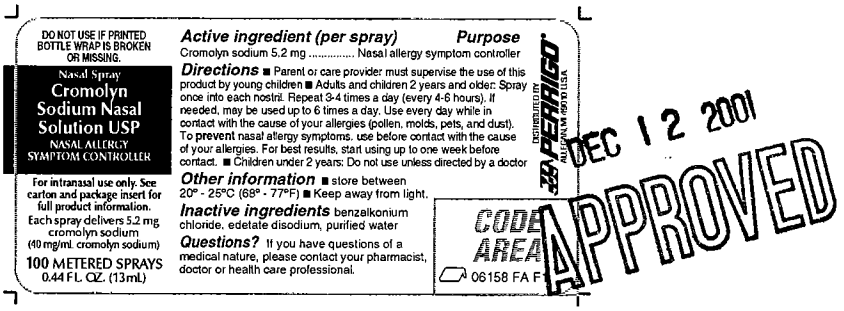
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-427

LABELING

FINAL PRINTED LABELING
BOTTLE LABEL



FINAL PRINTED LABELING
CARTON

APPROVED

DEC 12 2001

EFB 264

Cromolyn Sodium Nasal Solution USP

(Adults and children 2 years and older)

Drug Facts

Active ingredient (per spray) — **Purpose**

Cromolyn sodium 5.2 mg ..... Nasal allergy symptom controller

Uses to prevent and relieve nasal symptoms of hay fever and other nasal allergies:

- runny/itchy nose
- sneezing
- allergic stuffy nose

Warnings

Do not use
- if you are allergic to any of the ingredients

Ask a doctor before use if you have
- fever
- discolored nasal discharge
- sinus pain
- wheezing

When using this product
- it may take several days of use to notice an effect. Your best effect may not be seen for 1 to 2 weeks.
- brief stinging or sneezing may occur right after use
- do not use it to treat sinus infection, asthma, or cold symptoms
- do not share this bottle with anyone else as this may spread germs

Stop use and ask a doctor if
- shortness of breath, wheezing, or chest lightness occurs
- hives or swelling of the mouth or throat occurs
- your symptoms worsen
- you have new symptoms
- your symptoms do not begin to improve within two weeks
- you need to use for more than 12 weeks

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions
- see package insert on how to use pump
- parent or care provider must supervise the use of this product by young children
- adults and children 2 years and older:
  - spray once into each nostril. Repeat 3-4 times a day (every 4-6 hours). If needed, may be used up to 6 times a day.
  - use every day while in contact with the cause of your allergies (pollen, molds, pets, and dust)
  - to prevent nasal allergy symptoms, use before contact with the cause of your allergies. For best results, start using up to one week before contact.
  - if desired, you can use this product with other medicines, including other allergy medicines.
- children under 2 years: Do not use unless directed by a doctor

Drug Facts (continued)

Other information
- store between 20° - 25°C (68° - 77°F)
- keep away from light
- keep carton and package insert. They contain important instructions.

Inactive ingredients
benzalkonium chloride, edetate disodium, purified water

Questions?
If you have questions of a medical nature, please contact your pharmacist, doctor or health care professional.

Before using any medication read all label directions. Keep carton and package insert. They contain important information.

DO NOT USE IF PRINTED BOTTLE WRAP IS BROKEN OR MISSING.

This product is convenient and easy to administer using the metered spray pump. See package insert for spray pump directions.

DISTRIBUTED BY
PERRIGO®
ALLEGAN, MI 49010 U.S.A.

Nasal Spray

Cromolyn Sodium Nasal Solution USP

NASAL ALLERGY SYMPTOM CONTROLLER

Nasal Spray

Cromolyn Sodium Nasal Solution USP

NASAL ALLERGY SYMPTOM CONTROLLER

Prevents and Relieves Nasal Allergy Symptoms:

- runny/itchy nose
- sneezing
- allergic stuffy nose

Without Drowsiness

Full Prescription Strength

Safe For Ages 2 Years & Older

100 METERED SPRAYS

Each spray delivers 5.2 mg cromolyn sodium

0.44 FL. OZ. (13mL)

What Makes This Product Unique?

Nasal Allergy Symptom Prevention
This product can prevent nasal allergy symptoms when used before exposure to the cause of your nasal allergies, and will build protection against future symptoms as long as you continue to use this product as directed.

Effective Relief
This product provides original prescription-strength relief of nasal allergy symptoms, including congestion, sneezing and runny or itchy nose.

Works only in your nose
This product is a nasal spray that works only in your nose – where nasal allergies attack. It helps to stop the cells in your nose from reacting to pollen, pet dander, and other allergies, so you don't experience nasal allergy symptoms.

Safe
- No drowsiness
- No jitters
- No "rebound" nasal congestion
- Safe to use with other medicines, including other allergy medicines
- Non habit forming
- Safe to use throughout your allergy season
- Good for year-round allergies
- Safe for children as young as two years old

LOT NO.

EXP.

06158 FA C1

45

FINAL PRINTED LABELING
BOTTLE LABEL

DO NOT USE IF PRINTED BOTTLE WRAP IS BROKEN OR MISSING.

Nasal Spray

Cromolyn Sodium Nasal Solution USP

NASAL ALLERGY SYMPTOM CONTROLLER

For intranasal use only. See carton and package insert for full product information.

Each spray delivers 5.2 mg cromolyn sodium (40 mg/mL cromolyn sodium)

200 METERED SPRAYS
0.88 FL. OZ. (26mL)

Active ingredient (per spray) ***Purpose***
Cromolyn sodium 5.2 mg ... Nasal allergy symptom controller

Directions ■ Parent or care provider must supervise the use of this product by young children ■ Adults and children 2 years and older: Spray once into each nostril. Repeat 3-4 times a day (every 4-6 hours). If needed, may be used up to 6 times a day. Use every day while in contact with the cause of your allergies (pollen, molds, pets, and dust). To **prevent** nasal allergy symptoms, use before contact with the cause of your allergies. For best results, start using up to one week before contact. ■ Children under 2 years: Do not use unless directed by a doctor

Other information ■ store between 20° - 25°C (68° - 77°F) ■ Keep away from light.

Inactive ingredients benzalkonium chloride, edetate disodium, purified water

Questions?
If you have questions of a medical nature, please contact your pharmacist, doctor or health care professional.

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CODE AREA
06160 FA F1

DEC 12 2001
APPROVED

APPROVED

DEC 12 2001

FINAL PRINTED LABELING
CARTON

DO NOT USE IF PRINTED BOTTLE WRAP IS BROKEN OR MISSING.

Cromolyn Sodium Nasal Solution USP

(Adults and children 2 years and older)

Drug Facts

Active ingredient (per spray) — **Purpose**

Cromolyn sodium 5.2 mg ..... Nasal allergy symptom controller

Uses to prevent and relieve nasal symptoms of hay fever and other nasal allergies:

- runny/itchy nose
- sneezing
- allergic stuffy nose

Warnings

Do not use
- if you are allergic to any of the ingredients

Ask a doctor before use if you have
- fever
- discolored nasal discharge
- sinus pain
- wheezing

When using this product
- it may take several days of use to notice an effect. Your best effect may not be seen for 1 to 2 weeks.
- brief stinging or sneezing may occur right after use
- do not use it to treat sinus infection, asthma, or cold symptoms
- do not share this bottle with anyone else as this may spread germs

Stop use and ask a doctor if
- shortness of breath, wheezing, or chest lightness occurs
- hives or swelling of the mouth or throat occurs
- your symptoms worsen
- you have new symptoms
- your symptoms do not begin to improve within two weeks
- you need to use for more than 12 weeks

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions
- see package insert on how to use pump
- parent or care provider must supervise the use of this product by young children
- adults and children 2 years and older:
  - spray once into each nostril. Repeat 3-4 times a day (every 4-6 hours). If needed, may be used up to 6 times a day.
  - use every day while in contact with the cause of your allergies (pollen, molds, pets, and dust)
  - to prevent nasal allergy symptoms, use before contact with the cause of your allergies. For best results, start using up to one week before contact.
  - if desired, you can use this product with other medicines, including other allergy medicines.
- children under 2 years: Do not use unless directed by a doctor

Other information
- store between 20° - 25°C (68° - 77°F)
- keep away from light
- keep carton and package insert. They contain important instructions.

Drug Facts (continued)

Inactive ingredients
benzalkonium chloride, edetate disodium, purified water

Questions?
If you have questions of a medical nature, please contact your pharmacist, doctor or health care professional.

Before using any medication read all label directions. Keep carton and package insert. They contain important information.

This product is convenient and easy to administer using the metered spray pump. See package insert for spray pump directions.

DISTRIBUTED BY
PERRIGO®
ALLEGAN, MI 49010 U.S.A.

Nasal Spray

Cromolyn Sodium Nasal Solution USP

NASAL ALLERGY SYMPTOM CONTROLLER

Nasal Spray

Cromolyn Sodium Nasal Solution USP

NASAL ALLERGY SYMPTOM CONTROLLER

Prevents and Relieves Nasal Allergy Symptoms:

- runny/itchy nose
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- allergic stuffy nose

Without Drowsiness

Full Prescription Strength

Safe For Ages 2 Years & Older

200 METERED SPRAYS

Each spray delivers 5.2 mg cromolyn sodium

0.88 FL. OZ. (26mL)

LOT NO.

EXP.

06160 FA C1

EFB 265

What Makes This Product Unique?

Nasal Allergy Symptom Prevention
This product can prevent nasal allergy symptoms when used before exposure to the cause of your nasal allergies, and will build protection against future symptoms as long as you continue to use this product as directed.

Effective Relief
This product provides original prescription-strength relief of nasal allergy symptoms, including congestion, sneezing and runny or itchy nose.

Works only in your nose
This product is a nasal spray that works only in your nose – where nasal allergies attack. It helps to stop the cells in your nose from reacting to pollen, pet dander, and other allergies, so you don't experience nasal allergy symptoms.

Safe
- No drowsiness
- No jitters
- No "rebound" nasal congestion
- Safe to use with other medicines, including other allergy medicines
- Non habit forming
- Safe to use throughout your allergy season
- Good for year-round allergies
- Safe for children as young as two years old

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Nasal Spray

Cromolyn Sodium Nasal Solution USP

Nasal Allergy Symptom Controller

PREVENTS AND RELIEVES NASAL ALLERGY SYMPTOMS

WHAT MAKES THIS PRODUCT UNIQUE?

Nasal Allergy Symptom Prevention

This product can prevent nasal allergy symptoms when used before exposure to the cause of your nasal allergies, and will build protection against future nasal allergy symptoms as long as you continue to use this product as directed.

Effective Relief

This product provides original prescription-strength relief of nasal allergy symptoms, including congestion, sneezing and runny or itchy nose.

Works Only In Your Nose

This product is a nasal spray that works only in your nose – where nasal allergens attack. It helps to stop the cells in your nose from reacting to pollen, pet dander, and other allergens, so you don't experience nasal allergy symptoms.

Safe

- No drowsiness
- No jitters
- No "rebound" nasal congestion
- Non habit forming
- Safe to use with other medicines, including other allergy medicines
- Safe to use throughout your allergy season
- Good for year-round allergies
- Safe for children as young as two years old

APPROVED

DEC 12 2001

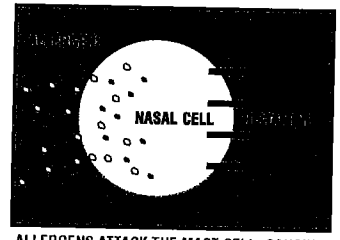
WHAT CAUSES NASAL ALLERGY SYMPTOMS?

Nasal allergies are caused by airborne pollens from trees, grasses, or ragweed, and by mold, animals and dust. Exposure to these nasal allergy-causing substances may cause mast cells in your nose to release histamine. When histamine is released it causes nasal allergy symptoms: sneezing, runny/itchy nose, and allergic stuffy nose.

HOW DOES THIS PRODUCT WORK?

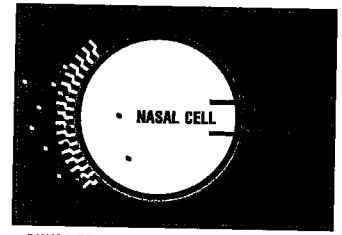
This product is neither an antihistamine nor a decongestant nor a corticosteroid. It's a nasal mast cell stabilizer. In addition to treating nasal allergy symptoms, it decreases the allergic reaction by reducing the release of histamine, the trigger of allergy symptoms, from mast cells.

WITHOUT THIS PRODUCT



ALLERGENS ATTACK THE MAST CELL, CAUSING IT TO ERUPT AND RELEASE HISTAMINE

WITH THIS PRODUCT



ONLY A FEW NASAL ALLERGENS GET TO THE CELL, SO LESS HISTAMINE IS RELEASED

HOW DO I TELL IF IT'S AN ALLERGY OR A COLD?

Some nasal allergy symptoms may seem like cold symptoms. There are several clues that you're suffering from nasal allergy symptoms, instead of a cold. Colds are caused by viral infections, and symptoms often include fever, body aches, discolored nasal discharge or cough. It is rare for nasal allergies to produce these symptoms. If you have them, please call your doctor before beginning this product. Nasal allergy symptoms include runny/itchy nose, sneezing and stuffy nose. Seasonal allergies occur the same time each year, and are linked to plant pollens, spores, or molds. Some allergies occur year round, and may be connected to microscopic particles in common household dust, animal dander, or indoor molds. This product can help you with the nasal symptoms of allergy.

WHO SHOULD USE THIS PRODUCT?

This product is suitable for most people with nasal allergies including children as young as 2.

This product is safe to use if you are taking other medicines, even other allergy medicines, because this product does not cause any known drug interactions.

Don't use this product if you are allergic to the ingredients. If this product causes irritation to your nose, discontinue use.

HOW TO USE THIS PRODUCT

Begin use 1-2 weeks before you are exposed to nasal allergens.

To prevent nasal allergy symptoms, start using this product before you think your symptoms will begin. Use your experience as a guide. For example: if you are allergic to cats, start this product one week before you visit a house with cats. If you can't predict your allergy season, begin this product at the first sign of nasal allergy symptoms. This product also relieves nasal allergies while it builds full protection against further symptoms.

Use this product 3-4 times a day, every day while in contact with the cause of your nasal allergy, whether you have symptoms or not. Spray once in each nostril in the morning, at noon, at dinner, and at bedtime. Some people may get brief nasal stinging and/or sneezing right after the use of this product.

Full protection may take as long as 1-2 weeks with regular use so continue using this product during that time. Regular use is important to achieve full protection.

Use this product throughout your allergy season.

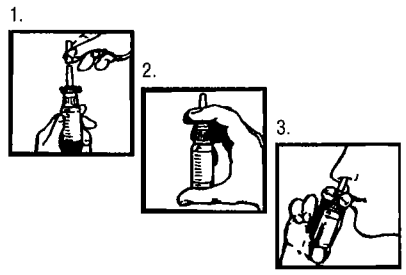
This product can be used safely up to 6 times a day, for up to 12 weeks. If you need this product beyond 12 weeks, speak to your doctor. Also speak to your doctor if your symptoms worsen, new symptoms occur, or symptoms do not begin to improve within two weeks. Your symptoms may indicate some other underlying condition.

STOP AFTER 2 WEEKS IF YOU DON'T GET ANY RELIEF

STOP USE AND ASK A DOCTOR

if shortness of breath, wheezing, chest tightness, hives, or swelling of the mouth or throat occur while using this product. You may be allergic to this product and require further medical attention.

Do not use this product if allergic to any of its ingredients.



SPRAY PUMP DIRECTIONS

For Adults and Older Children

Blow your nose before using this product.

1. Remove the clear plastic cap and safety clip. (Picture 1)
2. Hold the pump with thumb at bottom and the nozzle between fingers. If this is the first time you are using the pump, or if you have not used the pump for several days, spray in the air until you get a fine mist. (Picture 2)
3. Hold the bottle as shown in the picture. Insert nozzle into nostril. Spray upward while breathing in through the nose. This will release one dose of medication. Repeat in other nostril. Some people may get brief stinging and/or sneezing right after the use of this product. (Picture 3)
4. To keep clean, wipe the nozzle. Put clear plastic cap and safety clip back on the bottle.
5. Do not share this bottle with anyone else as this may spread germs.

For Very Young Children

1. Only an adult should administer the product.
2. Use care when inserting the nozzle into the nose to avoid injury.

NASAL ALLERGY CONTROLLING TIPS

Many people are allergic to the dust mites that live in carpeting and bedding. Put mattresses and pillows in airtight covers and, if practical, get rid of all carpets. Use an air purifier with a HEPA (High Efficiency Particulate Air) filter to clean the air. People with nasal allergies to animals should limit their contact with these animals. It is the animal's dander (skin flakes) that causes allergies, not the hair length. People who are allergic to pollen and mold should use an air conditioner as much as possible. When you open the windows in your house, you let in pollen and mold spores. Ask your doctor or healthcare professional for more tips on how to allergy-proof your home.

Store between 20°-25° C (68°-77° F).

Keep away from light.

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PERRIGO®
ALLEGAN, MI 49010 U.S.A.

06100 FA J1

FINAL PRINTED LABELING
BOTTLE WRAP

75-427
AP 12/12/01

DEC 12 2001

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-427

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-427 **Date of Submission:** July 31, 1998

Applicant's Name: L. Perrigo Company

Established Name: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray

Labeling Deficiencies:

1. GENERAL COMMENTS:

   In your application, you have identified [redacted] as the manufacturer, however, on your labeling you indicate Perrigo is the manufacturer. Please revise and/or comment.

2. CONTAINER (13 mL and 26 mL)

   a. See GENERAL COMMENT.

3. CARTON (13 mL and 26 mL)

   a. See GENERAL COMMENT.

4. NASAL ALLERGY SYMPTOM PREVENTION AND RELIEF LEAFLET

   a. See GENERAL COMMENT.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels for the 13 mL and 26 mL containers, and 12 copies of final printed carton and patient leaflet labeling.

APPEARS THIS WAY
ON ORIGINAL

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance? Yes No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?	X		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST: The innovator's _____ _____. The applicant's _____ differs. It is _____. Is this acceptable? To be determined.

_____

_____

FOR THE RECORD:

1. The reference listed drug for this product is OTC-Nasalcrom® by McNeil (20-463; Approved January 3, 1997).

2. The USP name for this product is Cromolyn Sodium Nasal Solution. USP requires it be preserved in tight, light-resistant containers.

3. The applicant certifies that a New Product Exclusivity is in effect through January 3, 2000 and that it will not market until after that date. No patents exist for this product. See Vol. 1.1, pages 9-10.

4. The product is manufactured by _____ for L. Perrigo 117 Water Street, Allegan, MI 49010. However, the labels and labeling indicate that the product is manufactured by L. Perrigo. The applicant has been referred to 21 CFR 201.1(h)(5) for guidance. See Vol. 1.1, page 112.

5. Outside firms are used for testing only. See Vol. 1.1, page 116.

6. Container/Closure:

   Bottle: HDPE _____ for 13 mL and 26 mL package.
   Sprayer w/ overcap & safety clip for 13 mL and 26 mL package.

   See Vol. 1.1, page 332.

7. Product line:

   5.2 mg/spray in 13 mL and 26 mL bottles.

   See Vol.1.1, page 32-33.

8. Components/Composition

NDA: Each mL contains:
Active: 40 mg Cromolyn sodium
Inactive: Purified water
benzalconium chloride (preservative)
edetate disodium

ANDA: Each mL contains:
Active: 40 mg Cromolyn sodium
Inactive: Purified water
benzalkonium chloride
disodium EDTA

Vol. 1.1, page 65.

9. Storage/Dispensing

NDA: 15-30°C (59°-86°F). Keep away from light.
ANDA: 15-30°C (59°-86°F). Keep away from light.

Vol. 1.1, page 21.

Date of Review: 9-15-98 **Date of Submission:** July 31, 1998

Primary Reviewer: J. Watts **Date:** 9/16/98

Team Leader: John D. Grace **Date:** 9/17/98

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

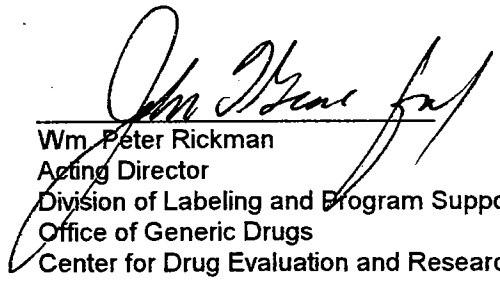
ANDA Number: 75-427 **Date of Submission: March 31, 2000**
Applicant's Name: L. Perrigo Company
Established Name: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray
Labeling Deficiencies:

1. GENERAL COMMENTS: Please note that the reference listed drug labeling which you submitted for your side-by-side has not yet been approved. Therefore, revise your labels and labeling to be in accord with the currently approved labeling for the reference listed drug, NASALCROM® (McNeil; NDA#20-463; approved January 3, 1997). In addition, labeling making a distinction for "Children's NASALCROM®" has not yet been approved. Therefore, we will be unable to approve similar labeling for your ANDA. We have enclosed a copy of the innovator's labeling for your convenience.
2. CONTAINER (13 mL and 26 mL) - Please include the NDC # and exp. date.
3. CARTON (13 mL and 26 mL)- Front and right side panels - See GENERAL COMMENT. In addition, rather than using " this product" please site the product name. Please Use capital letters for " Poison Control Center". Include the NDC# and exp. date.
4. NASAL ALLERGY SYMPTOM PREVENTION AND RELIEF LEAFLET- See GENERAL COMMENT.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container, carton labels and patient leaflet labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval. We suggest that you routinely monitor the following website for any approved changes – http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes or NO
Container Labels:(13 mL and 26 mL)
Carton Labeling:(13 mL and 26 mL)
Patient Package Insert Labeling:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: OTC-NASALCROM®
NDA Number: 20-463
NDA Drug Name: Cromolyn Sodium Nasal Solution USP, 4%
NDA Firm: McNeil Consumer Products Company
Date of Approval of NDA Insert and supplement #: January 3, 1997; FPL February 28, 1997
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side by side comparison w/innovator labels in file folder.
Basis of Approval for the Carton Labeling: Side by side comparison w/RLD carton in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	

Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug for this product is OTC-Nasalcrom by McNeil (20-463; Approved January 3, 1997). However at the time of this review the orange book site Pharmacia Upjohn as the NDA applicant holder. Pharmacia Upjohn will market the product.
2. The USP name for this product is Cromolyn Sodium Nasal Solution. USP requires it be preserved in tight, light-resistant containers.
3. The applicant certifies that a New Product Exclusivity is in effect through January 3, 2000 and that it will not market until after that date. No patents exist for this product. See Vol. 1.1, pages 9-10.
4. The product is manufactured by [redacted] for L. Perrigo 117 Water Street, Allegan, MI 49010. However, the labels and labeling indicate that the product is manufactured by L. Perrigo. See Vol. 3.1, page 129. Labels and labeling in the march 31 review now identifies L. Perrigo as the distributor.
5. Outside firms are used for testing only. See Vol. 1.1, page 116.
6. Container/Closure:
   Bottle: HDPE [redacted] for 13 mL and 26 mL package.
   Sprayer w/ overcap & safety clip for 13 mL and 26 mLpackage. See Vol. 1.1, page 332.
7. Product line: 5.2 mg/spray in 13 mL and 26 mL bottles.See Vol.1.1, page 32-33.
8. Components/Composition
   NDA: Each mL contains:
   Active: 40 mg Cromolyn sodium
   Inactive: Purified water, benzalconium chloride (preservative), edetate disodium
   ANDA: Each mL contains:
   Active: 40 mg Cromolyn sodium
   Inactive: Purified water, benzalkonium chloride, disodium EDTA Vol. 1.1, page 65.
9. Storage/Dispensing
   NDA: 15-30°C (59°-86°F). Keep away from light.
   ANDA: 15-30°C (59°-86°F). Keep away from light. Vol. 1.1, page 21.
10. The generic firm submitted labeling for "Children's Cromolyn Sodium" the submitted a side-by-side comparison with innovator labeling that they found in the marketplace for "Children's NasalCrom". This labeling has not yet been approved. It has been submitted as a Special Supplement Changes Being Effected to the New Drug Division. If approved the labeling will include dosing for children ages 2 and up. It currently is indicated for children ages 6 and up. Per Babbet Merrit in New Drug Division. It may also receive exclusivity rights. It is in an approvable status as of the date of this review. See office folder. the holder of the NDA was informed that these changes needed prior approval before place in the market. SE5/002

Date of Review: December 21, 2000
Date of Submission: March 31, 2000

Reviewer: Angela M. Payne **Date:**
Team Leader: [signature] **Date:** 1-19-2001

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cc:
ANDA: 75-427
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:\FIRMSNZ\PERRIGO\LTRS&REV\75427NA2.I

apayne 01-18-01

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Superseded by other reviews

ANDA Number: 75-427 Date of Submission: Feb. 15 & 16 , 2001
Applicant's Name: L. Perrigo Company
Established Name: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray

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APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels:(13 mL and 26 mL) vol 5.1 pages 29-76 satisfactory in FPL
Carton Labeling:(13 mL and 26 mL) vol 5.1 pages 29-76 satisfactory in FPL
Patient Package Insert Labeling: vol 5.1 pages 29-76 satisfactory in FPL

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: OTC-NASALCROM®
NDA Number: 20-463
NDA Drug Name: Cromolyn Sodium Nasal Solution USP, 4%
NDA Firm: McNeil Consumer Products Company
Date of Approval of NDA Insert and supplement #: January 3, 1997; FPL February 28, 1997
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side by side comparison w/innovator labels in file folder.
Basis of Approval for the Carton Labeling: Side by side comparison w/RLD carton in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	

Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug for this product is OTC-Nasalcrom by McNeil (20-463; Approved January 3, 1997). However at the time of this review the orange book site Pharmacia Upjohn as the NDA applicant holder. Pharmacia Upjohn will market the product.
2. The USP name for this product is Cromolyn Sodium Nasal Solution. USP requires it be preserved in tight, light-resistant containers.
3. The applicant certifies that a New Product Exclusivity is in effect through January 3, 2000 and that it will not market until after that date. No patents exist for this product. See Vol. 1.1, pages 9-10.
4. The product is manufactured by [redacted] for L. Perrigo 117 Water Street, Allegan, MI 49010. However, the labels and labeling indicate that the product is manufactured by L. Perrigo. See Vol. 3.1, page 129. Labels and labeling in the march 31 review now identifies L. Perrigo as the distributor.
5. Outside firms are used for testing only. See Vol. 1.1, page 116.
6. Container/Closure:
   Bottle: HDPE [redacted] for 13 mL and 26 mL package.
   Sprayer w/ overcap & safety clip for 13 mL and 26 mLpackage. See Vol. 1.1, page 332.
7. Product line: 5.2 mg/spray in 13 mL and 26 mL bottles.See Vol.1.1, page 32-33.
8. Components/Composition
   NDA: Each mL contains:
   Active: 40 mg Cromolyn sodium
   Inactive: Purified water, benzalconium chloride (preservative), edetate disodium
   ANDA: Each mL contains:
   Active: 40 mg Cromolyn sodium
   Inactive: Purified water, benzalkonium chloride, disodium EDTA Vol. 1.1, page 65.
9. Storage/Dispensing
   NDA: 15-30°C (59°-86°F). Keep away from light.
   ANDA: 15-30°C (59°-86°F). Keep away from light. Vol. 1.1, page 21.
10. The generic firm submitted labeling for "Children's Cromolyn Sodium" the submitted a side-by-side comparison with innovator labeling that they found in the marketplace for "Children's NasalCrom". This labeling has not yet been approved. It has been submitted as a Special Supplement Changes Being Effected to the New Drug Division. If approved the labeling will include dosing for children ages 2 and up. It currently is indicated for children ages 6 and up. Per Babbet Merrit in New Drug Division. It may also receive exclusivity rights. It is in an approvable status as of the date of this review. See office folder. The holder of the NDA was informed that these changes needed prior approval before place in the market. SE5/002

Date of Review: April 23, 2001 **Date of Submission:** Feb. 15 & 16th 2001

cc: ANDA: 75-427
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:/firmsnz/perrigo/let&rev/75427ap.l
Review

4/23/01
5/3/2001

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-427 **Date of Submission: 7/12/01**
Applicant's Name: L. Perrigo Company
Established Name: Cromolyn Sodium Nasal Solution USP, 5.2 mg/ Nasal Spray

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APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels:(13 mL and 26 mL) vol 7.1 satisfactory in FPL submitted 7/12/01
Carton Labeling:(13 mL and 26 mL) vol 7.1 satisfactory in FPL submtted 7/12/01
Patient Package Insert Labeling: vol 7.1 satisfactory in FPL submitted 7/12/01
BASIS OF APPROVAL:

Patent data for 20-463 : THERE ARE **NO UNEXPIRED PATENTS.**

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact

Exclusivity data for NDA 20-463:

Supplement No.	Use Code	Description	Expiration date	Generic Labeling Impact
s-002/approved March 27, 2001		For use in children down to 2 years of age.	Was not granted a 3 yr wax/hauc protection because firm did not do clinical studies. They submitted only pk data.	Same as RLD

Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: OTC-NASALCROM®
NDA Number: 20-463
NDA Drug Name: Cromolyn Sodium Nasal Solution USP, 4%
NDA Firm: McNeil Consumer Products Company
Date of Approval of NDA Insert and supplement #: S-002, approved Mar 27, 2001.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side by side comparison w/innovator labels in file folder.
Basis of Approval for the Carton Labeling: Side by side comparison w/RLD carton in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		

Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug for this product is OTC-Nasalcrom by McNeil (20-463; Approved Mar. 27, 2001). However at the time of this review the orange book site Pharmacia Upjohn as the NDA applicant holder. Pharmacia Upjohn will market the product.
2. The USP name for this product is Cromolyn Sodium Nasal Solution. USP requires it be preserved in tight, light-resistant containers.
3. The applicant certifies that a New Product Exclusivity is in effect through January 3, 2000 and that it will not market until after that date. No patents exist for this product. See Vol. 1.1, pages 9-10.
4. The product is manufactured by [redacted] for L. Perrigo 117 Water Street, Allegan, MI 49010. However, the labels and labeling indicate that the product is manufactured by L. Perrigo. See Vol. 3.1, page 129. Labels and labeling in the march 31 review now identifies L. Perrigo as the distributor.
5. Outside firms are used for testing only. See Vol. 1.1, page 116.
6. Container/Closure:
   Bottle: HDPE [redacted] for 13 mL and 26 mL package.
   Sprayer w/ overcap & safety clip for 13 mL and 26 mL package. See Vol. 1.1, page 332.
7. Product line: 5.2 mg/spray in 13 mL and 26 mL bottles.See Vol.1.1, page 32-33.
8. Components/Composition
   NDA: Each mL contains:
   Active: 40 mg Cromolyn sodium
   Inactive: Purified water, benzalconium chloride (preservative), edetate disodium
   ANDA: Each mL contains:

Active: 40 mg Cromolyn sodium
Inactive: Purified water, benzalkonium chloride, disodium EDTA Vol. 1.1, page 65.

9. Storage/Dispensing
NDA: 15-30°C (59°-86°F). Keep away from light.
ANDA: 15-30°C (59°-86°F). Keep away from light. Vol. 1.1, page 21.

10. The generic firm submitted labeling for "Children's Cromolyn Sodium" the submitted a side-by-side comparison with innovator labeling that they found in the marketplace for "Children's NasalCrom". This labeling has not yet been approved. It has been submitted as a Special Supplement Changes Being Effected to the New Drug Division. If approved the labeling will include dosing for children ages 2 and up. It currently is indicated for children ages 6 and up. Per Babbet Merrit in New Drug Division. It may also receive exclusivity rights. It is in an approvable status as of the date of this review. See office folder. The holder of the NDA was informed that these changes needed prior approval before place in the market. SE5/002. S-002 is now approved see date above.

Date of Review: **August 21, 2001** **Date of Submission:** **7/12/2001**

---

cc: ANDA: 75-427
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:/firmsnz/perrigo/let&rev/75427ap.2L
Review

8/21/2001
8/21/01

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-427

CHEMISTRY REVIEWS

1. ***CHEMIST's REVIEW #1*** [*Courier New 12*]

2. **ANDA 75-427**

3. APPLICANT, Name/Address/Telephone/Fax:
L. Perrigo Co.
Attention: Lisa Gould McNeil
117 Water Street
Allegan, MI 49010
☎ 616-673-8451/*fax* 616-673-7655

4. LEGAL BASIS FOR ANDA SUBMISSION: *505(j)*

5. Supplement: n/a

6. PROPRIETARY Name: none

7. **Non-PROPRIETARY Name**: **Chromolyn Sodium Nasal Solution, USP**

Innovator's Product Name: Nasalcrom®
Pharmacia & Upjohn
[Exclusivity expires 1-3-2000]

OA File: 1st generic ———

8. Supplement Provides For: n/a

9. AMENDMENTS & Other DATES.
A. **FIRM**:
*07-31-98 original appl.
11-20-98 bio amendment

B. **FDA**:
09-15-98 labeling unsat.
11-03-98 Bio deficiencies

10. PHARMACOLOGICAL CATEGORY:

11. Rx or OTC: R_x

12. RELATED ANDA's: -

13. DOSAGE Form: nasal solution delivered via a manual metered dose pump

14. POTENCY: 5.2 mg/spray = **4%**

15. CHEMICAL Name: Cromolyn sodium:
Disodium 5,5'-[(2-hydroxytrimethylene) dioxy]*bis*[4-oxo-4*H*-1-benzopyran-2-carboxylate]
MW 512.34 *[15826-37-6]*

16. Records & Reports: n/a

17. COMMENTS.

A. General Comments:
USP drug substance and drug product.

B. Comments for the Action Letter, see section 38:

18. CONCLUSIONS & RECOMMENDATIONS:
NA with MAJOR amendment.

19. Reviewer/Branch Chief:

Robert W. Trimmer
BRANCH II, DIV. OF CHEMISTRY I, OGD

Michael J. Smela, Jr.
TEAM LEADER

Date Started: 12-01-98
Date Completed: 01-29-99
revised: 02-19-99

APPEARS THIS WAY
ON ORIGINAL

Redacted 28 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

APPEARS THIS WAY
ON ORIGINAL

file# *X:/new/firmsnz/Perrigo/*75427r1.brt

cc:
ANDA 75-427
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/Chemist/RWTrimmer/ 2-24-99
HFD-625/Chemistry Team Leader/MJSmela/2/22/99 MJSmela 2/25/99

Project Manager:

HFD-617/DPHuie/2/22/99 DPHuie 2/23/99
F/t by: gp/2/22/99

CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

1. ***CHEMIST's REVIEW #2***

2. **ANDA 75-427**

3. APPLICANT, Name/Address/Telephone/Fax:
L. Perrigo Co.
Attention: Valerie Gallagher
117 Water Street
Allegan, MI 49010
☎ 616-673-8451/*fax* 616-673-7655

4. LEGAL BASIS FOR ANDA SUBMISSION: *505(j)*

5. Supplement: n/a

6. PROPRIETARY Name: none

7. **Non-PROPRIETARY Name:** **Cromolyn Sodium Nasal Solution, USP**

Innovator's Product Name: Nasalcrom®
Pharmacia & Upjohn NDA 20-463
[Exclusivity expired 1-3-2000]

QA File: 1st generic ——— There is no patent.

Teresa Watkins' labeling review says the RLD is by McNeil, but I haven't found anything to support her statement. Teresa doesn't recall the details, per E-mail 8/29/00.

8. Supplement Provides For: n/a

9. AMENDMENTS & Other DATES.

Vol. A1.1:

07-31-98 original appl.
09-01-98 Acceptable for filing 8/3/98
11-03-98 Bio deficiencies
11-20-98 bio amendment
03-05-99 NA-Major - Chemistry and labeling
03-30-99 Bio deficiencies

Vol. A2.1:

04-20-99 DMPQ concurrence with CHI-DO recommendation to withhold approval of this ANDA, based on inspection of finished dosage form manufacturing facility, ———————————

Vol. A3.1 to A3.4:

03-31-00 **Major amendment** in response to 03-05-99 for chemistry and labeling (A3.1 and A3.2)

Perrigo is further amending this ANDA to address a manufacturing site change and container/closure system changes:

Perrigo is changing its contract manufacturer [redacted]

The chemistry responses contained in this major amendment are based on a new exhibit batch manufactured at [redacted] using a new container/closure system.

New information in this amendment that supports the changes in manufacturing site and C/C system will be marked by the symbol "✏".

03-31-00 Amendment in response to 03-30-99 for bioequivalence (A3.3 and A3.4)

06-20-00 Bio deficiencies (A3.1)

10. PHARMACOLOGICAL CATEGORY: Anti-asthmatic (prophylactic)

11. Rx or OTC: OTC

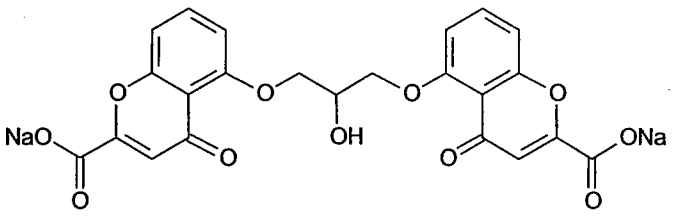
12. RELATED ANDA's: -

13. DOSAGE Form: nasal solution delivered via a manual metered dose pump

14. STRENGTH: 5.2 mg/spray = 4%

15. CHEMICAL Name: Cromolyn sodium:
Disodium 5,5'-[(2-hydroxytrimethylene) dioxy]*bis*[4-oxo-4*H*-1-benzopyran-2-carboxylate]
MW 512.34 *[15826-37-6]*

4*H*-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroy-1,3-propanediyl)bis(oxy)]bis[4,-oxo-, disodium salt]. $C_{23}H_{14}Na_2O_{11}$.



16. Records & Reports: n/a

17. COMMENTS:

Acknowledgement:

The first chemistry review was completed by Dr. Robert Trimmer. For efficiency, I am using his review #1 as a template for my review #2.

There are **deficiencies** in the following Review Points:

24, 25, 26, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product, because it is a nasal spray, not an inhalation solution.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

USP drug substance and drug product.

32. LABELING

On hold due to questions re OTC Guidance and "Drug Facts" format, per E-mail from Teresa Watkins 8/29/00.

33. ESTABLISHMENT INSPECTION

A new EER needs to be issued because of the change in the finished dosage manufacturer for the drug product. The new facility is:

[ ] CFN ———

_____ should be deleted from the EER because this company will no longer be employed by the applicant for this ANDA.

The following new contract testing labs also need to be added to the EER because they might be used to test the drug substance:

The functions are shown on pages 129 and 131-132 of the chemistry amendment of 3/31/00.

34. BIOEQUIVALENCE STATUS

Deficiencies were sent to Perrigo 6/20/00.

18. CONCLUSIONS & RECOMMENDATIONS:
NA with MAJOR amendment.

19. Reviewer/Branch Chief:

Eugene L. Schaefer, Ph.D.
BRANCH II, DIV. OF CHEMISTRY I, OGD

Michael J. Smela, Jr.
TEAM LEADER

Date Completed: 9/25/00
Revised: 10/3/00

APPEARS THIS WAY
ON ORIGINAL

Redacted 26 page(s)

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information from

CHEMISTRY REVIEW #2

cc:

ANDA 75-427
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/Chemist/ELSchaefer/10/3/00
HFD-625/Chemistry Team Leader/MJSmela/10/10/00

Project Manager:

HFD-617/MDillahunt/10/10/00

F/t by: gp/10/10/00

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CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

APPEARS THIS WAY
ON ORIGINAL

1. ***CHEMIST's REVIEW #3***

2. **ANDA 75-427**

3. APPLICANT, Name/Address/Telephone/Fax:
L. Perrigo Co.
Attention: Valerie Gallagher
515 Eastern Avenue
Allegan, MI 49010
☎ 616-673-9367/*fax* 616-673-7655

4. LEGAL BASIS FOR ANDA SUBMISSION: *505(j)*

5. Supplement: n/a

6. PROPRIETARY Name: none

7. **Non-PROPRIETARY Name:** **Cromolyn Sodium Nasal Solution, USP**

Innovator's Product Name: Nasalcrom®
McNeil NDA 20-463
[Exclusivity expired 1-3-2000]

QA File: 1st generic ——— There is no patent.

8. Supplement Provides For: n/a

9. AMENDMENTS & Other DATES.

Vol. A1.1:

07-31-98 original appl.
09-01-98 Acceptable for filing 8/3/98
11-03-98 Bio deficiencies

03-05-99 NA-Major - Chemistry and labeling

Vol. A2.1:

11-20-98 bio amendment
03-30-99 Bio deficiencies
04-20-99 DMPQ concurrence with CHI-DO recommendation to withhold approval of this ANDA, based on inspection of finished dosage form manufacturing facility, ———————————

Vol. A3.1 to A3.4:

03-31-00 Major amendment in response to 03-05-99 for chemistry and labeling (A3.1 and A3.2)

Perrigo further amended this ANDA to address a manufacturing site change and container/closure system changes:

Perrigo changed its contract manufacturer [redacted]

The chemistry responses contained in the amendment of 03-31-00 were based on a new exhibit batch manufactured at [redacted] using a new container/closure system.

New information in the amendment of 03-31-00 that supported the changes in manufacturing site and C/C system was marked by the symbol "✏".

03-31-00	Amendment in response to 03-30-99 for bioequivalence (A3.3 and A3.4)
06-20-00	Bio deficiencies (A3.1)
10-13-00	NA-Major - chem only
10-27-00	Memo from HFD-324 [redacted]
11-02-00	Telecon re 10-13-00
01-19-01	Labeling deficiencies

Vol. A4.1 to A4.4:

11-30-00	Bio amendment in response to 06-20-00

Vol. A5.1:

01-19-01	Labeling deficiencies (Same as in A3.1)
01-24-01	**Major amendment - chemistry (the subject of this review)**
01-26-01	Bio amendment
04-30-01	Bio deficiencies
02-15-01	Labeling amendment in response to 01-19-01

10. PHARMACOLOGICAL CATEGORY: Anti-asthmatic (prophylactic)

11. Rx or OTC: OTC

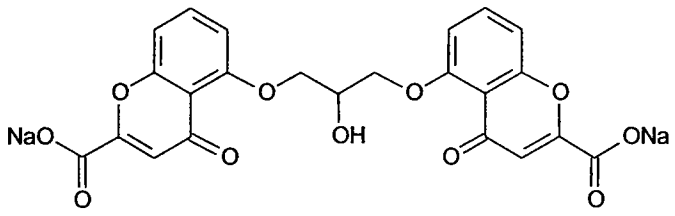
12. RELATED ANDA's: -

13. DOSAGE Form: nasal solution delivered via a manual metered dose pump

14. STRENGTH: 5.2 mg/spray = 4%

15. CHEMICAL Name: Cromolyn sodium:
Disodium 5,5'-[(2-hydroxytrimethylene) dioxy]*bis*[4-oxo-4*H*-1-benzopyran-2-carboxylate]
MW 512.34 *[15826-37-6]*

4*H*-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroy-1,3-propanediyl)bis(oxy)]bis[4,-oxo-, disodium salt]. $C_{23}H_{14}Na_2O_{11}$.



16. Records & Reports: n/a

17. COMMENTS:

A summary of Perrigo document revisions is provided in Section 19. Some of these revisions are discussed in the Responses. Other revisions are minor and are not discussed in this review. Documents that were revised but not noted in the Responses are located in Section 20.

There are **deficiencies** in the following Review Points:

28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product, because it is a nasal spray, not an inhalation solution.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

USP drug substance and drug product.

32. LABELING

Labeling deficiencies were sent 1/19/01. Labeling amendment of 2/15/01 **acceptable,** as of 5/3/01.

33. ESTABLISHMENT INSPECTION

A new EER needs to be issued because of the change in the residual solvents tester for the drug substance.

[redacted] needs to be deleted from the EER.

The new facility is:

[redacted]

See Response #14 in the cover letter of the amendment of 1/24/01. See GMP certification behind Tab 14, on page 71.

34. BIOEQUIVALENCE STATUS

Deficiencies were sent to Perrigo 4/30/01.

18. CONCLUSIONS & RECOMMENDATIONS:
NA with MINOR amendment requested.

19. Reviewer/Branch Chief:
Eugene L. Schaefer, Ph.D.
BRANCH II, DIV. OF CHEMISTRY I, OGD

Michael J. Smela, Jr.
TEAM LEADER

Date Completed: 7/5/01 Revised: 7/9/01

cc:

ANDA 75-427
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates): ES 7/12/01

HFD-625/Chemist/ELSchaefer/7/9/01
HFD-625/Chemistry Team Leader/MJSmela/7/11/01 MJSmela 7/12/01

Project Manager:

HFD-617/MDillahunt/7/11/01 MDillahunt 7/11/01

F/t by: gp/7/11/01

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CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

1. ***CHEMIST's REVIEW # 4***

CHEMISTRY CLOSE

2. **ANDA 75-427**

3. APPLICANT, Name/Address/Telephone/Fax:
L. Perrigo Co.
Attention: Valerie Gallagher
515 Eastern Avenue
Allegan, MI 49010
☎ 616-673-9367/*fax* 616-673-7655

4. LEGAL BASIS FOR ANDA SUBMISSION: *505(j)*

5. Supplement: n/a

6. PROPRIETARY Name: none

7. **Non-PROPRIETARY Name:** **Cromolyn Sodium Nasal Solution, USP**

Innovator's Product Name: Nasalcrom®
McNeil NDA 20-463
[Exclusivity expired 1-3-2000]

QA File: 1st generic ------ There is no patent.

8. Supplement Provides For: n/a

9. AMENDMENTS & Other DATES.

Vol. A1.1:

07-31-98 original appl.
09-01-98 Acceptable for filing 8/3/98
11-03-98 Bio deficiencies
03-05-99 NA-Major - Chemistry and labeling

Vol. A2.1:

11-20-98 bio amendment
03-30-99 Bio deficiencies
04-20-99 DMPQ concurrence with CHI-DO recommendation to withhold approval of this ANDA, based on inspection of finished dosage form manufacturing facility, [redacted]

Vol. A3.1 to A3.4:

03-31-00 Major amendment in response to 03-05-99 for chemistry and labeling (A3.1 and A3.2)

Perrigo further amended this ANDA to address a manufacturing site change and container/closure system changes:

Perrigo changed its contract manufacturer [redacted]

The chemistry responses contained in the amendment of 03-31-00 were based on a new exhibit batch manufactured at [redacted] using a new container/closure system.

New information in the amendment of 03-31-00 that supported the changes in manufacturing site and C/C system was marked by the symbol "✏".

03-31-00	Amendment in response to 03-30-99 for bioequivalence (A3.3 and A3.4)
06-20-00	Bio deficiencies (A3.1)
10-13-00	NA-Major - chem only
10-27-00	Memo from HFD-324 [redacted]
11-02-00	Telecon re 10-13-00
01-19-01	Labeling deficiencies

Vol. A4.1 to A4.4:

11-30-00	Bio amendment in response to 06-20-00

Vol. A5.1:

01-19-01	Labeling deficiencies (Same as in A3.1)
01-24-01	Major amendment - chemistry
01-26-01	Bio amendment
04-30-01	Bio deficiencies
02-15-01	Labeling amendment in response to 01-19-01
07/13/01	NA-Minor - Chem only

Vol. A6.1 and 6.2:

06/29/01	Bio amendment

Vol. A7.1:

07/12/01	Labeling amendment

Vol. A8.1:

07/26/01 Bio telephone amendment
07/31/01 **Chemistry minor amendment (the subject of this review)** in response to 07/13/01

10. PHARMACOLOGICAL CATEGORY: Anti-asthmatic (prophylactic)

11. Rx or OTC: OTC

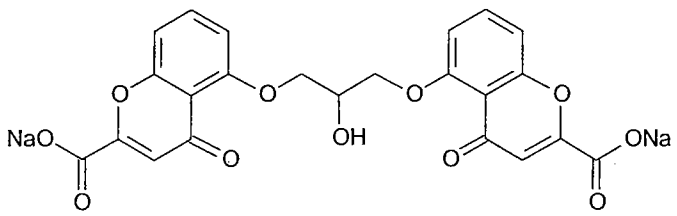
12. RELATED ANDA's: -

13. DOSAGE Form: nasal solution delivered via a manual metered dose pump

14. STRENGTH: 5.2 mg/spray = 4%

15. CHEMICAL Name: Cromolyn sodium:
Disodium 5,5'-[(2-hydroxytrimethylene) dioxy]*bis*[4-oxo-4*H*-1-benzopyran-2-carboxylate]
MW 512.34 *[15826-37-6]*

4*H*-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroy-1,3-propanediyl)bis(oxy)]bis[4,-oxo-, disodium salt]. $C_{23}H_{14}Na_2O_{11}$.



16. Records & Reports: n/a

17. COMMENTS:

The chemistry deficiencies have been **resolved.**

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product, because it is a nasal spray, not an inhalation solution.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

USP drug substance and drug product.

32. LABELING

Labeling amendment of 2/15/01 **acceptable**, as of 5/3/01.

Perrigo submitted FPL on 7/12/01.

33. ESTABLISHMENT INSPECTION

On 7/16/01, **OC recommended that we withhold approval** of ANDA 75-427.

34. BIOEQUIVALENCE STATUS

Deficiencies were sent to Perrigo 4/30/01. Perrigo submitted a Bio amendment on 6/29/01, and a Bio telephone amendment (coded as NC) on 7/26/01. **These amendments are under review.**

18. CONCLUSIONS & RECOMMENDATIONS:

The chemistry deficiencies have been resolved. A microbiology review and a methods validation are not needed. Draft labeling is acceptable. FPL has been submitted but not reviewed. Office of Compliance is recommending withhold. Bio amendment is under review.

ANDA 75-427 can be approved when final printed labeling, establishment evaluation and bioequivalence are all acceptable.

Therefore, I am doing a **CHEMISTRY CLOSE.**

19. Reviewer/Branch Chief:

Eugene L. Schaefer, Ph.D.
BRANCH II, DIV. OF CHEMISTRY I, OGD

Michael J. Smela, Jr.
TEAM LEADER

Date Completed: 8/10/01

Redacted 10 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #4

cc:

ANDA 75-427
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates): ES 8/10/01

HFD-625/Chemist/ELSchaefer/
HFD-625/Chemistry Team Leader/MJSmela/ MJSmela 8/17/01

Project Manager:

HFD-617/MDillahunt/

F/t by:

V:\FIRMSNZ\PERRIGO\LTRS&REV\75427cr4.doc

CHEMISTRY CLOSE

APPEARS THIS WAY
ON ORIGINAL

1. ***CHEMIST's REVIEW # 4***

ADDENDUM

2. **ANDA 75-427**

3. APPLICANT, Name/Address/Telephone/Fax:
L. Perrigo Co.
Attention: Valerie Gallagher
515 Eastern Avenue
Allegan, MI 49010
☎ 616-673-9367/*fax* 616-673-7655

7. **Non-PROPRIETARY Name:** **Cromolyn Sodium Nasal Solution, USP**

13. DOSAGE Form: nasal solution delivered via a manual metered dose pump

14. STRENGTH: 5.2 mg/spray = 4%

9. AMENDMENTS & Other DATES.

Vol. A1.1:

07-31-98 original appl.

Vol. A6.1 and 6.2:

06/29/01 Bio amendment

Vol. A7.1:

07/12/01 Labeling amendment

Vol. A8.1:

07/26/01 Bio telephone amendment
07/31/01 Chemistry minor amendment

17. COMMENTS:

The chemistry deficiencies have been **resolved.**

The conditions of the **other disciplines** are as follows:

32. LABELING

FPL submitted on 7/12/01 found **satisfactory** by Angela Payne 8/21/01.

33. ESTABLISHMENT INSPECTION

On 7/16/01, **OC recommended that we withhold approval** of ANDA 75-427. No change, as of 9/7/01.

34. BIOEQUIVALENCE STATUS

Perrigo submitted a Bio amendment on 6/29/01, and a Bio telephone amendment (coded as NC) on 7/26/01. **Deficiencies** were sent to Perrigo 8/31/01.

18. CONCLUSIONS & RECOMMENDATIONS:

ANDA 75-427 is **NOT APPROVED - FAX AMENDMENT requested,** because of the Bio deficiencies. Otherwise, the only remaining issue is the withhold recommendation from OC.

19. Reviewer/Branch Chief:

Eugene L. Schaefer, Ph.D.
BRANCH II, DIV. OF CHEMISTRY I, OGD

Michael J. Smela, Jr.
TEAM LEADER

Date Completed: 9/7/01

APPEARS THIS WAY
ON ORIGINAL

22. **SYNTHESIS:** **Satisfactory** in Review #1
Manufacturer of the Bulk Drug Substance: [redacted]
[redacted] DMF #[redacted]
Last **sat.** review 9/20/99; **no amendments since then, as of 9/7/01.**

33. ESTABLISHMENT INSPECTIONS: **Not Satisfactory**

On 7/16/01, **OC recommended that we withhold approval** of ANDA 75-427 because a warning letter has been issued to Perrigo. This recommendation is still in effect, as of 9/7/01.

Comment: The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

34. BIOEQUIVALENCE STATUS: **Not Satisfactory**

Deficiency: Bioequivalence for this product has not been established. Please respond to the deficiencies provided to you on August 31, 2001.

36. ORDER of REVIEW.
The application submissions covered by this review was taken in the date order of receipt? Yes x
If no, explain reason below:

37. DMF CHECKLIST For ANDA #75-427 REVIEW #4 Addendum

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT of REVIEW	Date REVIEW COMPLETED
[redacted]	II/[redacted]	3	adequate	9/20/99

Comments: no amendments since then, as of 9/7/01.

Page 1 of 1. *ELSchaefer* Reviewer [redacted] Signature 9/7/01 Date

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-427

APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray

The deficiency presented below represents a FAX deficiency:

A. Deficiency:

Bioequivalence for this product has not been established. Please respond to the deficiencies provided to you on August 31, 2001.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comment in your response:

The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

Sincerely yours,

Paul Schwerd for 9/14/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-427
ANDA DUP
DIV FILE
Field Copy

Endorsements: ES 9/13/01

HFD-625/Chemist/ELSchaefer/9/7/01
HFD-625/MShaikh for/Team Leader/MJSmela/9/10/01
HFD-617/Project Manager/MDillahunt/9/10/01 MDillahunt 9/11/01

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F/T by: DJ 9/10/01

CHEMISTRY REVIEW - NOT APPROVABLE - FAX

M Smela
9/13/01

APPEARS THIS WAY
ON ORIGINAL

1. ***CHEMIST's REVIEW # 5***

CHEMISTRY CLOSE

A chemistry close and an addendum were also performed for CR#4.

2. **ANDA 75-427**

3. APPLICANT, Name/Address/Telephone/Fax:
L. Perrigo Co.
Attention: Valerie Gallagher
515 Eastern Avenue
Allegan, MI 49010
☎ 616-673-9367/*fax* 616-673-7655

7. **Non-PROPRIETARY Name:** **Cromolyn Sodium Nasal Solution, USP**

13. DOSAGE Form: nasal solution delivered via a manual metered dose pump

14. STRENGTH: 5.2 mg/spray = 4%

9. AMENDMENTS & Other DATES.

Vol. A1.1:

07-31-98 original appl.

Vol. A6.1 and 6.2:

06/29/01 Bio amendment

Vol. A8.1:

07/26/01 Bio telephone amendment
07/31/01 Chemistry minor amendment
08/31/01 Bio deficiencies were faxed to Perrigo
09/17/01 NA-FAX from chemistry
10/17/01 FAX Chemistry Amendment

Vol. A9.1:

10/17/01 Bio amendment

17. COMMENTS:

33. ESTABLISHMENT INSPECTION

On 7/16/01, **OC recommended that we withhold approval** of ANDA 75-427. No change, as of 11/14/01.

34. BIOEQUIVALENCE STATUS

The Bio amendment of 10/17/01 is pending review, as of 11/14/01.

18. CONCLUSIONS & RECOMMENDATIONS:

All CMC issues have been resolved. Therefore, I recommend a **CHEMISTRY CLOSE.**

19. Reviewer/Branch Chief:

Eugene L. Schaefer, Ph.D.
BRANCH II, DIV. OF CHEMISTRY I, OGD

Michael J. Smela, Jr.
TEAM LEADER

Date Completed: 11/14/01

APPEARS THIS WAY
ON ORIGINAL

22. **SYNTHESIS:** **Satisfactory** in Review #1
Manufacturer of the Bulk Drug Substance: [redacted]
[redacted] DMF #[redacted]
I found DMF [redacted] to be **adequate** on 11/14/01.

33. ESTABLISHMENT INSPECTIONS: **Not Satisfactory**

On 7/16/01, **OC recommended that we withhold approval** of ANDA 75-427 because a warning letter has been issued to Perrigo. This recommendation is still in effect, as of 11/14/01.

Comment: The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

Response: Acknowledged.

34. BIOEQUIVALENCE STATUS: **Incomplete**

Deficiency: Bioequivalence for this product has not been established. Please respond to the deficiencies provided to you on August 31, 2001.

Response: Perrigo submitted a Bio amendment on 10/17/01. The submission is pending review, as of 11/14/01.

36. ORDER of REVIEW.
The application submissions covered by this review was taken in the date order of receipt? No x
If no, explain reason below:

The submission was a FAX amendment.

37. DMF CHECKLIST For ANDA #75-427 REVIEW #5

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT of REVIEW	Date REVIEW COMPLETED
[redacted]	II/[redacted]	1	adequate	11/14/01

Comments:

Page 1 of 1. *ELSchaefer* Reviewer — Signature — 11/14/01 Date

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-427

APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray

None

cc: ANDA 75-427
ANDA DUP
DIV FILE
Field Copy

ES 11/14/01

Endorsements:

HFD-625/ELSchaefer, Chemist/
HFD-625/MLShaikh for MJSmela, Team Leader/ Mujahid Shaikh 11/15/01
HFD-617/MDillahunt, Project Manager/

V:\FIRMSNZ\PERRIGO\LTRS&REV\75427cr5.doc
F/T by:

CHEMISTRY CLOSE

APPEARS THIS WAY
ON ORIGINAL

1. ***CHEMIST's REVIEW # 5***

ADDENDUM

There have been no changes in Composition, DS specs, DP specs or stability specs since Chemistry Review #4.

2. **ANDA 75-427**

3. APPLICANT, Name/Address:
L. Perrigo Co.
Attention: Valerie Gallagher
515 Eastern Avenue
Allegan, MI 49010

7. **Non-PROPRIETARY Name:** **Cromolyn Sodium Nasal Solution, USP**

13. DOSAGE Form: nasal solution delivered via a manual metered dose pump

14. STRENGTH: 5.2 mg/spray = 4%

9. AMENDMENTS & Other DATES.

Vol. A1.1:
07-31-98 original appl.

Vol. A9.1:
10/17/01 Bio amendment

17. COMMENTS:

33. ESTABLISHMENT INSPECTION *

On 7/16/01, **OC recommended that we withhold approval** of ANDA 75-427. No change, as of 11/26/01.

34. BIOEQUIVALENCE STATUS
Bio had no further questions on 11/16/01.

18. CONCLUSIONS & RECOMMENDATIONS:
ANDA 75-427 can be **APPROVED**, pending an acceptable Establishment Evaluation.

19. Reviewer/Branch Chief:
Eugene L. Schaefer, Ph.D. — BRANCH II, DIV. OF CHEMISTRY I, OGD
Michael J. Smela, Jr. — TEAM LEADER

*EER revised to acceptable on 11/29/01
M Smela

22. **SYNTHESIS:** **Satisfactory** in Review #1
Manufacturer: [redacted]

I found DMF [redacted] to be **adequate** on 11/14/01. No more submissions, as of 11/26/01.

33. ESTABLISHMENT INSPECTIONS: **Not Satisfactory**

On 7/16/01, **OC recommended that we withhold approval** of ANDA 75-427 because a warning letter has been issued to Perrigo. This recommendation is still in effect, as of 11/26/01.

34. BIOEQUIVALENCE STATUS: **Satisfactory** in the Addendum to CR#5

Deficiency: Bioequivalence for this product has not been established. Please respond to the deficiencies provided to you on August 31, 2001.

Response: Perrigo submitted a Bio amendment on 10/17/01. Bio had no further questions on 11/16/01.

cc: ANDA 75-427
ANDA DUP
DIV FILE
Field Copy

ES 12/3/01

Endorsements:

HFD-625/ELSchaefer, Chemist/11/27/01
HFD-625/MJSmela, Team Leader/11/27/01

MJSmela
12/3/01

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F/T by: gp/11/28/01

OFFICE OF COMPLIANCE HAS RECOMMENDED "WITHHOLD APPROVAL". OTHERWISE, ANDA 75-427 CAN BE APPROVED.

ANDA APPROVAL SUMMARY

ANDA: 75-427	CHEMIST: Eugene L. Schaefer, Ph.D.	DATE: 11/26/01
DRUG PRODUCT: Cromolyn Sodium Nasal Solution, USP		
FIRM: L. Perrigo Co.		
DOSAGE FORM: Nasal Solution	STRENGTH: 5.2 mg/spray = 4%	
cGMP: On 7/16/01, **OC recommended that we withhold approval** of ANDA 75-427. No change, as of 11/26/01.*		
BIO: Bio had no further questions on 11/16/01.		
VALIDATION - (Description of dosage form received by FDA lab same as in firm's ANDA?): N/A USP DS and DP		
STABILITY: The containers in the stability studies are the same as those in the container section.		
LABELING: Container, carton, and insert labeling were approved by Angela Payne on 8/21/01.		
STERILIZATION VALIDATION (If applicable): N/A		
SIZE OF BIO BATCH (Firm's source of NDS ok?): Yes N/A		
SIZE OF STABILITY BATCHES (If different from bio batch, were they manufactured via the same process?): N/A The size of the stability batch was ———		
PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?: Yes The maximum size of production batches will be ———		
Signature of chemist: Es 11/26/01 Eugene L. Schaefer, Ph.D.	Signature of Team Leader: M Smela 11/27/01 Michael Smela	

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* EER changed to acceptable on 11/29/01
M Smela

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-427

BIOEQUIVALENCE REVIEW

Cromolyn Sodium Nasal Solution USP
5.2 mg/spray (40 mg/mL)
ANDA # 75-427
Reviewer: Andre J. Jackson
WP # 75427W.798

L. Perrigo Company
Allegan, Michigan
Submission Date:
July 31, 1998

Review of a Waiver Request

The firm has requested a waiver from in vivo bioavailability requirements for its Cromolyn Sodium Nasal Solution, 40 mg/mL, in accordance with 21 CFR 320.22 (b) (3) (i).

Comments:

1. The test product is an inhalation solution.

2. The formulation of the test product is identical, quanlitatively and quantitatively, to that of the currently approved Nasalcrom® Nasal Spray, 40 mg/mL, manufactured by Pharmacia and Upjohn Co., as shown below:

Ingredients	Test Formula	Nasalcrom®'s Formula
Cromolyn Sodium	40 mg/mL	40 mg/mL
Edetate Disodium	———	———
Benzalkonium Chloride	———	———
Water	q.s. to 100%	q.s. to 100%

Deficiency:

Since Cromolyn Sodium Nasal Solution USP is packaged in a manual metered dose pump, it must be demonstrated through *in vitro* testing that the delivery system of the test product performs the same as the delivery system of the reference listed drug. Information demonstrating the sameness should include but is not limited to:

a. droplet size distribution

b. uniformity of unit spray content, based on single actuation data, and including priming data.

c. spray pattern

d. plume geometry

Although the test product is not a pressurized metered dose inhaler, the firm is referred to the metering performance and uniformity of unit spray content sections of Chapters 601 and 905 of the U.S. Pharmacopeia, and to the Division of Bioequivalence June 27, 1989 Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers). As noted in this Guidance, comparative data from two methods of droplet size distribution determination should be reported. Each method should be validated, and provide true droplet size distributions, including mass median aerodynamic diameter and geometric standard deviation, in the appropriate droplet size range, for the products.

Because there are a number of unresolved issues regarding the testing of manual metered dose pumps for the documentation of in vitro bioequivalence, the firm is advised to submit a protocol outlining its planned studies. This protocol may be based in part on the considerations discussed in the above references.

Recommendations:

The waiver request of *in vivo* bioequivalence requirements for the test product, L. Perrigo Company's Cromolyn Sodium Nasal Solution, USP, 40 mg/mL, has been found **unacceptable** due to the reasons cited in the deficiency above.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 10/24/98

Concur: Date: 10/27/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-427 (original, duplicate), HFD-652(Huang, Jackson), Drug File, Division File

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-427 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray (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:

Since Cromolyn Sodium Nasal Solution USP is packaged in a manual metered dose pump, it must be demonstrated through *in vitro* testing that the delivery system of the test product performs the same as the delivery system of the reference listed drug. Information demonstrating the sameness should include but is not limited to:

a. droplet size distribution

b. uniformity of unit spray content, based on single actuation data, and including priming data.

c. spray pattern

d. plume geometry

Although the test product is not a pressurized metered dose inhaler, you are referred to the metering performance and uniformity of unit spray content sections of Chapters 601 and 905 of the U.S. Pharmacopeia, and to the Division of Bioequivalence June 27, 1989 Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers). As noted in this Guidance, comparative data from two methods of droplet size distribution determination should be reported. Each method should be validated, and provide true droplet size distributions, including mass median aerodynamic diameter and geometric standard deviation, in the appropriate droplet size range, for the products.

Because there are a number of unresolved issues regarding the testing of manual metered dose pumps for the documentation of in

vitro bioequivalence, you are advised to submit a protocol outlining its planned studies. This protocol may be based in part on the considerations discussed in the above references.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 75-427
ANDA DUPLICATE
DIVISION FILE
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ Jackson

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Printed in final on / /98

Endorsements: (Final with Dates)
HFD-652/ Jackson
HFD-652/ YHuang 10/27/98
HFD-650/ D. Conner 10/27/98

WAIVER (WAI)

Strengths: 40 mg/mL
Outcome: UN

Outcome Decisions:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

WINBIO COMMENTS:

Cromolyn Sodium Nasal Solution USP
5.2 mg/spray (40 mg/mL)
ANDA # 75-427
Reviewer: Andre J. Jackson
WP # 75427W.N98

L. Perrigo Company
Allegan, Michigan
Submission Date:
November 20, 1998

Review of an Amendment to a Waiver Request

Background

The firm has requested a waiver from in vivo bioavailability requirements for its Cromolyn Sodium Nasal Solution, 40 mg/mL, in accordance with 21 CFR 320.22 (b) (3) (i) on July 31, 1998.

The firm was informed that they would be required to submit information demonstrating the sameness of their product to the RLD Nasalcrom® manufactured by Pharmacia and Upjohn. The information requested was to include but not limited to:

1. Uniformity of unit spray content, based on single actuation data, and including priming data.
2. Droplet size distribution by at least two methods.
3. Spray pattern.
4. Plume geometry.

Although the test product is not a pressurized metered dose inhaler, the firm was referred to the metering performance and uniformity of unit spray content sections of Chapters 601 and 905 of the U.S. Pharmacopoeia, and to the Division of Bioequivalence June 27, 1989 Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers). As noted in this Guidance, comparative data from two methods of droplet size distribution determination should be reported. Each method should be validated, and provide true droplet size distributions, including mass median aerodynamic diameter and geometric standard deviation, in the appropriate droplet size range for the products.

Correspondence from the Office of Generic Drugs also advised the firm that many unresolved issues remained and it was suggested that they submit a protocol for review by the Division of Bioequivalence.

The firm's responses to those comments are as follows:

Firm's Response #1

Based on the above comments, we believe that the Division of Bioequivalence did not have access to the submitted results of in-vitro comparative testing performed to demonstrate the equivalence of the delivery systems of the test and reference drug products. That information was provided in section 14 of the ANDA on pages 411 through 441 and included the following test results:

a. Comparative Droplet Size Distribution Analysis
b. 1) Content Uniformity of Unit Sprays - single actuation, average of 10, and % RSD for each device tested.
   2) Individual, Average and Range of Sprays Delivered per bottle (26 mL and 13 mL)
c. Comparative Spray Pattern (Geometry) Analysis with analysis of symmetry factors
d. Comparative Plume Geometry Analysis

To facilitate your review of this documentation, an additional copy of these pages is enclosed in this amendment.

FDA Replies to Items in Firm Response #1:

a. Particle Droplet Sizing:
The particle sizing data provided by the firm in vol. 1.1, page 435 for Nasalcrom 13 mL and 26 mL spray bottles and for the test product in vol. 1.1 page 439 has been found to be incomplete.

Droplet size distribution by laser diffraction (e.g. [redacted]) should be determined at the beginning, middle, and end of use life for the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. Data should be reported in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Data should be reported based on mass (volume). All instrument/computer printouts should also be submitted, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration(fractional loss of energy from the laser beam caused by particle scattering) should be reported for each run, along with the

instrument manufacturer's recommended obscuration ranges.

In addition the firm should supply data from cascade impaction to characterize particles in a smaller size range than the expected range for aqueous nasal sprays. This is useful to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor data should account for mass balance and be reported in the following groups:

Adaptor to throat or separator,

Stage 0 to stage 3, and

Stage 4 to filter.

Because the purpose of the cascade impactor data for the aqueous nasal sprays is to characterize fines only, not to provide a particle size distribution, the firm is requested to provide cascade impactor studies only at the beginning and end of canister through-life testing.

The firm may, if it wishes, also provide comparative data by additional methods such as time-of-flight laser.

b. 1 and 2. Unit Dose and Content Uniformity:
The content uniformity of unit sprays-single actuation data, average of 10 data provided by the firm in vol. 1.1, page 412 and the individual, average and range of sprays delivered per bottle vol. 1.1, pages 414 and 415(26 mL and 13 mL)are also incomplete.

In order to show consistency with the Potency Test described in the 27 June 1989 *Division of Bioequivalence Guidance for the in vitro portion of bioequivalence requirements for metaproterenol sulfate and albuterol inhalation aerosols (metered dose inhalers)*, the content uniformity of unit sprays test should be performed at the beginning, middle, and end of use life of the product after product priming.

A dose is defined as the minimum number of sprays or actuations defined in the product labeling as the recommended dose. The amount of drug per single spray (not the mean of two or more consecutive sprays) should be determined using a validated biochemical/chromatographic assay. All raw data should be submitted

for review.

c. Spray Patterns:
Spray patterns should be determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent. A drug-specific reagent will not develop color when tested with placebo. Photographs of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max}) diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{min}/D_{max}), along with photographs and markings indicating D_{min} and D_{max}.

d. Plume Geometry

The comparative plume geometry data in vol. 1.1, 418-433 is incomplete.

The plume geometry should describe two side views of the plume, at 90^0 angles to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. The firm should provide plume geometry based on high-speed photography. Plume geometry may be performed only at the beginning of use life. Plumes should be characterized at three or more different times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. The firm is requested to provide all photographs and data characterizing plume dimensions.

Firm Response #2

We have considered your comments regarding the testing specified in USP <601> and <905> and the application of the June 27, 1989, guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers) and provide the following comments:

USP <601>

The Metering Performance testing described in USP <601> for pressurized inhalers fitted with actuators is designed to measure the variation in the weights of the delivered sprays and to detect changes in the dose delivered that may be caused by dynamic effects, including leakage, on the pressurized system. Page 414 of the enclosed documentation from the original ANDA provides results of a similarly designed test to measure the spray delivery of 10 units of each bottle size. The test is adapted for the non-pressurized system and provides a calculated number of sprays delivered per bottle. The results are well within the USP requirements.

FDA Reply #2:

The data presented on page 414 is incomplete. See FDA reply to firm's comment #1 related to content uniformity

Firm's Comment #3:

USP <905>
The Uniformity of Unit Spray Content described in USP <601> and <905> are designed to measure the content of active ingredient in the discharged spray for a pressurized metered-dose inhaler. This test was performed on the proposed sprayer using a method to collect the entire spray content appropriate for a nasal solution rather than a device which is designed to sample a suspension for an inhalation route of administration. Comparative results from testing of 10 sprayers of the listed and proposed drug are enclosed (page 412 of the original ANDA). The results meet the requirements stated in USP <601>.

FDA Reply #3:

In order to show consistency with the Potency Test described in the 27 June 1989 *Division of Bioequivalence Guidance for the in vitro portion of bioequivalence requirements for metaproterenol sulfate and albuterol inhalation aerosols (metered dose inhalers)*, the content uniformity of unit sprays test should be performed at the beginning, middle, and end of use life of the product after product priming, and it should be based on at least 10 units(10 different bottles) of the test product and 10 units of the RLD. Also three batches of the test and reference product are required.

Firm's Comment #4:

In general, the tests described in "Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)", the referenced guidance are specific for pressurized metered dose inhalation aerosols of particles in suspension; both Metaproterenol Sulfate and Albuterol Inhalation Aerosols are microcrystalline suspensions of drug in a liquefied propellant contained in a pressurized metal canister. Cromolyn Sodium Nasal Spray is an aqueous solution delivered by a mechanical metering pump from a non-pressurized plastic bottle.

Several of the tests described in the guidance and in USP <601> are specific to determining the size of solid particles expelled from the delivery device. Thus it is not possible to perform the tests for particle size on a solution product using the various impactor devices or by microscopic examination as all of these tests are designed to measure the diameters of particles captured on impactor stages or glass slides. It is also not possible to determine the mass median aerodynamic diameter and geometric standard deviation as these parameters are derived from the impactor data.

FDA Reply #4:

The Division of Bioequivalence does not require particle sizing of solution products. However, for nasal solutions delivered by manual metered pumps, determination of comparative droplet size(not solid particles) distribution is recommended.

Firm's Comment #5:

Further, according to USP <601> the purpose of performing the various tests described for particle size is to ensure that particles are of no greater than 10 microns in diameter in order to ensure deposition in the lung during inhalation. The results of the analysis of the test and reference drugs for droplet size indicate that the delivery devices produce droplets with median size of approximately 60 microns and that 90% of the droplets are larger than about 30 microns. This large diameter of droplet size coupled with the nasal route of administration ensures that the product will be properly delivered to the site of action in the

nasal cavity.

The November 13, 1998, draft Guidance for Industry on Metered Dose Inhaler (NMI) and Dry Powder Inhaler (DPI) Drug Products - Chemistry, Manufacturing, and Controls Documentation lists these same tests but specifies the guidance does not address inhalation solutions and aqueous nasal sprays.

FDA Reply #5:

The particle sizing data submitted by the firm using [redacted] Laser Diffraction is incomplete for the reasons listed under FDA reply # 1. Also the data presented by the firm was for only 3 bottles/product. The requirement is at least 10 bottles from each of the 3 lots of test and reference used in the testing at the beginning, middle and end of the use life for the product. This data was not supplied by the firm.

Firm's Comment #6:

In summary, we have provided results from testing which is appropriate to demonstrate the comparability of the delivery devices of the test and reference products. As the drug product is a true solution, the test and reference drug products are assumed to be equivalent in physical form and only those tests that measure any potential differences in the performance of the metered dose sprayer are possible. To demonstrate this comparability, we have conducted the testing described herein.

FDA Reply #6:

The FDA does not agree that Perrigo Company has provided sufficient information to establish the equivalency of their product to the RLD. In addition the firm must provide data on the products priming and tail off performance.

Deficiencies:

1. The Division of Bioequivalence requires that pumps should be actuated mechanically to increase reproducibility and

- No fewer than 10 units (i.e., 10 bottles and associated

delivery devices) each of the test and reference products should be tested in a blinded manner.

- For all *in vitro* tests, data from three batches of the reference product, and two or three batches of the test products as available should be submitted for review. Batch records for all batches of the test product should be submitted.

- SOP's for all tests effective at the time of testing should be submitted. SOP's should describe the mechanical actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s).

- Raw data for all tests should be submitted in the form of paper copies as well as electronic files (Excel 5.0 spread sheets).

- For tests such as content uniformity, which is performed at the beginning (B), middle (M), and end (E) or B and E of use life sectors, equivalence must be assessed at each sector.

2. The test product must show equivalence to the RLD in performance during the initial use and priming of the product. The sponsor should submit data to support that the test product's performance is equivalent to the RLD during priming. In addition, evidence for comparable tail off characteristics should be submitted. Data should be based on the amount of drug per actuation using a biochemical/chromatographic assay. The product is labeled to deliver 100 doses, the firm is advised to combine determination of priming, uniformity of unit dose and tail off in suitable ranges of doses delivered to be consistent with the beginning, middle and end of use life.

3. The particle sizing data provided by the firm in vol. 1.1, page 435 for Nasalcrom 13 mL and 26 mL spray bottles and for the test product in vol. 1.1 page 439 has been found to be incomplete.

Droplet size distribution by laser diffraction (e.g. ——— ——— should be determined at the beginning, middle, and end of use life for the product. Measurements should be made at three

distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. Data should be reported in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Data should be reported based on mass (volume). All instrument/computer printouts should also be submitted, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration(fractional loss of energy from the laser beam caused by particle scattering) should be reported for each run, along with the instrument manufacturer's recommended obscuration ranges.

In addition the firm should supply data from cascade impaction to characterize particles in a smaller size range than the expected range for aqueous nasal sprays. This is useful to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor data should account for mass balance and be reported in the following groups:

Adaptor to throat or separator,

Stage 0 to stage 3, and

Stage 4 to filter.

Because the purpose of the cascade impactor data for the aqueous nasal sprays is to characterize fines only, not to provide a particle size distribution, the firm is requested to provide cascade impactor studies only at the beginning and end of canister through-life testing.

The firm may, if it wishes, also provide comparative data by additional methods such as time-of-flight laser.

4.Spray patterns should be determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent. A drug-specific reagent will not develop color when tested with placebo. Photographs of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max})diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{min}/D_{max}), along with photographs and markings

indicating D_{min} and D_{max}.

5.The comparative plume geometry data in vol. 1.1, 418-433 is incomplete.

The plume geometry should describe two side views of the plume, at 90^0 angles to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. The firm should provide plume geometry based on high speed photography. Plume geometry may be performed only at the beginning of use life. Plumes should be characterized at three or more different times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. The firm is requested to provide all photographs and data characterizing plume dimensions.

6. The device and formulation are integral components of a nasal spray, therefore to support the sameness of test and reference devices, the sponsor should provide to the extent possible a side-by-side comparison of the pumps and actuators used in the test and reference products. This information should include the manufacturer, model numbers of the pumps and actuators, model numbers of actuator inserts and the overcaps. Technical drawing with dimensions should also be submitted for both the test and reference products, if available.

7.Data from the following test should be provided in order to obtain a waiver of the *in vivo* bioequivalence requirements for the 13 mL Nasalcrom spray bottle. These test are:

Unit dose(beginning and end of use life sectors)
Priming
Loss of Prime
Droplet size distribution (beginning of use life)
Spray pattern(beginning of use life)

Recommendations:

The waiver request of *in vivo* bioequivalence requirements for the test product, L. Perrigo Company's Cromolyn Sodium Nasal Solution, USP, 40 mg/mL, has been found **unacceptable** due to the reasons cited in the deficiency above.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 1/28/99

Concur: _____ Date: 3/9/99
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-427 (original, duplicate), HFD-652(Huang, Jackson), Drug File, Division File

Cromolyn Sodium Nasal Solution USP
5.2 mg/spray (40 mg/mL)
ANDA # 75-427
Reviewer: Andre J. Jackson
V:\Firmsnz\Perrigo\Ltr&Rev\75427A.300

L. Perrigo Company
Allegan, Michigan
Submission Date:
March 31, 2000

Review of an Amendment to a Waiver Request

Background

The firm has requested a waiver from in vivo bioavailability requirements for its Cromolyn Sodium Nasal Solution, 40 mg/mL, in accordance with 21 CFR 320.22 (b) (3) (i) on July 31, 1998.

The firm was informed that they would be required to submit information demonstrating the sameness of their product to the RLD Nasalcrom® manufactured by Pharmacia and Upjohn. The information requested was to include but not limited to:

1. Uniformity of unit spray content, based on single actuation data, and including priming data.
2. Droplet size distribution by at least two methods.
3. Spray pattern.
4. Plume geometry.

The firm responded to these agency requests in their submission of November 20, 1998. However, the data submitted was found to be incomplete since many of the requested tests were done incorrectly. The current submission is the firm's response to the deficiencies in the November 20, 1998 submission.

The firm has also informed the Division of Bioequivalence that the responses are based upon a new exhibit batch manufactured at [redacted] using a new container/closure system and the documentation necessary to support a new exhibit batch and container/closure system.

Deficiency 1.

1. The Division of Bioequivalence requests that pumps should be actuated mechanically to increase reproducibility and

No fewer than 10 units (i.e., 10 bottles and associated

delivery devices) each of the test and reference products should be tested in a blinded manner.

RESPONSE:

The testing conducted to support this amendment was done in consideration of the comments received from the Division of Bioequivalence regarding mechanical activation of pumps, the number of units to be evaluated, and testing in a blinded manner.

FDA Reply:

The firm stated in vol. 3.4 page 1682 that the validation data for the automated actuators would be supplied in the in vitro study report. However, this data could not be identified by the Division of Bioequivalence. The settings were given in vol. 3.4 page 1664 but it was never stated if these settings were used for all studies. The firm should supply the validation data for their [redacted] actuation station and clearly state if the same settings were used for all studies.

Deficiency 2.

2. For all in vitro tests, data from three *batches of* the reference product, and two or three *batches of the test* products as *available should be submitted for* review. *Batch records* for all batches of the test product *should* be submitted.

RESPONSE:

The testing conducted to support this amendment was done in consideration of the comments received from the Division of Bioequivalence and in consideration of the FDA Draft Guidance Documents for Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products related to Chemistry, Manufacturing, and Controls Documentation and Bioavailability and Bioequivalence Studies that issued in May and June of 1999.

A split-fill sublot plan was developed using the rationale noted in the FDA Draft Guidance document entitled, "Bioavailability and *Bioequivalence Studies* for *Nasal* Aerosols *and Nasal Sprays* for *Local* Action" Page 9, Paragraph 2. ANDA's states, "For nasal *sprays formulated as* solutions, in vitro *BE* tests can

alternatively be performed on three sublots *of* product prepared from one *batch of* the solution."

A detailed explanation of the split-fill sublot plan employed for the submission batch manufactured to support this amendment and the executed batch records are included with this amendment in Section 12, Page 192.

FDA Reply:

The firm's explanation of their split-fill sublot procedure is acceptable to the Division of Bioequivalence.

Deficiency 3.

3. SOP's for all tests effective at the time *of* testing *should be* submitted. SOP's *should describe* the *mechanical actuation devices used* for each experiment, and procedures used for *blinding test* and RLD products from the analyst(s).

RESPONSE:

In accordance with the above comment, the methods and the bioequivalence study protocol used to conduct the in vitro tests to support this amendment are included in Section 23. The methods and/or protocols, where appropriate, describe mechanical actuation devices and blinding processes.

FDA Reply:

The information in the referenced Section 23 are the data resulting from the in vitro testing. The protocol information supplied by the firm is in vol. 3.2 section 15 under drug product methods, which included the following:

Testing Conditions: Mechanical actuation, without human intervention was used for the testing. This was done according to procedure No. 1735.1 page 793 vol. 3.2. Each sprayer was actuated 5 times to prime. The amount actuated was measured by HPLC assay.

Tests were performed only for spray content uniformity and through life not at the beginning, middle and end of unit life as requested in the guidance. The firm should supply a detailed SOP for their methods. All raw data should be *submitted in the* form

of paper copies as well as electronic files (excel spreadsheets).

Deficiency 4.

4. Raw data for all tests *should* be *submitted in the* form *of* paper copies as well as electronic files (excel 5.0 spreadsheets)

RESPONSE:

Bioequivalence Study Data Packages for the in vitro tests conducted to support this amendment have been submitted in the form of paper copies as well as electronic files (Excel 5.0 formats) where appropriate, in accordance with the comment above (see Section 23).

FDA Reply:

All data submitted by the firm were summary data. Appropriate raw data should be submitted using the format in appended Tables 1-7. In addition for droplet size distribution 20% of the data sheets containing histograms from the ———————— analyses should be submitted. The firm should also submit 20% of the sample chromatograms used in the assay validation for cromolyn.

Deficiency 5.

5. For tests such as content uniformity, which is performed at the beginning (B), Middle (M), and end (E) or B and E of use life sectors, equivalence must be assessed at each sector.

RESPONSE:

For tests such as spray content uniformity through end of container life, equivalence assessments of the Perrigo product sample and the Reference Listed Drug were conducted at each sector, beginning (B), middle (M), and end (E) or B and E, in accordance with the above comment.

FDA Reply:

The data supplied by the firm on CD and paper were summary data. The type of data requested is the individual data for each of the 10 bottles tested. Comparative raw data should be presented to support the summary results presented in vol. 3.1. Data should

be presented for the 13 mL and 26 mL bottles. The data should be presented as excel spreadsheets.

Deficiency 6.

6. Your test product must show equivalence to the RLD in performance during the initial use and priming of the product. You should submit data to support that the test product's performance is equivalent to the RLD during priming. In addition, evidence for comparable tail off characteristics should be submitted. Data should be based on the amount of drug per actuation using a biochemical chromatographic assay. The product is labeled to deliver 100 doses, the firm is advised to combine determination of priming, uniformity of unit dose and tail off in suitable ranges of doses delivered to be consistent with the beginning, middle and end of use of life.

RESPONSE:

Equivalence assessments of priming performance, initial use, and tail off characteristics have been conducted in accordance with this comment. The specific tests conducted included Droplet Size Distribution, Spray Content Uniformity Through Life of Container, and Cascade Impaction.

The data generated for the Spray Content Uniformity Through Life of Container was based on the amount of drug per actuation using chromatographic assay method 1735 (see Section 15, Page 792). The data generated by this testing is located in Section 4, Page 6 and Page 9.

For the Droplet Size Distribution and Cascade Impaction testing, summaries of the comparative data generated by the testing are filed in Section 23 at Page 977 and Page 1182. The Bioequivalence Study Data Packages are filed in Section 23, Page 990 and Page 1184 and are also supplied in Excel 5.0 file format on the computer data disc supplied with this amendment.

The data generated by all three tests indicates equivalent performance for the Perrigo test product and the Reference Listed Drug during all assessment phases.

FDA Reply:

Raw data for priming and tail off were not included in the submission. All raw data should be submitted in electronic format as excel spreadsheets.

The data for droplet size distribution is incomplete since raw data were not submitted for the beginning, middle and end of use life. Also the data for spray content uniformity through life of container is incomplete since data was not presented for each of the 10 individual bottles at the beginning, middle and end of use life. The cascade impaction data was summary data.

Data from individual bottles should be presented showing the drug amounts deposited on the throat [redacted] and stages 0, 1, 2, 3 and filter of the [redacted] Cascade Impactor instrument determined by a validated HPLC assay. The tests should be performed at the beginning and end of use life. The raw data should be from 10 actuations per test and 10 bottles each of test and reference products batches tested. This data should be supplied for the 13 mL and 26 mL bottles. The current submission only contains summary data for the 26 ml bottle. The formats the firm should use to present the raw data are presented in attached Table 4 for cascade impaction and attached Table 5 for laser diffraction. The data *should* be *submitted in the* form *of* paper copies as well as electronic files (excel spreadsheets).

Deficiency 7.

7. The particle sizing data you provided in vol. 1.1, page 435 for Nasalcrom 13 mL and 26 mL spray bottles and for the test product in vol. 1.1 page 439 has been found to be incomplete.

Droplet size distribution by laser diffraction (e.g., [redacted]) should be determined at the beginning, middle, and end of use life for the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. Data should be reported in the form of D10, D50, D90 and SPAN [(D90-D10/D50)]. Data should be reported based on mass (volume). All instrument/computer printouts should also be submitted, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration (fractional loss of energy from the laser beam caused by particle scattering) should

be reported for each run, along with the instrument manufacturer's recommended obscuration ranges.

In addition you should supply data from cascade impaction to characterize particles in a smaller size range than the expected range for aqueous nasal sprays. This is useful to assure that there is not an excess mass of 'Fines" in the test product relative to the RLD. Cascade impactor data should account for mass balance and be reported in the following groups:

Adaptor to throat or separator,

Stage 0 to stage 3, and

Stage 4 to filter.

Because the purpose of the cascade impactor data for the aqueous nasal sprays is to characterize fines only, not to provide a particle size distribution, you are requested to provide cascade impactor studies only at the beginning and end of canister through-life testing.

You may, if you wish, also provide comparative data by additional methods such as time-of-flight laser.

RESPONSE:

Droplet Size Distribution

Droplet Size Distribution testing was conducted by laser diffraction at the beginning, middle and end of use of life for the product. Measurements were made at three distances from the orifice to the laser beam. At each distance, measurements were made at different delay times to characterize the plume upon formation (B), as the plume started to dissipate (E), and at an intermediate time (Lowest). A Summary is filed in Section 23 at Page 977. The bioequivalence Study Data Package noting D10, D50, D90 and SPAN is filed in Section 23, Page 990, of this amendment. Excel 5.0 file formats of the Bioequivalence Study Data Package are also filed with this amendment on a computer data disc.

Data is reported based on mass (volume). Representative samples of the ——— instrument/computer print outs for a Perrigo sample and a Reference Listed Drug sample are submitted in Section 23, Page 984 and include cumulative percent undersize

tables and histograms of particle size distribution. Percent of transmission is reported for each run (obscuration may be derived from this data). The ——— instrument manufacturer's recommended transmission range is ———. Because this testing generated thousands of pages of data, each individual print out has not been submitted with this amendment. Print outs for each run are on file with ——— and can be supplied to the FDA if deemed necessary.

The data generated by this testing amounted to 9,720 individual pieces of data for the Perrigo product and 9,720 individual pieces of data for the Reference Listed Drug. Again, because of the sheer volume of data generated by this testing, the data set was broken down into more manageable groups and a summary comparison was generated. The comparison covers 5 cm, D50 Lowest, and Span Lowest results for the Perrigo product and the Reference Listed Drug, providing an indication of median and relative variability. Each of these data sets contains 270 values for the Perrigo product and 270 values for the Reference Listed Drug. The 5cm distance was chosen because it is the maximum distance at which samples were tested. D50 was chosen because it represents the median diameter, i.e., 50% of the sample is smaller and 50% of the sample is larger than the median diameter.

The results indicate that the means were within 5% of each other with comparable standard deviations and that the Perrigo product compared favorably with the Reference Listed Drug.

Cascade Impaction

Cascade impaction testing comparing the Perrigo product with the Reference Listed Drug was conducted. A summary of the comparative cascade impaction data filed in Section 23, Page 1182, accounts for mass balance and reports data in the following groups*:

-Group 1 (pump nozzle, nasal chamber, and cone) -Group 2 (Stage 0 and 1) -Group 3 (Stage 2 - filter)

*In accordance with FDA Draft Guidance for Industry, *"Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action"*, issued

The summary report indicates that the Perrigo product and the Reference Listed Drug compare favorably.

The Bioequivalence Study Data Package is filed in Section 23, Page 1184, of this amendment. Excel 5.0 file formats of the Bioequivalence Study Data Package is filed with this amendment on a computer data disc.

FDA Reply:

The Division of Bioequivalence realizes that the tests for droplet size distribution and cascade impaction generates numerous pages of data. The Division requests that **all raw data** should be submitted and a representative amount of supportive data such as computer sheets (20%) for the _____ system showing generated histograms should be included. The data should be presented in excel spreadsheets using the format presented in appended Table 3 with data for D50 and span for the beginning, middle and end for 10 bottles at 3 distances. The format for cascade impaction data for the different stages for the 3 lots of 10 bottles is presented in attached Table 4.

Deficiency 8.

8. Your products spray pattern should be determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug specific reagent. A drug-specific reagent will not develop color when tested with placebo. Photographs of spray patterns, in color if appropriate, should be analyzed to measure the shortest (Dmin) and (Dmax) diameters. Reported data should include values of Dmin, Dmax and ovality ratio (Dmin/Dmax), along with photographs and markings indicating Dmin and Dmax.

RESPONSE:

In accordance with the comment above, comparative spray pattern testing was conducted at three distances from the TLC plate at beginning and end of life sectors. A drug-specific reagent was not used to facilitate

visualization of the spray patterns because the products tested are solutions, not suspensions or aerosols. Representations of the spray patterns were used to measure Dmin and Dmax diameters. Special Assay Report 16126 (see Section 23, Page 1397) was generated using Perrigo Method 109 (See Section 15, Page 811) and reports values for Dmax, Dmin, and the ovality ratio. Representations of the spray patterns are attached to Special Assay Report 16126 (see Section 23, Page 1398).

FDA Reply:

The data submitted by the firm is incomplete since it was only summary data. The Division of Bioequivalence requests that the firm should submit **all raw data** for spray pattern at three distances from the TLC plate at beginning and end of life sectors. In addition paper copies for 20% of the supportive spray pattern images with markings used for quantitation should be submitted. The data for 10 bottles should be presented as an excel worksheet using the format in attached Table 6 including Dmin and ovality ratio for the beginning and end of bottle contents for test and reference at 3 distances from the chromatographic plate.

Deficiency 9:

9. *Since the device and* the formulation are integral *components of* your test nasal spray *and in* order to support the sameness *of* test and reference devices, you *should* provide to the extent possible a side-by-side comparison *of* the pumps *and* actuators used in the test *and reference* products. This information should include the manufacturer, model *numbers of* the pumps and actuators, model numbers of actuator inserts, *and the* overcaps. Technical drawings with *dimensions* should also *be submitted for* both the test *and* reference products, if available.

RESPONSE:

To the extent possible, the Perrigo pump and actuator have been compared with that of the Reference Listed Drug (RLD). The comparison table is located in Section 13 of this amendment and includes information regarding the manufacturer, model numbers, critical dimensions, and performance attributes.

The Perrigo pump and actuator system and the RLD pump and actuator system are both manufactured by ———. Information that is considered proprietary by ——— was not available to Perrigo for review. However, assurance was received from ——— that the —— pump and —— actuator and their associated components have no significant differences from the pump and actuator used by the RLD. The side-by-side comparison in Section 13, Page 617 confirms the assertion made by ———. A detailed table of contents for the ——— DMF is also included in Section 13, Page 514. Samples of the fully assembled and disassembled Perrigo pump/actuator system and the fully assembled and disassembled Reference List Drug pump/actuator system are enclosed with this amendment.

FDA Reply:

The firm's response is acceptable.

Deficiency 10.

10. Your comparative plume geometry data in vol. 1.1, 418-433 is incomplete.

The plume geometry should *describe two* side views *of* the plume, at 90° angles to each other *and relative* to the axis *of* the plume, *of* the aerosol cloud when actuated into space. You should provide plume geometry *based on* high speed photography. Plume geometry may be performed only at the *beginning of use* life. Plumes should be *characterized at* three or more different times after actuation. These times should be *chosen to* characterize the plume early upon formation, as the plume has started to dissipate, *and at* some intermediate time. Photographs of *spray* plumes should be used to measure plume *length, plume* width, and plume *(spray* cone) angle. You are *requested to* provide all photographs and data characterizing plume dimensions.

RESPONSE:

Comparative plume geometry data was generated using high-speed photography. Because there is not a reproducible method available to measure plume length and width, only 90° and 0° plume angle data is presented. Plumes were characterized at five different times after actuation. Because of the sheer volume of data generated by this

testing, not all plume sequence photographs are included with this amendment. However, all plume sequence photographs are on file at ——— and can be supplied to FDA if deemed necessary. Representative samples of the plume sequence photographs that were collected for each Perrigo sample and each Reference Listed Drug sample are filed in Section 23, Page 1256.

A summary of the comparative plume geometry data is filed in Section 23, Page 1255. The Bioequivalence Study Data Package is filed in Section 23, Page 1266. Excel 5.0 file formats of the Bioequivalence Study Data Package are filed with this amendment on a computer data disc.

The data generated by this testing indicates that the Perrigo product and the Reference Listed Drug compare favorably.

FDA Reply:

The firm's data is incomplete. The firm should submit all raw data related to plume geometry as excel spreadsheets using the format in attached Table 7. The data should include plume width, plume length and plume angle for 10 cans for each of 3 lots of test and reference at three or more times after actuation. 20% of the plume sequence photographs as paper copies should also be submitted with markings used for quantitation.

Recommendations:

The waiver request of *in vivo* bioequivalence requirements for the test product, L. Perrigo Company's Cromolyn Sodium Nasal Solution, USP, 40 mg/mL, has been found **unacceptable** due to the reasons cited in the deficiencies above.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 5/10/2000

Concur: Date: 6/2/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-427 (original, duplicate), HFD-652(Huang, Jackson), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-427 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray (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. You stated in vol. 3.4 page 1682 that the validation data for the automated actuators would be supplied in the in vitro study report. However, this data could not be identified by the Division of Bioequivalence. The settings were given in vol. 3.4 page 1664 but it was never stated if these settings were used for all studies. You should supply the validation data for your ——— actuation station and clearly state if the same settings were used for all studies.

2. The information you supplied in the referenced Section 23 of the submission are the data resulting from the in vitro testing. Your protocol information was in vol. 3.2 section 15 under drug product methods, which included the following:

Testing Conditions: Mechanical actuation, without human intervention was used for the testing. This was done according to procedure No. 1735.1 page 793 vol. 3.2. Each sprayer was actuated 5 times to prime. The amount actuated was measured by HPLC assay.

Tests were performed only for spray content uniformity and through life not at the beginning, middle and end of unit life as requested in the guidance. You should supply a detailed SOP for the methods. All raw data should be *submitted in the* form *of* paper copies as well as electronic files (excel spreadsheets).

3. The data you supplied for tests such as content uniformity on CD and paper were summary data. The type of data required is the individual data for each of the 10 bottles tested. Comparative raw data should be presented to support the summary results presented in vol. 3.1. Data should be presented for the 13 mL and 26 mL bottles.

4. Raw data for priming and tail off were not included in the submission. All raw data should be submitted in electronic format as excel spreadsheets using the format in appended Tables 1-7.

The data for droplet size distribution is incomplete since raw data were not submitted for the beginning, middle and end of use life. Also the data for spray content uniformity through life of container is incomplete since data was not presented for each of the 10 individual bottles at the beginning, middle and end of use life. The cascade impaction data was summary data.

Data from individual bottles should be presented showing the drug amounts deposited on the throat (————————————) and stages 0, 1, 2, 3 and filter of the———— Cascade Impactor instrument determined by a validated HPLC assay. The tests should be performed at the beginning and end of use life. The raw data should be from 10 actuations per test and 10 bottles each of test and reference products batches tested. This data should be supplied for the 13 mL and 26 mL bottles. Your current submission only contains summary data for the 26 ml bottle. The formats you should use to present the raw data are presented in attached Table 4 for cascade impaction and attached Table 5 for laser diffraction. The data *should* be *submitted in the* form *of* paper copies as well as electronic files (excel spreadsheets).

5. The Division of Bioequivalence realizes that the tests for droplet size distribution and cascade impaction generates numerous pages of data. The Division requests that **all raw data** should be submitted and a representative amount of supportive data such as computer sheets (20%) for the ———————— system showing generated histograms should be included. The data should be presented in excel spreadsheets using the format presented in appended Table 3 with data for D50 and span for the beginning, middle and end for 10 bottles at 3 distances. The format for cascade impaction data for the different stages for the 3 lots of 10 bottles is presented in attached Table 4.

6. Your data for plume geometry is incomplete. You should submit all raw data related to plume geometry as excel spreadsheets

spreadsheets using the format in attached Table 7. The data should include plume width, plume length and plume angle for 10 cans for each of 3 lots of test and reference at three or more times after actuation. 20% of the plume sequence photographs as paper copies should also be submitted with markings used for quantitation.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

Table 1: Unit Dose Data*....(ANDA # .....)

Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p*(Tvs.R)**
TEST	1	Beg														
		Mid														
		End														
	2	Beg														
		Mid														
		End														
	3	Beg														
		Mid														
		End														
REF	1	Beg														
		Mid														
		End														
	2	Beg														
		Mid														
		End														
	3	Beg														
		Mid														
		End														

** For Nasal sprays, Beginning (Beg) and End only.*

*** Based on combined data of three lots, separately at Beg, Middle (Mid) and End*

Table 2: Priming Data....(ANDA # .....)

(Similar table for Repriming Data, where applicable per REF labeling)

Product	Lot #	Actuation #	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
TEST	1	1														
		2														
		3														
		To the first full medication dose														
	2	1														
		2														
		3														
		To the first full medication dose														
	3	1														
		2														
		3														
		To the first full medication dose														
REF	1	1														
		2														
		3														
		To the first full medication dose														
	2	1														
		2														
		3														
		To the first full medication dose														
	3	1														
		2														
		3														

*** Based on combined data of three lots.*

Table 3: Tail Off Data....(ANDA # .....)

Product	Lot #	Actuation #	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p*(Tvs.R)**
TEST	1	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
	2	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
	3	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
REF	1	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
	2	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
	3	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														

*** Based on combined data of three lots.*

Table 4: Cascade Impaction Data....(ANDA # .....)

(For nasal aerosols & nasal sprays, data may be combined into three groups per the draft Nasal BA/BE Guidance)
(Table format is based on the Andersen Cascade Impactor. It should be modified appropriately for other devices)

				Drug Deposition on (Mass Units)										
PROD	SECTOR	Lot #	Can #	Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
TES	BEG		5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

PROD	SECTOR	Lot #	Can #	Drug Deposition on (Mass Units) Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
TES	END		4												
			5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

TeS/REF (Grand Mean)	BEG
	END

*p (Tvs.R)***	BEG	
	END	

*** Based on combined data of three lots, separately at Beg & End*

APPEARS THIS WAY
ON ORIGINAL

Table 4: Cascade Impaction Data....(ANDA # .....)

'For nasal aerosols & nasal sprays, data may be combined into three groups per the draft Nasal BA/BE Guidance)
'Table format is based on the Andersen Cascade Impactor. It should be modified appropriately for other devices)

				Drug Deposition on (Mass Units)										
PROD	SECTOR	Lot #	Can #	Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
REF	BEG		5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

PROD	SECTOR	Lot #	Can #	Drug Deposition on (Mass Units) Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
REF	END		4												
			5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

Table 5: Particle Sizing by Laser Diffraction....(ANDA # .....)

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
(3, 5 and 7 cm are provided as examples. Other distances may be appropriate for specific products)	TEST	1	Beg														
			Mid														
			End														
		2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
3 cm	REF	1	Beg														
			Mid														
			End														
		2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
5 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
7 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
			Beg														

*** Based on combined data of three lots, separately at Beg, Mid & End*

3	Mid	
	End	

Table 5: Particle Sizing by Laser Diffraction....(ANDA # .....)

SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p*(Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
3 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p*(Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
5 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
7 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
			Beg														

*** Based on combined data of three lots, separately at Beg, Mid & End***

3 Mid
End

Table 6: Spray Pattern Data....(ANDA # .....)

Dmin

Distance	Product	Lot #	Lot #	Stage	Bottle/Can # 1 2 3 4 5 6 7 8 9 10	Mean	%CV	Test/Ref	p(Tvs.R)**
(3, 5 and 7 cm are provided as examples. Other distances may be appropriate for specific products)		1	1	Beg					
				End					
	TEST	2	2	Beg					
				End					
		3							
			3	Beg					
				End					
3 CM		1	1	Beg					
				End					
	REF	2	2	Beg					
				End					
		3	3	Beg					
				End					

*** Based on combined data of three lots, separately at Beg & End*

Dmin

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1 2 3 4 5 6 7 8 9 10	Mean	%CV	Test/Ref	p(Tvs.R)**
		1	1	Beg					
				End					
	TEST	2	2	Beg					
				End					
		3							
			3	Beg					
				End					
5 CM									
		1	1	Beg					
				End					
	REF	2	2	Beg					
				End					
		3							
			3	Beg					
				End					

*** Based on combined data of three lots, separately at Beg & End***

Dmin

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
10 Cm																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

*** Based on combined data of three lots, separately at Beg & End*

Table 6: Spray Pattern Data....(ANDA # .....)

Dmax

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1 2 3 4 5 6 7 8 9 10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	1	Beg					
				End					
	TEST	2	2	Beg					
				End					
		3							
			3	Beg					
				End					
3 CM									
		1	1	Beg					
				End					
	REF	2	2	Beg					
				End					
		3	3	Beg					
				End					

*** Based on combined data of three lots, separately at Beg & End*

Dmax

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	1	Beg														
				End														
	TEST	2	2	Beg														
				End														
		3	3	Beg														
				End														
5 CM																		
		1	1	Beg														
				End														
	REF	2	2	Beg														
				End														
		3																
			3	Beg														
				End														

** *Based on combined data of three lots, separately at Beg & End*

Dmax

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1 2 3 4 5 6 7 8 9 10	Mean	%CV	Test/Ref
		1	1	Beg				
				End				
	TEST	2	2	Beg				
				End				
		3	3	Beg				
				End				
10 Cm								
		1	1	Beg				
				End				
	REF	2	2	Beg				
				End				
		3	3	Beg				
				End				

*** Based on combined data of three lots, separately at Beg & End*

Table 6: Spray Pattern Data....(ANDA # .....)

Ovality Ratio (Dmax/Dmin)

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
3 CM																	
		1	Beg														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			End														

** *Based on combined data of three lots, separately at Beg & End*

Ovality Ratio

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)*
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
5 CM																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

*** Based on combined data of three lots, separately at Beg & End***

Ovality Ratio

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	** Based on combined data of three lots, separately at Beg & End
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
10 Cm																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

Table 7: Plume Geometry Data....(ANDA # .....)

Plume Width

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
		0.015														
		0.030														
		0.045														
	1	0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
TEST	2	0.045														
		0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
	3	0.045														
		0.060														
		0.090														
		0.120														
		.														

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
		0.015														
		0.030														
		0.045														
	1	0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
REF	2	0.045														
		0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
	3	0.045														
		0.060														
		0.090														
		0.120														
		.														

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

Table 7: Plume Geometry Data....(ANDA # .....)

Plume Length

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
		0.015														
		0.030														
		0.045														
	1	0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
TEST	2	0.045														
		0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
	3	0.045														
		0.060														
		0.090														
		0.120														
		.														

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
		0.015														
		0.030														
		0.045														
	1	0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
REF	2	0.045														
		0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
	3	0.045														
		0.060														
		0.090														
		0.120														
		.														

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

Table 7: Plume Geometry Data....(ANDA # .....)

PROD	LOT	Time* (Sec)	Plume Angle Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p(Tvs.R)**
		0.015															0.015													
		0.030															0.030													
		0.045															0.045													
	1	0.060														1	0.060													
		0.090															0.090													
		0.120															0.120													
		.															.													
		0.015															0.015													
		0.030															0.030													
TEST	2	0.045													REF	2	0.045													
		0.060															0.060													
		0.090															0.090													
		0.120															0.120													
		.															.													
		0.015															0.015													
		0.030															0.030													
	3	0.045														3	0.045													
		0.060															0.060													
		0.090															0.090													
		0.120															0.120													
		.															.													

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

CC: ANDA 75-427
ANDA DUPLICATE
DIVISION FILE
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ Jackson

v:\firmsnz\perrigo\ltrs&rev\75427A.300
Printed in final on / /

Endorsements: (Final with Dates)
HFD-652/ Jackson
HFD-652/ YHuang 5/10/2000
HFD-650/ D. Conner 6/2/00

~~**AMENDMENT TO A WAIVER**~~ (WAI) Strengths: 40 mg/mL 5.2mg/Spray
STUDY AMENDMENT (STA) orc **Outcome: UN**

UN - Unacceptable
WINBIO COMMENTS: 6/22/00

APPEARS THIS WAY
ON ORIGINAL

Cromolyn Sodium Nasal Solution USP,
5.2 mg/spray (40 mg/mL)
ANDA # 75-427
Reviewer: Andre J. Jackson
V:\Firmsnz\Perrigo\Ltr&Rev\75427A.N00

L. Perrigo Company
Allegan, Michigan
Submission Date:
November 30, 2000
January 26, 2001

Review of an Amendment

History:

Date: July 31, 1998 The firm submitted a waiver request for their product based upon the test product being quantitatively and qualitatively the same as the reference listed drug. The waiver was denied and the firm was informed that because there were a number of unresolved issues regarding the testing of manual metered dose pumps for the documentation of in vitro bioequivalence, they were advised to submit a protocol outlining its planned studies. This protocol was based in part on the considerations related to the metering performance and uniformity of unit spray content sections of Chapters 601 and 905 of the U.S. Pharmacopeia, and to the Division of Bioequivalence June 27, 1989 Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers).

Date : November 20, 1998- The firm responded to the deficiency from the July 31, 1998 submission. The Division of Bioequivalence provided the firm more specifics related to the required in vitro testing requirements.

Date : March 31, 2000-The firm responded to the deficiencies from the November 20, 1998 submission. However, the submitted data was incomplete. Raw data was not submitted for all the tests. Appended to the deficiency letter to the firm, the FDA provided a format to use for raw data presentation as an Excel spreadsheet.

Date : January 17, 2001 -The firm was contacted by phone and requested to supply information regarding droplet size determination with the laser beam. The information sought and their replies are at the end of this review.

Background Information on drug product and pump

Formulation:

Composition of the test product is quantitatively and qualitatively the same as the reference listed drug (see earlier review dated January 25, 1999).

Drug Products:

Test: L. Perrigo Cromolyn Sodium Nasal Solution 5.2 mg/Spray-[redacted]. Lot # 9KV008
(batch size [redacted] was divided into 6 split-fill sublots. These were:
9KV008 9KV009 9KV0010 - 13 ml size
9KV0011 9KV0012 9KV0013- 26 ml size

Reference: Pharmacia & Upjohn(vol. 3.1)

NasalCrom Lot # 52DCB, ——— -13 mL size
NasalCrom Lot # 32DKA, ——— -26 mL size

The information supplied by the firm on the reference lots is incomplete and the firm is requested to clarify the #52DCB and #32DKA lots with the those used in the in vitro tests.

Comparability of Spray Devices:

——— developed and provided to L. Perrigo a nasal spray pump ——— Actuator which was almost identical to that of the innovator product. A physical comparison between the L. Perrigo pump and NasalCrom[R] pump is shown in Vol. 3.2, page 617, a copy of the drawing for L. Perrigo's pump is included in Vol. 3.2 page 620.

The spray device is acceptable to the Division of Bioequivalence.

Procedures and Information Applicable to All Tests:

All actuations of the nasal spray products were done using a mechanical actuator to actuate the nasal sprays in a reproducible manner. The mechanical actuator used was a proprietary unit designed by ———, for nasal spray actuation. Final settings were as follows:

Force setting	5.6 kg
Dosing Time	11-15 ms
Hold Time	2 s
Return Time	35-40 ms

Objective:

The firm has replied to the comments made by the Division of Bioequivalence (DBE) related to their March 31, 2000 submission (*In Vitro* Performance Studies on Cromolyn Sodium Nasal Solution 5.2 mg/Spray).

Review of November 30, 2000 Amendment

FDA COMMENT

1. *You stated in vol. 3.4 page 16 that the validation data for the automated actuators would be supplied in the in vitro study report. However, this data could not be identified by the Division of Bioequivalence. The settings were given in vol. 3.4 page 1664 but it was never stated if these settings were used for all studies. You should supply the validation data for your ——— actuation station and clearly state if the same settings were used for all studies.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above comment, please note the following information:

———————— 's validation report — 02-01, *Report on the Qualification of the Use of an Automated Actuator to Advance Perrigo Company Cromolyn Sodium Nasal Spray from Beginning through Middle and End of Life Stage,* was filed with the March 30, 2000, amendment in the Methods Validation Section on page 1436. In accordance with the above comment, an addendum to — 02-01 noting the settings that were used throughout all testing conducted by ———————— is located on page 55 of this amendment.

———————— 's validation report — 02-02, *Report on the Qualification of the Use of an Automated Actuator to Advance Nasalcromo Cromolyn Sodium Nasal Spray from Beginning through Middle and End of Life Stage,* was filed with the March 30, 2000, amendment in the Methods Validation Section on page 1477. In accordance with the above comment, an addendum to — 02-02 noting the settings that were used throughout all testing conducted by ———————— is located on page 54 of this amendment.

———————— 's test method TM — 02-PG, *Plume Geometry for Cromolyn Sodium Nasal Spray Product,* was filed with the March 30, 2000, amendment in the Methods Validation Section on page 1671. In accordance with the above comment, an addendum to TM — 02-PG noting the settings that were used throughout all testing conducted by ———————— is located on page 52 of this amendment.

FDA Reply:

The firm's reply is acceptable.

FDA COMMENT:

2. *The information you supplied in the referenced Section 23 of the submission are the data resulting from the in vitro testing. Your protocol information was in vol. 3.2 Section 15 under drug product methods, which included the following:*

   ***Testing Conditions:** Mechanical actuation, without human intervention was used for the testing. This was done according to Procedure No. 1735. 1 page 793 vol. 3.2 Each sprayer was actuated 5 times to prime. The amount actuated was measured by HPLC assay.*

   Tests were performed only for spray content uniformity and through life not at the beginning, middle and end of unit life as requested in the guidance. You should supply a detailed SOP for the methods. All raw data should be submitted in the form of paper copies as well as electronic files (excel) spreadsheets.

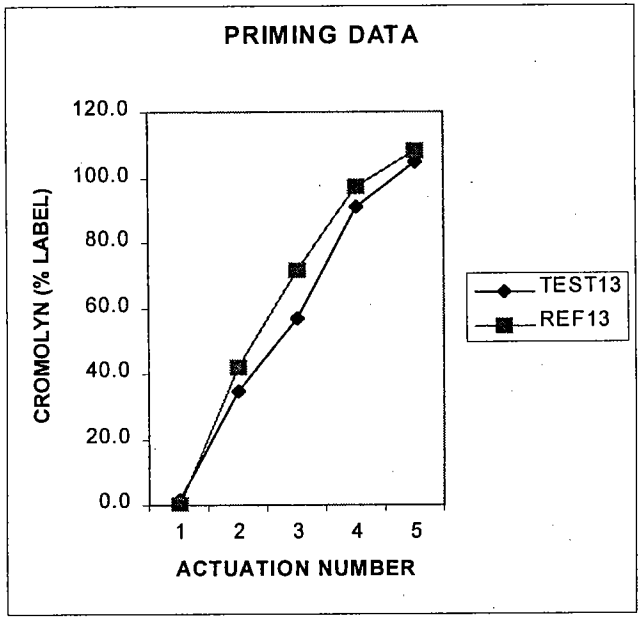
L. PERRIGO COMPANY RESPONSE:

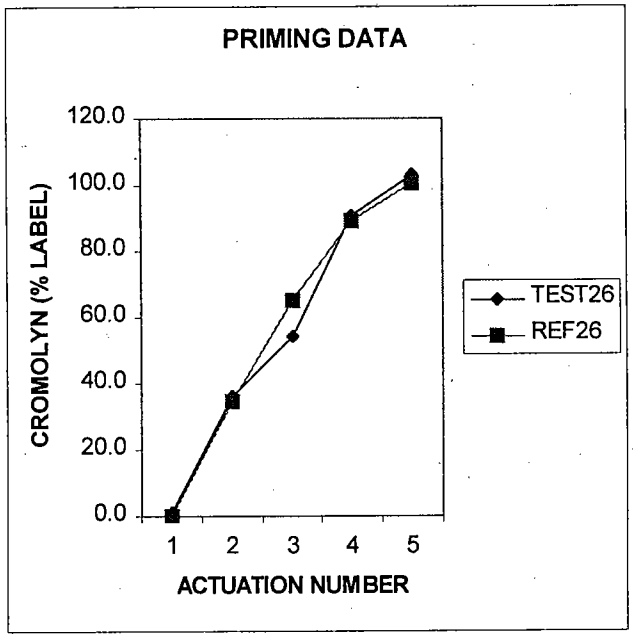
In accordance with the above FDA comment, raw data for spray content uniformity testing and through life testing performed at the beginning, middle and end of unit life is supplied on page 191 of this amendment. The protocol used to conduct the testing is filed on page 57 and the protocol validation report is filed on page 66. Note that the same protocol was used to conduct the priming, through life, and tail-off bioequivalence testing. Electronic Excel spreadsheets of data tables are located on the CD accompanying this amendment.

SPACE INTENTIONALLY LEFT BLANK

FDA Comments on Priming and Tail-off Procedures:

The through life study was conducted by priming the 13 mL and 26 mL bottles with 5 actuations of the automated actuation station to prime the pump. The initial sample is taken, the spray is pumped 48 and 98 times respectively for the initial samples. The middle samples are obtained following 49 and 99 actuations respectively. Tail-off was after the 101st spray for the 13 ml size and following the 201st spray for the 26 mL size. This was continued up to the 52nd spray after that designated to begin tail-off measurements. The resulting data is presented in Figure 1 priming data-13 mL and Figure 2 priming data-26mL.



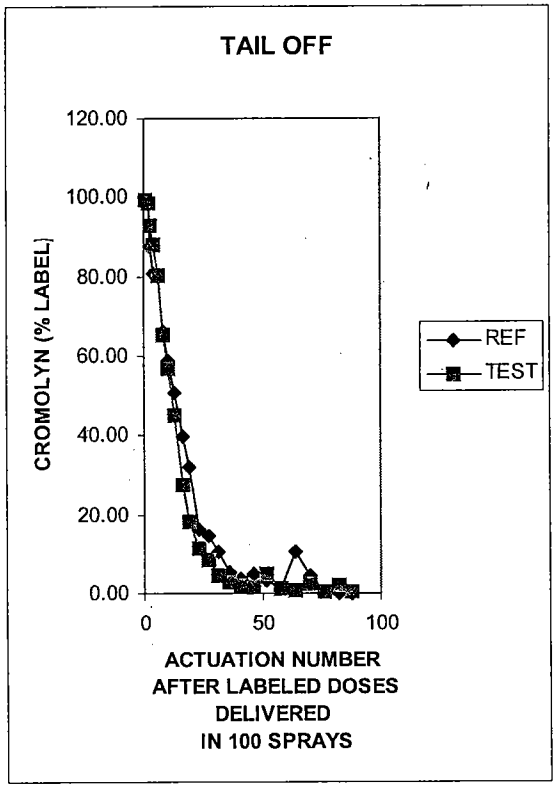


Actuation after the 100th dose

spray	% Label 13 ML	
	REF	TEST
1	98.41	99.21
2	99.22	98.47
3	87.54	93.02
4	80.88	87.86
6	80.22	80.23
8	66.26	65.28
10	58.63	56.93
13	50.83	44.95
16	39.75	27.55
19	31.89	18.24
23	16.17	11.45
27	14.78	8.66
31	10.42	4.64
36	5.47	2.98
41	3.82	1.88
46	5.03	1.56
52	3.27	5.02
58	1.20	1.05
64	10.55	1.00
70	4.30	2.40
76	0.50	0.60
82	0.00	2.20
88	0.00	0.30

Actuation after the 200th dose

spray	% Label 26 ML	
	REF	TEST
1	98.41	99.21
2	99.22	98.47
3	87.54	93.02
4	80.88	87.86
6	80.22	80.23
8	66.26	65.28
10	58.63	56.93
13	50.83	44.95
16	39.75	27.55
19	31.89	18.24
23	16.17	11.45
27	14.78	8.66
31	10.42	4.64
36	5.47	2.98
41	3.82	1.88
46	5.03	1.56
52	3.27	5.02
58	1.20	1.05
64	10.55	1.00
70	4.30	2.40
76	0.50	0.60
82	0.00	2.20
88	0.00	0.30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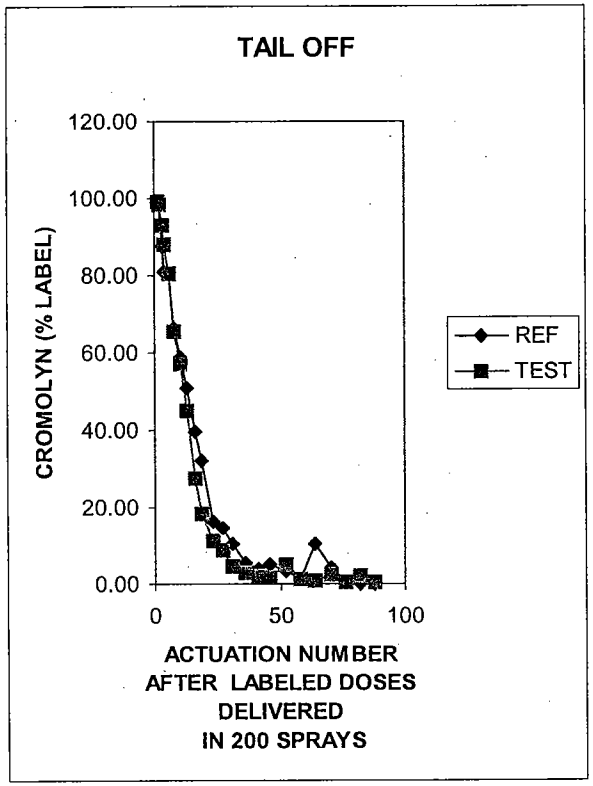
AFTER LABELED DOSES
DELIVERED
IN 100 SPRAYS
REF
TEST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CROMOLYN (% LABEL)
0
50
100
ACTUATION NUMBER
AFTER LABELED DOSES
DELIVERED
IN 200 SPRAYS
REF
TEST

The following table provides a summary of content uniformity based on the reviewer's calculations.

Table 1. Content uniformity for the 26 mL nasal spray (A) and the 13 mL nasal spray (B).

A

			VARIABILITY	MEAN OF LOG	%CV					
PRODUCT	SECTOR	MEAN	TOTAL %CV		WITHIN		BETWEEN	T/R	T/R	P
					LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST	BEG	108.35	2.33	4.67	1.04	2.5	1.24	1.03	1.01	0.4079
	MID	108.35	2.60	4.69	1.16	2.39	2.27	1.05	1.05	0.0011
	END	104.58	7.80	4.65	1.99	10.09	2.97	1.04	1.04	0.0485
REF	BEG	105.66	3.85	4.66	3.25	4.28	1.49			
	MID	103.29	7.09	4.63	0.81	7.69	6.40			
	END	100.52	7.39	4.61	5.41	9.90	1.92			

B

			VARIABILITY	MEAN OF LOG	%CV					
PRODUCT	SECTOR	MEAN	TOTAL %CV		WITHIN		BETWEEN	T/R	T/R	P
					LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST	BEG	108.24	2.79	4.68	1.58	2.20	2.46	0.98	0.98	0.0048
	MID	110.44	2.40	4.70	0.83	1.53	2.49	0.99	0.99	0.0749
	END	109.18	3.12	4.69	1.22	3.84	1.59	1.00	1.00	0.7184
REF	BEG	110.09	1.43	4.70	1.63	4.79	0.38			
	MID	111.51	1.63	4.71	1.06	2.12	0.81			
	END	109.72	6.85	4.70	1.09	11.06	1.74			

** The unit dose data are expressed % of label claim. P value calculated assuming unequal variance*

The weight of individual sprays was determined by weighing bottles before and after each spray collection, and the amount of drug per spray was determined by HPLC analysis.

FDA Comments on the Unit Dose Data Submitted

1. The mean values for test and reference were comparable at all 3 sectors. Reference values were slightly higher for the 13 mL size and smaller on average for the 26 mL size. Per cent CV values were comparable. Two p values were significant for the 13 mL and 26 mL bottle sizes. Test/Ref ratios were within the limits of 90-110% as discussed in the draft nasal BA/BE guidance.

2. The unit dose data also conform to the recommendations made in the draft guidance. The mean values were within 85-115% and no value was outside 80-120% of the label claim.

3. Based upon the mean values, the unit dose did not change with the life sector. There was an increase in variability (i.e., increase in % cv range) with life sector especially within lots.

4. The priming and tail-off data in Figures 1 and 2 are comparable.

5. Based upon unit dose data, the labeled dose is delivered by the 6th actuation for the test and reference products. This is consistent with the innovator patient package insert. Based on the foregoing, the firm's response to the DBE comment on unit dose and content uniformity is acceptable.

FDA COMMENT :

3. *The data you supplied for tests such as content uniformity on CD and paper were summary data. The type of data required is the individual data for each of the 10 bottles tested. Comparative raw data should be presented to support the summary results presented in vol. 3. 1.* ***Data should be presented for the 13 mL*** *and 26 mL bottles.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, the data tables filed on page 191 detail the individual raw data for content uniformity testing for each of the 10 bottles tested from each of the three lots of 13 mL and 26 mL bottles. Comparative raw data is also presented for the RLD product. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

FDA Reply:

The firm's response is acceptable based upon the data presented to address FDA comment 2.

FDA COMMENT :

4. *Raw data for priming and tail off were not included in the submission. All raw data should be submitted in electronic format as excel spreadsheets using the format in the appended tables I - 7.*

The data for droplet size distribution is incomplete since raw data were not submitted for the beginning, middle, and end of use life. Also the data for spray content uniformity through life of container is incomplete since data was not presented for each of the 10 individual bottles at the beginning, middle and end of use life. The cascade impaction data was summary data. Data from individual bottles should be presented showing the drug amounts deposited on the throat ——— ——— and stages 0, 1, 2, 3, and filter of the ——— Cascade Impactor instrument determined by a validated HPLC assay. The tests should be performed at the beginning and end of use life. The raw data should be from 10 actuations per test and 10 bottles each of test and reference products batches tested. This data should be supplied for the 13 mL and 26 mL bottles. Your current submission only contains summary data for the 26 mL bottle. The formats you should use to present the raw data are presented in attached Table 4 for cascade impaction and attached Table 5 for laser diffraction. The data should be submitted in the form of paper copies as well as electronic files (excel spreadsheets).

L. PERRIGO COMPANY RESPONSE:,

In accordance with the above FDA comment, the raw data for priming and tail off testing is detailed in the data tables filed on page 73 and page 192. The tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. The protocol used to conduct the testing is filed on page 57 **of this amendment and** the protocol validation report is filed on page 66. Note that the same protocol was used to conduct the priming, through life, and tail-off bioequivalence testing. The same samples were used to conduct the priming and through life testing. Different samples were used to conduct the tail-off testing. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

Additionally, the raw data for droplet size distribution testing (particle sizing by laser diffraction) conducted at the beginning, middle and end of use life is detailed in the data tables filed on page 701. Because the only difference between the sprayer used with the 26 mL bottle and the sprayer used with the 13 mL bottle is the length of the dip tube, testing was conducted on the 26 mL configuration only. Electronic Excel spreadsheets of data tables are located on the CD accompanying this amendment.

The raw data for spray content uniformity through life of container is detailed in the data tables filed on page 191 and include data for each of the 10 individual bottles tested at the beginning, middle, and end of use life. The tables are formatted

similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. Note that the same protocol was used to conduct the priming, through life, and tail-off bioequivalence testing. The same samples were used to conduct the priming and spray content uniformity through life testing. Different samples were used to conduct the tail-off testing. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.
The raw data for cascade impaction testing is detailed in the data tables filed on page 397. A validated HPLC assay method was used to conduct the testing. Please reference the test method TM- — 02-01 B, HPLC Assay of Cromolyn Sodium in Cromolyn Sodium Nasal Spray, filed with the March 30, 2000, amendment on page 1652 and the method validation report also filed with the March 30, 2000, amendment on page 1410. Because the only difference between the sprayer used with the 26 mL bottle and the sprayer used with the 13 mL bottle is the length of the dip tube, testing was conducted on the 26 mL configuration only. The cascade impaction testing data tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

FDA Comment on droplet size determination procedures

The droplet size distribution was determined at 3 distances 1cm, 2.5 cm and 5 cm from the ——————————. At each combination of life sector and distance, droplet size distribution was determined at the beginning of plume formation, fully formed plume and plume dissipation. These stages were determined based upon 90% transmission. The beginning of plume formation was characterized by a drop in % transmission to 90%. The fully formed plume was characterized by a % transmission of $\leq$ 90% while during plume dissipation % transmission rose above 90%. Time delays were not calculated by the firm (see January 26, 2001 amendment respone #1). Collected data for beginning, middle and end sectors is presented based upon particle size distribution. The droplet size distribution is based upon D10,D50 and D90, the particles which comprise 10%, 50% and 90% of the population of particles, respectively. This data is presented in Table 3 for the test product.

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Table 3. Test and reference data for droplet size distribution D50 um (particles comprising 50% of the mass).

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		Lot	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	1CM	SPBEG	86.55	53.83	4.36	25.64	67.67	10.26	1.43	1.32	0.0057
	BEG	1CM	SPMID	50.35	34.31	3.89	4.45	49.55	13.45	1.02	0.99	0.7872
	BEG	1CM	SPEND	77.78	71.82	4.22	23.89	84.2	25.49	1.32	1.16	0.0755
REF	BEG	1CM	SPBEG	60.59	19.61	4.09	17.58	21.85	2.36			
	BEG	1CM	SPMID	49.46	9.16	3.9	6.81	9.82	6.93			
	BEG	1CM	SPEND	58.8	14.29	4.06	9.79	21.85	5.71			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	2.5CM	SPBEG	105.82	52.42	4.55	47.88	60.45	3.85	0.92	0.86	0.4402
	BEG	2.5CM	SPMID	39.74	15.10	3.67	9.33	22.04	1.68	0.89	0.88	0.0008
	BEG	2.5CM	SPEND	151.48	33.41	4.97	25.68	54.43	10.76	0.73	0.74	0.0007
REF	BEG	2.5CM	SPBEG	115.35	32.70	4.70	30.41	35.88	6.24			
	BEG	2.5CM	SPMID	44.89	11.73	3.80	7.94	12.90	5.81			
	BEG	2.5CM	SPEND	207.68	33.47	5.27	29.11	35.88	5.73			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	

TEST	BEG	5CM	SPBEG	78.98	48.93	4.27	28.92	55.56	24.24	0.96	0.90	0.7143
	BEG	5CM	SPMID	32.46	5.87	3.48	4.71	7.81	1.30	0.96	0.96	0.0372
	BEG	5CM	SPEND	126.06	40.68	4.77	28.92	46.54	9.53	0.76	0.75	0.0045
REF	BEG	5CM	SPBEG	81.91	24.38	4.38	19.48	31.76	5.22			
	BEG	5CM	SPMID	33.84	8.78	3.52	6.86	8.46	5.20			
	BEG	5CM	SPEND	165.99	32.12	5.06	19.48	34.66	1.21			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	MID	1CM	SPBEG	155.21	41.60	4.96	36.69	40.06	19.52	0.79	0.84	0.0513
	MID	1CM	SPMID	105.35	58.43	4.49	55.57	56.26	23.67	0.96	0.94	0.785
	MID	1CM	SPEND	214.72	44.76	5.24	36.69	42.79	14.61	0.97	1.03	0.8035
REF	MID	1CM	SPBEG	197.11	48.28	5.14	37.28	56.42	14.86			
	MID	1CM	SPMID	109.63	54.29	4.55	52.76	58.83	6.33			
	MID	1CM	SPEND	221.63	52.71	5.22	56.42	59.65	14.28			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	MID	2.5CM	SPBEG	105.17	39.51	4.59	32.94	48.44	6.84	0.63	0.62	0.0001
	MID	2.5CM	SPMID	39.61	55.97	3.60	9.61	78.16	13.58	0.73	0.80	0.0772
	MID	2.5CM	SPEND	121.84	11.68	4.80	11.84	48.44	2.46	0.75	0.79	0.0004
REF	MID	2.5CM	SPBEG	166.54	27.52	5.07	22.54	32.26	10.77			
	MID	2.5CM	SPMID	54.00	69.58	3.82	68.06	70.04	18.99			
	MID	2.5CM	SPEND	161.78	33.27	5.03	27.00	38.09	9.09			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	MID	5CM	SPBEG	71.77	32.51	4.24	11.12	45.35	9.72	0.73	0.75	0.0008
	MID	5CM	SPMID	31.04	5.23	3.43	3.11	6.28	1.65	0.95	0.95	0.0009
	MID	5CM	SPEND	98.92	15.53	4.58	11.12	17.06	4.13	0.73	0.75	0.0001
REF	MID	5CM	SPBEG	97.67	33.22	4.52	27.02	35.56	13.91			
	MID	5CM	SPMID	32.78	6.60	3.49	3.45	8.34	3.30			
	MID	5CM	SPEND	135.01	26.06	4.88	27.02	31.51	6.35			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	END	1CM	SPBEG	141.17	28.38	4.91	20.16	29.84	16.21	0.72	0.71	0.0001
	END	1CM	SPMID	65.21	44.55	4.11	23.26	54.20	11.54	1.24	1.18	0.0287
	END	1CM	SPEND	198.04	18.81	5.27	18.10	22.79	3.26	0.81	0.81	0.0001
REF	END	1CM	SPBEG	195.68	23.37	5.25	19.73	26.64	4.00			
	END	1CM	SPMID	52.45	18.53	3.95	10.07	25.33	5.92			
	END	1CM	SPEND	245.96	18.05	5.49	15.71	26.64	6.35			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	END	2.5CM	SPBEG	105.45	41.93	4.59	28.22	46.35	14.69	0.64	0.61	0.0001
	END	2.5CM	SPMID	35.74	12.32	3.57	9.58	15.79	3.13	0.95	0.95	0.0958

	END	2.5CM	SPEND	129.34	13.82	4.85	10.98	46.35	6.63	0.76	0.77	0.0001
REF	END	2.5CM	SPBEG	165.54	24.09	5.08	19.04	29.68	6.71			
	END	2.5CM	SPMID	37.75	12.75	3.62	11.53	13.38	5.41			
	END	2.5CM	SPEND	170.59	21.75	5.12	18.71	23.87	7.77			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	END	5CM	SPBEG	76.97	41.77	4.28	49.96	15.23	10.92	0.72	0.71	0.0006
	END	5CM	SPMID	32.56	6.37	3.48	4.66	7.43	2.77	0.95	0.95	0.0089
	END	5CM	SPEND	103.61	18.90	4.62	14.81	21.59	1.78	0.79	0.81	0.0021
REF	END	5CM	SPBEG	106.79	29.70	4.63	36.92	25.35	7.21			
	END	5CM	SPMID	34.24	7.90	3.53	6.61	8.69	3.53			
	END	5CM	SPEND	130.66	31.20	4.83	25.35	35.28	12.87			

Table 4. Test data for droplet size span (D90-D10/D50).

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	1CM	SPANB	1.83	19.29	0.58	13.38	23.77	9.20	0.99	1.00	0.8847
	BEG	1CM	SPANM	1.75	9.78	0.56	7.45	9.80	5.48	0.87	0.89	0.0135
	BEG	1CM	SPANE	1.56	24.86	0.42	19.79	32.69	10.56	0.99	0.97	0.8554
REF	BEG	1CM	SPANB	1.84	26.49	0.58	15.84	36.53	6.53			
	BEG	1CM	SPANM	2.03	26.81	0.68	13.61	32.57	11.53			
	BEG	1CM	SPANE	1.58	14.20	0.45	7.30	21.06	4.67			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	2.5CM	SPANB	1.92	20.23	0.63	17.72	23.45	6.12	0.83	0.84	0.0025
	BEG	2.5CM	SPANM	2.11	16.94	0.74	11.74	21.66	6.73	0.83	0.89	0.0871
	BEG	2.5CM	SPANE	1.32	18.97	0.26	17.25	23.45	4.05	1.16	1.18	0.0247
REF	BEG	2.5CM	SPANB	2.30	22.96	0.81	17.84	25.84	9.14			
	BEG	2.5CM	SPANM	2.53	49.34	0.86	27.66	47.65	10.10			
	BEG	2.5CM	SPANE	1.14	30.32	0.09	25.01	28.93	6.29			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	5CM	SPANB	2.56	51.80	0.87	27.52	49.22	40.76	0.94	0.90	0.5402
	BEG	5CM	SPANM	1.51	23.44	0.34	10.86	37.12	7.63	0.85	0.80	0.0007
	BEG	5CM	SPANE	1.63	23.90	0.37	11.11	41.72	1.88	1.16	1.07	0.0259
REF	BEG	5CM	SPANB	2.73	26.36	0.97	19.88	32.34	2.04			
	BEG	5CM	SPANM	1.78	11.79	0.57	10.46	11.71	6.21			
	BEG	5CM	SPANE	1.41	25.02	0.31	17.89	28.02	8.53			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	MID	1CM	SPANB	2.20	34.27	0.73	31.16	35.92	14.38	1.25	1.31	0.0494

	MID	1CM	SPANM	3.02	43.50	1.01	35.53	49.59	10.19	0.89	0.91	0.317
	MID	1CM	SPANE	1.54	54.93	0.30	31.16	54.08	23.29	0.91	1.00	0.5643
REF	MID	1CM	SPANB	1.77	51.47	0.46	37.82	63.06	17.15			
	MID	1CM	SPANM	3.40	47.09	1.11	38.36	55.26	4.83			
	MID	1CM	SPANE	1.69	69.28	0.30	63.06	71.82	17.49			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	MID	2.5CM	SPANB	2.20	24.17	0.76	18.39	28.03	10.22	1.14	1.15	0.0611
	MID	2.5CM	SPANM	1.90	8.61	0.64	3.20	13.53	2.21	0.97	0.99	0.4661
	MID	2.5CM	SPANE	1.52	7.34	0.42	6.57	20.79	1.80	1.17	1.19	0.0001
REF	MID	2.5CM	SPANB	1.92	30.51	0.62	23.91	34.14	11.82			
	MID	2.5CM	SPANM	1.96	21.63	0.64	16.33	24.47	6.73			
	MID	2.5CM	SPANE	1.29	19.37	0.24	17.02	24.26	4.03			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	MID	5CM	SPANB	2.39	44.09	0.83	25.05	62.05	12.02	1.13	1.07	0.2523
	MID	5CM	SPANM	1.39	23.55	0.26	12.14	33.68	5.53	0.94	0.92	0.269
	MID	5CM	SPANE	1.80	21.71	0.49	12.83	44.07	6.60	1.08	0.95	0.1944
REF	MID	5CM	SPANB	2.13	33.56	0.76	23.26	49.62	0.68			
	MID	5CM	SPANM	1.48	20.66	0.34	9.58	32.37	5.88			
	MID	5CM	SPANE	1.67	23.52	0.54	16.80	38.87	8.25			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	END	1CM	SPANB	2.17	19.27	0.76	13.13	23.47	7.68	1.46	1.46	0.0001
	END	1CM	SPANM	2.96	25.41	1.05	19.30	29.17	8.55	1.03	1.02	0.5607
	END	1CM	SPANE	1.45	18.15	0.35	15.00	19.85	4.79	1.35	1.36	0.0001
REF	END	1CM	SPANB	1.49	19.58	0.38	17.90	22.72	4.31			
	END	1CM	SPANM	2.86	19.51	1.03	13.34	26.64	5.57			
	END	1CM	SPANE	1.07	21.50	0.05	14.77	22.82	5.80			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	END	2.5CM	SPANB	2.14	23.56	0.74	19.59	28.22	5.10	1.24	1.23	0.0007
	END	2.5CM	SPANM	1.98	10.93	0.68	2.66	16.08	3.32	1.00	1.00	0.9004
	END	2.5CM	SPANE	1.57	14.23	0.44	14.67	19.59	6.00	1.19	1.19	0.0001
REF	END	2.5CM	SPANB	1.73	21.27	0.53	16.17	28.90	3.47			
	END	2.5CM	SPANM	1.97	6.01	0.68	5.26	6.93	0.53			
	END	2.5CM	SPANE	1.32	15.03	0.27	13.93	17.17	7.76			

PROD	UNIT	DIST	PLUME	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
	LIFE		FORM		%CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
							%CV		%CV			VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	END	5CM	SPANB	2.12	39.47	0.67	33.15	43.30	18.46	0.96	1.06	0.7083
	END	5CM	SPANM	1.39	10.43	0.32	9.55	11.26	4.05	0.97	0.94	0.4606

	END	5CM	SPANE	1.86	14.84	0.61	10.51	35.99	1.83	1.05	1.07	0.2612
REF	END	5CM	SPANB	2.20	37.54	0.62	32.29	47.37	5.79			
	END	5CM	SPANM	1.44	23.52	0.39	14.11	37.40	2.74			
	END	5CM	SPANE	1.76	20.88	0.54	16.90	47.37	13.95			

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FDA Comments on Droplet Size Distribution Data

1. Evaluation of the test and reference product's equivalence with regard to droplet size distribution is based on the D50 and SPAN data for the fully formed spray (SPMID values).

2. The T/R geometric mean ratio for the D50 data for the fully formed spray were in the range of 0.80 – 0.99. The T/R ratio of 0.88 for the 2.5 cm distance data is outside the acceptable range of 0.90-1.11 stipulated in the draft Nasal BA/BE guidance. However, it was noted that for the 2.5 cm D50 data, the reference product total variability (%CV = 11.73-69.58%) exceeded that of the test product (CV=11.68-55.97%). Therefore, the D50 data for the 2.5 and 5 cm distances were analyzed by the population bioequivalence (PBE) approach outlined in the draft guidance. The statistical methodology based on that approach takes into consideration the relative variability of the test and reference products in determining bioequivalence.

   The PBE analyses were performed by ——————— at the ——————— . Because values of two parameters (i.e., $sigma_{T0}$ - the variance terms offset, and epsilon – the scaling variance) to be used for the methodology outlined in the draft guidance are still under consideration, ——————'s analysis of D50 data utilized all possible combinations (i.e., $sigma_{T0}$ values of 0.1 and 0.2, and epsilon values of 0.0, 0.01, 0.03, and 0.05, where 0.0 represents the most stringent criterion). In addition the average bioequivalence (ABE) limits of 1.11 and 1.25 were used. The test product meets equivalence criterion based on all combinations of ABE, $sigma_{T0}$ and epsilon (see the attached sheet). Therefore the D50 data are acceptable.

3. The SPAN data were also analyzed in the manner described for the D50 data.

   When the 2.5 cm and 5 cm SPAN data were analyzed by the methodology outlined in the guidance. The analyses revealed the following five outlier values:

Distance	Product	Sector	Lot	Bottle	SPAN
2.5 cm	REF	Beg	R1	7	7.60
2.5 cm	REF	Beg	R1	1	5.72
5.0 cm	TEST	Beg	T1	1	0.10
5.0 cm	REF	Mid	R3	5	0.20
5.0 cm	TEST	Mid	T3	2	0.10

   The Division of Bioequivalence (DBE) recalculated the above SPAN values using the relevant D10, D50 and D90 values submitted by the firm. Based on the DBE analysis, the first two values were found to be correct. However, the latter three values were found to be incorrect, the correct values are:

Distance	Product	Sector	Lot	Bottle	SPAN
5.0 cm	TEST	Beg	T1	1	1.62
5.0 cm	REF	Mid	R3	5	1.46
5.0 cm	TEST	Mid	T3	2	1.31

The correct SPAN values were substituted for the incorrect ones, the T/R ratio of geometric means of SPAN values at various distances were found to be in the range of 0.91-0.96. PBE analysis was also performed using the ABE, sigma T0 and epsilon combinations mentioned above. The test product meets equivalence criterion based on all combinations (see the attached sheet). Therefore the SPAN data are acceptable.

The droplet size distribution tested by Perrigo is acceptable.

FDA Comments on Cascade Impaction Procedures

Cascade impaction: The cascade impactor characterizes particles in a smaller size range than the expected range for aqueous nasal sprays. However, it is useful as to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor ——— data accounts for mass balance and is reported in the following groups:

Group-1: Pump, Nozzle, Nasal Chamber
Group-2: Plate 1
Group-3: Plate 2 to ▬ plus filter

The firm was asked to provide cascade impactor studies only at the beginning and end of canister through-life testing.

The firm submitted the following data:

The drug deposited on corresponding stages was determined separately by HPLC method. For the HPLC method, the LOQ was ——— ..

Ten units from each of the 3 unit lots of test and reference products were used to obtain cascade impaction data equipped with *USP throat*. Each unit was tested at the beginning and end of life.

The procedure for determination of particle size distribution using ———————— Cascade Impactor (using Automated Spray Pump Actuation Station ————————) and HPLC method for the assay of Cromolyn was validated for precisian, accuracy, specificity and linearity (Vol. 3.4, page 1410). A summary of cascade impaction data based on the reviewer calculation is presented in the Table 5:

Table 5

Material Recovered(%)

MATERIAL RECOVERED (%)-PUMP NOZZLE CHAMBER

PROD	SECTOR	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
			% CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
					%CV		%CV			VARIANCE
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	114.53	3.74	4.74	2.76	3.33	2.70	1.05	1.05	0.0006
	END	116.95	16.98	4.72	2.13	30.73	6.97	1.06	1.02	0.089
REF	BEG	108.85	6.73	4.69	5.13	8.87	1.42			
	END	110.25	6.09	4.70	5.10	7.18	2.46			

MATERIAL RECOVERED (%)-PLATE 1 >5.8um <9.0um

PROD	SECTOR	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
			% CV		LOT Range		LOT	ARITH	GEOM MEAN	UNEQUAL
					%CV		%CV			VARIANCE
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	0.28	41.23	-1.30	22.56	50.09	5.71	1.10	1.12	0.2965
	END	0.29	35.13	-1.32	30.17	40.08	6.84	1.02	1.00	0.7827

REF	BEG	0.25	29.83	-1.41	17.83	30.51	19.39			
	END	0.28	32.10	-1.31	19.91	41.68	12.00			

MATERIAL RECOVERED (%)-PLATE 2 TO ⌐ PLUS FILTER ≤ 5.8um

PROD	SECTOR	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
			% CV		LOT		LOT	ARITH	GEOM MEAN	UNEQUAL
					%CV		%CV			VARIANCE
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	0.01	33.48	-5.22	25.24	41.33	1.09	1.27	1.26	0.0099
	END	0.01	41.38	-4.81	36.02	47.86	3.27	1.17	1.14	0.1534
REF	BEG	0.00	35.96	-5.45	28.94	38.60	13.65			
	END	0.01	40.14	-4.94	25.73	48.76	21.5			

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FDA Comment on Cascade Impaction Data :

1. The Cascade Impacting results indicated that the amount of drug deposited in Group 1(Pump, Nozzle, Nasal Chamber) is similar between test and reference products. and there is not an excess mass of fines in the test product relative to the reference product. The T/R ratios were within the acceptable range of 90-110%. Based on mass balance data, >99% of drug deposition was within Group 1 for the test and reference products. Determination of equivalence of drug deposited in Groups 2 and 3 is not important since the total amount of drug is < 0.3%.

2. The firm's response to the comment is acceptable.

FDA COMMENT :

5. The Division of Bioequivalence realizes that the tests for droplet size distribution and cascade impaction generates numerous pages of data. The Division requests that all raw data should be submitted and a representative amount of supportive data such as computer sheets (20%) for the ————————system showing generated histograms should be included. The data should be presented in excel spreadsheets using the format presented in the appended Table 3 with data for D50 and span for the beginning, middle and end for 10 bottles at 3 distances. The format for cascade impaction data for the different stages for 3 lots of 10 bottles is presented in attached Table 4.

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, 20% of the computer sheets from the ————————System showing generated histograms are included with this amendment on page 739. The raw test data for the droplet size distribution (particle sizing by laser diffraction) testing is detailed in the data tables filed on page 701, with data for D50 and **SPAN** for the beginning, middle, and end for 10 bottles at 3 distances for the L. Perrigo drug product and the RLD product. The droplet size distribution (particle sizing by laser diffraction) testing data tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

The raw test data for the cascade impaction testing is presented in the data tables filed on page 397. The cascade impaction testing data tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment. Sample result printouts representing 20% of the data generated by ————————during the cascade impaction bioequivalence testing are filed on page 404.

FDA Reply:

The firm's reply is acceptable based upon the reviewer's analysis of the firm's data.

FDA COMMENT:

6. *Your data for plume geometry is incomplete. You should submit all raw data related to plume geometry as excel spreadsheets using the format in attached Table 7. The data should include plume width, plume length and plume angle for 10 cans for each of 3 lots of test and reference at three or more times after actuation. 20% of the plume sequence photographs as paper copies should also be submitted with markings used for quantitation.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, the raw data related to plume geometry angle and length and width testing is detailed in the data tables filed on page 1711 and page 1904. The Excel spreadsheets are formatted similarly to the tables supplied with the June 20, 2000, correspondence from FDA. The data includes plume width, plume length, and plume angle data for 10 bottles from each of 3 lots of the L. Perrigo product and the RLD product at three or more times after actuation. The ——— Bioequivalence Study Appendix 1 entitled, "Commentary on Plume Angle, Width, and Length Measurements" is filed on page 1714. This document provides justification for the test method utilized during the plume geometry bioequivalence testing conducted by ——— Additionally, 20% of the plume sequence photographs with the markings used for quantification are filed with this amendment on page 1723. Electronic Excel spreadsheets of data tables are located on the CD accompanying this amendment.

The following documentation is also filed with this amendment:

- **Addendum to ——— Protocol —02-0213E, Bioequivalence Study Protocol for Perrigo Company for Testing of 4% Cromolyn Sodium Nasal Spray, to add plume geometry length and width testing. (Page 1980)**

- **———: Test Method TM — 02-PGLW, Plume Geometry Length and Width Measurements for Cromolyn Sodium Nasal Spray. (Page 1987)**

——— Plume Geometry Length and Width Method Qualification For Cromolyn Sodium 4% Nasal Spray. (Page 1990)

——— Bioequivalence Study Appendix 1 entitled "Commentary on Plume Angle, Width and Length Measurements". This document provides justification for the test method utilized during the plume angle bioequivalence testing conducted by ——— (Page 1714)

FDA Comment on Plume Geometry Procedures:

Plume geometry describes two side views, at a 90^0 angle to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. The firm has provided plume geometry based on high speed photography. Plume geometry was performed only at beginning of use life. Plumes were characterized at three delay times after actuation. These times were chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at an intermediate time. Photographs of spray plumes were used to measure plume length, plume width, and plume (spray cone) angle. The firm provided 20% of all photographs and data characterizing plume dimensions including scaling information to indicate actual size.

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Table 8. Data for plume geometry

PROD	DELAY	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	TEST/REF	TEST/REF	P
	SEC		%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			0 DEGREE VIEW-PLUME WIDTH							
TEST	0.002	10.39	13.96	2.33	11.83	16.90	17.71	1.10	1.13	0.0826
	0.105	21.00	12.51	3.04	7.91	15.99	34.08	1.00	1.00	0.968
	0.208	21.98	14.14	3.08	10.62	15.38	18.30	0.98	0.98	0.5232
REF	0.002	9.44	27.24	2.21	11.60	15.26	14.27			
	0.105	21.03	14.79	3.04	9.55	17.95	31.19			
	0.208	22.53	15.92	3.10	12.74	16.81	13.74			

PROD	DELAY	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	TEST/REF	TEST/REF	P
	SEC		%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			90 DEGREE VIEW-PLUME WIDTH							
TEST	0.002	10.63	14.89	2.35	14.02	16.39	7.94	1.10	1.13	0.0794
	0.105	21.17	12.67	3.04	10.49	14.19	17.65	1.09	1.09	0.0199
	0.208	22.37	13.10	3.10	11.19	13.65	9.93	1.05	1.06	0.1341
REF	0.002	9.63	27.01	2.23	10.25	18.71	35.62			
	0.105	19.47	14.35	2.96	8.23	19.70	42.89			
	0.208	21.21	14.06	3.05	10.54	17.03	23.66			

PROD	DELAY	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	TEST/REF	TEST/REF	P
	SEC		%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			0 DEGREE VIEW-PLUME LENGTH							
TEST	0.002	14.97	14.25	2.70	9.91	15.96	23.95	1.16	1.17	0.003
	0.105	32.94	10.85	3.49	8.50	9.63	6.39	1.05	1.04	0.0805

	0.208	40.05	12.23	3.68	8.17	11.62	17.44	1.02	1.02	0.4685
REF	0.002	12.92	22.45	2.54	8.92	10.22	8.26			
	0.105	31.52	8.00	3.45	7.11	8.93	13.18			
	0.208	39.22	9.80	3.66	8.06	10.52	13.71			

PROD	DELAY	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	TEST/REF	TEST/REF	P
	SEC		%CV		LOT %CV Range		LOT	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			90 DEGREE VIEW-PLUME LENGTH							
TEST	0.002	15.00	15.89	2.70	10.60	20.66	32.62	1.08	1.10	0.1436
	0.105	32.69	9.60	3.48	4.31	9.16	35.78	1.03	1.03	0.1988
	0.208	39.78	11.35	3.68	8.71	11.85	15.30	1.02	1.02	0.3719
REF	0.002	13.88	24.43	2.60	8.45		21.45			
	0.105	31.73	8.03	3.45	7.58	7.76	1.30			
	0.208	38.83	9.21	3.66	8.16	10.34	11.81			

PROD	DELAY	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	TEST/REF	TEST/REF	P
	SEC		%CV		LOT %CV Range		LOT	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			0 DEGREE VIEW-PLUME ANGLE							
TEST	0.002	69.09	15.21	4.22	7.68	25.03	72.64	0.91	0.90	0.0053
REF	0.002	76.12	10.62	4.33	8.93	12.17	15.35			

PROD	DELAY	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	TEST/REF	TEST/REF	P
	SEC		%CV		LOT %CV Range		LOT	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			90 DEGREE VIEW-PLUME ANGLE							
TEST	0.002	69.11	16.39	4.22	6.97	25.89	66.00	0.89	0.88	0.0021
REF	0.002	77.24	10.11	4.34	9.34	11.02	8.21			

FDA Comments on Plume Geometry Data:

1. Plume width and plume length were measured at time delays of 2 , 105 and 208 msec. The 2 msec delay represents early plume formation whereas delay times of 105 and 208 msec represents the fully formed and dissipating plumes. The T/R ratios of geometric means for the fully formed plume were in the acceptable range of 0.9-1.1 as defined in the nasal draft guidance. There was comparable variability, %CV, for the test and reference products.

2. The firm provided plume angle data for only the 2msec distance, which represents the very early stage of plume formation.

3. The plume geometry data is incomplete.

Spray Pattern

The November 30, 2000 amendment also contained information on spray pattern although it was not specifically requested in the deficiency letter of March 31, 2000.

FDA Comments on Spray Pattern Procedures:

The data for Spray pattern was determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products.

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A summary of the spray pattern data based on the reviewer's calculations is presented in Table 8.

Table 8. Data for spray pattern (Dmax , Dmin and Ovality at the 3 distances(3cm, 4cm and 5 cm)for the 13 mL and 26 mL bottles of Cromolyn.

PRODUCT	SECTOR	PARAMETER	DIST	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST	BEG	DMAX13	3CM	6.41	7.30	1.85	4.14	9.51	1.86	0.95	0.96	0.2075
	END	DMAX13	3CM	6.57	9.07	1.88	6.66	12.05	2.98	0.97	0.98	0.4597
REF	BEG	DMAX13	3CM	6.71	22.06	1.89	4.48	25.67	8.72			
	END	DMAX13	3CM	6.79	22.06	1.90	7.60	32.83	8.12			
PROD	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST	BEG	DMAX13	4CM	7.99	7.32	2.08	4.85	7.66	4.30	0.99	1.00	0.7686
	END	DMAX13	4CM	8.05	8.73	2.08	5.74	11.85	2.77	0.99	0.99	0.7298
REF	BEG	DMAX13	4CM	8.04	10.49	2.08	6.50	9.49	4.28			
	END	DMAX13	4CM	8.12	10.49	2.09	6.78	13.11	5.00			
PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST	BEG	DMAX13	5CM	9.64	8.16	2.26	6.81	8.51	3.79	1.00	1.01	0.8432
	END	DMAX13	5CM	9.44	8.00	2.24	5.32	11.17	1.68	0.99	0.99	0.707
REF	BEG	DMAX13	5CM	9.60	9.36	2.26	7.05	9.83	5.19			
	END	DMAX13	5CM	9.52	9.24	2.25	6.40	9.87	5.14			
PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN		BETWEEN	T/R	T/R	P

						OF LOG						
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST	BEG	DMAX26	3CM	6.42	10.18	1.86	6.41	12.79	4.69	1.00	1.00	0.9694
	END	DMAX26	3CM	6.72	24.77	1.89	7.26	34.70	12.38	1.07	1.06	0.1846
REF	BEG	DMAX26	3CM	6.43	10.64	1.86	5.93	11.61	6.98			
	END	DMAX26	3CM	6.28	10.81	1.83	8.98	11.09	5.66			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST	BEG	DMAX26	4CM	7.99	6.93	2.08	5.68	6.64	4.40	1.00	1.00	1
	END	DMAX26	4CM	8.10	17.73	2.08	6.88	23.24	10.55	1.03	1.02	0.4266
REF	BEG	DMAX26	4CM	7.99	10.15	2.07	7.07	9.55	7.15			
	END	DMAX26	4CM	7.86	10.02	2.06	5.08	10.82	5.63			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	DMAX26	5CM	9.63	8.41	2.26	6.21	11.29	2.78	1.00	1.00	0.9198
	END	DMAX26	5CM	9.48	14.53	2.24	8.41	19.97	5.79	1.00	1.00	0.9449
REF	BEG	DMAX26	5CM	9.60	10.10	2.26	5.25	10.45	8.03			
	END	DMAX26	5CM	9.46	8.09	2.24	3.60	3.60	5.16			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL

												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	DMIN26	3CM	5.85	9.32	1.76	5.08	11.34	2.67	0.98	0.98	0.4222
	END	DMIN26	3CM	6.07	22.27	1.79	8.09	28.57	13.77	1.04	1.03	0.3621
REF	BEG	DMIN26	3CM	5.98	11.57	1.78	8.98	12.40	6.95			
	END	DMIN26	3CM	5.81	11.43	1.75	9.99	12.39	4.74			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	DMIN26	4CM	5.85	9.32	1.76	5.08	11.34	2.67	0.98	0.98	0.4222
	END	DMIN26	4CM	6.07	22.27	1.79	8.09	28.57	13.77	1.04	1.03	0.3621
REF	BEG	DMIN26	4CM	5.98	11.57	1.78	8.98	12.40	6.95			
	END	DMIN26	4CM	5.81	11.43	1.75	9.99	12.39	4.74			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	DMIN26	5CM	8.78	11.19	2.17	7.32	15.78	3.73	0.99	0.99	0.6789
	END	DMIN26	5CM	8.71	16.49	2.15	8.29	22.37	8.06	1.00	0.99	1
REF	BEG	DMIN26	5CM	8.89	12.63	2.18	9.77	13.06	8.53			
	END	DMIN26	5CM	8.71	8.13	2.16	7.29	9.22	2.50			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	DMIN13	3CM	6.01	6.36	1.79	4.50	7.24	3.42	1.01	1.02	0.5995
	END	DMIN13	3CM	6.11	9.73	1.80	3.50	12.00	6.16	1.00	1.01	0.9265

REF	BEG	DMIN13	3CM	5.93	11.73	1.77	7.81	15.78	5.15			
	END	DMIN13	3CM	6.08	20.42	1.79	4.40	31.53	7.24			
PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	DMIN13	4CM	7.45	9.46	2.00	5.25	9.82	7.63	1.02	1.02	0.3768
	END	DMIN13	4CM	7.54	9.83	2.02	5.81	11.44	6.52	1.03	1.03	0.2342
REF	BEG	DMIN13	4CM	7.29	9.41	1.98	4.43	12.94	4.61			
	END	DMIN13	4CM	7.32	9.22	1.99	5.22	12.94	3.54			
PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	DMIN13	5CM	8.97	9.19	2.19	6.35	8.68	7.11	1.03	1.03	0.1909
	END	DMIN13	5CM	8.85	7.94	2.18	3.75	11.54	3.95	1.02	1.02	0.4626
REF	BEG	DMIN13	5CM	8.69	9.14	2.16	6.13	11.84	4.43			
	END	DMIN13	5CM	8.71	8.37	2.16	5.75	9.57	5.07			
PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	OVAL13	3CM	1.07	4.77	0.06	3.92	5.96	1.56	0.94	0.95	0.0101
	END	OVAL13	3CM	1.08	4.87	0.07	3.16	4.45	3.95	0.97	0.97	0.0172
REF	BEG	OVAL13	3CM	1.13	10.42	0.12	5.25	14.77	4.24			
	END	OVAL13	3CM	1.12	5.79	0.11	4.59	6.90	0.96			
PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN		BETWEEN	T/R	T/R	P

						OF LOG						
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	OVAL13	4CM	1.08	5.06	0.07	2.23	4.62	4.39	0.97	0.97	0.035
	END	OVAL13	4CM	1.07	4.84	0.07	2.63	4.00	4.28	0.96	0.96	0.0239
REF	BEG	OVAL13	4CM	1.11	6.40	0.10	4.61	9.03	0.81			
	END	OVAL13	4CM	1.11	7.22	0.10	4.72	8.78	1.6			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	OVAL13	5CM	1.08	5.79	0.07	4.76	5.95	3.48	0.97	0.98	0.1299
	END	OVAL13	5CM	1.07	5.57	0.06	2.35	6.07	4.21	0.98	0.98	0.1226
REF	BEG	OVAL13	5CM	1.11	7.04	0.10	5.38	9.33	1.13			
	END	OVAL13	5CM	1.09	6.41	0.09	4.58	8.40	0.37			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	OVAL26	3CM	1.10	9.55	0.09	4.87		2.41	1.02	1.02	0.2753
	END	OVAL26	3CM	1.11	7.27	0.10	5.69	8.44	2.12	1.02	1.02	0.1716
REF	BEG	OVAL26	3CM	1.08	5.78	0.07	4.36	7.45	1.34			
	END	OVAL26	3CM	1.08	5.70	0.08	5.09	6.59	1.30			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL

												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	OVAL26	4CM	1.09	8.24	0.09	6.74	10.36	0.88	1.01	1.01	0.4722
	END	OVAL26	4CM	1.09	7.01	0.08	5.20	9.97	0.46	1.00	1.00	0.8502
REF	BEG	OVAL26	4CM	1.08	5.98	0.07	3.98	6.80	2.22			
	END	OVAL26	4CM	1.08	5.43	0.08	4.72	5.86	2.56			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN OF LOG	WITHIN		BETWEEN	T/R	T/R	P
					%CV		LOT %CV Range		LOT %CV	ARITH	GEOM MEAN	UNEQUAL
												VARIANCE
				N=30	N=30	N=30	N=10		N=3	N=1	N=1	
TEST	BEG	OVAL26	5CM	1.10	9.17	0.09	7.41	10.57	1.00	1.02	1.02	0.3839
	END	OVAL26	5CM	1.09	8.59	0.09	5.63	10.77	2.25	1.01	1.00	0.7355
REF	BEG	OVAL26	5CM	1.08	6.05	0.08	4.89	6.83	0.94			
	END	OVAL26	5CM	1.09	5.75	0.08	3.90	7.31	2.73			

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FDA Comments on Spray Pattern Data Analysis:

The spray pattern data submitted by the firm are unacceptable, due to failure to characterize and quantitate the size or shape of spray patterns. It is not clear if the sponsor used a drug specific reagent to visualize the spray patterns. The representative photocopies submitted by the firm show rectangles drawn around the spray patterns to determine Dmax and Dmin. However, these rectangles fail to reflect the size and shape of spray patterns.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (Dmax and Dmin) by definition should intersect the center of the spray pattern.

The firm should submit revised spray pattern data after proper quantitation.. The sponsor may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, Dmax and Dmin) along with identity of distance, product, and lot number.

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Review of January 26, 2001 Amendment

FDA Question 1.

What were the three, time delays-at formation, fully developed and dissipation or the sprays?

Firm's Reply:

For these droplet size measurement studies, ——— employed a ——————— instrument with ——— software. Nasal sprays were automatically generated using an ——————— ——actuation station.

This overall approach was taken to select these aerosol spray events for TM —02-MA.

FDA Comment:

The firm's reply is acceptable.

FDA Question 2.

How were the times selected?

Firm's Reply:

See discussion in question 1 above.

FDA Comment:

The firm's reply is acceptable.

FDA Question 3:

What was the duration of sampling time at each of the three phases of plume life?

Firm's Reply:

The data acquisition rate for the method is 50OHz. This indicates the number of data points acquired per second (i.e. one signal every 2ms, or 500 per second). In addition. the Acquisition Duty Cycle of the method is set at ——. This indicates the percentage of data that immediately precedes the actual data time point selected and measured and is used to average and smooth the data point.

FDA Comment:

The firm's reply is acceptable.

FDA Question 4.

Provide representative plots of percent transmission vs. time. (D5O,D90, and D10 vs. time on the same plot.

Firm's Reply:

Figures 1, 2 and 3 show representative plots of transmission vs. time as well as the D50, D90, and D10 droplet size distribution data for a single spray collected I cm from the laser beam (Figure 1), 2.5 Cm from the laser beam (Figure 2) and 5 cm from the laser beam (Figure 3). The spray duration can be determined from the time scale at the bottom of each graph. % Transmission data is represented by the top line data plot **and is related to the scale at the left** of the chart. D10, D50, and D90 data is shown as the lower three line **plots and is related to the** scale at the right of the chart. A summary of the results is given in the lower table key on the figures.

FDA Comment:

The firm's reply is acceptable.

Overall Comments:

1. The composition of the test product is qualitatively and quantitatively the same as the reference product.

2. Based on the test/reference ratios the unit dose data indicate that the test and reference products are similar at the beginning and end of unit life.

3. The tail-off characteristics of the test product are similar to those of the reference product.

4. The ——— laser diffraction data demonstrate that the distribution of droplet size in the test product spray is similar to that of the reference product spray. The Cascade Impaction data was similar for the test and reference products.

Deficiencies:

1.The firm should explain the relationship between the NasalCrom lots # 's 52DCB and 32DKA listed in vol. 3.1 pages 6-8 to the lot numbers listed in the studies which were

13mL	26mL
86DUY	13DSP
47DYC	44DHC
46DYC	49DYC

2.The firm should supply repriming data consistent with use instructions in the package insert. The bottles should be primed, wasting 5 sprays, with the 6th spray assayed(i.e. prime attained). Bottles should then be set aside for 14 days. After 14 days the bottles should be reprimed by wasting 2 sprays with the 3rd spray assayed (i.e., prime attained). This should be done using 3 lots of test and reference products.

3.The firm's plume geometry data are incomplete. The firm should provide plume angle data for the delay times greater than 2 msec (e.g., 20 and 50 msec).

4.The spray pattern data submitted by the firm are unacceptable, due to failure to characterize and quantitate the size or shape of spray patterns. It is not clear if the sponsor used a drug specific reagent to visualize the spray patterns. The representative photocopies submitted by the firm show rectangles drawn around the spray patterns to determine Dmax and Dmin. However, these rectangles fail to reflect the size and shape of spray patterns.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (Dmax and Dmin) by definition should intersect the center of the spray pattern.

The firm should submit revised spray pattern data after proper quantitation. The sponsor may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, Dmax and Dmin) along with identity of distance, product, and lot number.

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Recommendation:

The *in vitro* performance testing conducted by L. Perrigo on its Cromolyn Nasal Spray, 40 mg/mL comparing it with the reference product, Nasalcrom®, nasal solution (Pharmacia and Upjohn) has been found to be incomplete by the Division of Bioequivalence due to deficiencies 1-5.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 3/12/2001

Concur: Date: 4/19/2001
for Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

cc: ANDA 75-427 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

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BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-427 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray

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

Deficiencies:

1.You should explain the relationship between the NasalCrom lots # 's 52DCB and 32DKA listed in vol. 3.1 pages 6-8 to the lot numbers listed in the studies which were :

13mL	26mL
86DUY	13DSP
47DYC	44DHC
46DYC	49DYC

2. You should supply repriming data consistent with use instructions in the package insert. The bottles should be primed, wasting 5 sprays, with the 6th spray assayed (i.e., prime attained). Bottles should then be set aside for 14 days after which the bottles should be reprimed by wasting 2 sprays with the 3rd spray assayed (i.e., prime attained). This should be done using 3 different lots of test and reference.

3.Your plume geometry data are incomplete. You should provide plume angle data for the delay times greater than 2 msec (e.g., 20 and 50 msec).

4. Your spray pattern data are unacceptable, due to failure to characterize and quantitate the size or shape of spray patterns. It is not clear if you used a drug specific reagent to visualize the spray patterns. The representative photocopies submitted show rectangles drawn around the spray patterns to determine Dmax and Dmin. However, these rectangles fail to reflect the size and shape of spray patterns.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (Dmax and Dmin) by definition should intersect the center of the spray pattern.

You should submit revised spray pattern data after proper quantitation. You may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, Dmax and Dmin) along with identity of distance, product, and lot number.

Sincerely yours,

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

CC: ANDA 75-427
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD- 652 /Reviewer
HFD-652 /Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner
HFD-655/G.Singh COPS 3/30/01
Insert Path and File Name Here (V:\Firmsnz\Perrigo\Ltr&Rev\75427A.N00)
BIOEQUIVALENCY - DEFICIENCIES Submission Date: November 30, 2000

1. **STUDY AMENDMENT** (STA) (November 30, 2000) Strengths: 5.2 mg/spray **Outcome: IC**

2. **STUDY AMENDMENT** (STA) (January 26, 2001) Strengths: 5.2 mg/spray **Outcome: IC**

Outcome Decisions:
IC - Incomplete

WinBio Comments

Redacted 26 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW OF 11/30/2000 and 1/26/2001 SUBMISSIONS
(ATTACHMENTS)

Cromolyn Sodium Nasal Solution USP,
5.2 mg/spray (40 mg/mL)
ANDA # 75-427
Reviewer: Andre J. Jackson
V:\Firmsnz\Perrigo\Ltr&Rev\75427A.601

L. Perrigo Company
Allegan, Michigan
Submission Date:
June 29, 2001

Review of an Amendment

History:

Date: July 31, 1998 The firm submitted a waiver request for their product based upon the test product being quantitatively and qualitatively the same as the reference listed drug. The waiver was denied and the firm was informed that because there were a number of unresolved issues regarding the testing of manual metered dose pumps for the documentation of in vitro bioequivalence, they were advised to submit a protocol outlining its planned studies. This protocol was based in part on the considerations related to the metering performance and uniformity of unit spray content sections of Chapters 601 and 905 of the U.S. Pharmacopeia, and to the Division of Bioequivalence June 27, 1989 Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers).

Date : November 20, 1998- The firm responded to the deficiency from the July 31, 1998 submission. The Division of Bioequivalence provided the firm more specifics related to the required in vitro testing requirements.

Date : March 31, 2000-The firm responded to the deficiencies from the November 20, 1998 submission. However, the submitted data was incomplete. Raw data was not submitted for all the tests. Appended to the deficiency letter to the firm, the FDA provided a format to use for raw data presentation as an Excel spreadsheet.

Date : November 30, 2000- The firm submitted an amendment to address the deficiencies from the March 31 submission.

Date : January 17, 2001 -The firm was contacted by phone and requested to supply information regarding droplet size determination with the laser beam. The firm was issued a deficiency letter based upon their November submission.

Date : June 29, 2001- The firm submitted an amendment to address the deficiencies in the November 30, 2000 submission.

Deficiencies:

Deficiency 1.

1.The firm should explain the relationship between the NasalCrom lots # 's 52DCB and 32DKA listed in vol. 3.1 pages 6-8 to the lot numbers listed in the studies which were

13mL	26mL
86DUY	13DSP
47DYC	44DHC

46DYC 49DYC

L. PERRIGO COMPANY RESPONSE:

In light of the above comment, a review was conducted of the documentation submitted thus far to the FDA regarding this drug product. We believe the above comment is referencing Section 4 of the Major Amendment submitted on March 31, 2000.

Section 4 of the March 31, 2000, Major Amendment provided a comparison between the Perrigo drug product and the Reference Listed Drug. Comparative analysis reports for the exhibit batch and the Reference Listed drug were submitted in Special Assay Report Nos. 14900, 14901, and 14913.

The comparative analysis reports contained data from testing conducted on two randomly selected lots of the Reference Drug available in the retail market, 52DCB (13 mL) and 32DKA (26 ml).

As noted in the above FDA comment, several additional lots of the Reference Listed Drug were used to facilitate the bioequivalence studies submitted in Perrigo's November 30, 2000, Bioequivalence Amendment. Perrigo was unable secure a sufficient number of 52DCB and 32DKA lot number samples to facilitate the additional testing required to support the amendment. Therefore, additional lots with sufficient sample quantities to support the testing were randomly selected from those lots of the Reference Listed Drug available for purchase in the retail market.

FDA Comments:

The firm's reply is acceptable to the Division of Bioequivalence.

Deficiency 2.

2.The firm should supply re-priming data consistent with use instructions in the package insert. The bottles should be primed, wasting 5 sprays, with the 6th spray assayed(i.e. prime attained). Bottles should then be set aside for 14 days. After 14 days the bottles should be re-primed by wasting 2 sprays with the 3rd spray assayed (i.e., prime attained). This should be done using 3 lots of test and reference products.

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, repriming data consistent with the use instructions in the package insert is filed in Section 3 of this amendment. The bottles were primed, wasting 5 sprays, with the 6th spray assayed (i.e., prime attained). Bottles were then set aside for at least 14 days after which the bottles were reprimed by wasting 2 sprays with the 3rd spray assayed (i.e., prime attained). This testing was done using 10 bottles of 3 different lots of 13 mL and 26 mL samples of test and reference listed drug product. The data indicates that the prime retention characteristics of the Perrigo drug product compares favorably to the reference listed drug product.

The L. Perrigo Company protocol entitled, "Protocol for Priming, Reprime, Through Life, and Tail-Off for Cromolyn Sodium Nasal Solution" has been revised to include sample preparation instructions for the prime and repriming testing and is filed in Section 3 of this amendment. Also filed in Section 3 of this amendment is a revised method validation report with regard to method 1735, as well as the sample result printouts for the data generated during the repriming testing.

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Prime and Re-Prime data submitted by the firm and re-analyzed by the reviewer.

PROD	SECTOR	MEAN	TOTAL	MEAN	WITHIN	LOTS	BETWEEN	TEST/ REF	TEST /REF	P
			%CV	OF LOG	%CV	RANGE	LOT %CV	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST 13ML	PRIME	106.43	6.32	4.67	5.69	7.26	106.43	1.00	1.00	0.93
	REPRIME	114.43	4.57	4.74	1.49	7.44	114.43	1.08	1.08	0.56
REF 13ML	PRIME	106.27	7.49	4.66	4.37	10.00	106.26			
	REPRIME	106.27	7.49	4.66	1.21	4.92	113.67			

PROD	SECTOR	MEAN	TOTAL	MEAN	WITHIN	LOTS	BETWEEN	TEST/ REF	TEST /REF	P
			%CV	OF LOG	%CV	RANGE	LOT %CV	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
TEST 26ML	PRIME	106.07	6.30	4.66	3.24	7.52	106.07	1.02	1.03	0.23
	REPRIME	112.40	3.64	4.72	1.34	3.69	112.40	1.02	1.02	0.14
REF 26ML	PRIME	103.77	7.62	4.64	6.84	8.26	103.77			
	REPRIME	110.73	4.02	4.71	2.58	4.10	110.73			

FDA Comments on the Priming and Repriming Data Submitted

1. The mean values for test and reference on priming and re-priming were comparable . Reference values following priming were slightly higher for the 13 mL size and smaller on average for the 26 mL size. On re-priming the mean values for the 26 mL size were larger than the 13 mL size. Per cent CV values were comparable. None of the p values were significant for the 13 mL and 26 mL bottle sizes. Test/Ref ratios were within the limits of 90-111% as employed by the Division of Bioequivalence for acceptance of solution nasal spray products.

   Based upon the bottles that were set aside after priming for at least 14 days after which the bottles were re-primed by wasting 2 sprays with the 3rd spray assayed (i.e., prime attained). The labeled dose is delivered by the 6th actuation for the test and reference products. This is consistent with the innovator patient package insert. Based on the foregoing, the firm's response to the DBE comment on priming and re-priming is acceptable

Deficiency 3.

3.The firm's plume geometry data are incomplete. The firm should provide plume angle data for the delay times greater than 2 msec (e.g., 20 and 50 msec).

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, plume angle testing for the delay times greater than 2 msec (e.g., 20 and 50 msec) was conducted by ———— ———— and the data is filed in Section 4 of this amendment. The data indicates that the Perrigo drug product compares favorably to the reference listed drug product.

———————— report entitled "Video Plume Geometry Method Qualification for Cromolyn Sodium Nasal Spray" is also filed in Section 4. The plume geomtery angle photographs generated by———————— during the plume geometry angle testing are also filed in Section 4.

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Plume Angle data submitted by the firm and re-analyzed by the reviewer.

PROD	DELAY	MEAN	TOTAL	MEAN OF LOG	WITHIN	LOTS	BETWEEN	TEST/ REF	TEST /REF	P
	MSEC		%CV		%CV	RANGE	LOT %CV	ARITH	GEOM	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			0 DEGREE VIEW-PLUME ANGLE							
TEST	20	41.08	23.1	3.71	9.6	28.8	10.6	1.15	1.15	0.018
REF	20	35.7	19.4	3.57	10.9	20.95	9.6			

PROD	DELAY	MEAN	TOTAL	MEAN OF LOG	WITHIN	LOTS	BETWEEN	TEST/ REF	TEST /REF	P
	MSEC		%CV		%CV	RANGE	LOT %CV	ARITH	GEOM	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			0 DEGREE VIEW-PLUME ANGLE							
TEST	50	47.13	23.4	3.85	18.4	28.4	9.5	1.02	1.03	0.6109
REF	50	45.78	20.1	3.82	16	26.2	14.8			

PROD	DELAY	MEAN	TOTAL	MEAN	WITHIN	LOTS	BETWEEN	TEST/ REF	TEST/ REF	P
	MSEC		%CV	OF LOG	%CV	RANGE	LOT %CV	ARITH	GEOM MEAN	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	N=1	N=1	VARIANCE
			90 DEGREE VIEW-PLUME ANGLE							

TEST	20	42.72	26.00	3.75	19.05	33.69	25.18	1.05	1.04	0.46
REF	20	40.72	22.80	3.71	14.32	26.90	21.11			

PROD	DELAY	MEAN	TOTAL	MEAN	WITHIN	LOT	BETWEEN	TEST/ REF	TEST/ REF	P
	MSEC		%CV	OF LOG	%CV	RANGE	LOT %CV	ARITH	GEOM	UNEQUAL
		N=30	N=30	N=30	N=10		N=3	MEAN	MEAN	VARIANCE
			90 DEGREE VIEW PLUME ANGLE							
TEST	50	47.52	23.07	3.86	16.4	29.59	22.11	0.95	0.96	0.38
REF	50	49.72	15.53	3.9	11.3	18.17	14.04			

FDA Comments on the Plume Geometry Data Submitted

The test/reference ratio for the plume angle data for the geometric means was within the acceptable range of 0.9-1.11, with the exception of the 20 msec 0^0 angle view data. Perusal of the data indicated a shift in the mean for the reference product to 35 from 45 at 20 msec compared to 50 msec.

Based upon the ongoing discussions in the CDER OINDP, many nasal spray products do not have predefined 0^0 and 90^0 Views. Therefore the units are placed at random. Consequently, the 0^0 and 90^0 views may not be absolute. Therefore the 0^0 and 90^0 view data may be combined. On the basis of the combined data, the test/reference ratios were within the acceptable range of 0.9-1.11 for both the 20 msec and 50 msec observations.

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Deficiency 4.

4.The spray pattern data submitted by the firm are unacceptable, due to failure to characterize and quantitate the size or shape of spray patterns. It is not clear if the sponsor used a drug specific reagent to visualize the spray patterns. The representative photocopies submitted by the firm show rectangles drawn around the spray patterns to determine Dmax and Dmin. However, these rectangles fail to reflect the size and shape of spray patterns.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (Dmax and Dmin) by definition should intersect the center of the spray pattern.

The firm should submit revised spray pattern data after proper quantitation. The sponsor may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, Dmax and Dmin) along with identity of distance, product, and lot number.

L. PERRIGO COMPANY RESPONSE:

In light of the above FDA comment, Perrigo contracted with ——————— to generate spray pattern quantification data from the spray patterns generated during the previous testing using an automated image analysis technique to reflect the true shape and size of the spray patterns and to reduce subjectivity and improve accuracy and precision. The data generated using the automated image analysis technique is filed in Section 5 of this amendment. The data indicates that the Perrigo drug product compares favorably to the reference listed drug product.
The spray pattern representations generated using ——————— automated image analysis technique include perimeter markings, Dmax and Dmin measurements, distance, product, and lot number. The automated image analysis system used by ——————— did not mark the intersection location of Dmax and Dmin on the image. The location is calculated automatically by the program and the Dmax and Dmin calculations are noted in the measurement data area of the print out. Please note that the spray pattern measurements and calculations generated during the spray pattern testing previously conducted by Perrigo appear on the spray pattern representations generated by ———————. The Perrigo-generated measurements and calculations were disregarded during the second analysis conducted by ——————— . The spray patterns captured on TLC plates were not generated using a drug specific reagent. A drug specific reagent was deemed unnecessary because the cromolyn sodium nasal spray solution is a solution, not a suspension. As noted in L. Perrigo Company's bioequivalence protocol for spray pattern testing, ——————— dye is added to the bottles of solution so that the spray pattern is visible when sprayed onto the TLC plate (See Section 26, page 2190, of L. Perrigo Company's 11/30/00 Bioequivalence Amendment). Therefore, because this product involves an API, cromolyn sodium, that is in a solution, not a suspended state, we believe there would be no significant change in the data submitted if a drug specific reagent were used to facilitate the testing.

FDA Comments on the Spray Pattern Data

The Division of Bioequivalence has reviewed the spray pattern data and found it to be unacceptable since the firm has tampered with the reference product by adding ~ mg of ——— dye in order to visualize the spray pattern. Tampering with either product is not permitted in Bioequivalence testing.

The spray pattern testing should be repeated without manipulation of either the test or reference products.The visualization agent/dye should be used post-actuation. The visualization agent should preferably be drug or formulation specific.. The firm should supply to the Division of Bioequivalence **the actual computer pictures** used to measure the Dmax and Dmin distances along with the computer printout of the values. The pictures should exhibit Dmax and Dmin lines.

Deficiency:

1. The spray pattern testing should be repeated without manipulation of either the test or reference products.The visualization agent/dye should be used post-actuation. The visualization agent should preferably be drug or formulation specific.. The firm should supply to the Division of Bioequivalence **the actual computer pictures** used to measure the Dmax and Dmin distances along with the computer printout of the values. The pictures should exhibit Dmax and Dmin lines.

Recommendation:

The *in vitro* performance testing conducted by L. Perrigo on its Cromolyn Nasal Spray, 40 mg/mL comparing it with the reference product, Nasalcrom®, nasal solution (Pharmacia and Upjohn) has been found to be incomplete by the Division of Bioequivalence due to deficiency 1.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 8/23/2001

Concur: Date: 8/29/01
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

cc: ANDA 75-427 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

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BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-427 APPLICANT: L.Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray (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. You should repeat the spray pattern testing without manipulation of either the test or reference products.The visualization agent/dye should be used post-actuation. The visualization agent should preferably be drug or formulation specific. You should supply to the Division of Bioequivalence **the actual computer pictures** used to measure the Dmax and Dmin distances along with the computer printout of the values. The pictures should exhibit Dmax and Dmin lines.

Sincerely yours,

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

CC: ANDA 75 427
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD- 652 /Reviewer
HFD- 652 /Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner 8/29/01
HFD-655 /GJP Singh
Insert Path and File Name Here (V:\Firmsnz\Perrigo\Ltr&Rev\75427A.601)

BIOEQUIVALENCY - DEFICIENCIES Submission Date: June 29, 2001

1. **STUDY AMENDMENT** (STA) IC

Strengths: 5.2 mg/spray _____
Outcome: IC

Outcome Decisions:

IC - Incomplete

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

Cromolyn Sodium Nasal Solution USP,
5.2 mg/spray (40 mg/mL)
ANDA # 75-427
Reviewer: Andre J. Jackson
V:\Firmsnz\Perrigo\Ltr&Rev\75427AO01

L. Perrigo Company
Allegan, Michigan
Submission Date:
October 17, 2001

Review of an Amendment

History:

Date: July 31, 1998 The firm submitted a waiver request for their product based upon the test product being quantitatively and qualitatively the same as the reference listed drug. The waiver was denied and the firm was informed that because there were a number of unresolved issues regarding the testing of manual metered dose pumps for the documentation of in vitro bioequivalence, they were advised to submit a protocol outlining its planned studies. This protocol was based in part on the considerations related to the metering performance and uniformity of unit spray content sections of Chapters 601 and 905 of the U.S. Pharmacopeia, and to the Division of Bioequivalence June 27, 1989 Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers).

Date : November 20, 1998- The firm responded to the deficiency from the July 31, 1998 submission. The Division of Bioequivalence provided the firm more specifics related to the required in vitro testing requirements.

Date : March 31, 2000-The firm responded to the deficiencies from the November 20, 1998 submission. However, the submitted data was incomplete. Raw data was not submitted for all the tests. Appended to the deficiency letter to the firm, the FDA provided a format to use for raw data presentation as an Excel spreadsheet.

Date : November 30, 2000- The firm submitted an amendment to address the deficiencies from the March 31 submission.

Date : January 17, 2001 -The firm was contacted by phone and requested to supply information regarding droplet size determination with the laser beam. The firm was issued a deficiency letter based upon their November submission.

Date : June 29, 2001- The firm submitted an amendment to address the deficiencies in the November 30, 2000 submission. The firm was issued a deficiency letter requesting that they should repeat the spray pattern testing without manipulation of either the test or reference products.

Date : October 17, 2001- The firm submitted an amendment to address the deficiencies in the June 29, 2001 submission.

Deficiency:

1. The spray pattern testing should be repeated without manipulation of either the test or reference products. The visualization agent/dye should be used post-actuation. The visualization agent should preferably be drug or formulation specific. The firm should supply to

the Division of Bioequivalence **the actual computer pictures** used to measure the Dmax and Dmin distances along with the computer printout of the values. The pictures should exhibit Dmax and Dmin lines.

L. PERRIGO COMPANY RESPONSE:

In accordance with the above comment, L. Perrigo Company contracted with ———————. (now known as ——————————) to conduct the repeat spray pattern bioequivalence testing. ———— is an outside laboratory that conducted previously-submitted bioequivalence testing to support this application. As requested by FDA, the test and reference products were tested without manipulation and the visualization agent/dye was used post-actuation.

Prior to initiating the retesting. L. Perrigo Company sought clarification from FDA regarding several issues. During a conference call on September 25, 2001, with Krista Scardina and Dr. Singh, FDA Division of Bioequivalence staff members, the following clarification information was provided to L. Perrigo Company:

When asked if using ———————— to facilitate visualization of the spray patterns would be acceptable, Dr. Singh indicated that a visualization process involving ———————— would probably be acceptable.

When asked what distances would be acceptable to facilitate the repeat spray pattern testing, Dr. Singh recommended distances of 2, 4, and 6 cm.

Dr. Singh Indicated that the repeat spray pattern testing should evaluate only the 26 mL test and reference product samples, if the 26 mL and 13 mL products have identical metering devices.

With regard to the Dmin/Dmax-lines being represented on the spray pattern printouts, Dr. Singh indicated that 20% of all the spray pattern printouts generated should be submitted to FDA for review and that half of the submitted spray patter printouts should have Dmin/Dmax lines drawn manually on the printouts.

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Actual size color printouts of 20% of the spray patterns generated during the spray pattern testing are filed in Section 15 of this amendment and reflect automated Dmin/Dmax calculations. Half of the 20% of the spray patterns submitted were also evaluated without the aid of an automated calculation system and those color printouts reflect manually calculated Dmin/Dmax lines and are filed in Section 14 of this amendment.

The printing system used by ————to generate the color printed spray patterns filed in Sections 14 and 15 portray the spray patterns In a reduced size format. ————, determined that the actual size on-screen spray patterns were reduced during the printing process by a factor of 1.82 by comparing the reduced size spray pattern printouts with the on-screen actual size spray patterns. The manual Dmin/Dmax measurements were generated using the reduced size spray pattern printouts and these measurements are recorded on the reduced size color printouts in Section 14 and in the Data Summary Table filed in Section12. The manual measurements from the Data Summary Table were transferred to the Result Table filed in Section 10 after applying the factor of 1.82. Although the color printed spray patterns in Section 15 portray reduced size images, the Measurement Data Box reflects automated measurements generated from the actual size on-screen images without applying the conversion factor. The first measurement reflected in the Measurement Data Boxes correlates with the upper most spray pattern image. The measurements reflected in the Measurement Data Boxes are noted in the Data Summary Table filed in Section 11 and the Result Table filed in Section 9.

The Test Result Tables and Summary Data Tables are formatted as Excel spreadsheets and are filed in Sections 10 through 13 of this amendment. Electronic versions of the files are supplied on the attached diskette. Please see the comprehensive Table of Contents for a complete listing of all documents submitted to support this amendment.

Spray pattern data submitted by the firm and re-analyzed by the reviewer is presented on the next page.

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PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT %CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL
												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	DMAX26	2CM	34.88	11.19	3.55	8.55	10.03	13.59	5.01	0.88	0.87	0.0001
	END	DMAX26	2CM	39.24	11.19	3.66	7.56	11.43	14.19	3.14	0.94	0.94	0.0158
REF	BEG	DMAX26	2CM	39.82	7.96	3.68	5.88	9.55	8.81	0.51			
	END	DMAX26	2CM	41.72	7.77	3.73	3.89	6.16	11.88	0.62			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT %CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL
												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	DMAX26	4CM	62.29	12.48	4.12	7.17	7.66	19.61	4.12	0.92	0.92	0.0033
	END	DMAX26	4CM	64.67	11.56	4.16	6.91	10.43	15.60	4.69	0.96	0.95	0.102
REF	BEG	DMAX26	4CM	67.44	7.07	4.21	5.81	6.73	8.97	1.03			
	END	DMAX26	4CM	67.57	8.79	4.21	3.41	7.03	13.03	3.63			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT %CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL
												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	DMAX26	6CM	79.03	13.55	4.36	8.50	10.83	19.81	4.03	0.93	0.92	0.0146
	END	DMAX26	6CM	83.30	10.52	4.42	6.45	9.18	14.13	4.52	0.98	0.98	0.5628
REF	BEG	DMAX26	6CM	85.05	8.78	4.44	9.17	7.15	10.27	1.86			
	END	DMAX26	6CM	84.68	11.32	4.43	9.76	10.70	12.36	4.98			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT						

							%CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL
												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	DMIN26	2CM	28.08	9.57	3.33	6.37	8.22	13.06	3.37	0.88	0.88	0.0001
	END	DMIN26	2CM	31.03	12.77	3.43	9.55	13.51	15.77	1.57	0.94	0.94	0.0345
REF	BEG	DMIN26	2CM	31.75	6.82	3.46	6.64	8.81	5.08	1.16			
	END	DMIN26	2CM	32.99	9.02	3.49	7.74	5.94	12.67	1.88			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT %CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL
												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	DMIN26	4CM	49.20	12.36	3.89	5.03	8.60	19.69	3.08	0.94	0.93	0.0099
	END	DMIN26	4CM	51.23	11.24	3.93	6.66	9.86	16.22	2.35	0.97	0.97	0.2166
REF	BEG	DMIN26	4CM	52.58	6.05	3.96	5.90	6.97	4.99	2.13			
	END	DMIN26	4CM	52.89	8.49	3.96	7.08	6.11	11.37	3.07			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT %CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL
												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	DMIN26	6CM	57.01	15.48	4.03	10.81	10.74	22.25	5.13	0.94	0.93	0.0703
	END	DMIN26	6CM	62.40	11.96	4.13	9.25	11.29	15.16	2.72	1.02	1.02	0.6294
REF	BEG	DMIN26	6CM	60.55	9.34	4.10	11.55	10.24	5.20	3.15			
	END	DMIN26	6CM	61.39	14.04	4.11	17.98	9.75	13.26	4.22			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT %CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL

												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	OVAL26	2CM	1.24	8.69	0.22	5.84	13.48	4.50	1.77	0.99	0.99	0.6146
	END	OVAL26	2CM	1.27	8.33	0.24	6.13	11.96	5.73	1.90	1.00	1.00	0.8539
REF	BEG	OVAL26	2CM	1.26	5.17	0.23	5.89	5.19	4.75	0.89			
	END	OVAL26	2CM	1.27	5.70	0.24	7.06	4.80	5.07	1.52			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT %CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL
												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	OVAL26	4CM	1.27	10.26	0.24	6.85	15.48	6.15	2.60	0.99	0.99	0.6442
	END	OVAL26	4CM	1.27	9.92	0.23	6.17	15.13	5.71	2.66	0.99	0.99	0.6601
REF	BEG	OVAL26	4CM	1.29	7.35	0.25	8.71	6.28	5.48	3.39			
	END	OVAL26	4CM	1.28	6.18	0.24	7.26	5.32	6.10	1.39			

PRODUCT	SECTOR	PARAMETER	DISTANCE	MEAN	TOTAL	MEAN	WITHIN			BETWEEN	T/R	T/R	P
						OF LOG							
					%CV		LOT %CV						
							RANGE			LOT %CV	ARITH	GEOM	UNEQUAL
												MEAN	VARIANCE
				N=30	N=30	N=30	N=10			N=3	N=1	N=1	
TEST	BEG	OVAL26	6CM	1.41	15.55	0.33	12.09	20.29	12.63	6.11	0.99	0.99	0.871
	END	OVAL26	6CM	1.35	13.83	0.29	10.75	18.88	8.40	5.82	0.97	0.97	0.3183
REF	BEG	OVAL26	6CM	1.41	12.33	0.34	14.96	11.13	8.41	5.07			
	END	OVAL26	6CM	1.40	11.74	0.33	16.52	6.42	10.41	2.2			

FDA Comments on the Spray Pattern Data Submitted

The firm has repeated the spray pattern study and has visualized the spray pattern data using ———— as suggested by DBE. The firm provides the average ,standard deviation and %sd for the longest/shortest axis measurement and the longest/shortest axis ratio in Table 1 for the ——visualization.

The geometric mean values for test and reference spray pattern (i.e., Dmax and Dmin) for the reference were slightly higher. Per cent coefficient of variation values for the 30 bottles was lower for the reference except at the end sector for Dmax 26 (2cm, 4cm and 6 cm) and end sector Dmin 26(6 cm). The p values for Dmax at 2 and 4 cm distance at the beginning of the spray were statistically significant. Values of p for Dmin at 2 and 4 cm at the beginning of the spray were also statistically significant. All Test/Ref ratios were within the limits of 90-111% as employed by the Division of Bioequivalence for acceptance of solution nasal spray products except for Dmax and Dmin for the beginning of the spray for the 2 cm distance which had ratios of 0.88. Because the parameter values do not change between the beginning and end sectors of the product, the Division of Bioequivalence accepts the analysis of pooled beginning and end sector data. Based upon this analysis the geometric mean ratios are within the acceptable range of 90-111%. Therefore the spray pattern data is acceptable.

Comment.

1. All previous in vitro testing for this product was found to be acceptable.

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Recommendation:

The *in vitro* performance testing conducted by L. Perrigo on its Cromolyn Nasal Spray, 40 mg/mL comparing it with the reference product, Nasalcrom®, nasal solution (Pharmacia and Upjohn) has been found to be acceptable by the Division of Bioequivalence. The waiver of in vivo bioequivalence study requirements for the 40 mg/mL Nasal Spray of the test product is granted. The 40 mg/mL of the test product is therefore deemed bioequivalent to Nasalcrom®, nasal solution manufactured by Pharmacia and Upjohn.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 11/14/2001

Concur: Date: 11/16/01
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

cc: ANDA 75-427 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

SPACE INTENTIONALLY LEFT BLANK

CC: ANDA 75-427
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer

V:\Firmsnz\Perrigo\Ltr&Rev\75427AO01
Printed in final on / /

Endorsements: (Final with Dates)
HFD-652/ Reviewer 11/16/01
HFD-652/ Bio team Leader 11/14/2001
HFD-650/ D. Conner 11/16/01
HFD-655/GJP Sing

BIOEQUIVALENCY - ACCEPTABLE submission date: October 17, 2001

6. Study Amendment (STA)
~~WAIVER (WAI)~~

Strengths: 40 mg/mL
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

APPEARS THIS WAY ON ORIGINAL

#2

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-427 SPONSOR : L.Perrigo Company
DRUG AND DOSAGE FORM : Cromolyn Sodium Nasal Solution, USP

STRENGTH(S) : 40 mg/mL

TYPES OF STUDIES : Waiver

CLINICAL STUDY SITE(S): N/A

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : adj DATE : 11/14/01

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : YCH DATE : 11/14/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 11/16/01

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-427 APPLICANT: Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Spray, 40 mg/ml

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

Please be advised that when conducting future studies of *in-vitro* bioequivalence testing, it is of utmost importance to comply with the Agency's regulations regarding retention of study drugs as described in 21 CFR 320.38 and 320.63.

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 no not approvable.

Sincerely yours,

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

CC: ANDA 75-427
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File

V:/firms nz/perrigo/ltrs&rev/75-427.dsi
Printed on final 12/13/01

Endorsements: (Final with dates)
HFD-650/Dale Conner 12/13/01
HFD-650/ Lizzie Sanchez
HFD-652/ Krista Scardina 12/13/01

HFD652/Andre Jaetson
HFD650/YC Hwang
for Chandra S. 12/13/2001

BIOEQUIVALENCY-ACCEPTABLE submission date: December 6, 2001

1. Other (OTH) strengths: 40mg/ml
Outcome: AC

Outcome Decision: AC - Acceptable

Winbio comments:

Please make a US document

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-427 SPONSOR : Perrigo Company

DRUG AND DOSAGE FORM : Cromolyn Sodium Nasal Spray, USP

STRENGTH(S) : 40mg/ml

DSI INSPECTION STATUS

Inspection needed: (YES) / NO	Inspection status:	Inspection results:
First Generic _____ New facility ___X__ For cause _____ Other _____	Inspection completed: (December 6, 2001)	DSI recommeded not to accept the study. DBE recommends the study is acceptable.

REVIEWER : Andre Jackson, BRANCH : I

INITIAL : AJ DATE : 12/13/01

TEAM LEADER : Yih-Chain Huang BRANCH I

INITIAL : for Chain S. Chen DATE : 12/13/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 12/13/01

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-427 APPLICANT: L. Perrigo Company

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-427

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

The firm received a major deficiency for ANDA 75-427(Cromolyn Sodium Nasal Spray) from the Agency dated October 13, 2000. The firm is requesting additional information on 2 of the comments.(see attached fax)

Mr. Mike Smela and Dr. Eugene Schaefer reviewed the fax and I called the firm with the following comments.

Comment 1:
I informed Ms. Gallagher that all firms that generated data in the ANDA are expected to be listed as well as a description of what they have done or will do in the future. It is expected that all data are generated under GMP conditions.
——— has provided certification for GLP'S and Device GMP's for ———. The Agency will need certification for Drug GMP.

Comment 17b:
The amount of time it may be stored by a patient is the typical time to exhaust a container when following the minimum dose specified in the label.
Since the container/closure system has been changed from ——— to ———, a separate qualification study will not be needed.

DATE
November 2, 2000

ANDA NUMBER
75-427

IND NUMBER

TELECON

INITIATED BY

X **SPONSOR**

FDA

PRODUCT NAME
Cromolyn Sodium Nasal Spray (OTC)

FIRM NAME
L. Perrigo

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Valerie Gallagher, ANDA Regulatory Affairs Project Manager

TELEPHONE NUMBER
(616) 673-9367

SIGNATURE
M.Dillahunt 11/3/00

CC: ANDA 75-427
Division File
Chem Div I, T-con Notebook

OGD APPROVAL ROUTING SUMMARY

NDA # 75-427 Applicant L. Perrigo

Cromolyn Sodium Nasal Solution USP Strength 5.2 mg/spray

APPROVAL ☑ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

DRAFT RECEIPT — Date 11/28/01 Initials MD

FINAL ACTION — Date 12/3/01 Initials MD

1. Project Manager MDillahunt
   Review Support Br 2

   Application Summary:
   Original Rec'd date 8/3/98
   Date Acceptable for Filing 8/3/98 ✓
   Patent Certification (type) 1
   Date Patent/Exclus.expires N/A
   Citizens Petition/Legal Case Yes ☐ No ☑
   (If YES, attach email from PM to CP coord)
   First Generic Yes ☐ No ☑
   (If YES, check PETS)
   Pediatric Exclusivity Tracking PETS)
   Date checked N/A NDA# _____
   Nothing Submitted ☐
   Written request issued ☐
   Study Submitted ☐

   EER Status Pending ☐ Acceptable ☑ OAI ☐
   Date of EER Status 11/29/01
   Date of Office Bio Review 11/16/01 (OSI pending)
   Date of Labeling Approv. Sum 8/21/01
   Date of Sterility Assur. App. N/A
   Methods Val. Samples Pending Yes ☐ No ☑
   30 Day Clock Start _____ End _____
   Commitment Rcd. from Firm Yes ☐ No ☐
   Modified-release dosage form: Yes ☐ No ☑
   Interim Dissol. Specs in AP Ltr: Yes ☐

   Previously reviewed and tentatively approved ☐ Date _____
   Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
   Comments:

2. Div. Dir./~~Deputy Dir~~.
   Chemistry Div. I ~~or II~~
   Comments:
   Date 12/3/01 Initials RAC
   Date 12/4/01 Initials RAC

   The one section is satisfactory

3. Frank Holcombe
   Assoc. Dir. For Chemistry
   Comments: (First generic drug review)
   Date _____ Initials _____
   Date _____ Initials _____

   N/A

   Both Alpharma (74-800) and Bausch + Lomb (75-702) are approved to mfg this drug product.

4. Pat Beers Block
   Supv., Review Support Branch
   EER Status: On leave. Refer to DLPS review below.
   Date _____ Initials _____
   Date _____ Initials _____

   Bioequivalence sites:
   Clinical site:
   Inspection needed: ☐ yes ☐ no
   Status: ☐acceptable ☐unacceptable ☐ pending
   Date of status: _____
   Reason:
   Bioequivalence office level sign off:

   Analytical site:
   Inspection needed: ☐ yes ☐ no
   Status: ☐acceptable ☐unacceptable ☐pending
   Date of status: _____
   Reason:

   Labeling Status:

   Microbiology status:
   Patent Certification:
   Controlled Correspondence/Cit.Pet:
   Comments: RLD =

REVIEWER: | DRAFT RECEIPT | FINAL ACTION

5. Greg Davis
Supv., Reg. Support Branch

Date 12/12/01 Initials RW | Date 12/12/01 Initials RW for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

#1
N/A
N/A
RLD- Nasalcrom Nasal Spray (MDI) Pharmacia and Upjohn Consumer Healthcare 5.2 mg/spray NDA 20-4

Comments: There are no unexpired patents or exclusivity on this drug product.

6. Peter Rickman
Acting Director, DLPS

Date 12/12/01 Initials RW | Date 12/12/01 Initials RW for

Comments: Acceptable EES dated 11/29/01 (Verified 12/12/01) NDO A.I. dated noted FPL acceptable 8/21/01 (endorsed 11/29/01) CMC acceptable 8/17/01; 11/15/01; 11/29/01. Methods validation waived- USP API + drug product. Bioequivalence (Q1&2 and in vitro performance testing) found acceptable 11/14/01. OSI inspectional status is satisfactory. Office-level bio endorsed 11/16/01.

7. Robert L. West
Acting Deputy Director, OGD

Date 12/12/01 Initials RW | Date 12/12/2001 Initials Robert L West

Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments:

This application is recommended for approval

8. Gary Buehler
Director, OGD
Comments:

Date 12/12/01 Initials RW | Date 12/12/2001 Initials RW for

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Michelle Dillahunt
Review Support Branch

Date _____ Initials _____ | Date _____ Initials _____

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
12/14 9:20 Time notified of approval by phone 9:25 Time approval letter faxed
waiting for memo from Bio. /DO

FDA Notification:
12/14 Date e-mail message sent to "OGD approvals" account
12/14 Date Approval letter copied to"//cder/drugapp" directory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-427

CORRESPONDENCE

PERRIGO®

Ack for filing
8/21/98
S. Middleton

July 31, 1998

Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

RE: Abbreviated New Drug Application
Cromolyn Sodium Nasal Solution, 5.2 mg/spray
Over-the-Counter Product

Dear Mr. Sporn:

The L. Perrigo Company is submitting for your review and approval, an ANDA for Cromolyn Sodium Nasal Solution, 5.2 mg/spray pursuant to 505(j) of the Federal Food, Drug, and Cosmetic Act. The L. Perrigo Company's Cromolyn Sodium Nasal Solution is identical in strength, indications, active ingredient, route of administration and dosage form to Pharmacia and Upjohn's Nasalcrom® 5.2 mg/spray.

Nasalcrom® (NDA #20-463) is listed in the Eighteenth Edition of *Approved Drug Products with Therapeutic Equivalence Evaluations,* as an OTC drug with exclusivity protection. Nasalcrom® has market exclusivity until January 03, 2000.

A request for a Bioequivalence waiver is included in this submission.

Attached is an additional copy of this cover letter. Please stamp the date of your receipt on it and return in the enclosed self-addressed, stamped envelope.

Should you require additional information, please contact me directly by telephone at 616-673-9182, by FAX at 616-673-7655, by E-mail at lmcneil@perrigo.com, or the address on this letterhead.

Thank-you for your prompt handling of this submission.

Respectfully submitted,

Lisa Gould McNeil
Regulatory Affairs

xc: B. Schuster
G. Boerner

RECEIVED
AUG 0 3 1998
GENERIC DRUGS

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

ANDA 75-427

L. Perrigo Company
Attention: Brian R. Schuster
117 Water Street
Allegan, MI 49010

SEP 1 1998

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray

DATE OF APPLICATION: July 31, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 3, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-427
cc: DUP/Jacket
Division File
Field Copy
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett

Endorsement: HFD-615/PRickman, Chief, RSB _____ date 8/25/98
HFD-615/SMiddleton, CSO _____ date 8/24
HFD-625/MSmela, Sup. Chem. _____ date
WP File X:\NEW\FIRMSNZ\PERRIGO\LTRS&REV\75427.ACK
F/T mjl/8/21/98
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

NOV 3 1998

ANDA 75-427

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: L. Perrigo Company PHONE: 616-673-8451

ATTN: Brian R. Schuster FAX: 616-673-7655

FROM: Elaine Hu PROJECT MANAGER (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on July 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cromolyn Sodium Nasal Solution, 5.2 mg/spray (40 mg/mL).

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Pmsa 11/3/98

X:\new\ogdadmin\glossary\biofax.frm

NOV 3 1993

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-427 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray (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:

Since Cromolyn Sodium Nasal Solution USP is packaged in a manual metered dose pump, it must be demonstrated through *in vitro* testing that the delivery system of the test product performs the same as the delivery system of the reference listed drug. Information demonstrating the sameness should include but is not limited to:

a. droplet size distribution

b. uniformity of unit spray content, based on single actuation data, and including priming data.

c. spray pattern

d. plume geometry

Although the test product is not a pressurized metered dose inhaler, you are referred to the metering performance and uniformity of unit spray content sections of Chapters 601 and 905 of the U.S. Pharmacopeia, and to the Division of Bioequivalence June 27, 1989 Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers). As noted in this Guidance, comparative data from two methods of droplet size distribution determination should be reported. Each method should be validated, and provide true droplet size distributions, including mass median aerodynamic diameter and geometric standard deviation, in the appropriate droplet size range, for the products.

Because there are a number of unresolved issues regarding the testing of manual metered dose pumps for the documentation of in

vitro bioequivalence, you are advised to submit a protocol outlining its planned studies. This protocol may be based in part on the considerations discussed in the above references.

Sincerely yours,

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

PERRIGO®

November 20, 1998

Mr. Douglas Sporn, Director
Food and Drug Administration
CDER, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Bioequivalency Amendment

NDA ORIG AMENDMENT

AB

RE: Abbreviated New Drug Application
Cromolyn Sodium Nasal Solution, 5.2 mg/spray (40 mg/mL)
ANDA 75-427

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application for Cromolyn Sodium Nasal Solution, 5.2 mg/spray (40 mg/mL), filed on August July 31, 1998. Further reference is made to the November 3, 1998, FDA letter which provided bioequivalency deficiencies.

We hereby amend this ANDA to provide the additional information requested in the November 3, 1998, letter. This is a Bioequivalency Amendment as designated in the FDA letter. The comments provided were as follows (copy of the letter is enclosed):

Since Cromolyn Sodium Nasal Solution USP is packaged in a manual metered dose pump, it must be demonstrated through in vitro testing that the delivery system of the test product performs the same as the delivery system of the reference listed drug. Information demonstrating the sameness should include but is not limited to

a. droplet size distribution
b. uniformity of unit spray content, based on single actuation data and including priming data.
c. spray pattern
d. plume geometry

Although the test product is not a pressurized metered dose inhaler, you are referred to the metering performance and uniformity of unit spray content sections of Chapters 601 and 905 of the U.S. Pharmacopoeia, and to the Division of Bioequivalence June 27, 1989 Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers). As noted in this Guidance, comparative data from two methods of droplet size distribution determination should be reported. Each method should be validated, and provide true droplet size distributions, including mass median aerodynamic diameter and geometric standard deviation, in the appropriate droplet size range for the products.

Because there are a number of unresolved issues regarding the testing of manual metered dose pumps for the documentation of in-vitro bioequivalence, you are advised to submit a protocol outlining its planned studies. This protocol may be based in part on the considerations discussed in the above references.

RECEIVED
NOV 23 1998
GENERIC DRUGS

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

Perrigo Company provides the following response:

Based on the above comments, we believe that the Division of Bioequivalence did not have access to the submitted results of *in-vitro* comparative testing performed to demonstrate the equivalence of the delivery systems of the test and reference drug products. That information was provided in section 14 of the ANDA on pages 411 through 441 and included the following test results:

a. Comparative Droplet Size Distribution Analysis

b. 1)Content Uniformity of Unit Sprays - single actuation, average of 10, and % RSD

2)Individual, Average and Range of Sprays Delivered per Bottle (26 and 13 mL)

c. Comparative Spray Pattern (Geometry) Analysis with analysis of symmetry factors

d. Comparative Plume Geometry Analysis

To facilitate your review of this documentation, an additional copy of these pages is enclosed in this amendment.

We have considered your comments regarding the testing specified in USP <601> and <905> and the application of the June 27, 1989, guidance for the *In Vitro* Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers) and provide the following comments:

USP <601>

The Metering Performance testing described in USP <601> for pressurized inhalers fitted with actuators is designed to measure the variation in the weights of the delivered sprays and to detect changes in the dose delivered that may be caused by dynamic effects, including leakage, on the pressurized system. Page 414 of the enclosed documentation from the original ANDA provides results of a similarly designed test to measure the spray delivery of 10 units of each bottle size. The test is adapted for the non-pressurized system and provides a calculated number of sprays delivered per bottle. The results are well within the USP requirements.

USP <905>

The Uniformity of Unit Spray Content described in USP <601> and <905> are designed to measure the content of active ingredient in the discharged spray for a pressurized metered-dose inhaler. This test was performed on the proposed sprayer using a method to collect the entire spray content appropriate for a nasal solution rather than a device which is designed to sample a suspension for an inhalation route of administration. Comparative results from testing of 10 sprayers of the listed and proposed drug are enclosed (page 412 of the original ANDA). The results meet the requirements stated in USP <601>.

Guidance for the *In Vitro* Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)

In general, the tests described in the referenced guidance are specific for pressurized metered dose inhalation aerosols of particles in suspension; both Metaproterenol Sulfate and Albuterol Inhalation Aerosols are microcrystalline suspensions of drug in a liquefied propellant contained in a pressurized metal canister. Cromolyn Sodium Nasal Spray is an aqueous solution delivered by a mechanical metering pump from a non-pressurized plastic bottle.

Several of the tests described in the guidance and in USP <601> are specific to determining the size of solid particles expelled from the delivery device. Thus it is not possible to perform the tests for particle size on a solution product using the various impactor devices or by microscopic examination as all of these tests are designed to measure the diameters of particles captured on impactor stages or glass slides. It is also not possible to determine the mass median aerodynamic diameter and geometric standard deviation as these parameters are derived from the impactor data.

Further, according to USP <601> the purpose of performing the various tests described for particle size is to ensure that particles are of no greater than 10 microns in diameter in order to ensure deposition in the lung during inhalation. The results of the analysis of the test and reference drugs for droplet size indicate that the delivery devices produce droplets with median size of approximately 60 microns and that 90% of the droplets are larger than about 30 microns. This large diameter of droplet size coupled with the nasal route of administration ensures that the product will be properly delivered to the site of action in the nasal cavity.

The November 13, 1998, draft Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - Chemistry, Manufacturing, and Controls Documentation lists these same tests but specifies the guidance does not address inhalation solutions and aqueous nasal sprays.

In summary, we have provided results from testing which is appropriate to demonstrate the comparability of the delivery devices of the test and reference products. As the drug product is a true solution, the test and reference drug products are assumed to be equivalent in physical form and only those tests that measure any potential differences in the performance of the metered dose sprayer are possible. To demonstrate this comparability, we have conducted the testing described herein.

As required by 21 CFR 314.94(d)(5), the Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. Perrigo certifies that the amendment contained in the "field copy" is a true copy of the amendment which was submitted to the FDA headquarters.

Should you require additional information, please contact me directly by telephone at 616-673-9745, by fax at 616-673-7655, or at the address on this letterhead.

Sincerely,

Brian R. Schuster
Manager, ANDA Submissions
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

MAJOR AMENDMENT

MAR 5 1999

ANDA 75-427

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: L. Perrigo Co. PHONE: (616) 673-8451

ATTN: Brian R. Schuster FAX: (616) 673-7655

FROM: Denise Huie PROJECT MANAGER (301) 827–5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cromolyn Sodium Nasal Solution, 5.2 mg/spray.

Reference is also made to your amendment dated November 20,1998.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (7 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

CMC and labeling comments are attached

Pmas 3/5/99

X:\new\ogdadmin\macros\faxmaj.frm

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

3/5/1999 FDA FAX

h. [redacted]

14. Your accelerated stability studies did not state the storage conditions of the containers. Per our Center's *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics (1987)*, drug product solutions should be stored on their side or inverted as well as upright. New accelerated studies (or restressed samples of the current batch) are necessary on new test batches due to the failure to include many important tests as referenced in this letter. The new batches should also be tested for all in-process and release tests included in the ANDA or referenced in this letter. Additionally, stability data with the pump in place for the amount of time it may be stored by a patient is necessary as a one time qualification study.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

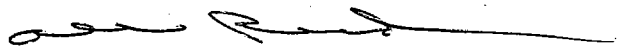
2. Since the subject drug product is an official article in the USP, the approval to use an analytical procedure that differs from that in the USP does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.

3. Please provide any additional long-term stability data, if available.

4. Your bioequivalence information is pending review.

5. Your response must also address the labeling deficiencies.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-427 **Date of Submission: July 31, 1998**

Applicant's Name: **L. Perrigo Company**

Established Name: **Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   In your application, you have identified [redacted] as the manufacturer, however, on your labeling you indicate Perrigo is the manufacturer. Please revise and/or comment.

2. CONTAINER (13 mL and 26 mL)

   a. See GENERAL COMMENT.

3. CARTON (13 mL and 26 mL)

   a. See GENERAL COMMENT.

4. NASAL ALLERGY SYMPTOM PREVENTION AND RELIEF LEAFLET

   a. See GENERAL COMMENT.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels for the 13 mL and 26 mL containers, and 12 copies of final printed carton and patient leaflet labeling.

APPEARS THIS WAY
ON ORIGINAL

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

John D. Grace for /

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

MAR 30 1999

ANDA 75-427

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: L. Perrigo Company PHONE: (616) 673-8451

ATTN: Brian R. Schuster FAX: (616) 673-7655

FROM: Elaine Hu PROJECT MANAGER (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on November 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cromolyn Sodium Nasal Solution, 5.2 mg/spray (40 mg/mL).

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 4 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

3/29/99

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MAR 30 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-427 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray (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 Division of Bioequivalence requires that pumps should be actuated mechanically to increase reproducibility and

- No fewer than 10 units (i.e., 10 bottles and associated delivery devices) each of the test and reference products should be tested in a blinded manner.

- For all *in vitro* tests, data from three batches of the reference product, and two or three batches of the test products as available should be submitted for review. Batch records for all batches of the test product should be submitted.

- SOP's for all tests effective at the time of testing should be submitted. SOP's should describe the mechanical actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s).

- Raw data for all tests should be submitted in the form of paper copies as well as electronic files (Excel 5.0 spread sheets).

- For tests such as content uniformity, which is performed at the beginning (B), middle (M), and end (E) or B and E of use life sectors, equivalence must be assessed at each sector.

2. Your test product must show equivalence to the RLD in performance during the initial use and priming of the product. You should submit data to support that the test product's performance is equivalent to the RLD during priming. In addition, evidence for

comparable tail off characteristics should be submitted. Data should be based on the amount of drug per actuation using a biochemical/chromatographic assay. The product is labeled to deliver 100 doses, the firm is advised to combine determination of priming, uniformity of unit dose and tail off in suitable ranges of doses delivered to be consistent with the beginning, middle and end of use life.

3. The particle sizing data you provided in vol. 1.1, page 435 for Nasalcrom 13 mL and 26 mL spray bottles and for the test product in vol. 1.1 page 439 has been found to be incomplete.

Droplet size distribution by laser diffraction (e.g. [redacted]) should be determined at the beginning, middle, and end of use life for the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. Data should be reported in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Data should be reported based on mass (volume). All instrument/computer printouts should also be submitted, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration(fractional loss of energy from the laser beam caused by particle scattering) should be reported for each run, along with the instrument manufacturer's recommended obscuration ranges.

In addition you should supply data from cascade impaction to characterize particles in a smaller size range than the expected range for aqueous nasal sprays. This is useful to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor data should account for mass balance and be reported in the following groups:

Adaptor to throat or separator,

Stage 0 to stage 3, and

Stage 4 to filter.

Because the purpose of the cascade impactor data for the aqueous nasal sprays is to characterize fines only, not to provide a particle size distribution, you are requested to provide cascade impactor studies only at the beginning and end of canister

through-life testing.

You may, if you wish, also provide comparative data by additional methods such as time-of-flight laser.

4.Your products spray patterns should be determined at three distances from the TLC plate at beginning and end life sectors. Spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent. A drug-specific reagent will not develop color when tested with placebo. Photographs of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max}) diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{min}/D_{max}), along with photographs and markings indicating D_{min} and D_{max}.

5. Since the device and the formulation are integral components of your test nasal spray and in order to support the sameness of test and reference devices, you should provide to the extent possible a side-by-side comparison of the pumps and actuators used in the test and reference products. This information should include the manufacturer, model numbers of the pumps and actuators, model numbers of actuator inserts and the overcaps. Technical drawings with dimensions should also be submitted for both the test and reference products, if available.

APPEARS THIS WAY
ON ORIGINAL

6.Your comparative plume geometry data in vol. 1.1, 418-433 is incomplete.

The plume geometry should describe two side views of the plume, at 90^0 angles to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. You should provide plume geometry based on high speed photography. Plume geometry may be performed only at the beginning of use life. Plumes should be characterized at three or more different times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. You are requested to provide all photographs and data characterizing plume dimensions.

Sincerely yours,

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

PERRIGO®

March 31, 2000

Mr. Gary Buehler, Acting Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CHEMISTRY
MAJOR AMENDMENT

ORIG AMENDMENT
N/AC

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the comments in the March 5, 1999, deficiency letter from the Divisions of Chemistry and Labeling.

It should be noted that L. Perrigo is also filing an amendment in response to the March 30, 1999, deficiency letter from the Division of Bioequivalence today with a separate response letter. Both response letters have been shipped together to FDA in one package. The response letters reference the same amendment documentation. Duplicate copies of the amendment documentation notebooks that support the response letters have been provided for each division for ease of review and archival (see the documentation distribution table on Page 2 of this letter).

L. Perrigo Company further amends this application to address a manufacturing site change and container/closure system changes.

In the initial submission, ——————— was listed as the contract manufacturer for this product. This amendment contains the necessary documentation to support replacing ——————— with ——————— as the new contract manufacturer, including new batch records and associated documentation and a description of the ——————— facility. ——————— is not a sterile manufacturing facility. Neither Perrigo nor the Reference Listed Drug claims that this product is sterile.

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117 Water Street
Allegan, Michigan 49010

Redacted 9 page(s)

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confidential commercial

information from

3/31/2000 PERRIGO LETTER

The new accelerated and room temperature stability studies are being conducted in consideration of the 3/5/99 comments received from the Division of Chemistry, the 3/30/99 comments received from the Division of Bioequivalence and the two FDA Draft Guidance Documents issued in May of 1999 for Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products. Section 16 of this amendment contains a description of the stability testing program, the stability specification and associated methods, post approval commitments, expiration dating period information, and the stability data reports. Note that the new stability study data reports indicate storage conditions and inverted or upright container orientations and include the testing noted in the original submission as well as the testing recommended in FDA letters dated 3/5/99 and 3/30/99.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. *The cGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.*

   RESPONSE:

   L. Perrigo acknowledges that the cGMP compliance of all the facilities listed in this application shall be evaluated by FDA's Office of Compliance and a satisfactory evaluation is required prior to the approval of this application

2. *Since the subject drug product is an official article in the USP, the approval to use an analytical procedure that differs from that in the USP does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.*

   RESPONSE:

   L. Perrigo acknowledges that since the subject drug product is an official article in the USP, the approval to use an analytical procedure that differs from that in the USP does not release L. Perrigo from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive

3. *Please provide any additional long-term stability data, if available.*

RESPONSE:

Because of the manufacturing site change and the container/closure change, there is no additional long-term stability data available at this time. The stability data available at this time is located in Section 16 of this amendment.

4. *Your bioequivalence information is pending review.*

RESPONSE:

A separate amendment has been filed with the Division of Bioequivalence on this date to respond to the March 30, 1999 comments from the Division of Bioequivalence.

5. *Your response must also address the labeling deficiencies.*

RESPONSE:

This amendment addresses the comments issued by the Division of Labeling on March 5, 1999. See Section B of this response letter for details.

B. Comments received from the Division of Labeling

1. *General Comments:*
In your application, you have identified [redacted] *as the manufacturer, however, on your labeling you indicate Perrigo is the manufacturer. Please revise or comment.*

RESPONSE:

Perrigo's original version labeling has been revised in accordance with the above comment. "Distributed by Perrigo" has replaced "Manufactured by Perrigo".

An additional change was necessary to accommodate the new container/closure system.

[redacted] have been deleted from the insert leaflet and the carton side panel.

Additionally, the Reference Listed Drug has revised its original version labeling since Perrigo filed its original ANDA. Therefore, Perrigo has revised its labeling accordingly.

All of the changes discussed above are noted in the side-by-side comparison provided in Section 5 of this amendment. Draft labeling for Perrigo's original version as well as samples of the Reference Listed Drug's currently marketed original version labeling are included with this amendment in Section 5.

This amendment also contains a children's version of the original labeling, in accordance with new labeling available on the market at the time of this filing for the Reference Listed Drug. The same drug product formula is used with the original version labeling as well as the children's version labeling. A side-by-side comparison of the Perrigo children's labeling version and the Reference Listed Drug's children's labeling version is provided in Section 5. The Perrigo labeling version indicates Distributed by Perrigo, in accordance with General Comment Number 1 above. Draft labeling for the Perrigo product and samples of the Reference Listed Drug's labeling are also provided in Section 5 of this amendment.

2. *Container (13 mL and 26 mL)*

   a. *See General Comment*

   RESPONSE:

   See Perrigo's response to the General Comment above.

3. *Carton (13 mL and 26 mL)*

   a. *See General Comment*

   RESPONSE:

   See Perrigo's response to the General Comment above.

4. *Nasal Allergy Symptom Prevention and Relief Leaflet*

   a. *See General Comment*

   RESPONSE:

   See Perrigo's response to the General Comment above.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels for the 13 mL and 26 mL containers, and 12 copies of final printed carton and patient leaflet labeling.

RESPONSE:

Because of the nature of the changes implemented to follow new Reference Listed Drug labeling, 4 copies of the draft labeling for each component and each size are included with this amendment in Section 5.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA headquarters.

We trust that this amendment provides all the necessary information to address the comments in the March 5, 1999, Chemistry Division deficiency letter as well as the manufacturing site change and the container/closure system changes. However, should additional information be required, please contact me directly by telephone at 616-673-9367 or by fax at 616-673-7655.

Sincerely,

Valerie Gallagher
ANDA Regulatory Affairs Project Manager

MAJOR AMENDMENT

ANDA 75-427

OCT 13 2000

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: L. Perrigo Company

TEL: (616) 673-8451

ATTN: Brian R. Schuster

FAX: (616) 673-7655

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray.

Reference is also made to your amendment dated March ~~5, 1999~~. 31 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance

SPECIAL INSTRUCTIONS:

10/13/00 NO

Redacted 5 page(s)

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information from

10/13/2000 FDA FAX

PERRIGO®

November 30, 2000

Gary Buehler, Acting Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT

ORIG AMENDMENT
N/AB

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence
- Perrigo Chemistry Amendment dated March 31, 2000
- Perrigo Bioequivalence Amendment dated March 31, 2000

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the comments in the June 20, 2000 deficiency letter from the Division of Bioequivalence.

AMENDMENT SUMMARY:

In light of the comments received from the FDA in the June 20, 2000, letter from the Division of Bioequivalence, L. Perrigo Company reviewed the documentation presented in the March 31, 2000, amendment related to in vitro bioequivalence testing.

As a result of that review and in accordance with specific comments in the June 20, 2000, letter from the Division of Bioequivalence, the following documentation is supplied with this amendment:

- An addendum to [redacted] Protocol — 02-01BE, Bioequivalence Study Protocol for Perrigo Company for Testing of 4% Cromolyn Sodium Nasal Spray, revising the term "suspensions" to "solutions". (Section 3)

- Statements from [redacted] clarifying that the same automated actuator system settings were used during the particle size distribution by laser light scattering testing (droplet sizing by laser diffraction), cascade impaction, and plume geometry angle and length/width bioequivalence testing. (Section 4)

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515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

- L. Perrigo Company protocol for priming, spray content uniformity, and tail-off bioequivalence testing. (Section 5)

- L. Perrigo Company justification report for the tail-off bioequivalence testing plan. (Section 6)

- L. Perrigo Company validation report for the priming, spray content uniformity, and tail-off bioequivalence testing protocol. (Section 7)

- Raw data generated by L. Perrigo Company during the priming bioequivalence testing presented in the table format suggested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 8)

    - Sample result printouts representing 20% of the data generated by L. Perrigo Company during the priming and spray content uniformity bioequivalence testing. Note that the same bottle samples were used to facilitate both tests. (Section 9)

- Raw data generated by L. Perrigo Company during the spray content uniformity bioequivalence testing presented in the table format suggested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 10)

    - Sample result printouts representing 20% of the data generated by L. Perrigo Company during the priming and spray content uniformity bioequivalence testing. Note that the same bottle samples were used to facilitate both tests. (Section 9)

- Raw data generated by L. Perrigo Company during the tail-off bioequivalence testing presented in the table format suggested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 11)

    - Sample result printouts representing 20% of the data generated by L. Perrigo Company during the tail-off bioequivalence testing. (Section 12)

- Raw data generated by [redacted] during the cascade impaction bioequivalence testing presented in the table format suggested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 13)

    - Sample result printouts representing 20% of the data generated by [redacted] during the cascade impaction bioequivalence testing. (Section 13.A.)

- Raw data generated by [redacted] during the particle sizing by laser diffraction bioequivalence testing presented in the table format suggested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 14)

During review of this data, FDA should also reference the previously submitted data tables filed at page 993 of the March 31, 2000 Amendment. The previously submitted data tables contain the individual test points reflected on the ——— Histograms noted below. The individual data points were then averaged together and were also noted on the previously submitted tables. As mentioned above, the averaged data was reformatted as requested in the June 20, 2000, letter from the Division of Bioequivalence.

- ——— histograms representing 20% of the printouts generated by ——— during the particle sizing by laser diffraction bioequivalence testing as requested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. The individual test points noted on the histograms are captured on the data tables previously submitted with the March 31, 2000, Amendment at page 993. (Section 15)

- Raw data generated by ——— during the plume geometry angle bioequivalence testing presented in the table format suggested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 16)

- ———Bioequivalence Study Appendix 1 entitled "Commentary on Plume Angle, Width, and Length Measurements". This document provides justification for the test method utilized during the plume angle and length and width bioequivalence testing conducted by ——— (Section 17)

- Plume geometry angle photographs representing 20% of the photographs generated by ——— during the plume geometry angle bioequivalence testing, as requested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 18)

- Raw data generated by ——— during the plume geometry length and width bioequivalence testing presented in the table format suggested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 19)

- Plume geometry length and width photographs representing 20% of the photographs generated by——— during the plume geometry length and width bioequivalence testing, as requested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 20)

- An addendum to the ——— Protocol —02-02BE, Bioequivalence Study Protocol for Perrigo Company for Testing of 4% Cromolyn Sodium Nasal Spray, providing for plume geometry length and width testing. (Section 21)

- ——————— Test Method TM —02-PGLW, Plume Geometry Length and Width Measurements for Cromolyn Sodium Nasal Spray Product. (Section 22)

- ——————— Plume Geometry Length and Width Method Qualification Report —02-09 for Cromolyn Sodium 4% Nasal Spray. (Section 23)

- Raw data generated by L. Perrigo Company during the spray pattern bioequivalence testing presented in the table format suggested by FDA in the June 20, 2000, letter from the Division of Bioequivalence. (Section 24)

    - Spray pattern images representing 20% of the images generated by L. Perrigo Company during the spray pattern bioequivalence testing. (Section 25)

    - L. Perrigo Company protocol for spray pattern bioequivalence testing. (Section 26)

    - L. Perrigo Company bioequivalence testing protocol addendum for Procedure 109, Spray Pattern Testing. (Section 27)

- The electronic versions of all the raw data tables mentioned above are located on the CD data disk enclosed with this amendment. The Excel-formatted file is entitled "Final BE Raw Data Tables". Within that file, each spreadsheet is clearly labeled on the file tabs, i.e., SCU, Priming, Tail-Off, etc.

In addition to the information noted above, the section below lists the specific comments received in the June 20, 2000, letter from the Division of Bioequivalence and the L. Perrigo Company responses.

FDA COMMENT:

1. *You stated in vol. 3.4 page 1682 that the validation data for the automated actuators would be supplied in the in vitro study report. However, this data could not be identified by the Division of Bioequivalence. The settings were given in vol. 3.4 page 1664 but it was never stated if these settings were used for all studies. You should supply the validation data for your ——————— actuation station and clearly state if the same settings were used for all studies.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above comment, please note the following information:

- ——————— validation report —02-01, *Report on the Qualification of the Use of an Automated Actuator to Advance Perrigo Company Cromolyn Sodium Nasal Spray from Beginning through Middle and End of Life Stage*, was filed with the March 30, 2000, amendment in the Methods Validation Section at page 1436. In accordance with the above comment, an addendum to —02-01 noting the settings that were used throughout all testing conducted by ——————— is located at page 55 of this amendment.

- ——————— validation report —02-02, *Report on the Qualification of the Use of an Automated Actuator to Advance Nasalcrom® Cromolyn Sodium Nasal Spray from Beginning through Middle and End of Life Stage*, was filed with the March 30, 2000, amendment in the Methods Validation Section at page 1477. In accordance with the above comment, an addendum to —02-02 noting the settings that were used throughout all testing conducted by ——————— is located at page 54 of this amendment.

- ——————— test method TM —02-PG, *Plume Geometry for Cromolyn Sodium Nasal Spray Product*, was filed with the March 30, 2000, amendment in the Methods Validation Section at page 1671. In accordance with the above comment, an addendum to TM —02-PG noting the settings that were used throughout all testing conducted by ——————— is located at page 52 of this amendment.

FDA COMMENT:

2. *The information you supplied in the referenced Section 23 of the submission are the data resulting from the in vitro testing. Your protocol information was in vol. 3.2 Section 15 under drug product methods, which included the following:*

***Testing Conditions**: Mechanical actuation, without human intervention was used for the testing. This was done according to Procedure No. 1735.1 page 793 vol. 3.2 Each sprayer was actuated 5 times to prime. The amount actuated was measured by HPLC assay.*

Tests were performed only for spray content uniformity and through life not at the beginning, middle and end of unit life as requested in the guidance. You should supply a detailed SOP for the methods. All raw data should be submitted in the form of paper copies as well as electronic files (excel) spreadsheets.

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, raw data for spray content uniformity testing and through life testing performed at the beginning, middle and end of unit life is supplied at page 191 of this amendment. The protocol used to conduct the testing is filed at page 57 and the protocol validation report is filed at page 66. Note that the same protocol was used to conduct the priming, through life, and tail-off bioequivalence testing. Electronic Excel spreadsheets of data tables are located on the CD accompanying this amendment.

FDA COMMENT:

3. *The data you supplied for tests such as content uniformity on CD and paper were summary data. The type of data required is the individual data for each of the 10 bottles tested. Comparative raw data should be presented to support the summary results presented in vol. 3.1. Data should be presented for the 13 mL and 26 mL bottles.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, the data tables filed at page 191 detail the individual raw data for content uniformity testing for each of the 10 bottles tested from each of the three lots of 13 mL and 26 mL bottles. Comparative raw data is also presented for the RLD product. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

FDA COMMENT:

4. *Raw data for priming and tail off were not included in the submission. All raw data should be submitted in electronic format as excel spreadsheets using the format in the appended tables 1 – 7.*

   The data for droplet size distribution is incomplete since raw data were not submitted for the beginning, middle, and end of use life. Also the data for spray content uniformity through life of container is incomplete since data was not presented for each of the 10 individual bottles at the beginning, middle and end of use life. The cascade impaction data was summary data.

Data from individual bottles should be presented showing the drug amounts deposited on the throat ——————— and stages 0, 1, 2, 3, and filter of the ——— Cascade Impactor instrument determined by a validated HPLC assay. The tests should be performed at the beginning and end of use life. The raw data should be from 10 actuations per test and 10 bottles each of test and reference products batches tested. This data should be supplied for the 13 mL and 26 mL bottles. Your current submission only contains summary data for the 26 mL bottle. The formats you should use to present the raw data are presented in attached Table 4 for cascade impaction and attached Table 5 for laser diffraction. The data should be submitted in the form of paper copies as well as electronic files (excel spreadsheets).

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, the raw data for priming and tail off testing is detailed in the data tables filed at page 73 and page 192. The tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. The protocol used to conduct the testing is filed at page 57 of this amendment and the protocol validation report is filed at page 66. Note that the same protocol was used to conduct the priming, through life, and tail-off bioequivalence testing. The same samples were used to conduct the priming and through life testing. Different samples were used to conduct the tail-off testing. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

Additionally, the raw data for droplet size distribution testing (particle sizing by laser diffraction) conducted at the beginning, middle and end of use life is detailed in the data tables filed at page 701. Because the only difference between the sprayer used with the 26 mL bottle and the sprayer used with the 13 mL bottle is the length of the dip tube, testing was conducted on the 26 mL configuration only. Electronic Excel spreadsheets of data tables are located on the CD accompanying this amendment.

The raw data for spray content uniformity through life of container is detailed in the data tables filed at page 191 and include data for each of the 10 individual bottles tested at the beginning, middle, and end of use life. The tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. Note that the same protocol was used to conduct the priming, through life, and tail-off bioequivalence testing. The same samples were used to conduct the priming and spray content uniformity through life testing. Different samples were used to conduct the tail-off testing. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

The raw data for cascade impaction testing is detailed in the data tables filed at page 397. A validated HPLC assay method was used to conduct the testing. Please reference the test method TM-—02-01B, HPLC Assay of Cromolyn Sodium in Cromolyn Sodium Nasal Spray, filed with the March 30, 2000, amendment at page 1652 and the method validation report also filed with the March 30, 2000, amendment at page 1410. Because the only difference between the sprayer used with the 26 mL bottle and the sprayer used with the 13 mL bottle is the length of the dip tube, testing was conducted on the 26 mL configuration only. The cascade impaction testing data tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

FDA COMMENT:

5. *The Division of Bioequivalence realizes that the tests for droplet size distribution and cascade impaction generates numerous pages of data. The Division requests that all raw data should be submitted and a representative amount of supportive data such as computer sheets (20%) for the ————————· system showing generated histograms should be included. The data should be presented in excel spreadsheets using the format presented in the appended Table 3 with data for D50 and span for the beginning, middle and end for 10 bottles at 3 distances. The format for cascade impaction data for the different stages for 3 lots of 10 bottles is presented in attached Table 4.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, 20% of the computer sheets from the ————————System showing generated histograms are included with this amendment at page 739. The raw test data for the droplet size distribution (particle sizing by laser diffraction) testing is detailed in the data tables filed at page 701, with data for D50 and SPAN for the beginning, middle, and end for 10 bottles at 3 distances for the L. Perrigo drug product and the RLD product. The droplet size distribution (particle sizing by laser diffraction) testing data tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

The raw test data for the cascade impaction testing is presented in the data tables filed at page 397. The cascade impaction testing data tables are formatted similarly to the data tables supplied with the June 20, 2000, correspondence from FDA. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment. Sample result printouts representing 20% of the data generated by ——————— during the cascade impaction bioequivalence testing are filed at page 404.

FDA COMMENT:

6. *Your data for plume geometry is incomplete. You should submit all raw data related to plume geometry as excel spreadsheets using the format in attached Table 7. The data should include plume width, plume length and plume angle for 10 cans for each of 3 lots of test and reference at three or more times after actuation. 20% of the plume sequence photographs as paper copies should also be submitted with markings used for quantitation.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, the raw data related to plume geometry angle and length and width testing is detailed in the data tables filed at page 1711 and page 1904. The Excel spreadsheets are formatted similarly to the tables supplied with the June 20, 2000, correspondence from FDA. The data includes plume width, plume length, and plume angle data for 10 bottles from each of 3 lots of the L. Perrigo product and the RLD product at three or more times after actuation. The ——————— Bioequivalence Study Appendix 1 entitled, "Commentary on Plume Angle, Width, and Length Measurements" is filed at page 1714. This document provides justification for the test method utilized during the plume geometry bioequivalence testing conducted by ——————— Additionally, 20% of the plume sequence photographs with the markings used for quantification are filed with this amendment at page 1723. Electronic Excel spreadsheets of data tables are located on the CD accompanying this amendment.

The following documentation is also filed with this amendment:

- Addendum to ——————— Protocol —02-02BE, Bioequivalence Study Protocol for Perrigo Company for Testing of 4% Cromolyn Sodium Nasal Spray, to add plume geometry length and width testing. (Page 1980)

- ——————— Test Method TM — 02-PGLW, Plume Geometry Length and Width Measurements for Cromolyn Sodium Nasal Spray. (Page 1987)

- ——————— Plume Geometry Length and Width Method Qualification For Cromolyn Sodium 4% Nasal Spray. (Page 1990)

- ——————— Bioequivalence Study Appendix 1 entitled "Commentary on Plume Angle, Width and Length Measurements". This document provides justification for the test method utilized during the plume angle bioequivalence testing conducted by ———————. (Page 1714)

ADDITIONAL L. PERRIGO COMPANY COMMENTS:

Although not specifically requested in the June 20, 2000, correspondence from the FDA, the raw data related to spray pattern testing is detailed in the data tables filed at page 2026. The Excel spreadsheets are formatted similarly to the tables supplied with the June 20, 2000, correspondence from FDA. The data includes Dmin, Dmax, and Ovality Ratio data for 10 bottles from each of the 3 lots of the 13 mL bottles and the 26 mL bottles for the L. Perrigo product and the RLD product. 20% of the spray pattern scans with the markings used for quantification are filed with this amendment at page 2044. The L. Perrigo Company bioequivalence testing protocol for spray pattern is filed with this amendment at page 2190 and the protocol validation report is filed at page 2193. Electronic Excel spreadsheets of the data tables are located on the CD accompanying this amendment.

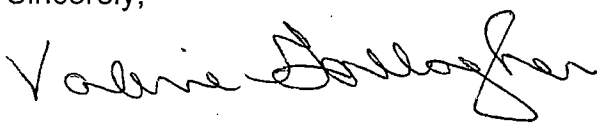
Please note that the contract laboratories used to conduct the testing outlined in this amendment are listed in Section 10 of the March 31, 2000, amendment. At this time, there are no additions or deletions.

L. Perrigo Company hereby restates its request for the FDA to waive the requirement for the submission of an *in vivo* bioavailability/bioequivalence study for this product based upon 21 CFR 320.22(b)(3) as made in the original ANDA submission and subsequent amendments

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA office in Rockville, MD.

We trust that the information supplied with this amendment and the previous amendments provides all the necessary information to address the comments in the June 20, 2000 deficiency letter. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,



Valerie Gallagher
ANDA Regulatory Affairs Project Manager

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

APPEARS THIS WAY
ON ORIGINAL

PERRIGO®

January 24, 2001

Gary Buehler, Acting Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR CHEMISTRY AMENDMENT

ORIG AMENDMENT
N/AC

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence
- Perrigo Chemistry Amendment dated March 31, 2000
- Perrigo Bioequivalence Amendment dated March 31, 2000
- FDA faxed deficiency letter dated June 20, 2000, from the Division of Bioequivalence
- FDA faxed deficiency letter dated October 13, 2000, from the Division of Chemistry
- Perrigo Bioequivalence Amendment dated November 30, 2000

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the comments in the October 13, 2000 deficiency letter from the Division of Chemistry.

FDA COMMENT:

1. Please provide cGMP certifications for ——— for compliance with human drug regulations in 21 CFR Parts 210 and 211.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 25 2001
OGD

RESPONSE:

In accordance with the above comment, a cGMP certification from ——— for compliance with human drug regulations in 21 CFR Parts 210 and 211 is filed in Section 1 at page 3 of this amendment.

L. Perrigo Company hereby ———

Section 10 of the March 31, 2000, amendment. In light of this situation, L. Perrigo Company submits the following documentation:

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

Redacted 11 page(s)

of trade secret and/or

confidential commercial

information from

1/24/2001 PERRIGO LETTER

FDA COMMENT:

19. We are awaiting your responding to the bioequivalence deficiencies which were sent to you on June 20, 2000.

RESPONSE:

Please be advised that L. Perrigo Company filed its response to the bioequivalence deficiencies dated June 20, 2000, with the FDA on November 30, 2000.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

FDA COMMENT:

1. Please provide any additional long-term stability data, if available.

RESPONSE:

In accordance with the above comment, the long-term stability reports have been updated with 12-month interval testing data. The updated long-term stability reports are filed in Section 18 at page 107 of this amendment.

FDA COMMENT:

2. Your labeling information is pending review.

RESPONSE:

In accordance with the above comment, L. Perrigo Company contacted the FDA Project Manager for a status update on the labeling review. Labeling comments were subsequently received by fax on January 19, 2001. L. Perrigo Company will respond to the comments in the near future.

FDA COMMENT:

3. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

RESPONSE:

L. Perrigo Company understands that the CGMP compliance of all the facilities listed in the ANDA application will be evaluated by FDA's Office of Compliance and that a satisfactory evaluation is required prior to the approval of this ANDA application.

ADDITTIONAL INFORMATION:

Please note that a Summary of Documentation Revisions table is included with this amendment in Section 19 at page 163. It details the documentation revisions noted in the above L. Perrigo Company responses as well as additional revisions made since the March 31, 2000, amendment. Additionally, those documents that were revised but not noted in the above L. Perrigo responses are filed in Section 20 at page 167 of this amendment.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA office in Rockville, MD.

We trust that the information supplied with this amendment and the previous amendments provides all the necessary information to address the comments in the October 13, 2000 deficiency letter. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,

Valerie Gallagher
ANDA Regulatory Affairs Project Manager

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

PERRIGO®

URGENT
FAX AMENDMENT

PERRIGO

ORIG AMENDMENT
N/AB

Regulatory Affairs Department
Fax: 616-673-7655

FACSIMILE TRANSMISSION

DATE: **January 26, 2001**

TO: **Krista Scardina**
Fax No. **301-594-0181**

FROM: **Valerie Gallagher**
ANDA Regulatory Affairs Project Manager

TEL. No. **616-673-9367**

Fax No. **616-673-7655**

NUMBER OF PAGES (INCLUDING COVER PAGE) 11

MESSAGE:

Attached you will find a Bioequivalence Amendment responding to the telephone comments I received from you on 1/17/01 regarding the ANDA noted below. Please call me if you have any questions.

ANDA No.: 75-427
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray

Please call Valerie Gallagher at (616) 673-9367 if there are transmission problems.

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

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BIOEQUIVALENCE AMENDMENT

Gary Buehler, Acting Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Faxed (301-594-0181) and mailed by Federal Express 1/26/01

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- L. Perrigo Company Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence
- L. Perrigo Company Chemistry Amendment dated March 31, 2000
- L. Perrigo Company Bioequivalence Amendment dated March 31, 2000
- FDA faxed deficiency letter dated June 20, 2000, from the Division of Bioequivalence
- FDA faxed deficiency letter dated October 13, 2000, from the Division of Chemistry
- L. Perrigo Company Bioequivalence Amendment dated November 30, 2000
- L. Perrigo Company Chemistry Amendment dated January 24, 2001
- FDA telephone comments received on January 17, 2001, from Division of Bioequivalence

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the telephone comments received on January 17, 2001, from Division of Bioequivalence Project Manager Krista Scardina.

FDA COMMENT:

Regarding the Droplet Size Distribution testing, please provide the following information:

1. What were the three time delays – at formation, fully developed, and at dissipation of the sprays?

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

2. How were the times selected? For example, were they chosen in relation to percent of transmission obscuration?

3. What was the duration of sampling time at each of the three phases of plume life?

4. Provide representative plots of percent transmission vs. time, D50, D90, and D10 vs. time on the same plot.

RESPONSE:

The Droplet Size Distribution bioequivalence testing for the cromolyn sodium nasal spray was conducted by ——————— for L. Perrigo Company. Please see the attached letter dated January 24, 2001, from ——————— Ph.D., Director, ——————————————————— ———————for responses to each of the above comments.

Please note that ——————— Test Method TM —02-MA referenced in the letter from ——— was previously submitted in L. Perrigo Company's 3/31/00 Major Amendment at page 1662.

L. Perrigo Company hereby restates its request for the FDA to waive the requirement for the submission of an *in vivo* bioavailability/bioequivalence study for this product based upon 21 CFR 320.22(b)(3) as made in the original ANDA submission and subsequent amendments

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA office in Rockville, MD.

We trust that the information supplied with this amendment provides all the necessary information to address the telephone comments received on January 17, 2001. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,

Valerie Gallagher
ANDA Regulatory Affairs Project Manager

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

PERRIGO®

LABELING AMENDMENT

Gary Buehler, Acting Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AF

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the fax comments received on January 19, 2001, from the Labeling Review Branch.

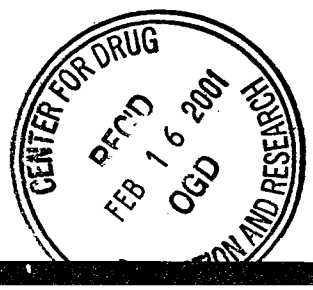
FDA COMMENT:

1. GENERAL COMMENTS:
Please note that the reference listed drug labeling which you submitted for your side-by-side has not yet been approved. Therefore, revise your labels and labeling to be in accord with the currently approved labeling for the reference listed drug, NASALCROM® (McNeil; NDA#20-463; approved January 3, 1997). In addition, labeling making a distinction for "Children's NASALCROM®" has not yet been approved. Therefore, we will be unable to approve similar labeling for your ANDA. We have enclosed a copy of the innovator's labeling for your convenience.

RESPONSE:

In response to the above comment, L. Perrigo Company has revised its labels and labeling to be in accord with the currently approved labeling for the reference listed drug, NASALCROM® (McNeil; NDA#20-463; approved January 3, 1997), as supplied with the January 19, 2001, fax comments from the Labeling Review Branch.

12 copies of final printed labeling for the bottle labels, the cartons, and the information leaflet are enclosed along with side-by-side comparison charts for each labeling component.



515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

FDA COMMENT:

2. CONTAINER (13mL and 26 mL)
Please include the NDC# and exp. date.

RESPONSE:

In response to the above comment, L. Perrigo Company does not usually note NDC numbers on labeling submitted to FDA for review for the reason that use of NDC numbers on product labeling is voluntary and customer specific. Therefore, NDC numbers have not been noted on the final printed labeling submitted with this amendment.

Also in response to the above comment, please note that the manufacturing lot number and product expiration date will be imprinted upon the bottle labels at the time of manufacture. This commitment is also noted in the Labeling Statement accompanying this amendment.

FDA COMMENT:

3. CARTON (13mL and 26 mL) – Front and right side panels – See GENERAL COMMENT. In addition, rather than using "this product" please site the product name. Please use capital letters for "Poison Control Center". Include NDC# and exp. date.

RESPONSE:

In response to the above specific comment, L. Perrigo Company respectfully declines to replace "this product" with the product title shown on the carton labeling principle display panel for the reason that L. Perrigo Company allows the customer to choose the product title used on the principle display panel while requiring use of "this product" elsewhere in the labeling for reasons of standardization.

Also in response to the above comment, capital letters have been used for "Poison Control Center" as requested in the labeling submitted with this amendment.

Please see L. Perrigo Company's response to FDA Comment 2 above regarding NDC numbers.

Please also note that "LOT NO." and "EXP." are located on the bottom panel of the product cartons. The actual manufacturing lot number and product expiration date will be imprinted on the carton in these locations at the time of manufacture. This commitment is also noted in the Labeling Statement accompanying this amendment.

FDA COMMENT:

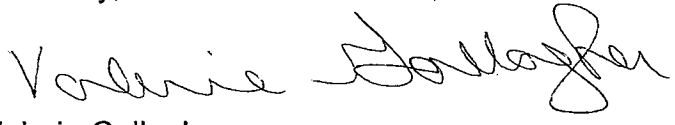
4. NASAL ALLERGY SYMPTOM PREVENTION AND RELIEF LEAFLET – See GENERAL COMMENT.

RESPONSE:

See L. Perrigo Company's response above to FDA's General Comment.

We trust that the information supplied with this amendment provides all the necessary information to address the fax comments received on January 19, 2001, from the Labeling Review Branch. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,



Valerie Gallagher
Supervisor, ANDA Regulatory Affairs

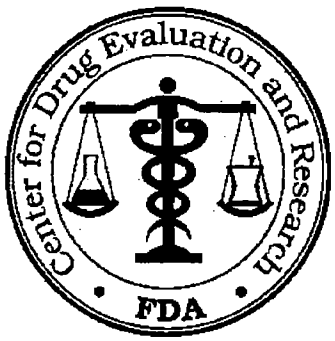
Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

BIOEQUIVALENCY AMENDMENT

ANDA 75-427

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APR 3 0 2001



TO: APPLICANT: L. Perrigo Company

TEL: 616-673-8451

ATTN: Brian R. Schuster

FAX: 616-673-7655

FROM: Krista M. Scardina, Pharm.D.

PROJECT MANAGER: 301-827-5847

Dear Mr. Schuster:

This facsimile is in reference to the bioequivalency data submitted on November 30, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray.

Reference is also made to your amendment(s) dated: January 26, 2001.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

(rs)

APR 3 0 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-427 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray

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

Deficiencies:

1.You should explain the relationship between the NasalCrom lots # 's 52DCB and 32DKA listed in vol. 3.1 pages 6-8 to the lot numbers listed in the studies which were :

13mL	26mL
86DUY	13DSP
47DYC	44DHC
46DYC	49DYC

2. You should supply repriming data consistent with use instructions in the package insert. The bottles should be primed, wasting 5 sprays, with the 6th spray assayed (i.e., prime attained). Bottles should then be set aside for 14 days after which the bottles should be reprimed by wasting 2 sprays with the 3rd spray assayed (i.e., prime attained). This should be done using 3 different lots of test and reference.

3.Your plume geometry data are incomplete. You should provide plume angle data for the delay times greater than 2 msec (e.g., 20 and 50 msec).

APPEARS THIS WAY
ON ORIGINAL

4. Your spray pattern data are unacceptable, due to failure to characterize and quantitate the size or shape of spray patterns. It is not clear if you used a drug specific reagent to visualize the spray patterns. The representative photocopies submitted show rectangles drawn around the spray patterns to determine Dmax and Dmin. However, these rectangles fail to reflect the size and shape of spray patterns.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (Dmax and Dmin) by definition should intersect the center of the spray pattern.

You should submit revised spray pattern data after proper quantitation. You may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, Dmax and Dmin) along with identity of distance, product, and lot number.

Sincerely yours,

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

PERRIGO®

June 29, 2001

MINOR BIOEQUIVALENCY AMENDMENT

Gary Buehler, Acting Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence
- Perrigo Chemistry Amendment dated March 31, 2000
- Perrigo Bioequivalence Amendment dated March 31, 2000
- FDA faxed deficiency letter dated June 20, 2000, from the Division of Bioequivalence
- FDA faxed deficiency letter dated October 13, 2000, from the Division of Chemistry
- Perrigo Bioequivalence Amendment dated November 30, 2000
- Perrigo Chemistry Amendment dated January 24, 2001
- FDA faxed deficiency letter dated January 19, 2001, from the Labeling Review Branch
- Perrigo Labeling Amendment dated February 15, 2001
- FDA faxed deficiency letter dated April 30, 2001, from the Division of Bioequivalence

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the comments in the April 30, 2001 deficiency letter from the Division of Bioequivalence.

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 02 2001
OGD

FDA COMMENT:

1. *You should explain the relationship between the NasalCrom lot #s 52DCB and 32DKA listed in vol. 3.1 pages 6-8 to the lot numbers listed in the studies which were:*

13mL	26mL
86DUY	13DSP
47DYC	44DHC
46DYC	49DYC

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

L. PERRIGO COMPANY RESPONSE:

In light of the above comment, a review was conducted of the documentation submitted thus far to the FDA regarding this drug product. We believe the above comment is referencing Section 4 of the Major Amendment submitted on March 31, 2000.

Section 4 of the March 31, 2000, Major Amendment provided a comparison between the Perrigo drug product and the Reference Listed Drug. Comparative analysis reports for the exhibit batch and the Reference Listed drug were submitted in Special Assay Report Nos. 14900, 14901, and 14913.

The comparative analysis reports contained data from testing conducted on two randomly selected lots of the Reference Drug available in the retail market, 52DCB (13 mL) and 32DKA (26 ml).

As noted in the above FDA comment, several additional lots of the Reference Listed Drug were used to facilitate the bioequivalence studies submitted in Perrigo's November 30, 2000, Bioequivalence Amendment. Perrigo was unable secure a sufficient number of 52DCB and 32DKA lot number samples to facilitate the additional testing required to support the amendment. Therefore, additional lots with sufficient sample quantities to support the testing were randomly selected from those lots of the Reference Listed Drug available for purchase in the retail market.

FDA COMMENT:.

2. *You should supply repriming data consistent with use instructions in the package insert. The bottles should be primed, wasting 5 sprays, with the 6th spray assayed (i.e., prime attained). Bottles should then be set aside for 14 days after which the bottles should be reprimed by wasting 2 sprays with the 3rd spray assayed (i.e., prime attained). This should be done using 3 different lots of test and reference.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, repriming data consistent with the use instructions in the package insert is filed in Section 3 of this amendment. The bottles were primed, wasting 5 sprays, with the 6th spray assayed (i.e., prime attained). Bottles were then set aside for at least 14 days after which the bottles were reprimed by wasting 2 sprays with the 3rd spray assayed (i.e., prime attained). This testing was done using 10 bottles of 3 different lots of 13 mL and 26 mL samples of test and reference listed drug product. The data indicates that the Perrigo drug product compares favorably to the reference listed drug product.

The L. Perrigo Company protocol entitled, "Protocol for Priming, Reprime, Through Life, and Tail-Off for Cromolyn Sodium Nasal Solution" has been revised to include sample preparation instructions for the prime and repriming testing and is filed in Section 3 of this amendment. Also filed in Section 3 of this amendment is a revised method validation report with regard to method 1735, as well as the sample result printouts for the data generated during the repriming testing.

FDA COMMENT:

3. *Your plume geometry data are incomplete. You should provide plume angle data for the delay times greater than 2 msec (e.g., 20 and 50 msec).*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above FDA comment, plume angle testing for the delay times greater than 2 msec (e.g., 20 and 50 msec) was conducted by ———— ———— and the data is filed in Section 4 of this amendment. The data indicates that the Perrigo drug product compares favorably to the reference listed drug product.

———————— report entitled "Video Plume Geometry Method Qualification for Cromolyn Sodium Nasal Spray" is also filed in Section 4. The plume geomtery angle photographs generated by ———————— during the plume geometry angle testing are also filed in Section 4.

FDA COMMENT:

4. *Your spray pattern data are unacceptable, due to failure to characterize and quantitate the size or shape of spray patterns. It is not clear if you used a drug specific reagent to visualize the spray patterns. The representative photocopies submitted show rectangles drawn around the spray patterns to determine Dmax and Dmin. However, these rectangles fail to reflect the size and shape of the spray patterns.*

Acceptable spray pattern quantification should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (Dmax and Dmin) by definition should intersect the center of the spray pattern.

You should submit revised spray pattern data after proper quantification. You may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative photographs/photocopies clearly indicative of the quantification (including marking for spray pattern perimeter, Dmax and Dmin) along with identity of distance, product, and lot number.

L. PERRIGO COMPANY RESPONSE:

In light of the above FDA comment, Perrigo contracted with ———————— to generate spray pattern quantification data from the spray patterns generated during the previous testing using an automated image analysis technique to reflect the true shape and size of the spray patterns and to reduce subjectivity and improve accuracy and precision. The data generated using the automated image analysis technique is filed in Section 5 of this amendment. The data indicates that the Perrigo drug product compares favorably to the reference listed drug product.

The spray pattern representations generated using ———— automated image analysis technique include perimeter markings, Dmax and Dmin measurements, distance, product, and lot number. The automated image analysis system used by ———— did not mark the intersection location of Dmax and Dmin on the image. The location is calculated automatically by the program and the Dmax and Dmin calculations are noted in the measurement data area of the print out. Please note that the spray pattern measurements and calculations generated during the spray pattern testing previously conducted by Perrigo appear on the spray pattern representations generated by ————. The Perrigo-generated measurements and calculations were disregarded during the second analysis conducted by ————.

The spray patterns captured on TLC plates were not generated using a drug specific reagent. A drug specific reagent was deemed unnecessary because the cromolyn sodium nasal spray solution is a solution, not a suspension. As noted in L. Perrigo Company's bioequivalence protocol for spray pattern testing, ———— dye is added to the bottles of solution so that the spray pattern is visible when sprayed onto the TLC plate (See Section 26, page 2190, of L. Perrigo Company's 11/30/00 Bioequivalence Amendment). Therefore, because this product involves an API, cromolyn sodium, that is in a solution, not a suspended state, we believe there would be no significant change in the data submitted if a drug specific reagent were used to facilitate the testing.

Please note that ———————— the contract laboratory used to conduct some of the testing outlined in this amendment, is listed in Section 10 of the March 31, 2000, amendment. At this time, there are no additions or deletions.

As previously requested by FDA, electronic Excel spreadsheets of the data tables presented in this amendment are located on the CD accompanying this shipment.

L. Perrigo Company believes that the large volume of in-vitro test data submitted in this amendment and the previous amendments demonstrates that the Perrigo drug product compares favorably with the reference listed drug product and hereby restates its request for the FDA to waive the requirement for the submission of an *in vivo* bioavailability/bioequivalence study for this product based upon 21 CFR 320.22(b)(3) as made in the original ANDA submission and subsequent amendments.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA office in Rockville, MD.

We trust that the information supplied with this amendment and the previous amendments provides all the necessary information to address the comments in the April 30, 2001, deficiency letter. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,

Valerie Gallagher
Supervisor, ANDA Regulatory Affairs

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

APPEARS THIS WAY
ON ORIGINAL

PERRIGO®

July 12, 2001

LABELING AMENDMENT

Gary Buehler, Acting Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo.Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998. L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to submit final printed labeling for the L. Perrigo Company Cromolyn Sodium Nasal Spray USP product that compares to the Reference Listed Drug (RLD) labeling that was approved by FDA on March 27, 2001.

This labeling amendment contains a labeling statement of similarity, side-by-side comparisons, a copy of the RLD labeling approval letter obtained from the FDA web site and copies of the approved labeling obtained from FDA as result of a request made by Perrigo, and final printed labeling for the L. Perrigo Company Cromolyn Sodium Nasal Spray USP product.

We trust that the information supplied with this amendment provides all the necessary information to facilitate approval of the final printed labeling. However, should additional information be required, please contact me as soon as possible by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,

Valerie Gallagher
Supervisor, ANDA Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 18 2001
OGD

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

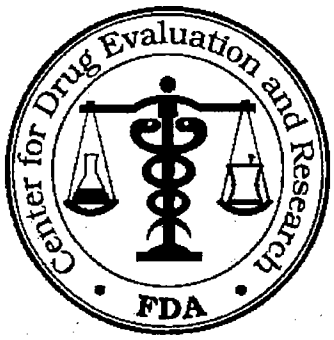
515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

MINOR AMENDMENT

ANDA 75-427

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL 13 2001



TO: APPLICANT: L. Perrigo Co. TEL: 616 673-9367

ATTN: ~~Brian R. Schuster~~ Valerie Gallagher FAX: 616 673-7655

FROM: Michelle Dillahunt PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray.

Reference is also made to your amendment(s) dated: January 24, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry comments included.

7/13/01 MD

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of trade secret and/or

confidential commercial

information from

7/13/2001 FDA FAX

PERRIGO®

July 26, 2001

BIOEQUIVALENCY TELEPHONE AMENDMENT

Gary Buehler, Acting Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/NC

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence
- Perrigo Chemistry Amendment dated March 31, 2000
- Perrigo Bioequivalence Amendment dated March 31, 2000
- FDA faxed deficiency letter dated June 20, 2000, from the Division of Bioequivalence
- FDA faxed deficiency letter dated October 13, 2000, from the Division of Chemistry
- Perrigo Bioequivalence Amendment dated November 30, 2000
- Perrigo Chemistry Amendment dated January 24, 2001
- FDA faxed deficiency letter dated January 19, 2001, from the Labeling Review Branch
- Perrigo Labeling Amendment dated February 15, 2001
- FDA faxed deficiency letter dated April 30, 2001, from the Division of Bioequivalence
- Telephone call from Krista Scardina, Division of Bioequivalence Project Manager, on July 26, 2001

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the comments received on July 27, 2001, from a voice mail message from Krista Scardina, a Division of Bioequivalence Project Manager.

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 27 2001

FDA COMMENT:

1. Please provide a data disc to replace the CD supplied with the Bioequivalence Amendment filed with FDA on 6/29/01. The data disc should contain Excel Spreadsheet formatted files and ASCII formatted files. FDA cannot read the CD supplied with the 6/29/01 documentation.

515 East Superior
Allegan, Michigan 49010
(616) 673-8451

L. PERRIGO COMPANY RESPONSE:

In accordance with the above request, enclosed with this amendment is a data disc containing copies of the Excel spreadsheets submitted on CD with the 6/29/01 Bioequivalence Amendment. As requested, ASCII formatted files of the same spreadsheets have also been supplied on the data disc.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA office in Rockville, MD.

We trust that the information supplied with this amendment and the previous amendments provides all the necessary information to facilitate final approval of this application. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,

Valerie Gallagher
Supervisor, ANDA Regulatory Affairs

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

PERRIGO®

July 31, 2001

MINOR CHEMISTRY AMENDMENT

ORIG AMENDMENT
N/AM

Gary Buehler, Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence
- Perrigo Chemistry Amendment dated March 31, 2000
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- Perrigo Labeling Amendment dated February 15, 2001
- FDA faxed deficiency letter dated April 30, 2001, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated June 29, 2001
- Perrigo Labeling Amendment dated July 12, 2001
- FDA faxed deficiency letter dated July 13, 2001, from the Division of Chemistry

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the comments in the July 13, 2001 deficiency letter from the Division of Chemistry.

FDA COMMENT:

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 02 2001
OGD

A. Deficiencies:

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

7/31/2001 PERRIGO LETTER

FDA COMMENT:

1. *Please provide any additional stability data, if available.*

L. PERRIGO COMPANY RESPONSE:

In accordance with the above comment, additional room temperature stability data through 18 months is filed in Section 5 of this amendment.

FDA COMMENT:

2. *In your stability reports, it would be more meaningful to represent beginning, middle and end by B, M, and E rather than A, B, and C.*

L. PERRIGO COMPANY RESPONSE:

L. Perrigo Company acknowledges and notes FDA's comment that it would be more meaningful to represent beginning, middle, and end by B, M, and E, rather than A, B, C. This comment will be considered when developing stability reports for future projects.

FDA COMMENT:

3. *The GMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.*

L. PERRIGO COMPANY RESPONSE:

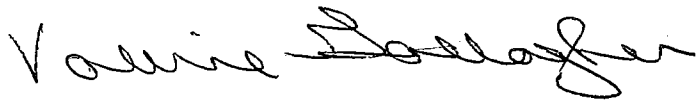
L. Perrigo Company acknowledges and notes FDA comment 3. above, and understands that the GMP compliance of all the facilities listed in our application will be evaluated by the Office of Compliance and that a satisfactory evaluation is required prior to approval of this application.

Please note that L. Perrigo Company further amended this application on July 12, 2001, to submit final printed labeling comparable to the Reference Listed Drug labeling that was approved by the FDA on March 27, 2001.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA office in Rockville, MD.

We trust that the information supplied with this amendment and the previous amendments provides all the information necessary to facilitate final approval of this application. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,



Valerie Gallagher
Supervisor, ANDA Regulatory Affairs

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

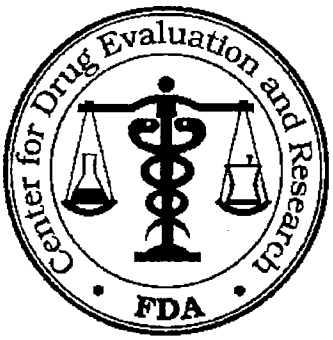
APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

ANDA 75-427

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

AUG 31 2001



TO: APPLICANT: L. Perrigo Company

TEL: 616-673-8451

ATTN: Brian R. Schuster

FAX: 616-673-7655

FROM: Krista M. Scardina, Pharm.D.

PROJECT MANAGER: 301-827-5847

Dear Mr. Schuster:

This facsimile is in reference to the bioequivalency data submitted on June 29, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

(14)

AUG 31 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-427 APPLICANT: L.Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray (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. You should repeat the spray pattern testing without manipulation of either the test or reference products.The visualization agent/dye should be used post-actuation. The visualization agent should preferably be drug or formulation specific. You should supply to the Division of Bioequivalence **the actual computer pictures** used to measure the Dmax and Dmin distances along with the computer printout of the values. The pictures should exhibit Dmax and Dmin lines.

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours,

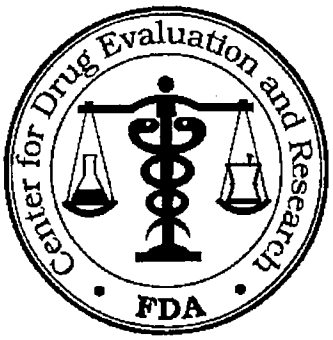
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FAX AMENDMENT

ANDA 75-427

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

SEP 17 2001



TO: APPLICANT: L. Perrigo

ATTN: Valerie Gallagher

TEL: 616- 673-8451

FAX: 616- 673-7655

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray (4%).

Reference is also made to your amendment(s) dated: February 15, July 12 and July 31, 2001.

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FAX AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS: Chemistry comments included.

9/17/01 NO

SEP 17 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-427

APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cromolyn Sodium Nasal Solution USP, 5.2 mg/spray

The deficiency presented below represents a FAX deficiency:

A. Deficiency:

Bioequivalence for this product has not been established. Please respond to the deficiencies provided to you on August 31, 2001.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comment in your response:

The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

Sincerely yours,

Paul Thoren for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

PERRIGO®

October 17, 2001

FAX CHEMISTRY AMENDMENT

Gary Buehler, Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

FA CHEM AMENDMENT

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence
- Perrigo Chemistry Amendment dated March 31, 2000
- Perrigo Bioequivalence Amendment dated March 31, 2000
- FDA faxed deficiency letter dated June 20, 2000, from the Division of Bioequivalence
- FDA faxed deficiency letter dated October 13, 2000, from the Division of Chemistry
- Perrigo Bioequivalence Amendment dated November 30, 2000
- Perrigo Chemistry Amendment dated January 24, 2001
- FDA faxed deficiency letter dated January 19, 2001, from the Labeling Review Branch
- Perrigo Labeling Amendment dated February 15, 2001
- FDA faxed deficiency letter dated April 30, 2001, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated June 29, 2001
- Perrigo Labeling Amendment dated July 12, 2001
- FDA faxed deficiency letter dated July 13, 2001, from the Division of Chemistry
- Perrigo Chemistry Amendment dated July 31, 2001
- FDA faxed deficiency letter dated August 31, 2001, from the Division of Bioequivalence
- FDA faxed deficiency letter dated September 17, 2001, from the Division of Chemistry
- Perrigo Bioequivalence Amendment dated October 17, 2001

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the comments in the September 17, 2001 deficiency letter from the Division of Chemistry.

Allegan, Michigan 49010
(616) 673-8451

FDA COMMENT

A. *Bioequivalence for this product has not been established. Please respond to the deficiencies provided to you on August 31, 2001.*

L. PERRIGO COMPANY RESPONSE:

After requesting and receiving clarification from the Division of Bioequivalence, L. Perrigo Company responded to the August 31, 2001, letter from the Division of Bioequivalence with an amendment dated October 17, 2001. A copy of the amendment letter is enclosed for your information.

FDA COMMENT

B. *The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.*

L. PERRIGO COMPANY RESPONSE:

L. Perrigo Company acknowledges and notes the above FDA comment and understands that the CGMP compliance of all the facilities listed in our application will be evaluated by FDA's Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA office in Rockville, MD.

We trust that the information supplied with this amendment and the previous amendments provides all the information necessary to facilitate final approval of this application. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,

Valerie Gallagher
Supervisor, ANDA Regulatory Affairs

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

APPEARS THIS WAY
ON ORIGINAL

PERRIGO®

October 17, 2001

BIOEQUIVALENCE AMENDMENT

Gary Buehler, Director
FDA, CDER, OPS, OGD
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AB

DRUG AMENDMENT

Re: Abbreviated New Drug Application
Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray
ANDA 75-427

Dear Mr. Buehler:

Reference is made to L. Perrigo Company ANDA 75-427 Cromolyn Sodium Nasal Spray USP, 5.2 mg/spray, filed on July 31, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA faxed deficiency letter dated November 3, 1998, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated November 20, 1998
- FDA faxed deficiency letter dated March 5, 1999, from the Divisions of Chemistry and Labeling
- FDA faxed deficiency letter dated March 30, 1999, from the Division of Bioequivalence
- Perrigo Chemistry Amendment dated March 31, 2000
- Perrigo Bioequivalence Amendment dated March 31, 2000
- FDA faxed deficiency letter dated June 20, 2000, from the Division of Bioequivalence
- FDA faxed deficiency letter dated October 13, 2000, from the Division of Chemistry
- Perrigo Bioequivalence Amendment dated November 30, 2000
- Perrigo Chemistry Amendment dated January 24, 2001
- FDA faxed deficiency letter dated January 19, 2001, from the Labeling Review Branch
- Perrigo Labeling Amendment dated February 15, 2001
- FDA faxed deficiency letter dated April 30, 2001, from the Division of Bioequivalence
- Perrigo Bioequivalence Amendment dated June 29, 2001
- Perrigo Labeling Amendment dated July 12, 2001
- FDA faxed deficiency letter dated July 13, 2001, from the Division of Chemistry
- Perrigo Chemistry Amendment dated July 31, 2001
- FDA faxed deficiency letter dated August 31, 2001, from the Division of Bioequivalence
- FDA faxed deficiency letter dated September 17, 2001, from the Division of Chemistry

L. Perrigo Company hereby amends this application in accordance with 21 CFR 314.96 to address the comments in the August 31, 2001 deficiency letter from the Division of Bioequivalence.

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

FDA COMMENT

You should repeat the spray pattern testing without manipulation of either the test or reference products. The visualization agent/dye should be used post-actuation. The visualization agent should preferably be drug or formulation specific. You should supply to the Division of Bioequivalence the actual computer pictures used to measure the Dmax and Dmin distances along with the computer print out of the values. The pictures should exhibit Dmax and Dmin lines.

L. PERRIGO COMPANY RESPONSE:

In accordance with the above comment, L. Perrigo Company contracted with ——— (now known as ———) to conduct the repeat spray pattern bioequivalence testing. ——— is an outside laboratory that conducted previously-submitted bioequivalence testing to support this application. As requested by FDA, the test and reference products were tested without manipulation and the visualization agent/dye was used post-actuation.

Prior to initiating the retesting, L. Perrigo Company sought clarification from FDA regarding several issues. During a conference call on September 25, 2001, with Krista Scardina and Dr. Singh, FDA Division of Bioequivalence staff members, the following clarification information was provided to L. Perrigo Company:

-When asked if using ——— to facilitate visualization of the spray patterns would be acceptable, Dr. Singh indicated that a visualization process involving ——— would probably be acceptable.

-When asked what distances would be acceptable to facilitate the repeat spray pattern testing, Dr. Singh recommended distances of 2, 4, and 6 cm.

-Dr. Singh indicated that the repeat spray pattern testing should evaluate only the 26 mL test and reference product samples.

-With regard to the Dmin/Dmax lines being represented on the spray pattern printouts, Dr. Singh indicated that 20% of all the spray pattern printouts generated should be submitted to FDA for review and that half of the submitted spray pattern printouts should have Dmin/Dmax lines drawn manually on the printouts.

Actual size color printouts of 20% of the spray patterns generated during the spray pattern testing are filed in Section 15 of this amendment and reflect automated Dmin/Dmax calculations. Half of the 20% of the spray patterns submitted were also evaluated without the aid of an automated calculation system and those color printouts reflect manually calculated Dmin/Dmax lines and are filed in Section 14 of this amendment.

The printing system used by ——— to generate the color printed spray patterns filed in Sections 14 and 15 portray the spray patterns in a reduced size format. ——— determined that the actual size on-screen spray patterns were reduced during the printing process by a factor of 1.82 by comparing the reduced size spray pattern printouts with the on-screen actual size spray patterns. The manual Dmin/Dmax measurements were generated using the reduced size spray pattern printouts and these measurements are recorded on the reduced size color printouts in Section 14 and in the Data Summary Table filed in Section12. The manual measurements from the Data Summary Table were transferred to the Result Table filed in Section 10 after applying the factor of 1.82. Although the color printed spray patterns in Section 15 portray reduced size images, the Measurement Data Box reflects automated measurements generated from the actual size on-screen images without applying the conversion factor. The first measurement reflected in the Measurement Data Boxes correlates with the upper most spray pattern image. The measurements reflected in the Measurement Data Boxes are noted in the Data Summary Table filed in Section 11 and the Result Table filed in Section 9.

The Test Result Tables and Summary Data Tables are formatted as Excel spreadsheets and are filed in Sections 10 through 13 of this amendment. Electronic versions of the files are supplied on the attached diskette. Please see the comprehensive Table of Contents for a complete listing of all documents submitted to support this amendment.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment that was submitted to the FDA office in Rockville, MD.

On October 17, 2001, L. Perrigo Company also filed an amendment with The Division of Chemistry in response to the September 17, 2001, Division of Chemistry letter requesting a response to the August 31, 2001, Division of Bioequivalence letter.

We trust that the information supplied with this amendment and the previous amendments provides all the information necessary to facilitate final approval of this application. However, should additional information be required, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at vgallagh@perrigo.com.

Sincerely,

Valerie Gallagher
Supervisor, ANDA Regulatory Affairs

Enc. -Review Copy of amendment documentation and response letter
-Archive Copy of amendment documentation and response letter

APPEARS THIS WAY
ON ORIGINAL