

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-067

Approval Letter

ANDA 75-067

JUL 19 1999

Alpharma, U.S. Pharmaceuticals Division
Attention: Martin Levy
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

This is in reference to your abbreviated new drug application dated January 31, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL.

Reference is also made to your amendments dated September 15, 1998, and April 12, and May 13, 1999.

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 labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Intal Nebulizer Solution, 20 mg/2 mL, of Rhone Poulenc Rorer Pharmaceuticals, Inc.).

Under 21 CFR 314.70, 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

Page 2

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

(Handwritten initials)
/S/

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

cc:

X *Schiffman EIR*

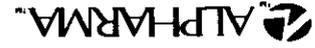
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-067

FINAL PRINTED LABELING

CROMOLYN SODIUM INHALATION SOLUTION USP
20 mg/2 mL

NDC 0472-0750-60



NDC 0472-0750-60

CROMOLYN SODIUM INHALATION SOLUTION USP
20 mg/2 mL

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION: Each 2 mL ampule contains 20 mg cromolyn sodium USP, in purified water.

NOTE: See package insert for full prescribing information including contraindications, warnings and precautions.

Cromolyn Sodium Inhalation Solution should be stored between 15°-30°C (59°-86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Store ampules in foil pouch until ready to use.

Keep out of the reach of children.

0750099782 VC100304

60 Ampules - 2 mL each

An aqueous solution for nebulization.
NOT FOR INJECTION.



611

19 39

Original

 ALPHARMA

NDC 0472-0750-60

CROMOLYN SODIUM INHALATION SOLUTION USP
20 mg/2 mL

CAUTION: Federal law prohibits dispensing without prescription.

60 Ampules - 2 mL each

An aqueous solution for nebulization.
NOT FOR INJECTION.

Manufactured by
Automatic Liquid Packaging, Inc.
Woodstock, IL 60098

Manufactured for
AlphaPharma USP Inc., Baltimore, MD 21244



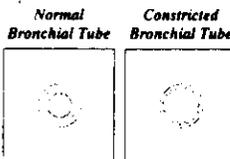


APPROVED

PHARMACEUT: Patient Instructions. Please do not remove.

Living a Full Life with Asthma

You or your child may be among the millions of Americans who have asthma. For most patients, asthma need not limit your lifestyle, if you closely follow the asthma management plan your doctor provides for you. Your doctor has given you this instruction sheet to help you learn more about asthma and ways to control it.



What is Asthma?

Asthma is a disease that causes patients to have difficulty breathing. Asthma "attacks" occur when the air passages (airways) to the lungs close up, blocking air from passing through. The closing up is caused by two things: 1) the muscles around the airways tighten (constrict) making the airway narrower, and 2) the passage lining swells and produces larger amounts of mucus (a sticky liquid normally found in the airways). This swelling is caused by a certain type of inflammation that can build up in the airways of patients with asthma. Inflammation and the airway sensitivity that results from it cause further attacks to occur.

What Causes These Attacks?

Asthma experts now know that patients with asthma have attacks because their airways are inflamed and overreactive. Their lungs become super-sensitive to certain irritants or "triggers", such as cold dry air, pollen, smoke, or cat dander. In the presence of such triggers, someone with asthma may have an attack, and attacks may occur more often.



Asthma triggers fall into 6 categories:

- 1) Substances that cause allergies (pollens, animal dander, molds, house dust, some foods and medicines)
- 2) Infections that affect breathing (colds, flu)
- 3) Emotional stress (difficult situations at home, school, work)
- 4) Strenuous exercise
- 5) Irritating gases (chlorine, perfume, tobacco smoke)
- 6) Sudden changes in temperature or humidity

How To Prevent Asthma Attacks

No medicine or procedure will "cure" asthma. The key to asthma relief, therefore, is to prevent attacks and to relieve attack symptoms if they do occur. A successful prevention plan* will do the following:



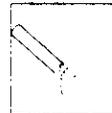
- 1) Keep your activities, including exercise, at normal levels.
- 2) Keep your lungs functioning normally or at a near normal level.
- 3) Prevent symptoms such as coughing or breathlessness that can keep you up at night, or occur in the early morning hours, or after exertion.
- 4) Prevent asthma attacks from happening.
- 5) Avoid unpleasant or harmful side effects that may result from using asthma medicine.

The best way to prevent asthma attacks is to avoid the triggers that bother you or your child. Try to identify the specific things that cause problems for you- things such as certain foods, house dust, or animal dander. Avoiding these triggers may be difficult or unpleasant. You may need to find a new home for a family pet or remove a carpet or a favorite stuffed toy. Even though these steps are difficult, they may be necessary in order to help prevent asthma attacks.

If house dust is a trigger, remove dust-collectors such as feather pillows, mattresses, quilts, and carpets from the bedroom. Mattresses and pillows can be covered with allergen-free covers. If a certain food triggers attacks, keep it out of your diet. Irritants in the air can be reduced by air conditioning, electrostatic air filters, or small-pore (HEPA) filters. Be careful of certain medicines. Aspirin and aspirin-like pain relievers, for example, can trigger attacks in some people and should be avoided if they do.

Other Do's and Don'ts

Anyone with asthma should stick to a healthy, balanced diet, get lots of rest and moderate exercise, and follow these do's and don'ts:



- 1) Don't smoke, and don't stay in the same room with people that do.
- 2) Avoid fresh paint.
- 3) Avoid sudden changes of temperature. Don't go in and out of extremely cool air-conditioned buildings during hot weather.
- 4) Stay home in extremely cold weather, if possible.
- 5) Stay away from people with colds or flu.
- 6) Try to avoid emotionally upsetting situations.
- 7) Drink lots of liquids.
- 8) Don't overdo, but follow a regular exercise plan, including activities that help develop lung capacity.
- 9) Don't take any medicine on your own without asking your doctor first.
- 10) Take all medicines your doctor prescribes, as much and as often as you are told.
- 11) Avoid taking sleeping pills or sedatives, even if asthma keeps you awake. Prop yourself up with extra pillows until your asthma medicine takes effect.
- 12) Avoid breathing in insecticides, deodorants, cleaning fluids, chlorine, or other irritating gases.

Asthma Medicines

Preventative Medicines:

Your doctor knows that, besides relieving an attack when it happens, it is also important to prevent attacks from occurring in the first place. Therefore, he or she has prescribed for you cromolyn sodium inhalation solution, a medicine that prevents asthma attacks by making airways less sensitive to asthma triggers. It works by stabilizing cells in the airway lining called mast cells. During an asthma attack, these cells become unstable and give off chemicals called mediators that cause inflammation and asthma attacks. By preventing mediator release, cromolyn sodium inhalation solution works to prevent asthma attacks.

Bronchodilators:

When someone is having an asthma attack, he or she needs a medicine called a bronchodilator to open up (dilate) the blocked airways in order to relieve asthma attacks. Your doctor may have already prescribed this medicine for you to use at that time.

*Adapted from the National Heart, Lung, and Blood Institute. Guidelines for the Diagnosis and Management of Asthma. National Asthma Education Program, Expert Panel Report, 1991.

How Will Cromolyn Sodium Inhalation Solution Work for You?

To get the best possible results, follow your doctor's instructions carefully when you first take cromolyn sodium inhalation solution.

Your doctor may tell you to take cromolyn sodium inhalation solution 10 to 15 minutes before you exercise or come into contact with a specific trigger, such as a cat. Usually, however, you will be told to take cromolyn sodium inhalation solution on a regular basis, probably starting at four times a day. **It is crucial that you take cromolyn sodium inhalation solution regularly, as often as your doctor recommends, even though you have no asthma symptoms at the time.** Cromolyn sodium inhalation solution starts working right away, but when you first begin taking it, you may have a lot of inflammation in your airways. Therefore, it may take up to two weeks (or perhaps one month) of regular treatment to bring your asthma under control. Do not stop taking cromolyn sodium inhalation solution or skip any doses without first talking to your doctor.

When you start using cromolyn sodium inhalation solution for the first time, your doctor may ask you to keep a diary showing when you have any symptoms, if and when you have trouble sleeping, how often you wheeze or cough, and other notes to help determine how effective cromolyn sodium inhalation solution will be to help you prevent asthma attacks. Your doctor may also recommend the use of a peak flow meter daily to help you better assess your progress.

While taking cromolyn sodium inhalation solution on a regular basis, you may need to take a bronchodilator-type medicine to treat occasional symptoms or attacks. While taking cromolyn sodium inhalation solution, you should continue taking your other medications until your doctor advises you otherwise.

Care & Storage

Cromolyn sodium inhalation solution should be stored between 15°-30°C (59°-86°F) and protected from light. Do not use if it contains a precipitate (particles or cloudiness) or becomes discolored. Keep out of the reach of children.

Store ampules in foil pouch until ready to use.

NOTE: In case of difficulty consult your doctor or pharmacist.

Instructions for the Use of Cromolyn Sodium Inhalation Solution

An aqueous solution for nebulization.

NOT FOR INJECTION

For best results, follow these instructions exactly and observe Care & Storage directions.

Method of Administration

Cromolyn sodium inhalation solution is recommended for use in a power driven nebulizer operated at an airflow rate of 6-8 liters per minute and equipped with a suitable face mask. Hand operated nebulizers are not suitable for the administration of cromolyn sodium inhalation solution. Your doctor will advise on the choice of a suitable nebulizer and how it should be used. Do not use any appliance without consulting your doctor.

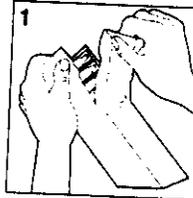
Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established. ✓

Dosage

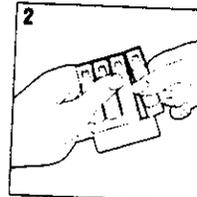
Nebulization should be carried out four times a day at regular intervals, or as directed by your doctor. Use the contents of a fresh ampule each time.

Inhalation

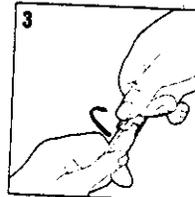
Once the nebulizer has been assembled and contains cromolyn sodium inhalation solution, hold the mask close to the patient's face and switch on the device. The patient should breathe in through the mouth and out through the nose in a normal, relaxed manner. Nebulization should take approximately five to ten minutes.



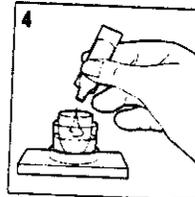
1. Open foil pouch by tearing at serrated edge as shown.



2. Remove a single ampule from the strip.



3. Open the ampule by twisting off the tabbed top section.



4. Squeeze the contents of the ampule into the solution container of your nebulizer. Discard the empty ampule.

Manufactured by
Automatic Liquid Packaging, Inc.
Woodstock, IL 60098

Manufactured for
Alpharma USPD Inc.
Baltimore, MD 21244

FORM NO. 0750-PL
Rev. 9/97 VC1353

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-067

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-067

3. NAME AND ADDRESS OF APPLICANT

Alpharma
U.S. Pharmaceutical Division,
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION

21CFR 314.94(a)(3) of the regulations.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Cromolyn Sodium Inhalation Solution USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

DOS 1/31/97; NA (Major), includes labeling and micro deficiencies 7/22/97; Bio letter (Waiver granted) 9/23/97; Amend (Major) 10/10/97; Amend (Major) 10/10/97; Label review 10/30/97; Chem. Review (Major) 3/26/98; Amend (Major) 9/15/98; Label review (Approval Summary) 9/30/98; NA (FAX) 3/24/99; FAX amend 4/12/99; Chem Close review 4/14/99; Amendment 5/13/99; Micro Review 6/15/99.

10. PHARMACOLOGICAL CATEGORY

Anti-asthmatic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Cromolyn Sodium
Inhalation
Solution U.S.P.

14. POTENCY

10 mg/mL of a 2 mL fill in a 3.2 mL
mL)

plastic ampule (20-mg/2

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory (see review #1)

16. RECORDS AND REPORTS N/A

17. COMMENTS

Chemistry remains acceptable.

Sterility review found acceptable on 6/13/99.

Labeling acceptable, Revisions needed post-approval. Reviewed on 9/30/98.

Bio waiver granted 9/23/97.

EER pending.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend that ANDA 75-067 should be approved.

19. REVIEWER:

DATE COMPLETED:

Stephen Sherken

6/17/99

Page(s)

7

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Information and are not
releasable.

Amnesty Review #5
6/17/99

Chemistry closed

1. CHEMISTRY REVIEW NO. 4
2. ANDA # 75-067
3. NAME AND ADDRESS OF APPLICANT

Alpharma
U.S. Pharmaceutical Division,
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION

21CFR 314.94(a)(3) of the regulations.

5. SUPPLEMENT(s)
6. PROPRIETARY NAME

N/A

N/A

7. NONPROPRIETARY NAME

Cromolyn Sodium Inhalation Solution USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

DOS 1/31/97; NA (Major), includes labeling and micro deficiencies 7/22/97; Bio letter (Waiver granted) 9/23/97; Amend (Major) 10/10/97; Amend (Major) 10/10/97*; Label review 10/30/97; Chem. Review (Major) 3/26/98; Amend (Major) 9/15/98*; Label review (Approval Summary) 9/30/98; NA (FAX) 3/24/99; FAX amend 4/12/99.

* Amendments not reviewed for Sterility assurance,

10. PHARMACOLOGICAL CATEGORY
11. Rx or OTC

Anti-asthmatic

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Cromolyn Sodium
Inhalation
Solution U.S.P.

14. POTENCY

10 mg/mL of a 2 mL fill in a 3.2 mL LDPE plastic ampule (20-mg/2 mL)

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory (see review #1)

16. RECORDS AND REPORTS N/A

17. COMMENTS

Chemistry is now acceptable..

Alpharma withdrew its 2-mL ampule from the application.

Sterility review pending.

Labeling acceptable, Revisions needed post-approval. Reviewed on 9/30/98.

Bio waiver granted 9/23/97.

EER returned acceptable for all listed facilities on 1/29/98.

18. CONCLUSIONS AND RECOMMENDATIONS

Chem-Close, pending Sterility review.

19. REVIEWER:

DATE COMPLETED:

Stephen Sherken

4/13/99

cc: ANDA 75 057

Endc

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Zuall
4/14/99

Page (s) 85

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Information and are not
releasable.

Chemistry Review # 4.

4/13/99

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-067

3. NAME AND ADDRESS OF APPLICANT

Alpharma
U.S. Pharmaceutical Division,
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION

21CFR 314.94(a)(3) of the regulations.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Cromolyn Sodium Inhalation Solution USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

DOS 1/31/97; NA (Major), includes labeling and micro deficiencies
7/22/97; Bio letter (Waiver granted) 9/23/97; Amend (Major) 10/10/97*;
Label review 10/30/97; Chem. Review (Major) 3/26/98; Amend (Major)
9/15/98*; Label review 9/30/98.

* Amendments not reviewed for Sterility assurance,

10. PHARMACOLOGICAL CATEGORY

Anti-asthmatic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Cromolyn Sodium
Inhalation
Solution U.S.P.

3.2 mL
(20 mg/2 mL)

14. POTENCY

10 mg/mL of a
2 mL fill in a
plastic ampule.

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory (see review #1)

16. RECORDS AND REPORTS N/A

Page(s) _____

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Chemistry Review #3
3/8/99

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-067

3. NAME AND ADDRESS OF APPLICANT

Alpharma
U.S. Pharmaceutical Division,
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION

21CFR 314.94(a)(3) of the regulations.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Cromolyn Sodium Inhalation Solution USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

DOS 1/31/97; NA (Major), includes labeling and micro deficiencies
7/22/97; Bio letter 9/23/97; Amend (Major) 10/10/97; NC 10/10/97

10. PHARMACOLOGICAL CATEGORY

Anti-asthmatic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Cromolyn Sodium Inhalation Solution U.S.P.

14. POTENCY

10 mg/mL in 2 mL fill
ampule (20 mg/2 mL)

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory (see review #1)

16. RECORDS AND REPORTS N/A

17. COMMENTS

Chemistry is not acceptable. Alpharma changed the size of the ampule from 10 mg/mL in 2 mL fill ampule to 20 mg/2 mL. This change requires a change in the Master Batch record, a new batch with an executed batch record, new COAs of the drug substance and drug product, and 3 months of accelerated stability data in the 2 mL vial at 40°C.

Micro review pending.

Labeling deficient.

Bio letter appears to be acceptable.

EER returned acceptable for all listed facilities on 1/29/98.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable (Major)

19. REVIEWER:

DATE COMPLETED:

Stephen Sherken

March 12, 1998

Page (s)

21

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releasable.

Chemistry Review # 2

3/12/98

Page(s) 2

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releasable.

7/22/97

Chemistry Review

#38

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-067

3. NAME AND ADDRESS OF APPLICANT

Alpharma
U.S. Pharmaceutical Division,
Baltimore, MD 21224

4. LEGAL BASIS FOR SUBMISSION

21CFR 314.94(a)(3) of the regulations.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Cromolyn Sodium Inhalation Solution USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

DOS 1/31/97

10. PHARMACOLOGICAL CATEGORY

Anti-asthmatic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 18-596
DMF-8164, Profarmaco Nobel SRL
Milano, IT.

13. DOSAGE FORM

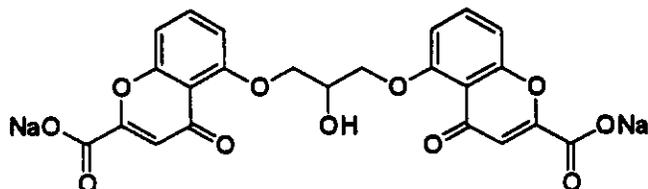
Cromolyn Sodium Inhalation Solution U.S.P.

14. POTENCY

10 mg/mL in 2 mL
ampule (20 mg/2 mL)

15. CHEMICAL NAME AND STRUCTURE

Cromolyn Sodium. $C_{23}H_{14}Na_2O_{11}$. 512.34. 4H-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(oxy)]bis[4,-oxo-, disodium salt]. 15826-37-6. Anti-asthmatic (prophylactic). USP 23, page 430.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Fairly complete application. There were 11 chemistry deficiencies and 8 microbiology deficiencies. Labeling was also found to be deficient. No bio review to date. EER is pending.

18. CONCLUSIONS AND RECOMMENDATIONS

Not-approvable (Major).

19. REVIEWER:

DATE COMPLETED:

Stephen Sherken

June 24, 1997

Page(s)

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Chemistry Review #1

6/24/97

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-067

BIOEQUIVALENCE REVIEW(S)

ANDA Number: 75-067

FIRM: Alparma DOSAGE FORM: Cromolyn Sodium Inhalation Solution
USP

STRENGTH 10 mg/mL; 2 mL fill in a 3.2 mL plastic ampule (20 mg/2 mL)

CGMP STATEMENT/EER UPDATE STATEMENT:

PENDING

BIO STUDY: Waiver granted on 9/23/97.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM)

Methods were verified by BLT-DO. BLT-DO tested lot #01096C per USP. All methods were found to be adequate.

STABILITY - ARE THE CONTAINERS USED IN STUDY IDENTICAL TO THOSE
IN CONTAINER SECTION

Lot 01096C was satisfactory tested for 3 months at 40°C/75% RH. The lot was packaged in a 3.2 mL (2 mL fill) unit dose vial. It's a ampule. Ampules were packaged in an Aluminum Laminated Foil Pouch. This was adequately described in the container section.

LABELING:

Labeling found adequate on 9/30/98.

STERILIZATION VALIDATION (IF APPLICABLE):

Sterility assurance found adequate on 6/13/99.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.): N/A

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE
THEY MANUFACTURED BY THE SAME
PROCESS?)

The size of Batch 01096C was rs.

PROPOSED PRODUCTION BATCHES - MANUFACTURING PROCESS THE SAME AS
BIO/STABILITY?

Size of proposed production batches is roduction
lots will be manufactured by the same process as batch 01096C
was.

Stephen Sherken 7/7/99

Prepared by Stephen Sherken on 6/17/99.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-067

SPONSOR: Alparma

DRUG: Cromolyn Sodium Inhalation Solution, USP

DOSAGE FORM: Inhalation Solution

STRENGTH: 20 mg/2 mL

REFERENCE PRODUCT: Intal® Inhalation Solution, 20 mg/2 mL (Fisons Corporation).

SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Cromolyn Sodium Inhalation Solution, USP, 20 mg/2 mL is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug Intal® Inhalation Solution, 20 mg/2 mL (Fisons Corporation).

PRIMARY REVIEWER: Zakariya Wahba, Ph.D. BRANCH: III

INITIAL: /S/ 2 DATE: 6/26/97

GROUP LEADER: Ramakant Mhatre, Ph.D. BRANCH: III

INITIAL: /S/ — DATE: 6/30/97

DIRECTOR: Nicholas Fleischer, Ph.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ — DATE: 10/23/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: — DATE: —

SEP 23 1997

ANDA 75-067

Alpharma, U.S. Pharmaceuticals Division
Attention: Vincent Andolina
John Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 23 1997

Alpharma, U.S. Pharmaceuticals Division
Attention: Vincent Andolina
John Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,



RS
Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 14 1997

Cromolyn Sodium Inhalation Solution, USP
20 mg/2 mL
ANDA # 75-067
Reviewer: Z.Z. Wahba
File #75067w.197

Alpharma
Baltimore, MD
Submission Date:
January 31, 1997

REVIEW OF A WAIVER REQUEST

BACKGROUND

1. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Cromolyn Sodium Inhalation Solution, USP, 20 mg/2 mL. The reference listed drug (RLD) is Intal® Inhalation Solution, 20 mg/2 mL (Fisons Corporation, NDA #18-596).
2. Cromolyn sodium inhalation is a solution dosage form indicated as a prophylactic agent in the management of bronchial asthma.

FORMULATION COMPARISON

Comparative compositions of the test and the reference Fisons' Intal® Inhalation Solution, 10 mg/1 mL, products are as follows:

Comparison of Formulation
(not for release under FOI)

Ingredient	Test Product (amount/2 mL)	RLD (amount/2 mL)
Cromolyn Sodium, USP	20 mg	20 mg
Purified Water, USP	qs to _____	qs to _____

Cromolyn sodium inhalation solution USP is clear, colorless, sterile, and has a target pH of 5.5.

COMMENTS

1. The drug product is classified "AN" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".
2. The firm's test solution product is identical, qualitatively and quantitatively, to the innovator product.
3. The waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR section 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-067

MICROBIOLOGY REVIEW(S)

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS
Microbiologist's Review #3
June 15, 1999

A. 1. ANDA: 75-067

APPLICANT: Alpharma
U.S. Pharmaceuticals Division
Attention: Vincent Andolina
The Johns Hopkins Bayview Campus
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224

MANUFACTURER: _____ Inc.

098

2. PRODUCT NAMES: **Cromolyn Sodium Inhalation Solution**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Sterile aqueous solution for nebulization - **20 mg/2 mL**

4. METHOD(S) OF STERILIZATION: _____

5. PRINCIPLE INDICATIONS: Prophylactic agent used for the management of patients with bronchial asthma

6. PHARMACOLOGICAL CATEGORY: Mast cell stabilizer
[Anti-inflammatory agent]

B. 1. DATE OF INITIAL SUBMISSION: January 31, 1997
(Received by OGD on 2/3/97)

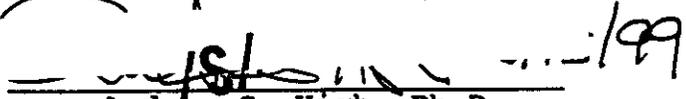
2. DATE OF AMENDMENT: May 13, 1999
- Subject of this Review (Received, May 17, 1999)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 6/15/99

- C. REMARKS: The amendment provides for the response to the Microbiology Deficiencies in the correspondence dated May 4, 1999.

- D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".



Andrea S. High, Ph.D.

cc:

067a2

Handwritten scribbles

Page(s) 1

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

Micro Review # 3

6/15/99

Microbiology Comments to be Provided to the Applicant

**ANDA: 75-067 APPLICANT: Alpharma,
U.S. Pharmaceuticals Division**

DRUG PRODUCT: Cromolyn Sodium Inhalation Solution USP 10 mg/mL

A. Microbiology Deficiencies:

Please clearly identify your amendment to this facsimile as
"RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

R.M. Patel

Rashmikant M. Patel, Ph.D.

Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #1

May 1, 1997

A. 1. **ANDA: 75-067**

APPLICANT: Alpharma
U.S. Pharmaceuticals Division
Attention: Vincent Andolina
The Johns Hopkins Bayview Campus
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224

MANUFACTURER:

2. **PRODUCT NAMES: Cromolyn Sodium Inhalation Solution**

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:**

Sterile aqueous solution for nebulization - **20 mg/2 mL**

4. **METHOD(S) OF STERILIZATION:**

5. **PRINCIPLE INDICATIONS:** Prophylactic agent used for the management of patients with bronchial asthma

6. **PHARMACOLOGICAL CATEGORY:** Mast cell stabilizer
-[Anti-inflammatory agent]

B. 1. **DATE OF INITIAL SUBMISSION:**

January 31, 1997 (Received by OGD on 2/3/97)

- Subject of this Review

2. **DATE OF AMENDMENT:** N/A; no amendments containing sterility assurance information were submitted by the time of this review

3. **RELATED DOCUMENTS:**

NDA 18-596 held by Fisons for Intal® Nebulizer Solution

drug substance, Cromolyn Sodium

4. **ASSIGNED FOR REVIEW:** April 24, 1997

C. REMARKS: The information provided in the application was insufficient to determine if the applicant is taking the necessary steps to ensure the sterility of the subject drug product (Cromolyn Sodium Inhalation Solution USP). For example, validation data were not provided for the steam-in-place process used to sterilize the B/F/S machine, batch tanks and transfer lines.

D. CONCLUSIONS: The submissions are therefore not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiologist's Comments to be Provided to the Applicant."

Kenneth H. ~~S~~ Mihvich, Ph.D.

*Rec'd
5/21/77*

cc:

Page (s) 5

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

Micro Review #1

5/1/97

1010

Microbiology Comments to be Provided to the Applicant

**ANDA: 75-067 APPLICANT: Alpharma,
U.S. Pharmaceuticals Division**

DRUG PRODUCT: Cromolyn Sodium Inhalation Solution USP 10 mg/mL

A. Microbiology Deficiencies:

~~Subject drug product~~

Please clearly identify your amendment to this facsimile as
"RESPONSE TO MICROBIOLOGY DEFICIENCIES"

Sincerely yours,

Rashmikant M. Patel

Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-067

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: ANDA 75067/000	Priority:	Org Code: 600
Stamp: 03-FEB-1997 Regulatory Due:	Action Goal:	District Goal: 03-APR-1998
Applicant: ALPHARMA USPD	Brand Name:	
333 CASSELL DR STE 3500	Established Name: CROMOLYN SODIUM	
BALTIMORE, MD 21224	Generic Name:	
	Dosage Form: SOL (SOLUTION)	
	Strength: 10 MG/ML INHALATION	
<hr/>		
FDA Contacts: D. HUIE (HFD-623) 301-827-5848 , Project Manager		
S. SHERKEN (HFD-625) 301-827-5848 , Review Chemist		
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader		

Overall Recommendation:

ACCEPTABLE on 19-JUL-1999 by S. FERGUSON (HFD-324) 301-827-0062

WITHHOLD on 16-JUL-1999 by M. EGAS (HFD-322) 301-594-0095

ACCEPTABLE on 29-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1110239**
ALPHARMA
7205 WINDSOR BLVD
BALTIMORE, MD 212442654

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Responsibilities: **FINISHED DOSAGE RELEASE**
TESTER
FINISHED DOSAGE STABILITY
TESTER

Establishment:

DMF No:
AADA No:

Profile: **SNI** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **29-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE**
MANUFACTURER

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities: **DRUG SUBSTANCE OTHER**
TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE OTHER**
Last Milestone: **OC RECOMMENDATION** **TESTER**
Milestone Date **08-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: DMF No:
AADA No:

RL

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE**
Last Milestone: **OC RECOMMENDATION** **MANUFACTURER**
Milestone Date **16-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Printed by Robert West
Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL **Date:** 16-Jul-1999 10:58am
From: Robert West
 WESTR
Dept: HFD-611 MPN2 271
Tel No: 301-827-5846 FAX 301-443-3847

TO: See Below

Subject: ANDA 75-067 FOR ALPHARMA'S CROMOLYN SODIUM INHALATION SOLN'

OGD presently has ANDA 75-067 for Alpharma's Cromolyn Sodium Inhalation undergoing final administrative review. All is in order from a review aspect; however, there is a "Potential OAI" alert status for the supplier of the sodium). (supplier of the cromolyn sodium).

In previous meetings, we have been informed that the inspection of _____ was completed in June and that OC is awaiting the arrival of the EIR report from the investigator before making a determination as to whether the OAI Alert applies to this application.

This is the second ANDA pending resolution of the status of _____ I previously sent you an inquiry about ANDA _____ Tablets which also uses _____

As we are awaiting a decision on two potential ANDA approvals, we respectfully request that the EIR be obtained and reviewed prior to the end of July. Any additional advice that you can provide regarding _____ d also be appreciated.

Thank you,

Bob

Distribution:

TC

CC:

CC:

CC

CC

CC:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: ANDA 75067/000
Stamp: 03-FEB-1997 Regulatory Due:
Applicant: ALPHARMA USPD
333 CASSELL DR STE 3500
BALTIMORE, MD 21224

Priority:
Action Goal:
Brand Name:
Established Name: CROMOLYN SODIUM
Generic Name:
Dosage Form: SOL (SOLUTION)
Strength: 10 MG/ML INHALATION

FDA Contacts: D. HUIE (HFD-623) 301-827-5848, Project Manager
S. SHERKEN (HFD-625) 301-827-5848, Review Chemist
M. SMELA JR (HFD-625) 301-827-5848, Team Leader

Overall Recommendation:

ACCEPTABLE on 29-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 1110239
ALPHARMA
7205 WINDSOR BLVD
BALTIMORE, MD 212442654

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Responsibilities: FINISHED DOSAGE RELEASE
TESTER
FINISHED DOSAGE STABILITY
TESTER

Profile: SNI OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-1997
Decision: WITHHOLD
Reason: FACILITY NOT DOING FUNCTION

NOTE: SNI is the code for "sterile, non-injectable, oc-sphthalmic drops." It was entered by error and does not apply to this application. "ctl" is the correct code and is acceptable.

Establishment:

No:
No:

Profile: SNI OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

responsibilities: FINISHED
MANUFAC

Establishment:

DMF No:
AADA No:

4/17/99
I spoke with
Jana (of OHA)
DEIO
yesterday +
she stated that
the performer
inspection was
done but she
has not gotten the
report yet. PB2

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 08-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE OTHER
TESTER

Establishment

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 08-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE OTHER
TESTER

Establishment:

IF No:
DA No:

Profile: CSN OAI Status: POTENTIAL OAI Responsibilities: DRUG SUBSTANCE
Last Milestone: INSPECTION PERFORMED MANUFACTURER
Milestone Date 17-JUN-1999

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: **ANDA 75067/000**
 Stamp: **03-FEB-1997** Regulatory Due:
 Applicant: **ALPHARMA USPD**
333 CASSELL DR STE 3500
BALTIMORE, MD 21224

Priority:
 Action Goal:
 Brand Name:
 Established Name: **CROMOLYN SODIUM**
 Generic Name:
 Dosage Form: **SOL (SOLUTION)**
 Strength: **10 MG/ML INHALATION**

Org Code: 600

District Goal: 03-APR-1998

FDA Contacts:	D. HUIE	(HFD-623)	301-827-5848	, Project Manager
	S. SHERKEN	(HFD-625)	301-827-5848	, Review Chemist
	M. SMELA JR	(HFD-625)	301-827-5848	, Team Leader

Overall Recommendation:

ACCEPTABLE on 19-JUL-1999 by S. FERGUSON (HFD-324) 301-827-0062

WITHHOLD on 16-JUL-1999 by M. EGAS (HFD-322) 301-594-0095

ACCEPTABLE on 29-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1110239**
ALPHARMA
7205 WINDSOR BLVD
BALTIMORE, MD 212442654

DMF No:
 AADA No:

Profile: **CTL** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **08-MAR-1999**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON FILE REVIEW**

Responsibilities: **FINISHED DOSAGE RELEASE
 TESTER
 FINISHED DOSAGE STABILITY
 TESTER**

Establishment:

DMF No:
 AADA No:

Profile: **SNI** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **29-MAR-1999**
 Decision: **ACCEPTABLE**
 Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE
 MANUFACTURER**

Establishment:

DMF No:
 AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities: **DRUG SUBSTANCE OTHER
 TESTER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: ANDA 75067/000	Priority:	Org Code: 600
Stamp: 03-FEB-1997 Regulatory Due:	Action Goal:	District Goal: 03-APR-1998
Applicant: ALPHARMA USPD	Brand Name:	
333 CASSELL DR STE 3500	Established Name: CROMOLYN SODIUM	
BALTIMORE, MD 21224	Generic Name:	
	Dosage Form: SOL (SOLUTION)	
	Strength: 10 MG/ML INHALATION	
<hr/>		
FDA Contacts: D. HUIE (HFD-615) 301-827-5862 , Project Manager		
S. SHERKEN (HFD-625) 301-827-5848 , Review Chemist		
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader		

Overall Recommendation:

ACCEPTABLE on 29-JAN-1998 by M. EGAS(HFD-322)301-594-0095

Establishment: **1110239**
ALPHARMA
7205 WINDSOR BLVD
BALTIMORE, MD 212442654

DMF No:
AADA No:

Profile: **CTL** OAI Status: **OAI ALERT**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **08-MAR-1999**

Responsibilities: **FINISHED DOSAGE RELEASE**
TESTER
FINISHED DOSAGE STABILITY
TESTER

Profile: **LIQ** OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-1997**
Decision: **WITHHOLD**
Reason: **FACILITY NOT DOING FUNCTION**

Establishment: **1419377**

DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **08-MAR-1999**

Responsibilities: **FINISHED DOSAGE**
MANUFACTURER

Establishment: **1225446**

DMF No:
AADA No:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: CTL OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 08-MAR-1999

Responsibilities: FINISHED DOSAGE OTHER
TESTER

Establishment:

QL

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 08-MAR-1999

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Establishment:

VD

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 08-MAR-1999

Responsibilities: DRUG SUBSTANCE OTHER
TESTER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: ANDA 75067/000	Priority:	Org Code: 600
Stamp: 03-FEB-1997 Regulatory Due:	Action Goal:	District Goal: 03-APR-1998
Applicant: ALPHARMA USPD	Brand Name:	
333 CASSELL DR STE 3500	Established Name: CROMOLYN SODIUM	
BALTIMORE, MD 21224	Generic Name:	
	Dosage Form: SOL (SOLUTION)	
	Strength: 10 MG/ML INHALATION	
FDA Contacts: ID = 122344		, Project Manager
M. SMELA JR (HFD-625)	301-827-5848	, Team Leader

Overall Recommendation:

ACCEPTABLE on 29-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1110239**
ALPHARMA
7205 WINDSOR BLVD
BALTIMORE, MD 212442654

DMF No:
AADA No:

Profile: **CTL** OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Profile: **LIQ** OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-1997**
Decision: **WITHHOLD**
Reason: **FACILITY NOT DOING FUNCTION**

Responsibilities: **FINISHED DOSAGE RELEASE**
TESTER
FINISHED DOSAGE STABILITY
TESTER

Establishment:

DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE**
MANUFACTURER

Establishment:

DMF No:
AADA No:

E L E C T R O N I C M A I L M E S S A G E

Date: 05-Mar-1999 11:13am EST
From: Michael Smela
SMELA
Dept: HFD-625 MPN2 204
Tel No: 301-827-5848 FAX 301-594-0180

TO: Frederic Marsik

(MARSIKF)

CC:
CC:
CC:
CC:

Subject: ANDA 75067

Fred...We are preparing a NA fax for this Cromolyn/ALPharma. Micro review of 10/10/97 and 9/15/98 amendments is pending.

Mike

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

ANDA Number: **75-067** Date of Submission: **September 15, 1998**

Applicant's Name: **Alpharma, U.S. Pharmaceuticals Division**

Established Name: **Cromolyn Sodium Inhalation Solution
USP, 20 mg/2 mL**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): 2 mL ampules, 12 ampules per foil pouch, cartons of 60 and 120, 20 mg/2 mL, September 15, 1998

Do you have 12 Final Printed Labels and Labeling? **Yes**

Unit Dose Ampule Label: September 15, 1998 (2 mL)

Foil Wrap: September 15, 1998 (12 ampules)

Unit Dose Carton Label:

October 10, 1997 (60 x 2 mL and 120 x 2 mL).

Professional Package Insert Labeling:

October 10, 1997 (Rev. 9/97).

Patient Package Insert Labeling:

October 10, 1997 (Rev. 9/97).

Revisions needed post-approval:

1. Professional Insert:

a. PREGNANCY - Begin a new paragraph with the last sentence.

b. DOSAGE AND ADMINISTRATION

i. Insert a space between paragraph three and four.

ii. Insert the following text at the end of this

section:

For additional information, see the accompanying leaflet entitled *Living a Full Life with Asthma*.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Intal® Nebulizer Solution

NDA Number: 18-596

NDA Drug Name: Intal® Nebulizer Solution

NDA Firm: Fisons Corporation

Date of Approval of NDA Insert and supplement #: S-026/May 27, 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:
Approved labels (March 18, 1996) in the file folder.

Basis of Approval for the Carton Labeling:
Approved labeling (March 18, 1996) in the 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 See USP supplement 1 for the title change from "Cromolyn Sodium Inhalation" to "Cromolyn Sodium Inhalation Solution".	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 ASEP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does NDA 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 NDA and applicant (page #) in the FTR			
Is the scoring configuration different than the NDA?			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:*****

*Noted 4/13/89
S. Sherke*

Please note new carton size of 120 that the firm proposes.

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Intal® Nebulizer Solution; Fisons; Approved May 27, 1997, Revised July 1996).

2. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this dosage form.

3. Storage/Dispensing Conditions:

NDA: Foil pouch, carton and insert: Store between -15° - 30°C (59° - 86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

ANDA: Carton and Insert: Store between 15° - 30°C (59° - 86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

USP: Preserve in single-unit double ended glass ampules or in low-density polyethylene ampules.

4. Product Line:

u
6

zes 01

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 056, Vol. 1.1.

6.

utilized for testing. See pages 089, vol. 1.1.

7. Container/Closure:

This product will be packaged in a 3.2 mL ampule with a 2 mL fill. The ampule will be made from a

and there will be 4 ampules per vial card. See pages 468 and 469, Vol. 1.2.

8. There has been only one other application for this drug product. It was approved in 1994. The package insert did not contain the patient leaflet. There is a FTR in the file folder from 1991 that states that we would not require the generic firms submit it at that time. After discussion between John Grace and myself (Carol Holquist) it was determined it is part of the approved labeling from 1996 and that we would request firms to submit it, however it would not have to be attached nor referenced in the PRECAUTIONS section of the insert. The innovator does not do this either. The leaflet contains informational material on how to live with asthma.
-
-

Date of Review: September 23, 1998

Date of Submission: September 15, 1998

Reviewer:

/S/

Date:

9/30/98

Team Leader:

*^
/S/*

Date:

9/30/98

cc:

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
BALTIMORE DISTRICT OFFICE

M E M O R A N D U M

DATE: July 16, 1997

FROM: Elaine Knowles Cole, District Director,
Baltimore District, HFR-MA200

SUBJ: Method Validation of the ANDA 75-067, Cromolyn Sodium
Inhalation, 20 mg/ 2 ml dosage strength,
Sample #97-734-166

TO: Kenneth Furnkranz, Review Chemist
CDER/OGD/DCI/ANDA Review Branch II, HFD-625

INFO: Director, Central Region, HFR-MA1
Director, Baltimore District Laboratory, HFR-MA260
Director, Philadelphia District Laboratory, HFR-MA160
Director, Office of Compliance, HFD-300
Director, Division of Field Science, HFC-140
Director, Compendial Operations, HFD-335

PRODUCT: Cromolyn Sodium Inhalation Solution, 20 mg/ 2ml,
lot # 0196C

APPLICANT: Alpharma, USPD
333 Cassell Drive
Suite 3500
Baltimore, MD 21224

ESTABLISHMENT: Alpharma USPD
(Testing facility only) 7205 Windsor Blvd
Baltimore, MD 21244-2654

DISTRICT RECOMMENDATION: Approve

COMMENTS:

Attached are the completed validating chemist's worksheets, summary of results with comments, and ANDA documents for the above referenced ANDA.

Baltimore District received the methods and sample on 6/10/97 from the manufacturer. Method verification was begun 6/30/97.

The finished product was analyzed for identification, assay, content uniformity and related compounds using current USP methodology.

The finished product met the USP specifications for all of the tests.

I recommend approval of this application. These comments do not take into account other factors relevant to the application.

~~IS/~~
Elaine Knowles Cole,
District Director

cc:

CDER Establishment Evaluation Report
for March 12, 1998

Application: **ANDA-75067/000**
Stamp: **03-FEB-1997** Regulatory Due:
Applicant: **ALPHARMA USPD**
333 CASSELL DR STE 3500
BALTIMORE, MD 21224

Priority:
Action Goal:
Brand Name:
Established Name: **CROMOLYN SODIUM**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **10 MG/ML INHALATION**

Org Code: **600**

District Goal: **03-APR-1998**

FDA Contacts: **S. OKEEFE (HFD-617)**
M. SMELA JR (HFD-625)

301-827-5848 , Project Manager
301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 29-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1110239**
ALPHARMA
7205 WINDSOR BLVD
BALTIMORE, MD 212442654

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE RELEASE**
TESTER
FINISHED DOSAGE STABILITY
TESTER

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-1997**
Decision: **WITHHOLD**
Reason: **FACILITY NOT DOING FUNCTION**

Establishment:

DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE**
MANUFACTURER

Establishment:

DMF No:
AADA No:

CDER Establishment Evaluation Report
for March 12, 1998

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-JAN-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE OTHER
TESTER

Establishment:

Jo:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-APR-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Establishment:

MF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-MAY-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE OTHER
TESTER

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

ANDA Number: **75-067** Date of Submission: **October 10, 1997**

Applicant's Name: **Alpharma, U.S. Pharmaceuticals Division**

Established Name: **Cromolyn Sodium Inhalation Solution
USP, 20 mg/2 mL**

Labeling Deficiencies:

1. UNIT DOSE CONTAINER (2 mL ampule)

Revise your label to qualify "Alpharma" as the distributor. We refer you to 21 CFR 201.1(h)(5) for further guidance.

2. FOIL WRAP (12s)

Satisfactory in draft.

3. UNIT DOSE CARTON (60 x 2 mL and 120 x 2 mL)

Satisfactory in final print.

4. INSERT

I. Professional Insert

Satisfactory in final print.

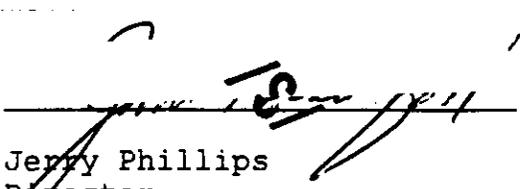
II. Patient Instructions Leaflet

Satisfactory in final print.

Please revise your unit dose ampule labels as instructed above, and submit final printed unit dose ampule labels and foil wrap 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.

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

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

3/30/98

Chemistry Review

#38

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

ANDA Number: **75-067** Date of Submission: **October 10, 1997**

Applicant's Name: **Alpharma, U.S. Pharmaceuticals Division**

Established Name: **Cromolyn Sodium Inhalation Solution
USP, 20 mg/2 mL**

Labeling Deficiencies:

1. UNIT DOSE CONTAINER (2 mL ampule)

Revise your label to qualify "Alpharma" as the distributor. We refer you to 21 CFR 201.1(h)(5) for further guidance.

2. FOIL WRAP (12s)

Satisfactory in draft.

3. UNIT DOSE CARTON (60 x 2 mL and 120 x 2 mL)

Satisfactory in final print.

4. INSERT

- I. Professional Insert

Satisfactory in final print.

- II. Patient Instructions Leaflet

Satisfactory in final print.

Please revise your unit dose ampule labels as instructed above, and submit final printed unit dose ampule labels and foil wrap 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.

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

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

Do you have 12 Final Printed Labels and Labeling? Yes

Unit Dose Ampule Label:

Foil Wrap:

Unit Dose Carton Label:

October 10, 1997 (60 x 2 mL and 120 x 2 mL).

Professional Package Insert Labeling:

October 10, 1997 (Rev. 9/97).

Patient Package Insert Labeling:

October 10, 1997 (Rev. 9/97).

Revisions needed post-approval:

1. Professional Insert:

a. PREGNANCY - Begin a new paragraph with the last sentence.

b. DOSAGE AND ADMINISTRATION

Insert a space between paragraph three and four.

ii. Insert the following text at the end of this section:

For additional information, see the accompanying leaflet entitled *Living a Full Life with Asthma*.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Intal® Nebulizer Solution

NDA Number: 18-596

NDA Drug Name: Intal® Nebulizer Solution

NDA Firm: Fisons Corporation

Date of Approval of NDA Insert and supplement #:

S-026/May 27, 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:

Approved labels (March 18, 1996) in the file folder.

Basis of Approval for the Carton Labeling:

Approved Labeling (March 18, 1996) in the file folder.

CONTAINER AND LABELING DEFICIENCIES

... (faded text) ...

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 See USP supplement 1 for the title change from "Cromolyn Sodium Inhalation" to "Cromolyn Sodium Inhalation Solution".	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 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 NLD 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 NLD and applicant (page #) in the PTR			
Is the scoring configuration different than the NLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (PTR: 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 from 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: (PTR: 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?: PTR: 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:*****

No CHC issue. H.S.M. 3/24/88

Please note new carton size of hat the firm proposes.

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Intal® Nebulizer Solution; Fisons; Approved May 27, 1997, Revised July 1996).

2. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this dosage form.

3. Storage/Dispensing Conditions:

NDA: Foil pouch, carton and insert: Store between 15° - 30°C (59° - 86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

ANDA: Carton and Insert: Store between 15° - 30°C (59° - 86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

USP: Preserve in single-unit double ended glass ampules or in low-density polyethylene ampules.

4. Product Line:

60s and 120s.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 056, Vol. 1.1.

6. utilized for testing. See pages 089, vol. 1.1.

7. Container/Closure:

This product will be packaged in a 3.2 mL ampule with a 2 mL fill. The ampule will be made from a

and there will be 4 ampules per vial card. See pages 468 and 469, Vol. 1.2.

8. There has been only one other application for this drug product. It was approved in 1994. The package insert did not contain the patient leaflet. There is a FTR in the file folder from 1991 that states that we would not require the generic firms submit it at that time. After discussion between John Grace and myself (Carol Holquist) it was determined it is part of the approved labeling from 1996 and that we would request firms to submit it, however it would not have to be attached nor referenced in the PRECAUTIONS section of the insert. The innovator does not do this either. The leaflet contains informational material on how to live with asthma.

Date of Review: October 30, 1997

Date of Submission: October 10, 1997

Reviewer:

Date: 11/4/97

Team Leader:

Date:

11/4/97

CC:

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

ANDA Number: **75-067** Date of Submission: **January 31, 1997**

Applicant's Name: **Alpharma, U.S. Pharmaceuticals Division**

Established Name: **Cromolyn Sodium Inhalation Solution USP,
20 mg/2 mL**

Labeling Deficiencies:

1. **UNIT DOSE CONTAINER (2 mL ampule)**
 - a. We acknowledge your comments regarding the embossing of the vial card and find them unsatisfactory. The embossing should be revised to read as follows:

FOR INHALATION USE ONLY

NOT FOR INJECTION

- b. Revise the established name on the principal display panel to read as follows:

Cromolyn Sodium Inhalation Solution USP

If space does not permit, you may abbreviate "Inhalation" and "Solution" as seen on the other text area. Do not utilize "INH" as an abbreviation for inhalation because it may be confused with "isoniazid".

2. **FOIL WRAP**
 - a. Include the temperature storage recommendations.
 - b. Include the following:

Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

- c. We encourage you to include a "manufactured by" statement as seen on your unit dose carton label and insert labeling.

3. UNIT DOSE CARTON (60 x 2 mL)

- a. Storage Temperature - Reverse the order of the degrees Fahrenheit and Celsius.
- b. Insert "the" in "Keep out of the reach of children."

4. INSERT

I. Professional Insert

a. TITLE

Place "For Inhalation..." and "Not For Injection..." in bold print.

b. DESCRIPTION

- i. Revise to read "molecular formula" rather than "empirical formula".
- ii. Revise to read "structural formula" rather than "molecular structure".
- iii. Revise the chemical name to be in accord with the second name listed in USP 23.
- iv. Revise the last paragraph to read as follows:

...ampule for inhalation use only
contains 20 mg cromolyn...

c. INDICATIONS AND USAGE

Delete "inhalation solution" from the first sentence of paragraph two.

d. WARNINGS

Insert the following text as the second paragraph:

Anaphylactic reactions with cromolyn sodium administration have been reported rarely.

e. PRECAUTIONS

- i. Information for Patients - Insert the following text as penultimate paragraph:

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

- ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

A) Delete "and" from the subsection heading.

B) Revise the subsection to read as follows:

Long term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg three days per week), hamsters (intraperitoneal administration at doses up to 53 mg/kg three days per week for 15 weeks followed by 17.5 mg/kg three days per week for 37 weeks), and rats (18 months subcutaneous treatment at doses up to 75 mg/kg six days per week) showed no neoplastic effects. These doses correspond to approximately 1.0, 0.3, and 2 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis.

Cromolyn sodium showed no mutagenic potential in Ames Salmonella/microsome plate assays, mitotic gene conversion in *Saccharomyces cerevisiae* and in an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day in males and 100 mg/kg/day in females. These doses are

approximately 18 and 10 times, respectively, the maximum recommended adult human daily inhalation dose, on a mg/m^2 basis.

iii. Pregnancy

- A) Revise the subsection heading to read:

Pregnancy: Teratogenic Effects,
Pregnancy Category B

- B) Revise the subsection to read as follows:

Reproduction studies with cromolyn sodium administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg and 164 mg/kg , respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg produced no evidence of fetal malformations. These doses represent approximately 27, 17, and 98 times, respectively, the maximum recommended adult human daily inhalation dose on a mg/m^2 basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses...

- iv. Drug Interaction During Pregnancy -
Revise to read as follows:

...dose up to 540 mg/kg (approximately 27 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (approximately 7 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) increased both resorptions and malformations. The addition of cromolyn sodium to isoproterenol appears to have increased the incidence of both resorptions and malformations.

- v. Nursing Mothers - Delete "inhalation solution" from the last sentence.

f. OVERDOSAGE

Revise to read as follows:

...has demonstrated that toxicity with cromolyn sodium occurs only with very high exposure levels, regardless of whether administration was parenteral, oral or by inhalation. Parenteral administration in mice, rats, guinea pigs, hamsters, and rabbits demonstrated median lethal dose of approximately 4000 mg/kg. Intravenous administration in monkeys also indicated a similar pattern of toxicity. The highest dose administered by the oral route in rats and mice was 8000 mg/kg, (approximately 261 and 130 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis) and at this dose level no deaths occurred. By inhalation, even in long term studies...

g. DOSAGE AND ADMINISTRATION

- i. Include the following text to appear as the second paragraphs:

Drug stability and safety of cromolyn sodium when mixed with other drugs in a nebulizer have not been established.

- ii. Non-steroidal agents:, first paragraph - Italicize "added."

g. HOW SUPPLIED

- i. Include the carton size.
- ii. We encourage the use of the NDC number in this section.
- iii. See comments c under FOIL WRAP and a and b under UNIT DOSE CARTON.

II. Patient Instructions Leaflet

- a. How to Prevent Asthma Attacks - Insert an asterisk "*" following "plan" in the last sentence of paragraph one. In addition, insert the following footnote at the bottom of the page:

* Adapted from the National Heart, Lung, and Blood Institute. Guidelines for the Diagnosis

and Management of Asthma. National Asthma Education Program, Expert Panel Report, 1991.

- b. See comments a and b under UNIT DOSE CARTON.
- c. Method of Administration - Include the following text:

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

Please revise your unit dose ampule labels, foil wrap, carton, leaflet and insert labeling, as instructed above, and submit final printed labels and 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.

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

THIS REVIEW SUPERSEDES THE REVIEW DATED APRIL 8, 1997

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

ANDA Number: **75-067** Date of Submission: **January 31, 1997**

Applicant's Name: **Alpharma, U.S. Pharmaceuticals Division**

Established Name: **Cromolyn Sodium Inhalation Solution USP,
20 mg/2 mL**

Labeling Deficiencies:

1. **UNIT DOSE CONTAINER (2 mL ampule)**
 - a. We acknowledge your comments regarding the embossing of the vial card and find them unsatisfactory. The embossing should be revised to read as follows:

FOR INHALATION USE ONLY

NOT FOR INJECTION

- b. Revise the established name on the principal display panel to read as follows:

Cromolyn Sodium Inhalation Solution USP

If space does not permit, you may abbreviate "Inhalation" and "Solution" as seen on the other text area. Do not utilize "INH" as an abbreviation for inhalation because it may be confused with "isoniazid".

2. **FOIL WRAP**
 - a. Include the temperature storage recommendations.
 - b. Include the following:

Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

- c. We encourage you to include a "manufactured by" statement as seen on your unit dose carton label and insert labeling.

3. UNIT DOSE CARTON (60 x 2 mL)

- a. Storage Temperature - Reverse the order of the degrees Fahrenheit and Celsius.
- b. Insert "the" in "Keep out of the reach of children."

4. INSERT

I. Professional Insert

a. TITLE

Place "For Inhalation..." and "Not For Injection..." in bold print.

b. DESCRIPTION

- i. Revise to read "molecular formula" rather than "empirical formula".
- ii. Revise to read "structural formula" rather than "molecular structure".
- iii. Revise the chemical name to be in accord with the second name listed in USP 23.
- iv. Revise the last paragraph to read as follows:

...ampule for inhalation use only
contains 20 mg cromolyn...

c. INDICATIONS AND USAGE

Delete "inhalation solution" from the first sentence of paragraph two.

d. WARNINGS

Insert the following text as the second paragraph:

Anaphylactic reactions with cromolyn sodium administration have been reported rarely.

e. PRECAUTIONS

- i. Information for Patients - Insert the

following text as penultimate paragraph:

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

- A) Delete "and" from the subsection heading.
- B) Revise the subsection to read as follows:

Long term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg three days per week), hamsters (intraperitoneal administration at doses up to 53 mg/kg three days per week for 15 weeks followed by 17.5 mg/kg three days per week for 37 weeks), and rats (18 months subcutaneous treatment at doses up to 75 mg/kg six days per week) showed no neoplastic effects. These doses correspond to approximately 1.0, 0.3, and 2 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis.

Cromolyn sodium showed no mutagenic potential in Ames Salmonella/microsome plate assays, mitotic gene conversion in *Saccharomyces cerevisiae* and in an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day in males and 100 mg/kg/day in females. These doses are approximately 18 and 10 times, respectively, the maximum recommended adult human daily inhalation dose, on a mg/m² basis.

iii. Pregnancy

- A) Revise the subsection heading to read:

Pregnancy: Teratogenic Effects,
Pregnancy Category B

- B) Revise the subsection to read as follows:

Reproduction studies with cromolyn sodium administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg and 164 mg/kg, respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg produced no evidence of fetal malformations. These doses represent approximately 27, 17, and 98 times, respectively, the maximum - recommended adult human daily inhalation dose on a mg/m² basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses...

- iv. Drug Interaction During Pregnancy -
Revise to read as follows:

...dose up to 540 mg/kg (approximately 27 times the maximum recommended adult human daily inhalation dose on a mg/m² basis) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (approximately 7 times the maximum recommended adult human daily inhalation dose on a mg/m² basis) increased both resorptions and malformations. The addition of cromolyn sodium to isoproterenol appears to have increased the incidence of both resorptions and malformations.

- v. Nursing Mothers - Delete "inhalation solution" from the last sentence.

f. OVERDOSAGE

Revise to read as follows:

...has demonstrated that toxicity with cromolyn sodium occurs only with very high exposure levels, regardless of whether administration was parenteral, oral or by inhalation. Parenteral administration in mice, rats, guinea pigs, hamsters, and rabbits demonstrated median lethal dose of approximately 4000 mg/kg. Intravenous administration in monkeys also indicated a similar pattern of toxicity. The highest dose administered by the oral route in rats and mice was 8000 mg/kg, (approximately 261 and 130 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis) and at this dose level no deaths occurred. By inhalation, even in long term studies...

g. DOSAGE AND ADMINISTRATION

- i. Include the following text to appear as the second paragraphs:

Drug stability and safety of cromolyn sodium when mixed with other drugs in a nebulizer have not been established.

- ii. Non-steroidal agents:, first paragraph - Italicize "added."

g. HOW SUPPLIED

- i. Include the carton size.
- ii. We encourage the use of the NDC number in this section.
- iii. See comments c under FOIL WRAP and a and b under UNIT DOSE CARTON.

II: Patient Instructions Leaflet

- a. How to Prevent Asthma Attacks - Insert an asterisk "*" following "plan" in the last sentence of paragraph one. In addition, insert the following footnote at the bottom of the page:

* Adapted from the National Heart, Lung, and

Blood Institute. Guidelines for the Diagnosis and Management of Asthma. National Asthma Education Program, Expert Panel Report, 1991.

- b. See comments a and b under UNIT DOSE CARTON.
- c. Method of Administration - Include the following text:

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

Please revise your unit dose ampule labels, foil wrap, carton, leaflet and insert labeling, as instructed above, and submit final printed labels and 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.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): 2 mL ampule, 20 mg/2 mL, 1/31/97

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

Unit Dose Ampule Label:

Foil Wrap:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Intal® Nebulizer Solution; Fisons; Approved March 18, 1996, Revised April 1994).

2. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this dosage form.

3. Storage/Dispensing Conditions:

NDA: Foil pouch, carton and insert: Store between 15° - 30°C (59° - 86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

ANDA: Carton and Insert: Store between 15° - 30°C (59° - 86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

USP: Preserve in single-unit double ended glass ampules or in low-density polyethylene ampules.

4. Product Line:

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 056, Vol. 1.1.

6. ~~F~~
I

utilized for testing. See pages 089, vol. 1.1.

7. Container/Closure:

This product will be packaged in a 3.2 mL ampule with a 2 mL fill. The ampule will be made from a and there will be 4 ampules per vial card. See pages 468 and 469, Vol. 1.2.

8. There has been only one other application for this drug product ANDA. It was approved in 1994. The package insert did not contain the patient leaflet. There is a FTR in the file folder from 1991 that states that we would not require the generic firms submit it at that time. After discussion between John Grace and myself (Carol Holquist) it was determined it is part of the approved labeling from 1996 and that we would request firms to submit it, however it would not have to be attached nor referenced in the PRECAUTIONS section of the insert. The innovator does not do this either. The leaflet contains informational material on how to live with asthma.

Date of Review: June 13, 1997

Date of Submission: January 31, 1997

Primary Reviewer: *TSI*

Date:

6/17/97

Secondary Reviewer: *TSI*

Date:

6/17/97

Team Leader: *TSI*

Date:

7/11/97

cc:

CDER Establishment Evaluation Report
for July 14, 1997

Establishment:

DMF No:

AADA No:

Profile: - CSN

OAI Status: NONE

Responsibilities:

Last Milestone: OC RECOMMENDAT 01-APR-1997

DRUG SUBSTANCE MANUFACTURER

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment:

DMF No:

AADA No:

Profile: NEC

OAI Status: NONE

Responsibilities:

Last Milestone: OC RECOMMENDAT 15-MAY-1997

DRUG SUBSTANCE OTHER TESTER

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

ANDA Number: **75-067** Date of Submission: **January 31, 1997**

Applicant's Name: **Alpharma, U.S. Pharmaceuticals Division**

Established Name: **Cromolyn Sodium Inhalation Solution USP,
20 mg/2 mL**

Labeling Deficiencies:

1. **UNIT DOSE CONTAINER (2 mL ampule)**
 - a. We acknowledge your comments regarding the embossing of the vial card and find them unsatisfactory. The embossing should be revised to read as follows:

 FOR INHALATION USE ONLY

 NOT FOR INJECTION
 - b. Revise the established name on the principal display panel to read as follows:

 Cromolyn Sodium Inhalation Solution USP

 If space does not permit, you may abbreviate "Inhalation" and "Solution" as seen on the other text area. Do not utilize "INH" as an abbreviation for inhalation because it may be confused with "isoniazid".

2. **FOIL WRAP**
 - a. Include the temperature storage recommendations.
 - b. Include the following:

 Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.
 - c. We encourage you to include a "manufactured by" statement as seen on your unit dose carton label and insert labeling.

3. UNIT DOSE CARTON (60 x 2 mL)
 - a. Storage Temperature - Reverse the order of the degrees Fahrenheit and Celsius.
 - b. Insert "the" in "Keep out of the reach of children."

4. INSERT

I. Professional Insert

a. TITLE

Place "For Inhalation..." and "Not For Injection..." in bold print.

b. DESCRIPTION

- i. Revise to read "molecular formula" rather than "empirical formula".
- ii. ~~Revise to read "structural formula" rather than "molecular structure".~~
- iii. Revise the last paragraph to read as follows:

...ampule for inhalation use only
contains 20 mg cromolyn...

c. INDICATIONS AND USAGE

Delete "inhalation solution" from the first sentence of paragraph two.

d. PRECAUTIONS

- i. Pregnancy - Revise the subsection heading to read:

Pregnancy: Teratogenic Effects,
Pregnancy Category B
- ii. Nursing Mothers - Delete "inhalation solution" from the last sentence.

e. HOW SUPPLIED

- i. Include the carton size.

- ii. We encourage the use of the NDC number in this section.
- iii. See comments c under FOIL WRAP and b and c under UNIT DOSE CARTON.

II. Patient Instructions Leaflet

How to Prevent Asthma Attacks - Insert an asterisk "*" following "plan" in the last sentence of paragraph one. In addition, insert the following footnote at the bottom of the page:

* Adapted from the National Heart, Lung, and Blood Institute. Guidelines for the Diagnosis and Management of Asthma. National Asthma Education Program, Expert Panel Report, 1991.

Please revise your unit dose ampule labels, foil wrap, carton, leaflet and insert labeling, as instructed above, and submit final printed labels and 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.

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

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:

Unit Dose Ampule Label:

Foil Wrap:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Intal® Nebulizer Solution

NDA Number: 18-596

NDA Drug Name: Intal® Nebulizer Solution

NDA Firm: Fisons Corporation

Date of Approval of NDA Insert and supplement #:

S-021/March 18, 1996

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:

Approved labels (March 18, 1996) in the file folder.

Basis of Approval for the Carton Labeling:

Approved labeling (March 18, 1996) in the 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 Z3 See USP supplement 1 for the title change from "Cromolyn Sodium Inhalation" to "Cromolyn Sodium Inhalation Solution".	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? Imprinting on the plastic ampule card. See comment to firm in review.	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). On ampule - See comment in review.	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASMP 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 NOW 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 NOW 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, Opespray?			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 C _{max} , T _{max} , 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?: FIR: 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:*****

Is the container/closure system adequate to meet the USP requirement for an container?

Yes. See item 26. of chemist's review

M. J. Smith
7/10/97

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Intal® Nebulizer Solution; Fisons; Approved March 18, 1996, Revised April 1994).

2. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this dosage form.

3. Storage/Dispensing Conditions:

NDA: Foil pouch, carton and insert: Store between 15° - 30°C (59° - 86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

ANDA: Carton and Insert: Store between 15° - 30°C (59° - 86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children. Store ampules in foil pouch until ready to use.

USP: Preserve in single-unit double ended glass ampules or in low-density polyethylene ampules.

4. Product Line:

60s.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 056, Vol. 1.1.

6. ⁱ
¹
utilized for testing. See pages 089, vol. 1.1.
7. Container/Closure:

This product will be packaged in a 3.2 mL ampule with a 2 mL fill. The ampule will be made from a and there will be 4 ampules per vial card. See pages 468 and 469, Vol. 1.2.
8. There has been only one other application for this drug product. It was approved in 1994. The package insert did not contain the patient leaflet. There is a FTR in the file folder from 1991 that states that we would not require the generic firms submit it at that time. After discussion between John Grace and myself (Carol Holquist) it was determined it is part of the approved labeling from 1996 and that we would request firms to submit it, however it would not have to be attached nor referenced in the PRECAUTIONS section of the insert. The innovator does not do this either. The leaflet contains informational material on how to live with asthma.

Date of Review: April 8, 1997

Date of Submission: January 31, 1997

Primary Reviewer:

Date:

4/25/97

Secondary Reviewer:

Date:

4/25/97

Team Leader:

Date:

4/29/97

CC:

Department of Health and Human Services
Public Health Service
Food and Drug Administration
ESTABLISHMENT EVALUATION REPORT
for March 13, 1997

Requestor's Name:	Division:	Phone:
Application: ANDA 75067	Brand Name:	
	Established Name: CROMOLYN SODIUM	
	Strength: 10 MG/ML INHALATION	Dosage Form: SOL
Sponsor: ALPHARMA USPD	Org Code: 600	Priority:
Office:		
Street: 333 CASSELL DR STE 3500		
City / State: BALTIMORE, MD 21224		District Goal: 03-APR-98
Action Goal:	User Fee Goal:	

Establishment: 1110239 **Name:** ALPHARMA
7205 WINDSOR BLVD
BALTIMORE, MD 212442654

Responsibilities	Dmf No	Profile	Status	Date
FINISHED DOSAGE STABILITY TESTER		LIQ		
Establishment:	Name:	INC		

Responsibilities	Profile	Status	Date
FINISHED DOSAGE MANUFACTURER	LIQ		
Establishment:	Name:		

Responsibilities	Profile	Status	Date
DRUG SUBSTANCE MANUFACTURER	CSN	PN	13-MAR-97

CSO	Date	Recommendation
-----	------	----------------

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-067

CORRESPONDENCE

May 13, 1999

RESPONSE TO MICROBIOLOGY DEFICIENCIES

CDER, FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Douglas Sporn, Director

NDA ORIG AMENDMENT

N/As

Re: ANDA 75-067
Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL

Dear Mr. Sporn:

Alpharma, U.S. Pharmaceutical Division hereby submits the response to the microbiology deficiency identified in our pending Abbreviated New Drug Application for Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL. Reference is made to the Agency's letter dated May 4, 1999 regarding the above referenced product application (attached).

Alpharma has responded, completely and comprehensively, to the question posed by the Agency in the aforementioned letter.

Alpharma is requesting a 24-month expiry dating for this product.

For ease of reference, your questions or comments should be addressed to Martin Levy, Director of Regulatory Affairs at Alpharma. My contact telephone number is 410-558-7250 ext. 205 and fax is 410-558-7262.

Sincerely,
ALPHARMA USPD INC.

Martin Levy

Martin Levy, FBIRA
Director, Regulatory Affairs
ML/fm



April 12, 1999

FACSIMILE AMENDMENT TO A PENDING APPLICATION

CDER, FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Douglas Sporn, Director

MAIL ROOM

Re: **ANDA #75-067**
Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL

Dear Mr. Sporn:

Pursuant to 21 CFR §314.96(a), Alpharma, U.S. Pharmaceuticals Division hereby submits a facsimile amendment to our pending abbreviated new drug application. Reference is made to the Agency's letter of March 24, 1999 (attached) and our abbreviated new drug application dated January 31, 1997. The Agency's comments have been restated and Alpharma's responses follow.

In addition to responding to this deficiency, please note that your sterility assurance information is pending review.

The applicant proposes the following specifications for the release and stability of Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL. These specifications mirror ICH requirements as they relate to drug products.

Proposed Release and Stability Specifications

Individual Unknown	()
Individual Known	()
Total	()

Proposed Release Specifications

Individual Known	()
Total	()

RECEIVED

APR 13 1999

GENERIC DRUGS



Cromolyn Sodium Inhalation
Solution, USP 20 mg/2 mL
ANDA 75-067/Fax Amend.
Cover letter/Page 2

We acknowledge the Agency's comment regarding the pending review of our sterility assurance information.

Your questions or comments on the proposed specifications should be directed to Martin Levy at 410-558-7250 ext. 205.

Sincerely,
ALPHARMA USPD, INC.

A handwritten signature in cursive script that reads "Martin Levy".

Martin Levy, FBIRA
Director, Regulatory Affairs
ML/fm
Enclosures

Page(s) _____

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

3/24/99
Chemistry Review



#38



September 15, 1998

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RECEIVED

N/AC

Re: **ANDA #75-067**
Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL
MAJOR AMENDMENT TO A PENDING APPLICATION INCLUDING RESPONSE TO LABELING DEFICIENCIES

Dear Mr. Sporn:

Pursuant to 21 CFR §314.96(a), Alpharma, U.S. Pharmaceuticals Division hereby submits a major amendment to our pending abbreviated new drug application. Reference is made to the Administration's letter of March 30, 1998 (attached) and our abbreviated new drug application dated January 31, 1997. The Administration's comments have been restated and Alpharma's responses follow.

A. Deficiencies

Page (s) 2

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

9/15/98

LABELING DEFICIENCIES:

Reference is made to the 4/22/98 telecommunication between the Administration (Sheila O'Keefe, CSO) and Alpharma (Francine McLeod) concerning the submission of FPL for the unit dose ampule. Alpharma requested that printer proofs be accepted for FPL because of the embossing process of the ampule. The ampule is produced and embossed at the time that the drug product is packaged (blow/fill/seal technology). The Administration agreed that final printers proof labeling would be acceptable. The unit dose ampule has been revised as requested.

Enclosed as attachment 5 are the following:

- Twelve copies of final "Printer's Proof" labeling of the unit dose ampule.

- Side by side comparison of the last submitted unit dose ampule labeling and the current labeling.

- Twelve copies of final printed labeling for the foil wrap. No revisions have been made from the last submitted foil labeling.

Alpharma USPD
Cromolyn Sodium Inhalation
Solution, USP 20 mg/2 mL
ANDA 75-067/Major Amend.
Cover letter/Page 6

We trust that our response fully addresses the Administration's concerns.

Sincerely,
Alpharma, USPD

Vincent Andolina
for

Ronald Bynum
Manager, Regulatory Affairs
RB/fm
Enclosures

FA\0750\submit\maj.amend2

In accordance with 21 CFR § 314.96(b), AlphaPharma certifies that the field copy is a true copy of this amendment and has been sent to the Baltimore, MD FDA District Office.

Nurcent Andolina 9/15/98 for

Ronald Bynum
Manager, Regulatory

Page (s) 2

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

9/15/98

October 10, 1997

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Steven Sherken, HFD-625
Metro Park North II
7500 Standish Place, Room 204
Rockville, Maryland 20855-2773

NEW CORRESP

KC noted NAI Saloff 10/22/97

Re: **ANDA #75-067**
Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL

MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sherken:

Reference is made to the Administration's letter of July 22, 1997 (attached) and our abbreviated new drug application dated January 31, 1997. The Administration requested that Alpharma, U.S. Pharmaceuticals Division submit a sample of the ampule card of the above referenced product to your attention.

Please find enclosed a sample of Cromolyn Sodium Inhalation Solution USP, 20 mg/2mL lot 01096C.

If you require additional samples please contact me at (410) 558-7250 ext 209.

Sincerely,

Ronald Bynum / for

Vincent Andolina
Manager, Regulatory Affairs

VA/fm
Enclosures

RECEIVED

OCT 15 1997

GENERIC DRUGS

*Andolina
10-21-97*



October 10, 1997

ANDA ORIG AMENDMENT

N/A C / FPL

Mr. Carl Draper
Director of Investigations and Enforcement Operations Branch
Food and Drug Administration
900 Madison Avenue
Baltimore, Maryland 21201

Re: **ANDA #75-067**
Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL

MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Draper:

Pursuant to 21 CFR § 314.96 (b), Alpharma, U.S. Pharmaceuticals Division of Baltimore, Maryland hereby submits a field copy of our major amendment to the above referenced abbreviated new drug application.

The undersigned official certifies that Alpharma's field copy is a true copy of that submitted to the Food and Drug Administration's headquarters.

Sincerely,

Ronald Bynum / for

Vincent Andolina
Manager, Regulatory Affairs

VA/fm
Enclosures

RECEIVED

OCT 14 1997

GENERIC DRUGS



October 10, 1997

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*Labels checked
10/30/97*

Re: **ANDA #75-067**

Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL

**MAJOR AMENDMENT TO A PENDING APPLICATION INCLUDING RESPONSE TO
MICROBIOLOGY AND LABELING DEFICIENCIES**

Dear Mr. Sporn:

Pursuant to 21 CFR §314.96(a), Alparma, U.S. Pharmaceuticals Division hereby submits a major amendment to our pending abbreviated new drug application. Reference is made to the Administration's letter of July 22, 1997 (attached) and our abbreviated new drug application dated January 31, 1997. The Administration's comments have been restated and Alparma's responses follow. This submission consists of one volume and four additional envelopes containing final printed carton labeling.

Chemistry Deficiencies

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

10/10/97

Chem + Micro deficiencies

LABELING DEFICIENCIES:

The unit dose ampule, foil wrap, carton, leaflet and insert labeling has been revised as instructed above. We have added an additional package size of ampules. Enclosed as attachment 16 are the following:

Twelve copies of final "Printer's Proof" labeling of the unit dose ampule and the foil wrap.

Twelve copies of final printed labeling for the carton (60 & 120 sizes), patient instructions leaflet and professional insert.

An annotated side-by-side comparison with the last labeling submitted for the unit dose ampule, foil wrap, carton, patient instructions leaflet and professional insert.

We trust that our response fully addresses the Administration's concerns.

Sincerely,
Alpharma, USPD

Ronald Bynum /for

Vincent Andolina
Manager, Regulatory Affairs
VA/fm
Enclosures

Alpharma USPD
Cromolyn Sodium Inhalation
Solution, USP 20 mg/2 mL
ANDA 75-067/Major Amend.

In accordance with 21 CFR §314.96 (b), the undersigned official certifies that Alpharma, U.S. Pharmaceuticals Division has provided a field copy of this major amendment to the FDA Baltimore district.

Ronald Bynum / for

10/10/97

Vincent Andolina
Manager, Regulatory Affairs



ALPHARMA

U.S. Pharmaceuticals Division

*Harvey Greenley
3/1/97*

January 31, 1997

Douglas Sporn, Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*Labeling
...
(...)*

**Re: Abbreviated New Drug Application
Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL**

Dear Mr. Sporn:

We are herewith submitting an Abbreviated New Drug Application pursuant to 21 CFR §314.94(a) and Section 505(j) of the Federal Food, Drug and Cosmetic Act for the drug product Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL.

The abbreviated application is being submitted as follows:

- 1) **Archival Copy** (Blue Folder)- consisting of one volume which contains items required for an ANDA per 21 CFR section 314.94(a) plus all the information required under section 505(j)(2)(A)(B) of the FD&C Act (see Table of Contents of this application). Under separate cover, as required by 21 CFR 314.94(d)(5), Alpharma, U.S. Pharmaceuticals Division hereby certifies that a field copy that contains (a) the technical section required by 21 CFR 314.94(a)(9), (b) a copy of the 356h form, and (c) a certification that the copy of the technical section is the same as that contained in the archival and review copies has been sent simultaneously to the Baltimore District Office.
- 2) **Review Copy**- which contains items for an ANDA per 21 CFR 314.94(d)(2) in two separate sections:
 - Red Folder** - Items described under 314.94(a)(2) through (a)(6), (a)(8), (a)(9), analytical methods, and analytical methods validation.
 - Orange Folder** - Items described under 314.94(a)(3), (a)(7), and (a)(8).

Sincerely,

Vincent Andolina

Vincent Andolina
Senior Manager, Regulatory Affairs

RECEIVED

FEB 05 1997

GENERIC DRUGS



January 31, 1997

Mr. Carl Turner
Director of Investigations
Food and Drug Administration
900 Madison Avenue
Baltimore, Maryland 21201

Re: Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL

ABBREVIATED NEW DRUG APPLICATION

Dear Mr. Turner:

Pursuant to 21 CFR § 314.94 (d) (5), Alpharma, U.S. Pharmaceuticals Division of Baltimore, Maryland hereby submits a field copy of our abbreviated new drug application, Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL.

The undersigned official certifies that Alpharm's field copy is a true copy of that submitted to the Food and Drug Administration's headquarters.

Sincerely,

Vincent Andolina
Sr. Manager, Regulatory Affairs

VA:fm

Enclosures