CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-271

CORRESPONDENCE

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-271 Applicant: Zenith Goldline Pharmaceuticals
Agent for Steripak Limited

Drug Product: Cromolyn Sodium Inhalation Solution USP, 10mg/mL

No chemistry manufacturing and controls deficiencies.

cc:

Endorsements:
HFD-625/K.Furnkranz/12-13-99 12/15/99
HFD-625/M.Smela, T/L/
HFD-617/M.Dillahunt, P/M/
V:\FIRMSNZ\STERIPAK\LTRS&REV\75271A04.DKF.DOC
FT by: bc/12-14-99
CHEMISTRY CLOSED

Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

Via Federal Express

DEC 01 1999

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT - Chemistry and Microbiology

RE: ANDA 75-271 - Cromolyn Sodium Inhalation Solution USP, 1.0% w/v

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated November 19, 1999 (copy provided in Reference), and to our Gratuitous Chemistry Amendment dated November 15, 1999 concerning our Abbreviated New Drug Application for the above referenced product. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your letter. As stated in your correspondence, this response should be considered a FACSIMILE AMENDMENT.

In response to the Agency's comments, we submit the following. Please note that several of the comments have previously been addressed in our Gratuitous Chemistry Amendment of 11/15/99. In these instances, we have provided the appropriate cross-references.

A. DEFICIENCIES

Page(s) 2

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12/1/99

4. *Please submit available long-term data generated on the exhibit batches since the last submission.*

   Response:
   Steripak has provided an updated Stability Report for the 9 month data as **Exhibit 5 of our Gratuitous Chemistry Amendment dated November 15, 1999**. As stated in our Gratuitous Amendment, the testing of the 40°C sample was inadvertently omitted from the 6 month time-point, however, the product was tested after a period of 10 months and the results were found to be satisfactory.

Zenith Goldline Pharmaceuticals, Inc., and Steripak Limited have made every effort to ensure that this response is complete and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions or require additional information, please contact our office at (201)767-1700, ext. 239/331

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Global Regulatory Affairs
Authorized US Agent for Steripak Ltd., UK

cc: Field Office

K:\Reg\CROMOLYN\CROMdeficiency response NOV.doc

Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

Via Federal Express

NOV 1 5 1999

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GRATUITOUS AMENDMENT - Chemistry

RE: ANDA 75-271 – Cromolyn Sodium Inhalation Solution, 1.0% w/v.

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for the above referenced product. Following receipt of chemistry deficiencies for another of Steripak's pending inhalation solution applications (ANDA 75-343 for Albuterol Sulfate Inhalation Solution, 0.083%; copies attached in Reference), we are submitting the enclosed additional information as a Gratuitous Amendment.

Responses to the chemistry deficiencies provided in Reference, which are applicable to Cromolyn Sodium Inhalation Solution, 1.0%, are provided below:

A. *CHEMISTRY DEFICIENCIES*

1 *Please state a maximum timeframe between manufacturing of a batch and the overwrap process for your future*

Page(s) _____

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

11/15/99

In addition, Steripak has provided an updated Stability Report for the 9 month data for Cromolyn Sodium Inhalation Solution, 1.0%, as *Exhibit 5.* It should be noted that the testing of the 40°C sample was inadvertantly omitted from the 6 month time-point, however, the product was tested after a period of 10 months and the results were found to be within specification.

Zenith Goldline has made a concerted effort to ensure that this response is complete and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions or require additional information, please contact our office at (201) 767-1700, ext. 239/331.

Sincerely yours,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Stacy Bate / for

Jason A. Gross, Pharm. D.
Director of Global Regulatory Affairs
Authorized US Agent for Steripak Limited, UK

Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

Via Federal Express

ORIG AMENDMENT

JUL 29 1999

AS

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RESPONSE TO MICROBIOLOGY DEFICIENCIES

RE: Cromolyn Sodium Inhalation Solution, USP, 1.0%
ANDA 75-271

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated July 15, 1999 (copy attached in Reference), concerning our Abbreviated New Drug Application for the above referenced product. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your letter. As stated in your correspondence, this response should be considered as a RESPONSE TO MICROBIOLOGICAL DEFICIENCIES.

In response to the Agency's comments, we submit the following:

A. MICROBIOLOGICAL DEFICIENCIES

1. The bacterial retention validation descriptions are too brief and no data generated during the

Page(s) 6

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7/29/99

3. ***Please clarify the meaning of "biannual basis" as it pertains to your media fill requalification program. This term may mean that requalification is completed either every 6 months (semi-annually) or every 2 years..***

Response

We conduct media simulation studies every 6 months therefore the words "Biannual basis" mean occurring twice a year.

This completes our Response to Microbiology Deficiencies in the Agency's comments of July 15, 1999. We trust that all outstanding deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Cross, Pharm. D.
Director of Global Regulatory Affairs
Authorized US Agent for Steripak Limited, UK

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express

JUN 2 4 1999

NDA ORIG AMENDMENT

N/AC

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT - Chemistry

RE: ANDA 75-271 - Cromolyn Sodium Inhalation Solution USP, 1.0% (10 mg/mL)

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Cromolyn Sodium Inhalation Solution USP, 1.0% (10 mg/mL), and to our Amendments dated August 26, 1998 (Major) and December 30, 1998 (Labeling). Further reference is made to OGD's Major Amendment deficiency letter dated March 8, 1999 (copy attached), in which the Agency advised Zenith Goldline of the unsatisfactory nature of our previous response pertaining to foil overwrapping of our [illegible] containers.

Pursuant to 21 CFR §314.120(a)(1), we are amending our application by responding to the chemistry deficiencies cited in the Agency's letter of March 8, 1999. In order to better meet OGD's requirements, we have revisited the container/closure data provided in our August 26, 1998 amendment, and request that the Agency consider our current response to Comment 2 as a replacement.

In response to the Agency's comments, we submit the following:

CHEMISTRY DEFICIENCIES

1. [illegible]

[illegible] both finish[illegible]

[illegible] *Cromolyn Sodium Inhalation Solution USP, 10 mg/mL (#K026)*, car[illegible] herewith in Exhibit 3.

140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0133 Fax (201) [illegible]
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Page(s) 1

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7/24/99

PLEASE NOTE AND ACKNOWLEDGE

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. *Labeling deficiencies, if any, should also be addressed in your reply.*

   Response:
   The response herein addresses the chemistry issues only. The labeling deficiencies listed in the Agency's communication of March 3, 1999 are currently being addressed, and the response will be submitted under separate cover.

2. *Your sterility assurance information is pending review.*

   Response:
   Steripak Limited acknowledges that the sterility assurance section of the ANDA is pending review, and that comments will be communicated separately upon completion of review.

This completes our Major Amendment response to the Agency's comments of March 8, 1999. We trust that all outstanding chemistry deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director of Global Regulatory Affairs
Authorized U.S. Agent for Steripak Limited, U.K.

Attachments

K:\Reg\CROMOLYN\second major defltr.rtf

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

NEW CORRESP
NC
NAE
DA 4/20/99

April 12, 1999

Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-271 - Cromolyn Sodium Inhalation Solution USP

Dear Mr. Sporn:

Reference is made to our March 9, 1999 request for a meeting with your office to discuss our pending application, a copy of which is attached. Reference is also made to our subsequent tele-conference with Mike Smela and Denise Huie.

Zenith Goldline Pharmaceuticals would like to thank Mr. Smela and the Office for responding to our request in such an expeditious manner.

Attached for your files is Zenith Goldline Pharmaceuticals meeting minutes. If the minutes do not reflect the issues as discussed, please let us know.

With best regards,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, State, Federal, and
International Regulatory Affairs

RECEIVED
APR 15 1999
GENERIC DRUGS

Attachment

JAG:dj

Nathan 4-15-99

140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0133 Fax (201) 767-3804

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Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Copy to File
3/17/99

March 9, 1999

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
CDER, FDA
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC

REQUEST FOR MEETING

Re: Cromolyn Sodium Inhalation Solution USP
ANDA 75-271

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application submitted for the above referenced product. This week we received a second Major deficiency letter for this application, and believe that it is necessary to request a meeting with the Agency. We hope that such a meeting will serve to clarify the outstanding requirements, in order that further deficiencies will be avoided.

The Agency's consideration of our meeting request is appreciated. Please contact the undersigned to make the necessary arrangements.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, State, Federal, and International
Regulatory Affairs

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MAR 10 1999
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Madine

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MAR 8 1999

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-271 Applicant: Zenith Goldline Pharmaceuticals
Agent for Steripak Limited

Drug Product: Cromolyn Sodium Inhalation Solution USP, 10mg/mL

The following comments represent MAJOR deficiencies:

A. Deficiencies:

1. In addition to the USP Related Compounds test, please provide a validated test for impurities/degradants to be used both for release and stability. For this test, we recommend that all major impurities are individually identified and limited and that total impurities should not exceed Unidentified impurities should also be limited.

2. Please provide the previously requested comparative data with at least 3 months of storage at 40°C, if you intend to market this product without an overwrap. Please provide the comparative studies with data using analytical methods appropriate to detect possible contaminants at sensitivities in the 100 ppb range. These comparative studies should be performed using other sensitive analytical methods in addition to those methods previously used. The vials that do not have a protective overwrap must be packaged identically as proposed for market (same inks, same adhesive, same labels, same cartons).

   The foil overwrap that you used in your comparative study led to contamination of the product. If you choose to use an overwrap to market the product, please select and validate one that does not cause the product to be contaminated.

3. Regarding the "Weight Loss" test, please provide the acceptance criteria in the stability specification.

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

1. Labeling deficiencies, if any, should also be addressed in your reply.

2. Your sterility assurance information is pending review.

Sincerely yours,

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

Zenith Goldline
PHARMACEUTICALS

Via Federal Express

DEC 30 1998

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/A F

LABELING AMENDMENT

RE: Cromolyn Sodium Inhalation Solution USP, 1.0% w/v (20 mg/2 mL)
ANDA 75-271

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Cromolyn Sodium Inhalation Solution USP, 1.0% w/v (20 mg/2 mL), ANDA 75-271, and to our Major Amendment filed on August 26, 1998, in which we committed to submitting Zenith Goldline's response to labeling deficiencies under separate cover. At this time, we are responding to the labeling deficiencies noted in the Agency's letter sent to Zenith Goldline via fax on July 1, 1998 (copy attached).

To facilitate review of this submission, and in accordance with 21 CFR §314.94(a)(8)(iv), we have provided side-by-side comparisons of the labeling proposed in this amendment (unit-dose container, unit-dose cartons, professional insert and patient insert) versus the last submitted labeling, with all differences annotated and explained. These can be found accompanying the final printed labels and labeling in Attachments 1 through 4 of this amendment.

LABELING DEFICIENCIES

1. *UNIT-DOSE CONTAINER*
   Revise as indicated in Comments 1.a. and 1.b.

   Response:
   We have revised our unit-dose container as instructed in Comments 1.a. and 1.b, and copies of the final printed label are provided in Attachment 1.

2. *UNIT-DOSE CARTON (30 x 2 mL, 60 x 2 mL and 120 x 2 mL)*
   Revise as indicated in Comments 2.a. through 2.d.

   Response:
   We have revised our unit-dose cartons as instructed in Comments 2.a. through 2.d. and copies of the final printed labeling for cartons of 30's, 60's and 120's are provided in Attachment 2.

RECEIVED

JAN 04 1999

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

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3. *INSERT*

   I. *PROFESSIONAL INSERT*

   Revise as indicated in Comments 3.I.a. through 3.I.k.

   Response:

   We have revised our professional insert as instructed in Comments 3.I.a. through 3.I.k., and copies of the final printed labeling are provided in Attachment 3.

   II. *PATIENT INSERT*

   Revise as indicated in Comments 3.II.a. through 3.II.d. Specify how many patient leaflets are provided in each carton.

   Response:

   We have revised our patient insert as instructed in Comments 3.II.a. through 3.II.d., and copies of the final printed labeling are provided in Attachment 4. Steripak Limited provides one professional insert in each carton of 30's, and one patient leaflet in each carton of both 60's and 120's. We respectfully remind the Agency that cartons of 30's are not labeled for individual sale, rather, they are intended for packaging into the cartons of 60's (2 x 30's) and 120's (4 x 30's).

This completes the Labeling Amendment response to the Agency's comments of July 1, 1998. We trust that all outstanding labeling deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely yours,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Stacy Bate for

Jason A. Gross, Pharm. D.
Director of State, Federal and
International Regulatory Affairs
U.S. Authorized Agent for Steripak Limited, UK

Attachments

K:\Reg\CROMOLYN\labelingamend.rtf

Zenith Goldline
PHARMACEUTICALS

October 9, 1998

Regulatory Affairs

Douglas L. Sporn
Director, Office of Generic Drug (HFD-600)
CDER, FDA
Metro Park North II, Document Room #150
7500 Standish Place
Rockville, MD 20855-2773

Re: Correspondence for the Microbiological Reviewer of:

→ **ANDA 75-271 Cromolyn Sodium Inhalation Solution**

Dear Mr. Sporn:

Each of the above referenced applications have proceeded through their first review cycles within your office, with two of the applications presently awaiting review of their respective subsequent amendments. We were initially informed that the sterility assurance reviews for each of these ANDA were pending. It our understanding, through follow-up conversations with the appropriate project managers, that the microbiological review queue is long due to limited Agency resources.

It is therefore the purpose of this correspondence is to offer information to the Agency which may alleviate some of the workload as it pertains to the micro-review of the above ANDAs. All three of the subject applications are manufactured at the same facility (Steripak, Cheshire, UK), utilizing the same equipment and similar processes. It is of special interest that the same microbiological information package was provided in each of these applications.

In light of this information and in order to maximize Agency resources, Zenith Goldline respectfully suggests that the microbiological reviews relevant to our above referenced ANDAs be performed concurrently by one reviewer since the information is identical.

We hope that our recommendation is well received, and serves to assist the Agency in reducing their backlog. Should you have any questions, please contact my office at your convenience.

With best regards,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, State, Federal and
International Regulatory Affairs

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140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-7700 (800) 387-0133 Fax (201) 784-1719
Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. V.I.

Zenith Goldline
PHARMACEUTICALS

ORIG AMENDMENT

N/A C

Regulatory Affairs

Via Federal Express

August 26, 1998

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

RE: **Cromolyn Sodium Inhalation Solution USP, 1.0%**
ANDA 75-271

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated July 1, 1998 (copy attached), concerning our Abbreviated New Drug Application for the above referenced product. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your "Not Approvable" letter. As stated in your correspondence, this response should be considered a MAJOR AMENDMENT.

A. Chemistry Deficiencies

Page(s) 3

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

8/26/98

Bioequivalency Review

We acknowledge that the Division of Bioequivalence has completed its review and has no further questions at this time. We understand that this comment is preliminary and may be subject to revision after review of the entire application.

This completes the Major Amendment response to the Agency's comments of July 1, 1998. We trust that all outstanding deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely yours,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director of State, Federal and
International Regulatory Affairs
US Authorized Agent for Steripak Limited, UK

Attachments
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Zenith Goldline
PHARMACEUTICALS

January 8, 1998

Mr. Douglas L. Sporn
Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(j) 2A OK 1/16/98

NEW CORRESP

Telephone Amendment

RE: Cromolyn Sodium Inhalation Solution USP, 1.0%
ANDA 75-271

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Cromolyn Sodium Inhalation Solution USP, 1.0%, submitted on December 11, 1997. Reference is also made to today's telephone conversation with Mr. Peter Rickman of your office. Mr. Rickman informed us that the reference listed drug was purchased from Fisons by Rhone Poulenc Rorer, and that a correction to our FDA Form 356h and the 505(j)(2)(A) statement reflecting the new owner was necessary. Therefore, we are amending our application accordingly. The revised FDA Form 356h and "Basis for Submission" documents are attached.

Additionally, since Zenith Goldline was made aware of this change after the application was compiled and submitted, we commit to revising relevant sections (i.e. labeling, etc.) as directed by the Agency.

We appreciate the Agency's advisement in this matter, and apologize for the oversight.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Regulatory Affairs

Attachments

kr\k:reg\cromolyn\rhonepou.doc

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JAN 09 1998
GENERIC DRUGS

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JUL 1 .998

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-271 Applicant: Zenith Goldline Pharmaceuticals
Agent for Steripak Limited

Drug Product: Cromolyn Sodium Inhalation Solution USP, 10mg/mL
The following comments represent MAJOR deficiencies:

A. Deficiencies:

1. Please provide revised Heavy Metals acceptance criteria for the drug substance. Your acceptance criteria for heavy metals (referencing Ph. Eur.) should read "< 10 ppm" rather than "20 ppm".

2. The inhalation product packaged in containers should employ a secondary overwrap such as a laminated foil or a pouch to ensure the identity, strength, quality, and purity of the product unless you can demonstrate that such an overwrap is unnecessary via comparative studies. Please give particular attention to the use of the overwrap to control water vapor permeation, gas permeation, extractables, and leachables (including heavy metals, adhesives and ink from the labeling). Your study assessing levels of vanillin and heavy metals is inadequate to justify the lack of an overwrap. You should compare vials that have been protected with an overwrap with vials that have not. The vials should be filled with drug product or purified water and stored at 40°c for at least 3 months. Testing should be conducted for the full range of potential volatile and semi-volatile contaminants at sensitivities in the 100 ppb range. The vehicle should be fully tested at the start of the study to serve as the control. The vials that do not have a protective overwrap must be packaged identically as proposed for market (same inks, same adhesive, same labels, same cartons).

3. Please provide a quantitative color test (APHA) in your release and stability specifications for your drug product.

4. Yearly testing for sterility should be induded in your stability protocol.

5. Please provide limits for each individual and total impurities/degradants based on your validated method for batch release and stability.

6. The stability data sheets are lacking the name of the manufacturer of the bulk drug substance, date of manufacture of the drug product, and the details of the container system. Please revise.

7. Please provide USP Biolgical Reactivity <87> test results for the LDPE resin.

8. OVI testing for the drug substance must be included in your specifications per USP, although you need not actually perform the test if you have verified the appropriate certification from the vendor.

9. Please update the drug substance limit test for to USP Supplement 7. Please provide representative spectra for this test.

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

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

2. Your response must also address the labeling deficiencies.

3. Your sterility assurance information is pending review.

4. Please provide any additional stability data may be available.

Sincerely yours,

Vilayat K Sayani for

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-271 APPLICANT: Zenith Goldline, US Agent for Steripak Limited

DRUG PRODUCT: Cromolyn Sodium Inhalation Solution USP

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

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

Sincerely yours,

Dale Conner

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-271 APPLICANT: Zenith Goldline, US Agent for Steripak Limited

DRUG PRODUCT: Cromolyn Sodium Inhalation Solution USP

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

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

Sincerely yours,

Dale Conner

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

ANDA 75-271

Zenith Goldline Pharmaceuticals
U.S. Agent for Steripak Limited
Attention: Jason A. Gross, Pharm D.
140 Legrand Avenue
Northvale, NJ 07647-2485

20 1998

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated January 8, 1997 and your correspondence dated January 8, 1997.

NAME OF DRUG: Cromolyn Sodium Inhalation Solution USP, 10 mg/mL

DATE OF APPLICATION: December 11, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 15, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

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

Zenith Goldline
PHARMACEUTICALS

December 11, 1997

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Subject: ANDA Filing for Cromolyn Sodium Inhalation Solution USP, 1.0%

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, and 21 CFR Parts 314.92 and 314.94, Zenith Goldline Pharmaceuticals, Inc., as US Authorized Agent for Steripak Limited, UK, is submitting an Abbreviated New Drug Application for Cromolyn Sodium Inhalation Solution USP, 1.0%. Steripak Limited and Zenith Goldline Pharmaceuticals, Inc., are wholly owned subsidiaries of IVAX Corporation. In accordance with OGD's Letter to Industry of December 24, 1996, concerning documentation of agent authorization, a letter from Steripak appointing Zenith Goldline as US Authorized Agent is provided directly following this cover letter.

A Certification Statement, as required by the Generic Drug Enforcement Act of 1992, can be found following the US Agent Authorization letter. In accordance with 21 CFR Part 314.94(d)(5), Zenith Goldline Pharmaceuticals, Inc., is providing a Field Copy of the technical section of this application for submission by CDER to the appropriate FDA district field office. Our Field Copy Certification is provided in the section following the Generic Drug Enforcement Act Certification.

This Abbreviated New Drug Application has been prepared in accordance with OGD's Guidance for Industry, dated April 1997. The Archival Copy, contained in the blue jackets, consists of three (3) volumes, labeled as Volume 1 through Volume 3. Volume 1 of the Archival Copy includes a waiver request for the requirement to submit Bioavailability/Bioequivalence Data. The Review Copy is divided into two parts. The first part, contained in the red jackets, consists of three (3) volumes, labeled as Volume 1 through Volume 3, and includes the Chemistry, Manufacturing and Controls Technical Section. The second part, contained in the orange jacket, consists of one (1) volume labeled as Volume 3a, and includes a waiver request for the requirement to submit Bioavailability/Bioequivalence Data, and other related information.

Accompanying this application are:

- Sterility Assurance Report #SAR-002 (Section XI and separately bound desk copy), in accordance with OGD's Letter to Industry of August 4, 1993.
- Three separately bound copies of the Methods Validation.

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583
Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

In support of this application, Steripak Limited has manufactured Cromolyn Sodium Inhalation Solution USP, 1.0%, exhibit (test) batch no. 7B3001, 700L. This batch was manufactured and fully packaged in compliance with Policy and Procedure Guide #22-90.

As an overview, and to facilitate review, an "Executive Summary", describing key aspects of this application immediately precedes the Table of Contents.

Pursuant to Section 5 USC Part 552(b)(4) of the Freedom of Information Act and 21 CFR Part 20.61, regarding privileged and confidential information, we declare that information on Cromolyn Sodium Inhalation Solution USP, 1.0%, as to its composition, method of manufacture, and test methods constitute trade secrets and confidential commercial information under the law, and are, therefore, not disclosable under the Freedom of Information Act.

We respectfully request a review of this application at your earliest convenience.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Regulatory Affairs
US Authorized Agent for Steripak Limited, UK

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/KRSB

Attachments

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-271 Applicant: Zenith Goldline Pharmaceuticals
Agent for Steripak Limited

Drug Product: Cromolyn Sodium Inhalation Solution USP, 10mg/mL

The following comments represent FAX deficiencies:

A. Deficiencies:

1. You have submitted data to support the use of a laminated foil pouch to protect the inhalation solution. However, it is necessary that you demonstrate that the laminated foil pouch does not contaminate the drug product. Your current methodology only demonstrated that the drug product meets all current specifications, and doesn't fully address potential contaminants from the pouch.

   This could be accomplished by evaluating chromatographic profiles comparing freshly manufactured solution vs solution stored in the exact market configuration for at least 3 months at 40°C. The sensitivity of the methods should be demonstrated to detect contaminants that might be present in the finished drug product as a result of the overwrap. You may wish to utilize other sensitive analytical methods (HPLC, GC, etc.) in addition to those methods previously used. As your pouch uses : to bind the layer, please demonstrate that your methods would detect monomer with at least 100 ppb sensitivity.

   Alternately, you may provide documentation that the pouch you propose to utilize has been approved by the FDA for marketing an inhalation solution in We will consider other valid scientific approaches to address this issue.

2. You have incorporated an extractable weight test into your Stability Protocol, but do not have a net fill test at release. Please incorporate the extractable weight/volume test as part of the release testing.

3. You have revised your Related Substances (TLC) acceptance criteria. Please explain why there are different acceptance criteria for Related Compounds at release and

for stability (Refer to pp. 3 and 19 of the 6/24/99 ANDA Amendment). The USP 23 requirement should be used for this test.

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

1. The sterility amendment of 7/29/99 is pending review. After the completion of review, comments, if any, will be communicated separately.

2. The firm's labeling was reviewed and found deficient, and the deficiencies were communicated to you on 3/3/99. As of this date, you have not responded to the labeling deficiencies enumerated at that time. Please respond.

3. A satisfactory compliance evaluation report is necessary prior to approval of the application. We have requested an evaluation from the Office of Compliance.

4. Please submit available long-term data generated on the exhibit batches since the last submission.

Sincerely yours,

11/19/99

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