CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75313

CORRESPONDENCE

ANDA 75-313

Zenith Goldline Pharmaceuticals
Attention: Jason A. Gross, Pharm.D.
140 Legrand Avenue
Northvale, New Jersey 07647

NOV 5

Dear Dr. Gross:

This refers to your pending abbreviated new drug application dated December 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Inhalation Solution, 0.02% (0.5 mg/2.5 mL).

Reference is also made to the telecon dated October 20, 1998 between you and Dr. Allen Rudman, Dr. Paul Schwartz, and Mr. Michael Smela of this Agency.

In that telecon, we informed you that the major deficiency fax dated July 27, 1998 did not include a deficiency concerning an overwrap issue. The deficiency is provided below:

> The inhalation product packaged in LDPE containers for which you are seeking approval 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). Studies assessing levels of vanillin and heavy metals were not provided 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). We acknowledge some limited comparative stability studies with and without the foil overwrap.

We would appreciate your prompt written response so we can continue our evaluation of your ANDA.

Sincerely yours,

/S/ 111594

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

cc: ANDA 75-313
Division File
Field Copy

Endorsements:

HFD-627/Takiar/ N. Takiar 10/29/98
HFD-627/PSchwartz/10/28/98 PS 10/29/98
HFD-617/JBuccine/10/28/98 JB 10/29/98
HFD-620/Rudman
F/T by: gp/10/29/98
INFORMATION REQUEST

ANDA 75-313

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

FEB 17 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 February 6, 1998 and your correspondence dated February 6, 1998.

NAME OF DRUG: Ipratropium Bromide Inhalation Solution, 0.02%

DATE OF APPLICATION: December 30, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 6, 1998

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

In addition, to be in compliance with 314.50(e)(2)(ii), you must provide four copies of the draft labeling in the archival copy of the application. Please provide three additional copies of the draft package insert for the archival copy. In the future please include four copies of the draft labels and labeling in **both** the archival and review copies of the application.

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

Should you have questions concerning this application, contact:

Joe Buccine
Project Manager
(301) 827-5848

Sincerely yours,

/S/

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

ANDA 75-313
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett

Zenith Goldline
PHARMACEUTICALS

December 3, 1998

NDA ORIG AMENDMENT
AA

Mr. Douglas L. Sporn
Director, Office of Generic Drugs (HFD-604)
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT

RE: ANDA 75-313 Ipratropium Bromide Inhalation Solution 0.02% w/v (0.5mg/2.5mL)

Dear Mr. Sporn,

Reference is made to the Agency's correspondence dated November 5, 1998 (copy attached) and a previous telecon of October 20, 1998 between Dr. Jason A. Gross of Zenith Goldline Pharmaceuticals and Dr. Allen Rudman, Dr. Paul Schwartz and Mr. Mike Smela of the Agency 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 deficiency cited in your letter of November 5, 1998. As discussed in the October 20, 1998 telecon, this response should be considered as an UNSOLICITED AMENDMENT.

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

DEFICIENCY

The inhalation product packaged in LDPE containers for which you are seeking approval 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 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 inks from the labeling). Studies assessing levels of vanillin and heavy metals were not provided to justify the lack of an overwrap. You should compare vials that have been protected by 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). We acknowledge some [illegible] stability studies with and without the foil overwrap.

RECEIVED
DEC 0 4 1998
GENERIC DRUGS

Response:

Steripak conducted studies on the packaged product with and without the foil pouch and characterized the potential migrants in the immediate container, secondary container and label. Both configurations were

placed on stability. The primary and secondary packaging components were tested to determine potential migrants and the stability samples were tested for these potential migrants. While testing in the proposed market container without the pouch met all the requirements, the testing in the foil pouch did not. When stored in the foil pouch, the product showed evidence of a contaminant at the 9 month time point after storage at 27.5°C/40%RH. The results obtained showed that the total "unknowns" exceed the upper limit of % whereas the total "unknowns" in the non overwrapped product still comply with the specification after 18 months storage at 27.5°C/40%RH. Steripak believes that this contamination arose from the foil overwrap, as the inside of the foil pouch consists of a plastic layer. While the foil obviates concerns about contaminants outside of the system, it also provides for the possibility of a problem occurring inside of the pouch. A full explanation, including the current stabilty data comparison for both overwrapped and non-overwrapped product may be found as Attachment 1. As it was always Steripak's intention to market the product without a pouch, these studies demonstrate the acceptability of this approach.

The proposed non-foil overwrapped market container configurations, labeled and cartoned, showed no evidence of contamination and meet the requirements for weight loss when tested under conditions more stringent than the required ICH guidelines. A more detailed explanation is provided in the Packaging Development Report found as Attachment 2.

This completes our Unsolicited Amendment response to the Agency's comments of November 5, 1998. We trust that the outstanding deficiency has 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 State, Federal and
International Regulatory Affairs
U.S. Authorized Agent for Steripak Limited, U.K.

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express and Telefax (301)827-4337

JAN 13 2000

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

NC

TELEPHONE AMENDMENT - Chemistry

RE: ANDA 75-313 - Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL)

Dear Mr. Sporn:

Reference is made to the Agency's telephone call on January 12, 2000, concerning our Abbreviated New Drug Application for the above referenced product. As specified by OGD, this response is classified as a TELEPHONE AMENDMENT, as it has been submitted within 10 days of FDA's telephone request.

In the conversation, Mr. Kenneth Furnkranz and Ms. Michelle Dilahunt advised Zenith Goldline that the methods validation package for this product has been reviewed, and that the Agency requires the firm to modify the potency assay for the Active Drug Substance to correct for water content. Please note that, as indicated in our application, Steripak tests the Ipratropium Bromide active drug substance in accordance with the most current compendia specified in the European Pharmacopoeia (1997, 3rd Edition; *Exhibit 1*). The potency is described as "not less than % and not more than %" of Ipratropium Bromide, "calculated with reference to the anhydrous substance". Therefore, Steripak calculates the potency based on the anhydrous substance.

We hope that this response provides the necessary clarification. Please do not hesitate to contact our office should you require additional information.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

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

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JAN 14 2000
OGD
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Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. V.I.

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express

DEC 14 1999

NDA ORIG AMENDMENT
N/AM

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: ANDA 75-313 - Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL)

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated December 10, 1999 (copy provided 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 the correspondence, this response should be considered a RESPONSE TO MICROBIOLOGY DEFICIENCIES.

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

A. MICROBIOLOGY DEFICIENCIES

OGD

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B. IN ADDITION

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

1. *Method Validation by the FDA district laboratory is in progress for the drug substance and the finished dosage form. We are currently awaiting the MV report from the laboratory.*

   Response:
   Steripak Limited acknowledges that the Method Validation is in progress, and the Agency is awaiting the report from the laboratory. We understand that comments, if any, will be communicated separately.

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

   Response:
   Steripak Limited acknowledges that a satisfactory compliance evaluation report is necessary prior to ANDA approval. Please note that Steripak was inspected by the FDA in April 1998, and was found to be acceptable.

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

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express

DEC 01 1999

Mr. Robert L. West, Director
Division of Labeling and Program Support
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

LABELING AMENDMENT

RE: ANDA 75-313 - Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL)

Dear Mr. West:

Reference is made to the Agency's correspondence dated November 2, 1999 (copy provided 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 be responding to the labeling deficiencies cited in your letter.

To facilitate review, 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 versus the last submitted labeling, with all differences annotated and explained. These can be found accompanying the final printed labeling in Exhibits 2 through 4 of this amendment.

LABELING DEFICIENCIES

1. *UNIT-DOSE CONTAINER (2.5 mL)*
   Submit a drawing of the unit-dose container with all pertinent information typed in where it is to appear on the vial.

   Response:
   Please refer to Exhibit 1, in which we have provided a drawing of the unit-dose container with all pertinent information typed in where it is to appear on the vial.

2. *FOIL POUCH (5 x 2.5 mL)*
   Revise as indicated in Comments 2.a. and 2.b.

   Response:
   We have revised our foil pouch labeling as instructed in Comments 2.a. and 2.b., and copies of the final printed labels are provided in Exhibit 2.

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3. *CARTON (25 x 2.5 mL, 30 x 2.5 mL and 60 x 2.5 mL)*
Revise as indicated in Comment 3.a.

Response:
We have revised our cartons as instructed in Comment 3.a., and copies of the final printed labeling for cartons of 25's, 30's and 60's are provided in Exhibit 3.

4. *PHYSICIAN INSERT*
Revise as indicated in Comments 4.a. through 4.c.

Response:
We have revised our physician insert as instructed in Comments 4.a. through 4.c., and copies of the final printed labeling are provided in Exhibit 4.

5. *PATIENT INSTRUCTIONS FOR USE INSERT*
Revise as indicated in Comments 5.a. and 5.b.

Response:
We have revised our patient insert as instructed in Comments 5.a. and 5.b., and copies of the final printed labeling are provided in Exhibit 4.

We acknowledge the Agency's right to request further changes to our 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.

Zenith Goldline Pharmaceuticals, Inc., and Steripak Limited have made a concerted effort to ensure that this response is complete and that the labeling 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 of Global Regulatory Affairs
Authorized U.S. Agent for Steripak Limited, U.K.

Exhibits

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Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express

OCT 22 1999

NEW CORRESP
NC
NW 1
Withdrawal
10/22/99

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

REQUEST FOR WITHDRAWAL OF GRATUITIOUS AMENDMENT DATED OCTOBER 15, 1999

RE: ANDA 75-313 - Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL)

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for the above referenced product, and to our Gratuitous Amendment of October 15, 1999. In the time since submission of our Gratuitous Amendment, we have received the Agency's Fax Communication dated October 18, 1999. Therefore, in order to avoid any confusion, we are requesting the withdrawal of the Gratuitous Amendment, without prejudice, so that we may respond directly to OGD's 10/18/99 Fax Communication. We anticipate submission of our Fax Amendment within a few days time.

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.

Jawerski /for

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

cc: District Office

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OCT 25 1999
EVALUATION AND

NW 10-22-99

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

Via Federal Express

OCT 1 5 1999

ORIG AMENDMENT
N/AA
Withdrawn
Per correspondence dated
10/21/99

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 75-313 - Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL)

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 Ipratropium Bromide Inhalation Solution, 0.02%, are provided below:

A. CHEMISTRY DEFICIENCIES

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

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Zenith Goldline
PHARMACEUTICALS
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Via Federal Express

JUL 15 1999

NDA ORIG AMENDMENT
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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: ANDA 75-313 - Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL)

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated June 3, 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 MICROBIOLOGY DEFICIENCIES.

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

A. MICROBIOLOGY DEFICIENCIES

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 16 1999
OGD

Continued...

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Conclusion

This confirms that the exposure of these filters to 0.02%w/v Ipartopium Bromide Inhalation Solution under simulated process conditions and a final challenge with organism suspended in the product does not affect the bacteria retentive properties of three different lots of filters, one of which is near to the filter manufacturers minimum specifications (low K_L value).

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 twice annually (without a set period of time between the 2 testing dates), 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 the microbiology deficiencies provided in the Agency's comments of June 3, 1999. Please do not hesitate to contact us should you require additional information.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Stacy Bate /for

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

Attachments

Zenith Goldline
PHARMACEUTICALS
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Via Federal Express

MAY 04 1999

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 DRUG AMENDMENT
Ac

MAJOR AMENDMENT - Chemistry

RE: Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL)
ANDA 75-313

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL), and to our Amendments dated August 24, 1998 (Major), and December, 3, 1998 (Unsolicited). Further reference is made to the OGD's Major Amendment deficiency letter dated March 10, 1999 (copy attached), in which the Agency advised Zenith Goldline of the unsatisfactory nature of our previous response pertaining to foil overwrapping of our LDPE containers.

Pursuant to 21 CFR §314.120(a)(1), we are responding to the deficiencies cited in the Agency's letter of March 10, 1999. Specifically, in order to better meet the agency requirements, we are amending our response to the container/closure data provided in our December 3, 1998 amendment.

CHEMISTRY DEFICIENCIES

Container:

Your response to the Agency's deficiency letter dated November 5, 1998, for the inhalation product packaged in LDPE containers for which you are seeking approval concerning the need to employ a secondary overwrap such as a laminated foil or a pouch to ensure the identity, strength, quality and purity of the product is not satisfactory.

Please provide the previously requested comparative data for at least 3 months of storage at accelerated conditions (40°C), if you intend to market this product without an overwrap. Also, provide the comparative studies 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, select one and perform the validation to show that it does not cause contamination in the product.

RECEIVED
MAY 06 1999

140 Legrand Ave., Northvale, New Jersey 07647 ▪ (201) 767-1700 (800) 387-0133 Fax (201) 767-1712

GENERIC DRUGS

Response:
At the time of the original submission, it was the firm's intention to package the product with a label and carton without a foil pouch. The firm provided information on the stability of the product in the carton and conducted migration studies on the carton and label, in an attempt to qualify the secondary packaging components. While the carton could be qualified at levels of extractables less than 100 ppb, the firm has been unable to test for label extractable material at those levels. The method and data provided in the December 3, 1998 response to this comment did not attain those levels of detection for the label. In addition, it was discovered that the original foil pouch material selected contained an inner EVA surface that contaminated the product. The contamination was detected using the method specified in Steripak's Finished Product Test Specification (document no. FDA/DP008/3), originally submitted in our August 24, 1998 amendment, and duplicated herein (Attachment 9) for ease of review. Using this method, which is validated in Section XVI of the original ANDA submission, the contamination was detected in all drug products packaged and stored using this foil.

Since the firm has been unable to develop analytical methods sensitive enough to detect labeling migrants at the 100 ppb level, it is now Steripak's intention to market the product in a foil pouch and emboss the nebule, as suggested by the Agency. To support this approach, the firm has identified foil pouch material that will not contaminate the drug product. The inner surface of the new foil pouch is a low-density polyethylene (LDPE) with no additives, the same type of resin used to manufacture the nebules themselves. The foil pre-treatment is applied using an aqueous solvent, obviating the need to test for organic residual solvents in the plastic layer. LDPE has the additional advantage that the sealing temperature is lower than that for EVA or polypropylene, thereby exposing the product to lower temperatures during heat sealing. Details regarding the foil pouch material and the selection process may be found in the "Packaging Development Report", provided in Attachment 1. Test results for the new foil pouch are also provided in this amendment.

In support of this proposed market container/closure system, a new Liter test batch (Lot #WO1131) was manufactured and fully packaged. This batch is % of the proposed final production batch. Samples were taken from the beginning, middle and end, and placed on Accelerated and Controlled Room Temperature Stability. Release and Stability Test Results are provided to demonstrate the stability of the product. Additional suitability and compatibility testing of the foil, with the product and with water, demonstrate the use of the proposed foil material.

PLEASE NOTE AND ACKNOWLEDGE

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

1. *Method Validation from the FDA district laboratory has been requested for the drug substance and the finished dosage form.*

   Response:
   Zenith Goldline Pharmaceuticals, Inc., acknowledges that Method Validation from the FDA district laboratory has been requested for the drug substance and the finished dosage form. Please note that we responded to this request by providing the appropriate data and samples to the district laboratory in packages sent on February 2, 1999 and February 22, 1999.

2. *The microbial section is pending review. After the completion of review, comments, if any, will be communicated separately.*

   Response:
   Zenith Goldline Pharmaceuticals, Inc., notes and acknowledges that the microbial section is pending review. After the completion of review, we understand that comments, if any, will be communicated separately.

3. *The labeling section is pending review due to its delayed submission. In the future, please make a statement in your cover letter for the delayed response.*

   Response:
   Zenith Goldline Pharmaceuticals, Inc., notes and acknowledges that the labeling section is pending review due to its delayed submission. We expect to submit this amendment to the Agency within a few days time. In the future, we will make a statement in our cover letter noting the delayed response.

This completes our Major Amendment Response to the Agency's comments of March 10, 1999. We trust that this information will satisfactorily address the Agency's concerns pertaining to the container/closure system for the drug product. Please do not hesitate to contact us should you have any questions.

Sincerely yours,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

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

Attachments

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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 75-343 Albuterol Sulfate Inhalation Solution
→ **ANDA 75-313 Ipratropium Bromide Inhalation Solution**
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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10-16-98

Zenith Goldline
PHARMACEUTICALS

ORIG AMENDMENT
N/AC

Regulatory Affairs

Via Federal Express

August 24, 1998

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

RE: Ipratropium Bromide Inhalation Solution, 0.02% (0.5 mg/2.5 mL)
ANDA 75-313

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated July 27, 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.

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

A. CHEMISTRY DEFICIENCIES

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pages of trade

secret and/or

confidential

commercial

information

Chemistry Deficiencies

B. IN ADDITION

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

1. *Methods Validation for the drug product by one of FDA's laboratories will be requested after validation and testing issues are resolved.*

   Response:

   Steripak Limited acknowledges that methods validation for the drug product by one of FDA's laboratories will be requested after validation and testing issues are resolved.

2. *The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP at the time of approval.*

   Response:

   Steripak Limited acknowledges that the firms referenced in the ANDA relative to the manufacturing and testing of the product must be in compliance with cGMP at the time of approval.

3. *The microbiological section is pending review. After the completion of review, comments, if any, will be communicated separately.*

   Response:

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

C. BIOEQUIVALENCY COMMENTS

1. *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.

   Response:

   Steripak Limited understands that there are no outstanding bioequivalence issues at this time. We acknowledge that the bioequivalence data may be subject to further review based on scientific or regulatory issues in the future, possibly resulting in the need for additional data or in the conclusion that the proposed formulation is not approvable.

This completes our Major Amendment response to the Agency's comments of July 27, 1998. 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. Gross, Pharm. D.
Director of State, Federal and
International Regulatory Affairs

/sb
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Attachments

Zenith Goldline
PHARMACEUTICALS

May 12, 1998
Via: Fed-Ex and Facsimile to (301)594-0181

Lizzy Sanchez, Pharm. D.
Project Manager
CDER, FDA
Document Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE TELEPHONE AMENDMENT

RE: Ipratropium Bromide Inhalation Solution, 0.02%, ANDA 75-313

Dear Dr. Sanchez:

This is in follow-up to your telephone conversation today with Ms. Stacy Bate, and to our April 29, 1998, correspondence concerning the above referenced application. Specifically, the purpose of this amendment is to address the discrepancy noted by yourself and Dr. Nguyen on page 58, Section D "Comparative Composition".

Regrettably, the Comparative Composition table contains a typographical error for the "weight/unit" value of ipratropium bromide, Ph. Eur, for both the Atrovent® and Steripak products. Instead of per ml, the correct value is "0.5 mg" per 2.5 ml. We have made the appropriate correction to this page (attached), and apologize for any inconvenience this may have caused. Further, we have checked the remainder of the application to assure that the rest of the calculations are correct.

We appreciate your kind assistance in this matter, and will be happy to provide any additional information as necessary.

With Best Regards,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

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

Attachment

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NEW CORRESP

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March 9, 1998

VIA FEDERAL EXPRESS

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

Correspondence to the Application

RE: Ipratropium Bromide Inhalation Solution, 0.02% w/v
ANDA 75-313

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Ipratropium Bromide Inhalation Solution, 0.02% w/v, submitted on December 30, 1997. It has come to our attention that the Blank Batch Record for Dilute Hydrochloric Acid NF (used in the manufacture of Ipratropium Bromide Inhalation Solution) was inadvertently omitted from SECTION XI.2. (page 200) of the initial filing. A copy of the missing document is attached to this correspondence.

We appreciate the Agency's consideration in this matter, and apologize for any inconvenience this may have caused.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

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

Attachments

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Zenith Goldline
PHARMACEUTICALS

February 24, 1998

NEW CORRESP
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VIA FEDERAL EXPRESS

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

Correspondence to the Application

RE: Ipratropium Bromide Inhalation Solution, 0.02% w/v
ANDA 75-313

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Ipratropium Bromide Inhalation Solution, 0.02% w/v, submitted on December 30, 1997. Further reference is made to OGD's acknowledgment letter dated February 17, 1998 (copy attached), in which the Agency informed us of the acceptability of the filing and requested that we provide three (3) additional copies of the draft package insert for the archival copy.

Attached please find the requested copies, which were inadvertently omitted from the initial filing. We appreciate the Agency's advisement in this matter, and apologize for any inconvenience this may have caused.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

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

Attachments

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Zenith Goldline
PHARMACEUTICALS

NEW CORRESP
NC

February 6, 1998

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

Correspondence to the Application

RE: Ipratropium Bromide Inhalation Solution, 0.02% w/v
ANDA 75-313

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Ipratropium Bromide Inhalation Solution, 0.02% w/v, submitted on December 30, 1997. Further reference is made to today's telephone conversation with Ms. Saundra Middleton of your office. Ms. Middleton informed us that the Form FDA 356h submitted with our ANDA filing cited the reference listed drug and application holder incorrectly, and that it is necessary for us to correct the form and submit it as a correspondence to the application.

We have revised the 356h form accordingly, and per Ms. Middleton's request, a copy of this correspondence has been faxed to her attention.

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

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OK to file
Middleton 2/6/98

Zenith Goldline
PHARMACEUTICALS

December 30, 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 Ipratropium Bromide Inhalation Solution 0.02% w/v

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 Ipratropium Bromide Inhalation Solution, 0.02% w/v. 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-003 (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.

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In support of this application, Steripak Limited has manufactured Ipratropium Bromide Inhalation Solution 0.02% w/v, exhibit (test) batch no. 7B4001, 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 Ipratropium Bromide Inhalation Solution 0.02% w/v, 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

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express and Telefax (301)827-4337

OCT 25 1999

NDA ORIG AMENDMENT
N/FA

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

FAX AMENDMENT - Chemistry

RE: ANDA 75-313 - Ipratropium Bromide Inhalation Solution, 0.02% w/v (0.5 mg/2.5 mL)

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated October 18, 1999 (copy provided 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 instructed, this response should be considered a FAX AMENDMENT, as we have provided the response within 30 calendar days of our receipt of the Agency's communication.

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

A. CHEMISTRY DEFICIENCIES

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B. IN ADDITION

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

1. *Method Validation from the FDA District Laboratory has been requested for the drug substance and the finished dosage form. We are currently awaiting the MV Report from the laboratory.*

   Response:
   Steripak Limited acknowledges that the OGD is currently awaiting the Methods Validation Report from the FDA District Laboratory.

2. *The sterility amendment of 7/15/99 is pending review. After the completion of the review, comments, if any, will be communicated separately.*

   Response:
   Steripak Limited acknowledges that the sterility amendment dated 7/15/99 is pending review. We understand that comments, if any, will be communicated separately after the review has been completed.

3. *The firm's labeling was reviewed and found deficient, and the deficiencies were communicated to you on 7/27/98. As of this date, you have not responded to the labeling deficiencies enumerated at that time. Please address the labeling deficiencies.*

   Response:
   Please note that our Labeling Amendment was submitted to the Agency on October 23, 1999.

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

   Response:
   Steripak Limited acknowledges that a satisfactory compliance evaluation report is necessary prior to ANDA approval. Please note that Steripak was inspected by the FDA in April 1998, and was found to be acceptable.

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

   Response:
   As requested, we have provided updated long-term stability data (9 months RT and 6 months Accelerated) herewith as *Exhibit 6*.

Zenith Goldline Pharmaceuticals, Inc., and Steripak Limited have 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.

P Jaworski /for

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

cc: district office

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