CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73045

APPROVAL LETTER

ANDA 73-045

AUG 19 1997

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

Dear Sir:

This is in reference to your abbreviated new drug application dated December 23, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Inhalation Aerosol, 90 mcg/Actuation.

Reference is also made to your amendments dated June 12, and 22, 1995; August 1, September 11, October 8, and November 15, 1996; January 6 and 22, May 23 and 27, July 17, and August 6, 1997.

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 Albuterol Inhalation Aerosol, 90 mcg/Actuation to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ventolin® Inhalation Aerosol, 90 mcg/Actuation, of Glaxo Wellcome, 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. 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 which 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-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73045

APPROVABLE LETTER

ANDA 73-045

Generics (UK) Limited
c/o Superpharm Corporation
Attention: Ms. Diana Sloane
1769 Fifth Avenue
Bayshore, NY 11706

JUN 26 1989

Dear Madam:

Please refer to your abbreviated new drug application dated December 23, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Inhalation Aerosol, 0.09 mg/inhalation.

Reference is also made to your amendments dated March 6, 1989 and May 16, 1989.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. Please revise your composition statement to include composition per aerosol container.

2. DMF [ ] and DMF [ ] are deficient. Both firms have been notified.

3. With respect to the drug substance controls:

   a) Please submit a copy of [ ] certificate of analysis per current BP and USP requirements.

   b) For the particle size determination, the upper limit of acceptance should be specified.

   c) Please clarify the micronization procedure with fluid energy milling equipment with respect to the types of potential contamination of the drug substance, both particulate and non-particulate.

   d) The certificate of analysis for the micronized drug substance should include microbial limits test.

4. The Division of Generic Drugs has eliminated the requirement of stability and full monograph testing at a laboratory in the U.S. of finished drug products manufactured at foreign facilities.

   Please re-state the facility where the full testing for product release and the stability testing will be conducted.

5. Although it is not stated in the application, it is noted that the microbial limits test for the finished product was performed by [ ] Please affirm your plan to use this laboratory.

6. With respect to the manufacture of the drug product:

   a) It is noted that trichlorofluoromethane is

   b) Please clarify if there is an on-line filter for dispensing dichlorodifluoromethane in the filling process. If so, what porosity filter is used?

   c) There are two sources for the drug substance. You have submitted data on the batch based on the drug substance from [ ]. Please submit a copy of the batch record of a production lot based on the drug substance from [ ] together with finished product test specifications and data. Please also submit 3-month accelerated stability data.

7. With respect to the container/closure system:

   a) Please certify that the components (the aluminum can, the metering valve, and the actuator with mouthpiece) meet CFR requirements for food contact surfaces.

   b) Extractable studies for each component are to be conducted using both standard organic solvents and the subject drug formulation under stressed conditions.

8. With respect to the finished product testing:

   a) The Division of Generic Drugs has prepared a 17-point document for in-vitro testing of inhalation aerosols. A copy is enclosed for your reference. Please incorporate the test parameters which are not already in your release specifications.

   b) You use laser techniques for particle size determination:

      i) The upper limit of acceptance is to be specified.
      ii) You have also submitted particle size determinations via image analysis and cascade impactor methods in support of the ANDA filing. We recommend that you add one of these two methods to the finished product testing. That is, particle size distributions should be determined using two different methods.
      iii) With the unit spray content determination, the amount retained on the mouthpiece is also to be determined.

9. With respect to stability testing:

   a) A one-time temperature cycling study is to be conducted. Please refer to the enclosed document.

b) The test parameters for stability monitoring should include all those parameters for product release. A few parameters may not need to be tested at all test stations. Please propose a reasonable testing frequency.

c) Some parameters (unit spray content, water content, microbial limits, leakage rate, assay/degradation products) should be conducted on canisters under simulated use conditions. That is, the canisters reserved for stability testing should be gradually emptied over the entire stability testing period (e.g., 2 actuations per week so that at the 12 month test station, the canisters are about half full).

d) With satisfactory accelerated data, the initial expiration dating period of 18 months is allowed.

10. In order for our laboratory to ascertain that your drug substance conforms to USP (if not USP, then appropriate) requirements, send the following materials to the address below:

Materials to be sent:

a) Albuterol (Drug Substance) [_____ (Manufacturers)]

Send three times the amount needed to perform all USP testing. Package the material in a tight, moisture-free container sealed in an outer container. Identify the manufacturer, the manufacturer's address, DMF number and lot number of the bulk sent.

b) A Certificate of Analysis (either yours or the manufacturer's) for the lot sent.

c) Standards - Reference, Impurity, and Internal - Send three times the amount required by the USP. [If you do not send the standard and the FDA Laboratory doesn't have it, the analysis will be delayed].

d) Copies of representative chromatograms and/or spectra (if applicable.)

e) Copy of the method of analysis if the drug substance is not compendial.

f) A Material Safety Data Sheet (OSHA Form 174) or equivalent information.

See comments under Container Label.

Insert Labeling - Not Satisfactory

A. Drug title above DESCRIPTION - Revise per Container Label (A) above.

B. DESCRIPTION

1. Line 1 - ...Albuterol Inhalation Aerosol is....

2. Line 7 - molecular (rather than "empirical").

3. Revise chemical description to read "Albuterol is a white, crystalline powder. It is soluble....

C. INDICATIONS AND USAGE: Albuterol Inhalation Aerosol is indicated....

D. CONTRAINDICATIONS: Albuterol Inhalation Aerosol is...

E. WARNINGS: line 1 - ...albuterol inhalation aerosol....

F. PRECAUTIONS

Paragraph 2, line 2 - pre-existing

G. HOW SUPPLIED

1. Albuterol Inhalation Aerosol is...

2. Specify the number of actuations per container.

H. Following the manufacturer of this product, please list the U.S. marketer.

I. Revise "albuterol aerosol inhaler" to read "albuterol aerosol" throughout the insert beginning at the CLINICAL PHARMACOLOGY section except as follows:

Revise as described in A, B, C, D, E, and G above.

Patient Leaflet - Not Satisfactory

A. Revise the product title at the heading of this leaflet to read "Albuterol Inhalation Aerosol."

B. WARNINGS (last line) - physician (spelling)

Address:

FDA/Division of Drug Analysis
Attention: Chief, Drug Monitoring Branch
1114 Market Street, Room 1002
St. Louis, MO 63101

These materials must be sent within 30 days of receipt of this letter. If you cannot send these materials by this date, please notify the Chief, Drug Monitoring Branch by letter. If you fail to send the requested materials, or properly notify the Drug Monitoring Branch Chief of any delay, this submission should be withdrawn. Send copies of all correspondence regarding the samples requested to the ANDA.

We recommend that you send the samples by registered mail/return receipt requested.

11. The finished dosage form is to be analyzed by our district laboratory.

    a) After you have revised your release specifications (see (8) above) and test methods, please submit 3 copies of:

        1) composition statement
        2) finished product testing specifications
        3) test methods and data

    b) You will be notified to send samples when a laboratory assignment is made.

12. Please submit one set of the components of the container/closure system and one unit of the finished dosage form to the attention of Florence Fang, the review chemist.

13. The facilities cited in this application are currently under CGMP evaluation by our Division of Manufacturing and Product Quality.

14. Your in-vivo bioequivalence study is under review.

15. Container Labels - Not Satisfactory

    A. Revise the product title to read "Albuterol Inhalation Aerosol."

    B. Include the name and address of the U.S. marketer of this product.

Carton Labeling - Not Satisfactory

C. See Insert Labeling (H) above.

Please revise your labels and labeling, then prepare and submit final printed container labels and carton labeling. We cannot request final printed insert labeling until your bio data has been found satisfactory and we have had a chance for review and comment.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

Enclosure

cc:
HFD-230, HFD-234
FFang/GJohnston/KTJohnson 6/2/89
R/D INIT. BY RPatel/RAJerussi
jth: 0080j 6/7/89

Not Approvable

Received 6/12/89

6/2/89

6-22-89

Review Note:

- The amendment dated 6/17/88 was fully responded to the Agency's letter 5/31/88. The information is adequate.

- The amendment dated 12/19/88 was fully responded to the Agency's letter 12/19/88. the information is adequate.

APPEARS THIS WAY
ON ORIGINAL

ANDA 73-045

APR 23 1990

Generics (UK) Limited
c/o Superpharm Corporation
Attention: Ms. Diana Sloane
1769 Fifth Avenue
Bayshore, NY 11706

Dear Madam:

Please refer to your abbreviated new drug application dated December 23, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Inhalation Aerosol, 0.09 mg/inhalation.

Reference is also made to your amendment dated August 28, 1989.

The application is deficient and therefore not approvable under Section 505 of the Act as follows:

1. Your revised Standard Control Procedure for the drug substance does not adequately reference, the method, of the several listed in SOP.M103 to be used to for this particular drug substance. The information should also be cited in the Procedure.

2. We await submission of your one-time temperature cycling study data and container extraction studies.

3. Your simulated use study should include the determination of moisture at each testing point.

4. We have requested that a district laboratory be assigned to analyze your finished dosage form. You will be notified when and where to send the samples of the drug product when the assignment is made.

5. We acknowledge your withdrawal of( )as one of your suppliers of the drug substance.

Also to labeling:

Insert: Not Satisfactory

A. DESCRIPTION

Line 2 - ...xylene - α, α'- diol
(add "α, α'")

B. CLINICAL PHARMACOLOGY

Line 1 - Italicize "In vitro" and in vivo"

C. Patient Instruction Leaflet

Before using your Albuterol Inhaler, read...

Please revise your insert labeling, then prepare and submit final printed copy.

The file is now closed. You are required to take an action described under Section 314.120 of the Regulations which will either amend or withdraw the application, or if you have substantial disagreement with our conclusions for not approving this application, you may request an opportunity for a hearing. For those deficiencies related to package insert labeling, we suggest that you incorporate the suggestions noted, then prepare and submit draft copy for our review and comment.

Sincerely yours,

/S/

for 4/20/90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc: HFD-634
JPiechocki/GJohnston/KTJohnson 4/18/90
ms: 4/10/90 (4390m)
R/D INITIALED BY RPatel/RAJerussi
Not Approvable

4-18-90 4-23-90 4/19/90

ANDA# 73-045

JUL 12 1991

Lachman Consultant Services, Inc.
Agent for: Genpharm Inc.
Attention: Dr. Leon Lachman
1600 Stewart Avenue
Westbury, NY 11590

Dear Sir:

Please refer to your abbreviated new drug application dated December 23, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Inhalation Aerosol, 0.09 mg/inhalation.

Reference is also made to your communications dated July 5, 1990 November 19, 1990, amending this application.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. Please provide data to show that your assay method for the analysis of the drug substance is equivalent to the method found in the USP's monograph for the drug substance. The final results between the two tests might be different, since you determine the end point in the assay electronically, while the USP requires the use of crystal-violet for end point detection.

2. Please explain why there was only one week of circular and X-Y humidity and temperature charts rather than the full six weeks of charts?

3. Please explain the large differences in median particle size diameters between the laser and the image analysis procedure, and the cascade impact method. Why shouldn't they almost be the same?

4. Please explain the sharp rise for total impurities between the 19th and 22nd month from [ ]% of lot 0291E1. Were these impurities ever identified and does any one of them correspond to the extracted peak at m/z and having a molecular weight of 186? Why wasn't this molecule identified?

5. Please provide all stability data accrued to date.

6. Regarding the labeling, we have the following comments:

COMMENTS:

A. General Comment.

Please submit container labels and carton labeling for the refill canister.

B. Container:

1. The label should be oriented on the canister so the product may be identified when inserted into the actuator.

2. The usual dosage guidelines should match those of the package insert.

3. The warning statement should be in bold type.

4. Revise To read "For oral inhalations with GENERICS (UK) LTD, adaptor only." Enclose the statement within a box.

5. 17 g should be placed on the main panel.

6. The shake well statement should be in bold.

C. Carton: Unsatisfactory

1. Enclose the statement "For oral inhalation with GENERICS (UK) LTD adaptor only" within a box.

2. PATIENT'S INSTRUCTION FOR USE

After "... read complete instructions carefully." insert the sentence, Children should use Albuterol Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

3. The DOSAGE, WARNINGS, storage and contents under pressure statements should be in bold type.

D. Insert

1. DESCRIPTION

a. Line 7, revise empirical formula to read molecular formula. Additionally, we prefer the numbers appear as subscripts in the molecular formula.

b. Line 8, revise ethanol to read alcohol.

2. WARNINGS

a. Line 1 ... albuterol inhalation aerosol ...(add "inhalation").

b. Paragraph 4 sentence 5, use a °symbol when describing temperature.

Please revise your labels and labeling, then prepare and submit final printed copy.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a ~~miner~~ major amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

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

cc: ANDA #73-045
DUP/Division File
HFC-130/JAllen
HFD-600 Reading File
HFD-638/JMolzon
HFD-634/RPatel/SSherken/06/19/91
HFD-634/VVashio/07/03/91
R/D initialed by RPatel
cls/06/20/91/b:73-045.LTR
F/T by cls/07/05/91
Not Approvable

ANDA 73-045

AUG 11 1994

A.L. Laboratories, Inc.
Attention: Ms. Deborah Winkel
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Madam:

This is in reference to your abbreviated new drug application dated December 28, 1988, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

Reference is also made to your amendments dated July 26, 1993 and February 4, 1994.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

4. We have the following comments regarding the stability of the drug product:

   a. Please revise your stability testing protocol to include final specifications for the content uniformity and extractables.

   b. Please revise your post-approval stability testing protocol to include tests for can content assay, can content weight, spray pattern, related substances (individual and total), and the Microbial Limit Test. Furthermore, a reasonable effort must be made to chemically identify the major impurities formed over the shelf life of the drug product.

   c. Please submit results of temperature cycling studies conducted for the exhibit batch in

accordance with the CDER Stability Guideline.

d. We note that you evaluate the particle size distribution by Laser Diffraction Method. We request that you conduct particle size distribution for the drug product by a second method - Cascade Impactor based on the method described in Supplement # 9 to USP XXII. Please submit validation of the method and propose specifications.

5. Please submit a signed certification stating that the facilities of CCL Industries, England are operated in compliance with all the appropriate environmental laws and regulations.

6. Bioequivalency of the proposed product has not been demonstrated. Please note that a new Interim Guidance for Documentation of In Vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers) was issued on January 27, 1994.

B. Labeling Deficiencies:

Container: Satisfactory

Refill Container: Satisfactory

Carton:

1. PATIENTS INSTRUCTIONS FOR USE

a. Comment #1, revise the following to be in bold print:

Then remove the cap from the mouthpiece.

b. Revise comment #2 to read:

...its upright position (see Figure 1) and...

c. Figure 1; Include the statement "UPRIGHT POSITION" and identify the cap and mouthpiece.

d. Figure 2; Include the statement "FOR ORAL INHALATION ONLY".

2. The statement [ ] is not appropriate for the complete unit. A statement informing the patient to save the adapter for use with the refill canister would be beneficial.

3. Revise to read:

   USUAL DOSAGE: Use only...

4. WARNINGS; Revise to read:

   ...consulting your physician. If symptoms get worse discontinue use and consult your physician immediately. Other inhaled medicines should be used only as prescribed by your physician.

5. The storage recommendations and the "Contents Under Pressure" statement is repeated on both side panels. We feel this is not necessary and would encourage removal of one of the duplicate statements. The additional space could be used to increase the size of the print and diagrams.

Refill Carton:

1. See comments 1, 3, 4, and 5 under Carton.

2. Revise the product name to read:

   ALBUTEROL INHALATION AEROSOL

   refill

Insert:

1. DESCRIPTION

   Revise the first paragraph to read:

   ...having the following structural formula:

2. CLINICAL PHARMACOLOGY

   Revise the last paragraph, last sentence as follows:

   ...at four hours in <u>a majority of the patients</u> and... (include the underline)

3. PRECAUTIONS

   a. **General**; revise the second paragraph as follows:

      ...and ketoacidosis. As with other beta-agonists, inhaled and intravenous albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

(Delete the last sentence

b. **Carcinogenesis, Mutagenesis, Impairment of Fertility**, revise to read:

...the rat at doses corresponding to 93, 463, and 2,315 times, respectively, the maximum inhalational dose for a 50 kg human. In another study...

c. **Pregnancy**; Revise to read:

i. Fourth sentence:

...corresponding to 1.15, 11.5, and 115 times, respectively, the maximum inhalational dose for a 50 kg human) showed cleft palate...

ii. Last sentence:

...corresponding to 2,315 times the maximum inhalational dose for a 50 kg human.

4. ADVERSE REACTIONS

Revise the second paragraph to read:

...a 13-week, double-blind... (add a comma)

5. OVERDOSAGE

Revise the first paragraph to read:

Manifestations of overdosage may include seizures, anginal pain,... (include "seizures")

6. PATIENT INSTRUCTION LEAFLET

See comments 1. b. and c. under Carton.

Please revise your carton and insert labeling, then prepare and submit final printed container labels, carton and insert labeling. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

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

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of

Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please be advised that samples of the drug product will be requested for methods validation at a later date after the testing issues are resolved.

3. Please submit any additional room temperature stability data that may be available.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

8/11/94

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

cc: ANDA 73-045
ANDA 73-045/DUP/Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-625/MShaikh/7/23/94 Mujahid Shaikh 8/8/94
HFD-625/MSmela/8-3-94 MSmela 8/10/94
HFD-617/VVashio/8-3-94 Washio 8/9/94
HFD-613/MGonitzke/8-3-94 MGonitzke 8/9/94
J. Phillips 8/10/94
X:\WPFILE\CARLOS\SHAIKH\73045LTR.94
F/T by MM 8-6-94
NOT APPROVABLE MAJOR AMENDMENT

ANDA 73-045

A.L. Laboratories, Inc.
Attention: Deborah Winkel
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

MAY 26 1995

Dear Madam:

This is in reference to your abbreviated new drug application dated December 28, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

Reference is also made to your amendments dated December 2, 1994, and January 27, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

B. Labeling Deficiencies:

CONTAINER: Satisfactory.

REFILL CONTAINER: Satisfactory.

CARTON: Satisfactory.

REFILL CARTON: Satisfactory.

INSERT:

1. DESCRIPTION

Revise the molecular weight to read "239.32" to be in accord with USP 23.

2. CLINICAL PHARMACOLOGY

Paragraph 4, last sentence - Italicize the *"O"* "...-*O*-methyl...".

3. PRECAUTIONS

a. Due to changes in the labeling of the listed drug please revise the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection to read as follows:

...in the rat at oral doses of 2, 10, and 50 mg/kg, corresponding to 93, 463, and 2,315 times...

b. Revise the **Pediatric Use** subsection to read as follows:

...in pediatric patients below...

4. ADVERSE REACTIONS

Paragraph 1, line 3 - ...is lower with albuterol.

PATIENTS INSTRUCTION FOR USE INSERT:

1. Revise instruction #2 to read as follows:

...its upright position (see Figure 1) and...

2. Relocate instruction number 2 to appear before the illustration for figure 2.

Please revise your package insert labeling, then prepare and submit final printed package insert labeling. Should further information become available in relation to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

C. Bioequivalence Deficiencies:

Bioequivalency of this product has not been established. An appropriate study has not been submitted.

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

1. Please be advised that a satisfactory methods validation is required prior to approval of this ANDA. We will request that the method validation study be initiated when your bioequivalence study is submitted.

2. A satisfactory compliance evaluation is required prior to approval of the ANDA. We will request an evaluation when your bioequivalence study is submitted.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 5/26/98

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

ANDA 73-045

A.L. Laboratories, Inc.
Attention: Ms. Deborah Mirran
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

JAN 29 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated December 28, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

Reference is also made to your amendment dated August 1, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Chemistry Deficiencies:

Please commit to put through these specifications within six months post-approval of this ANDA. You may submit a "Special Supplement - Changes Being Effected" with your results and methods validation to detect all the impurities.

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

1. Please be advised that we have instructed the FDA's International and Technical Operations Branch to collect samples of the drug product from the manufacturing facility of the drug product (i.e, CCL Industries, England) for the validation of the analytical methods. A satisfactory methods validation is required prior to approval of this ANDA.

2. A satisfactory compliance evaluation is required prior to approval of the ANDA.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 1/29/96

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

cc: ANDA 73-045
Dup
Division File
Field Copy
HFD-600/Reading File

Endorsements:

/S/ 1/17/96

HFD-625/MShaikh/12/20/96
HFD-625/SSherken for MSmela/1/3/96 Stephen Sherken 1/17/96
HFD-617/SO'Keefe/1/3/96 SOKeefe 1/16/96

NOT APPROVABLE - MAJOR AMENDMENT

ANDA 73-045

A.L. Laboratories, Inc.
Attention: Deborah Miran
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

APR 8 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated December 28, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

Reference is also made to your amendment dated February 23, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reason:

DMF ( ) remains deficient. Please request them to respond to all outstanding deficiencies cited by the FDA letter dated March 11, 1996. Please be advised that all the deficiencies must be resolved prior to approval of this application.

In addition to responding to the deficiency, please note and acknowledge the following in your response:

A satisfactory compliance evaluation is required prior to approval of the ANDA.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a

MAJOR AMENDMENT. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 4/4/96

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

cc: ANDA 73-045
Dup File
Division File
Field Copy
HFD-600/Reading File
HFD-82

Endorsements:
HFD-625/M.Shaikh/4-1-96
HFD-625/M.Smela/S.LUI for/4-2-96
HFD-617/SO'Keefe/4-3-96

/S/ 4/4/96
for Smela 04/4/96
4/4/96

Not Approval - Minor Amendment