

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

73045

ADMINISTRATIVE DOCUMENTS

ELECTRONIC MAIL MESSAGE

Date: 17-Jun-1994 04:12pm DST
From: Mujahid Shaikh
SHAIKHM
Dept: HFD-634 MFN2 204
Tel No: 301-594-0365 FAX 301-594-0180

TO: James Wilson (WILSONJ)

CC: Michael Smela (SMELA)

CC: Valerie Vashio (VASHIO)

Subject: ANDA 73-045

Jim:

I submitted a EER for ANDA 73-045 on 6-6-94. Please contact the Compliance to cancel this request. An EER requested will be made on a later date, when necessary. I have left a copy of EER on your desk.

Thank for your patience.

Mujahid L. Shaikh

MINUTES OF PHONE CALL

DATE: August 1, 1997

SUBJECT: ANDA 73-045, Albuterol Inhalation Aerosol, 90 ug/application

ORGANIZATION: Alpharma

PARTICIPANTS: Allen Rudman
Ron Bynum

Ron Bynum was contacted and asked to amend ANDA 73-045, Albuterol Inhalation Aerosol, 90 ug/application, application as follows:

1. Inclusion of an test for the release of the drug product (in addition to the ID test).
2. Reduction of the Unit Spray Content test limits from % to %.

Ron said that the firm will probably agree to the above, but that he would have to confer with the plant before giving a final answer. If Alpharma agrees to the changes, then they can be submitted as a commitment in a telephone amendment.

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING #5

Orig. Amendment (Major)

FPL

DATE OF REVIEW: February 27, 1995

ANDA #: 73-045

NAME OF FIRM: A. L. Laboratories, Inc.

NAME OF DRUG: Albuterol Inhalation Aerosol, 90 mcg/Inhalation

DATE OF SUBMISSION: December 2, 1994

COMMENTS:

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.

*OK to
Strip!*
~~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.~~

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their package insert labeling, then prepare and submit final printed package insert labeling. Should further information become available relation to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

FOR THE RECORD:

1. This review was based on the labeling of the listed drug Ventolin® (Allen & Hanburys; Approved February 2, 1994; Revised July 1993).
2. Storage/Dispensing Recommendations

USP: Not the subject of a USP monograph.

NDA: Store between 15° and 30°C (59° and 86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.

ANDA: Store at CRT 15°-30°C (59°-86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.

3. Exclusivity exist for the indication "Prevention of Exercise-Induced Bronchospasm in Children Ages 4 to 10 Years", which expires on July 20, 1996. Firm will not market product until exclusivity expires.

Carol Zimmermann

cc: ANDA 73-045DEC.94
HFD-613/CZimmermann/APayne/JPhillips (no cc)
njg3\24\95\73045
Review
final

/S/

3/24/98
3/27/95

/S/

3/28/95

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4-1-96
FROM: Mujahid L. Shaikh
SUBJECT: MVP for ANDA 73-045
TO: Jim Allgire

JS
4/1/96

Per your request, attached herewith the MVP for this ANDA. Please note that I have also included the most recent revision to the methods filed in A. L. Labs.'s amendment dated February 23, 1996.

If you need additional information, please contact me or Mike Smela at 301- 594-0370.

Thanks

File in Open Volume

MEMORANDUM of TELEPHONE CONVERSATION

DATE: 2/29/96

REFERENCE: ANDA 73045

PARTIES INVOLVED and AFFILIATION:

Michael Smela, Jr. FDA\HFD-625
Debbie Winkel A. L. Labs

MSI
2/29/96

SUMMARY of DISCUSSION:

Ms. Winkel phoned in regard to the pending minor amendment response to this Albuterol MDI application and specifically to the methods validation issue. It was noted that OGD has recently requested sample collection and Methods Validation From the ITOB.

Ms. Winkel stated she had spoken to Nancy Haggard of ITOB and that the PAI of the facility in England appears to be scheduled for April. I said that I had heard the same.

She asked if it was possible to get the MV going before then to save time. I said that the CP/PAI directs the investigator to personally collect the MV samples. I said this has generally been agreed in FDA to be an overreaction to the generic drug scandal of the late 80s, and that we were moving to a process of once again having firms mail MV samples to the labs. I said we had already mentioned to Nancy Haggard that if ITOB wished to obtain the MV samples by mail, we would have no problem. I said the inspection and sample collection is an ITOB responsibility and A.L. Labs should work it out with them.

CC: ANDA 73045

RECORD OF TELEPHONE CONVERSATION

FROM: Michael Smela, Jr. HFD625 8/22/96

NAME/TITLE OF INDIVIDUAL: Debbie Miran Reg Affairs
FIRM: A.L. Pharma
PRODUCT NAME: Albuterol MDI ANDA 73045
OGD CONTROL DOCUMENT: N/A
TEL #: 410-558-7250
FAX #: N/A
ADDITIONAL PARTICIPANT: None

SUBJECT: Telephone Amendment Request

I phoned and asked that the Shot Weight test being done for stability be also used for batch release. I asked if her current updated specs for Drug Substance, Drug Product and Stability could also be included in the amendment to facilitate processing the ANDA. She agreed but asked if a commitment on the Shot Weight test would be adequate as it takes some time to process spec changes internally. I said that was fine.

I asked that a copy of the telephone amendment be faxed to Mr. Shaikh when ready and she indicated it may be done today.

SIGNATURE OF OGD REPRESENTATIVES:

[Signature] 8/22/96

DIVISION/BRANCH: Div. of Chemistry I, Branch #2

3/5/97

Ron Bynum
A.L. Pharma
Albuterol MDI/ANDA 73-045

1. Because drug delivery may change progressively through canister life, the Division of Bioequivalence believes that, as a bioequivalence criterion, a test product should meet USP <905> Content Uniformity requirements at beginning, middle and end of canister through-life. Therefore, the firm is requested to provide the following:
 - a. Content uniformity data on 30 canisters of test lot # 8457 at beginning, middle and end.
 - b. Content uniformity data on 10 canisters of test lots # 8671 and 8834 at beginning, middle and end. For each batch, if 10 canisters fail to meet the USP specification at each of beginning, middle and end, an additional 20 canisters should be tested as stated in USP <905>. Note that, consistent with the 27 June 1989 Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, the specifications will be evaluated separately at beginning, middle and end of canister through life.
 - c. Data may be provided in the same format as that on pages 430 and 431 of the 6 January 1997 submission.

2. Additional information is also requested by the Division of Bioequivalence:
 - a. The specific model of ✓Andersen 8 stage cascade impactor used by the firm for the data submitted on 6 January 1997.
 - b. The expiration dates for test product batches # 8671 and 8834.
 - c. Testing dates for the ✓twin impinger data submitted on 12 June 1995 and 27 July 1996.
 - d. ✓Conduct of the Microscopy Test (USP <601>) on canisters from test product batches # 8457, 8671, and 8834, and Ventolin MDI batch # 6ZP0756. The Division requests these comparative baseline data, noting that the test serves a number of purposes: determination of the number of particles larger than 10 microns; identification of unusual agglomeration; characterization of crystal morphology; and identification of foreign particulates not related to the drug substance.

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Branch 2 HFD-625

FROM: Michael J. Smela, Jr. Team Leader DATE: 7/16/97

NAME/TITLE OF INDIVIDUAL(S): Ron Bynum
FIRM: AL Pharma
PRODUCT NAME: Albuterol MDI
TEL #: 410-558-7250
Reference: ANDA 73045

Notes of Conversation: I phoned to request a telephone amendment. I mentioned that the DBE was satisfied with the in vitro data but some specification changes are recommended.

I asked confirmation that USP <905>, Content Uniformity is used for both release and stability.

I asked for the cascade impactor specs for both release and stability be revised to those found in the bio review endorsed on 7/14/97.

Mr Bynum asked if he could commit to revise the specs as such since spec revision takes some time internally. I said that was fine and asked that a fax copy of the telephone amendment be sent to Mr. Shaikh.

SIGNATURE OF OGD REPRESENTATIVES:

Location of Electronic Copy:

JS
7/16/97

RECORD OF TELEPHONE CONVERSATION

Spencer

DATE: July 10, 1996

PRODUCT NAME: Albuterol Inh Aerosol

ANDA NUMBER: 73-045

FIRM NAME: Alpharma / Barre- National

NAME OF PERSON WITH WHOM CONVERSATION WAS HELD: Vincent Andolina

PARTICIPANT'S TELEPHONE: 410-298-1000 x 324

BACKGROUND:

Mr. Andolina initially called on 7/2/96. I happened to pick up this call and the acting team leader was unavailable, as I recall. His inquiry concerned the May 3, 1996 Federal Register notice - Interim Rule - on CFC/ozone warning statements. He was engaged in a debate with his colleagues on which path to follow. One option allowed was to label as it has been under EPA regulations. So the question was, if it was ok with EPA, was it ok with FDA? The other option was the interim rule which allowed for two statements: one directed towards provider and one towards patient which avoids the use of "harms public health", a statement that may alarm a patient if they are using this product.

In this initial conversation, he stated his superiors (Debbie Mirin and Ron Biron -sp?) wanted to include some hybrid statement in the labeling crafted from the options available. He had also spoke to Kathy Shoemaker of NDE's Pulmonary Division who said "if it was ok with EPA it would be ok with FDA. Though FDA and EPA were to have gotten together to discuss the issue again, but they didn't really get back to it."

Mr. Andolina commented this was one big nebulous issue. He also informed me he had spoken with then acting team leader John Grace on 5/31/96. After I hung up, I e-mailed John and Adolph. I advised Mr. Andolina I was not in a position to provide a course of action. I had requested either John o Adolph return his call. He had not received a call by the 7/10 and he then called me back.

MINUTES OF CONVERSATION:

On 7-10-96, I relayed from John Grace that this was an interim rule which we cannot enforce until it is finalized. So, for now, their labeling is still satisfactory for approval and there is no need to revise for new FPL.

NAME OF OGD REPRESENTATIVE :

JS

7-17-96

David Konigstein, Labeling Reviewer

SUBJECT: Visit by ALPHARMA Representatives

DATES: 9/12-13/96

VISITORS: Francis J. Blacha
Director Operations Technical Service
ALPHARMA
7205 Windsor Boulevard
Baltimore, Maryland 21244
Telephone: (410)298-1000
FAX: (410)597-9627

Anastasia Loftus
Technical Manager
CCL Pharmaceuticals
Runcorn Facility
9 Arkwright Road, Astmoor Industrial Estate
Runcorn, Cheshire WA7 1NU. England
Telephone: 01928 567676
FAX: 01928 591063

They arrived at 8 am on Thursday 9/12. We had a meeting with
(and the 2 visitors. opened the meeting by voicing our
concerns that the method gave low results which could result in
good product failing the test. replied by saying
they were concerned with our results because they did not match
results they had seen. They had a concern that they did not know
the source of the unit spray apparatus we received. The first
apparatus was sent from CCL quality control by ; but it
was broken in shipment. They did not know who sent the second
apparatus but said he thought it might have been the
research section. They brought another sampler with them. On
comparison, the heights of the frits were different which
resulted in the frit on the new apparatus being totally submerged
with 25 mL of collection fluid while with the initial sampler the
collection fluid had to be increased to 30 mL to cover the frit.
said the sampler was purchased from a glassware
company in the UK and agreed to send or Fax part of the catalog
referring to the sampler.

said they had also brought an column because we
reported retention times in excess of what they had seen.
offered that had just received and tested a new
column and guard column which gave retention times that
matched ALPHARMA's retention time.

asked if he could look at the cascade impaction
results from our testing. We showed him pages 25, 30, 31, 36,
and 37 from our report. He asked for copies. We contacted Mike
Smela to see if this was possible and he said to give
the copies because he could get them under the Freedom of
Information anyway.

presented us with a set of modified methods that

incorporated our initial suggestions.

We adjourned to the laboratory to test 10 canisters brought by

We were going to use the Andersen Constant Flow Air Sampler. said they usually use the vacuum pump that came with the Twin Impinger. The glass induction port on the sampler matched the adapter to the rotometer attached to the Twin Impinger so airflow could be measured at the mouth of the unit spray apparatus. Because of her wishes we switched and used the vacuum pump on the Twin Impinger. prepared the collecting fluid by discharging 10 mL of water from a wash bottle into a 50 mL graduate cylinder then 15 mL of methanol was likewise added to the cylinder. This solution was then transferred to the unit spray bottle. When turned on the vacuum pump and adjusted the airflow to 30 L/minute she commented the bubbling and splashing seemed excessive. When the airflow was adjusted to what thought had the correct amount of bubbling the rotometer read approximately 12 L/minute. The airflow was checked with a second rotometer and the airflow on the 2 rotometers agreed. The sampler was connected to the Andersen air pump with similar observations. again adjust the airflow to what she thought was the appropriate amount of bubbling and the rotometer read approximately 8 L/minute. She then reconsidered and readjusted the airflow which now was approximately 12 L/minute. The differences were speculated to be: rotometer calibration, surface tension of the collecting solution, or altitude.

It was decided to ignore this problem at this time and test the canisters as planned at 30 L/minute using the twin impinger vacuum pump.

tested all 10 canisters with weighing some canisters while we observed. After the 10 canisters were sampled canister 6 was retested with a reduced airflow of 12 L/minute.

Several minor differences were noted between the way ran the procedure and the way we had. She shook the canisters more violently than we had. She used a wash bottle of methanol to rinse the sampling apparatus while we used disposable pipettes. commented that the additional force from the wash bottle may be needed. Also, we had washed the sampler then dried it in an oven and dried the rubber mouthpiece adapter with a stream of nitrogen after each test. wiped off the rubber adapter and the glass input adapter with a Kimwipe tissue and continued to the next test.

The samples were chromatographed using a Spectra Physics chromatograph with a SpectraFocus detector. This detector is of similar design to the Waters adjustable wavelength detector used by The mobile phase was 45/55/0.1 methanol/water/acetic acid.

The results are attached. Canister 10 was out of specification and the canister shot weights were in the appropriate range.

The average of the results for canisters 1 to 9 was % label. Canister 6 had good agreement between the results at 30 and 12 L/minute.

After some discussion about the results we called it a day. After the visitors left the Andersen airflow was checked with a dry gas flow meter (which agreed with the rotometers at 12 and 30 L/minute.

The visitors returned at 7:30 a.m. on Friday, 9/13.

Mr. Blacha said they had been in contact with the UK and that the product was formulated at % label/spray so the results for canisters 1-9 were acceptable. He proposed running canister 10 again at 30 and 12 L/min. with first running the procedure then with running the procedure. He also suggested running canister 6 as a control.

The test solutions were chromatographed using the same instrumentation as above but the mobile phase was changed to the ANDA mobile phase of 40/60/0.1 methanol/water/acetic acid.

The results are attached. All of the results were within the specified limits with the results for 12 L/min. airflow being slightly higher than those for 30 L/min..

On discussion about the degree of bubbling for the airflow it was decided that calibration of the rotometer is not the problem because the difference would be too great. Another possibility raised was that the units of the rotometers might be different.

Other discussion about the methods revealed that the company does not filter the mobile phase after the components are mixed and uses a helium purge at all times.

It was decided that / would rerun and re-evaluate the Unit Spray and Content Uniformity procedures with the new glassware and new column. was asked to leave her column in case of further problems with the stipulation that it would be returned when the testing is completed. This column will not be used unless there are problems with The initial unit spray sampler received was returned to who immediately dropped the bottle and impinger into the broken glass receptacle. kept the rubber adapter and the input adapter.

RESULTS FROM ALPHARMA VISIT

9/12/96

CANISTER	%LABEL
1	78.4
2	105.9
3	88.0
4	112.7
5	103.2
6	95.8
7	76.5
8	78.8
9	95.8
10	61.3
6	94.5 Reduced Airflow, 12 L/min.

9/13/96

CANISTER	AIRFLOW	% LABEL ALPHARMA	% LABEL
10	30	92.8	111.9
10	12	102.0	115.5
6	30	112.8	109.1



A. L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
RESEARCH • DEVELOPMENT • REGULATORY

Albuterol Inhalation Aerosol, 90 mcg/Inhalation
ANDA # 73-045

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96(b), A.L. Laboratories certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA Baltimore District Office.

Deborah Miran
Sr. Director, Regulatory Affairs

8/22/96

Date



A. L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
RESEARCH • DEVELOPMENT • REGULATORY

Albuterol Inhalation Aerosol, 90 mcg/Inhalation
ANDA # 73-045

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96(b), A.L. Laboratories certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA Baltimore District Office.

Ronald Bynum / for
Deborah Miran
Sr. Director, Regulatory Affairs

8/1/96
Date

RECORD OF TELEPHONE CONVERSATION/MEETING

<p>If the assay were run on more than 1 day then interday data should be provided. The time the assay was validated should be provided as well as information on which data set does the validation data applies to.</p> <p>5. We stated that we normally do not rely on data from expired bio batch lots. We explained that for the Office to consider the cascade impactor data obtained after expiry from the reanalyzed bio batch lot, it would be helpful if stability data on the batches could be provided.</p> <p>Mr. Bynum said the firm did not have stability data past expiry; they only re-did potency, spray pattern and the cascade impactor data, all of which have previously been provided.</p> <p>Dr. Adams asked that the data submitted with the 10/8/96 submission be provided on a diskette in ASCII format and readable on Excel. Mr. Bynum said he would do so.</p> <p>We asked if Mr. Bynum had any questions. He asked for clarification on the differences in the assay validation we were requesting vs the typical chemistry validation they use.</p> <p>Dr. Adams explained that the data submitted suggest analytical problems and we need the validation data to help clarify our concerns.</p>	<p>DATE 10/28/96</p>
	<p>ANDA NUMBER 73-045</p>
	<p>IND NUMBER</p>
	<p>TELECON</p>
	<p>INITIATED BY MADE <input type="checkbox"/> APPLICANT/ <input checked="" type="checkbox"/> BY SPONSOR TELE.</p> <p><input checked="" type="checkbox"/> FDA <input type="checkbox"/> IN PERSON</p>
	<p>PRODUCT NAME Albuterol MDI</p>
	<p>FIRM NAME AlPharma</p>
	<p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Ron Bynum</p>
	<p>TELEPHONE NUMBER 410-558-7250</p>
	<p>SIGNATURE /S/</p>



A. L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
RESEARCH • DEVELOPMENT • REGULATORY

Albuterol Inhalation Aerosol, 90 mcg/Inhalation
ANDA # 73-045

MINOR AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96(b), A.L. Laboratories certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA Baltimore District Office.

Vincent Andolina for

Deborah Miran
Sr. Director, Regulatory Affairs

2/23/96

Date

f:\...\1264\submit\012996dl.ama

Sent to L105 by Internal Mail on 1/17/96.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 20, 1995
FROM: Mujahid L. Shaikh, Review Chemist
Office of Generic Drugs (HFD-625)
SUBJECT: Sample Request for Methods Validation for A. L.
Laboratories, Baltimore, MD Albuterol Inhalation
Aerosol (ANDA 73-045)
TO: Nancy Haggard, Chief
International and Technical Operations Branch (HFC-134)
THROUGH: Michael Smela, Jr., Supervisory Chemist *M Smela 1/17/96*
Office of Generic Drugs (HFD-625)

It has been determined that A.L. Laboratory's Albuterol MDI specifications are based on the current FDA and USP 23 requirements for Aerosols <601> in ANDA 73-045. The firm has submitted their regulatory methods for Albuterol Inhalation Aerosol. Therefore, these proposed regulatory analytical methods should be validated by a FDA laboratory since this subject drug product does not have a USP monograph.

As instructed under the PRE-APPROVAL INSPECTION/INVESTIGATIONS program (7346.832) you are requested to collect samples of the subject drug product, including the impurity reference standards, from the applicant's manufacturing facility at the following address:

CCL Industries
9 Arkwright Road
Astmoor Industrial Estate
Runcorn
WA7 1NU, England

Per your instructions for foreign firms, I have not included a copy of the methods validation package for this drug product as instructed in Part IV of the compliance program. Methods Validation Package will be ready to be obtained from me before the investigator goes to collect the samples from the above address.

Upon completion of the district's portion of the methods validation, please send worksheets, all attachments, conclusions, and recommendations directly to the review chemist, Mr. Mujahid L. Shaikh (MPN II, OGD, HFD-625, Room 226), within five days of completion. If you have any additional questions, please call me at (301) 594-0370.

*Please send samples and MV package to the Division of Drug Analysis in St. Louis to the attention of Henry Drew. DDA is set up to handle this product.

LABELING REVIEW WORKSHEET

FIRM: A. L. Laboratories, Inc. ANDA: 73-045
DRUG: Albuterol Inhalation Aerosol, 90 mcg/Inhalation

LABELING OF THE LISTED DRUG

FIRM: Allen & Hanburys NDA# 18-473
APPROVAL DATE: February 2, 1994 REV.DATE: July 1993

CONTAINER LABELS

APPROVED COPY ON FILE? Yes

USP CONTAINER/CLOSURE REQUIREMENTS: Not the subject of a USP monograph.

RECOMMENDED STORAGE STATEMENT:

ANDA: Store at CRT 15°-30°C (59°-86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.

NDA: Store between 15° and 30°C (59°-86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.

OTHER KEY ISSUES:

INSERT LABELING

PATENT & EXCLUSIVITY ISSUES: Exclusivity exists for the indication "Prevention of Exercise-Induced Bronchospasm in Children Ages 4 to 11 years of age", which expires on July 20, 1996.

BIO ISSUES: Pending

ALL INACTIVE INGREDIENTS CITED? Yes

OTHER KEY ISSUES:

APPROVAL SUMMARY

CONTAINER LABELS (SUBMISSION DATE): Satisfactorily submitted on December 2, 1994 (200 metered canister and refill canister).

CARTON LABELING (SUBMISSION DATE): Satisfactorily submitted on December 2, 1994 (1 x 200 metered canister and refill canister).

INSERT LABELING (SUBMISSION DATE): Satisfactorily submitted on August 1, 1995 (REV. 5/95)

FORMULATION/SCORING SUMMARY: Not applicable - Inhalation

COMMENTS OR FUTURE REVISIONS NEEDED:

1° REVIEWER:

2° REVIEWER:

SUPERVISOR:

/S/

10/26/95

/S/

DATE:

10/27/95



A. L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
RESEARCH • DEVELOPMENT • REGULATORY

**ALBUTEROL INHALATION AEROSOL, 90 mcg / INHALATION
ANDA #73-045**

AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96 (b), A.L. Laboratories certifies that a field copy of this amendment to the application has been sent to the FDA District Office.

Deborah Winkel
Sr. Director, Regulatory Affairs

8/1/95

Date

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 26, 1991

FROM: Joseph T. Piechocki, Ph.D.
Review Chemist, Division 2
Division of Generic Drugs

SUBJECT: ANDA 73-045

TO: K. Furnkranz
Acting Supervisor
Division 2
Division of Generic Drugs

As per our conversation of this date, review of ANDA 73-045 will be postponed until such time as the real agent for Generics Ltd. is identified. Since the true agent's identity is in question no further action will be taken until the firm resolves this question.

Mr. G. Johnston, who first raised this question, has called the firm today and they promise to reply in a few days.

/S/

32619.

MEMO OF TELCON
DIVISION OF DRUG ANALYSIS
ST. LOUIS, MO
(314) 539-2011

Date: 8/26/96
Time: 10:15 a.m. CDT

Between
Henry Drew, PH.D.
James Allgire
Virginia Kleekamp
Division of Drug Analysis

AND

Ron Bynum
Debbie Miran,
Senior VP Regulatory Affairs
A.L. Labs
401-558-7250

Subject: ANDA 73-045

Ron Bynum had called Jim Allgire at 9:40 a.m. CDT. I told him I had been on vacation and needed a few minutes. I told him I would call him back at about 10:15.

He said he had been FAXed a portion of our report. He had the comments listed on the 8 methods and the Summary of Results. (It sounded like he did not have the portion of the report that was directed just to the review chemist.)

Mr. Bynum said most of the comments were of the sort where you should include ... or change this to ... but they were having trouble finding our exact problems with the [] test.

We said that L/min. flow rate was excessive. The USP uses 12 L/min. and states the sampling device is a low flow device. When we used the USP device the absorbing fluid was drawn into the vacuum pump. The A.L. Labs device gets around that by fluting the top of the gas washing bottle. The problem remains that the results are low. This could be caused by the canisters or loss of drug from the excess bubbling.

√ When Dr. Drew brought up the that the collection fluid does not cover the frit, Ms Miran quoted that the lab people said that the 25 mLs not covering the frit should not make a difference. Ms Miran also speculated the variability could be caused by excess bubbling. She offered to send their data to us and when

asked said the canisters were manufactured Nov '95 and analyzed Jan '96.

Ms. Miran asked if we went to the second stage testing for Content Uniformity and we said we had not. Dr. Drew asked if it was in the method. Mr. Bynum checked and found it was not mentioned in the method but it is mentioned in the product specifications.

Ms. Miran also offered that the overseas lab said they could run the test at 12 L/min. She asked if we had evaluated their product at 12 L/min. using either the USP device or their device. We had not, but that we have evaluated numerous other canisters at 12 L/min. on the USP device.

Mr. Bynum asked if the airflow was the issue or was the fact the apparatus was not commercially available more important. This question about commercial availability was not answered before other questions were asked.

The question was raised of how much additional testing would be required if the procedure were changed to 12 L/min. Dr. Drew replied that would be up to the review chemist.

Ms Miran asked about the chromatography problem. The %RSD for the System Suitability is outside the range for acceptability. We said this was difficult to meet at that low level because the absorbance was 2-3 mAU. This made it difficult to hit a 3 %RSD window. Ms. Miran then asked if this could be the problem with the results because the samples were 73.8% and 72.2% with a 75% lower limit and 63.2% with a 65% lower limit. We replied that the problem was the product did not meet the specifications set forth.

It was mutually agreed that we would confer with Mike Smela and the review chemist and either we or the review chemists would be back in touch with A.L. Labs.

Ms. Miran then clarified that they had been instructed by Mike Smela to contact us directly. We said that Mike had sent us an E-mail that said A.L. Labs would be contacting us.

RECORD OF TELEPHONE CONVERSATION

FROM: Michael Smela, Jr. HFD625 8/22/96

NAME/TITLE OF INDIVIDUAL: Debbie Miran Reg Affairs
FIRM: A.L. Pharma
PRODUCT NAME: Albuterol MDI ANDA 73045
OGD CONTROL DOCUMENT: N/A
TEL #: 410-558-7250
FAX #: N/A
ADDITIONAL PARTICIPANT: None

SUBJECT: Telephone Amendment Request

I phoned and asked that the Shot Weight test being done for stability be also used for batch release. I asked if her current updated specs for Drug Substance, Drug Product and Stability could also be included in the amendment to facilitate processing the ANDA. She agreed but asked if a commitment on the Shot Weight test would be adequate as it takes some time to process spec changes internally. I said that was fine.

I asked that a copy of the telephone amendment be faxed to Mr. Shaikh when ready and she indicated it may be done today.

SIGNATURE OF OGD REPRESENTATIVES:

JS 8/22/96

DIVISION/BRANCH: Div. of Chemistry I, Branch #2

RECORD OF TELEPHONE CONVERSATION

FROM: Michael Smela, Jr. August 27, 1996

NAME/TITLE OF INDIVIDUAL: Debbie Miran
FIRM: A.L. Pharma
PRODUCT NAME: Albuterol MDI
TEL #: 410-558-7250

SUBJECT: Method Validation

I phoned as Gordon Johnston told me he spoke to her yesterday and she was expecting my call. I was unaware of why. She said she had spoken to Jim Allgire and Hank Drew of DDA about the problems with the spray assay test. She said they spoke in general but that DDA believes is it OGD's decision how A.L. Pharma should address the problem. I said I had not heard from DDA but will check.

I said that she could take the position that nothing is wrong with the test in which case we would ask DDA to reconfirm their results. She could also change the test per DDA recommendations and with data and we would revalidate the new test. I asked how we would regulate their product since the apparatus is not available. Debbie said DDA may keep the one they loaned them. She also asked if a A.L. Pharma rep could travel to DDA and work with them on running the test. I said that is possible if it comes to that.

After speaking with Hank Drew and Jim Allgire of DDA, I called back to further discuss options. I said that 3 options exist:

1. Applicant may maintain that the test method is adequate. I advised in this case OGD would ask DDA to repeat the test. Further action on the ANDA would then depend on the repeat test.
2. Applicant may maintain that the test is adequate but has some nuances. I advised that DDA would allow their analyst to come there and work the test with them. Further action again would depend on results.
3. Applicant may revise the method. I restated the recommendations of DDA and advised that DDA feels these recommendations would increase collection efficiency. The flow rate should be decreased from _____ L/min per the USP recommendation. They could continue to use their collection apparatus or change to the USP recommendation. DDA acknowledged they may keep the loaned apparatus if applicant does not change. Also advised that the method could refer to the apparatus as "or equivalent USP" which would further help the regulatory situation as a validated equivalent could be used. Also advised that the

System Suitability criteria for RSD are considered too stringent for the low level of analyte and should be relaxed. I said if this option is chosen, we would want:

1. Revised method 2. New release test data with the revised method 3. Revalidation of the revision by DDA and 4. They need to discuss whether they need to redo the comparative spray data for bio. I said that since the revision would be made to improve the accuracy of the method, it would seem these data will need to be repeated but that is bio's call.

Debbie stated she would like to discuss these options with the England facility and would let me know what they decide.

She called back about 30 minutes later and stated they do not desire to change their test. They prefer Option 2. I stated that they should then work out the arrangements directly with DDA.

Debbie said they expect to submit a Telephone Amendment within a week addressing the Method Validation comments. For the test at issue, they will maintain it is an adequate test and will refer to this phone call stating they will be sending a person to DDA. I said that such an amendment would be complete and therefore we would be obligated to accept it.

SIGNATURE OF OGD REPRESENTATIVES: *JS/* 8/27/96

DIVISION/BRANCH: Div. of Chemistry I, Branch #2

REVIEW OF PROFESSIONAL LABELING

Orig. Amendment

DRAFT

DATE OF REVIEW: March 27, 1990

ANDA #: 73-045

NAME OF FIRM: Superpharm

NAME OF DRUG:

Generic: Albuterol Inhalation Aerosol, 0.09 mg/Inh.

DATE OF SUBMISSION: August 28, 1989

COMMENTS:

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"

Patient Instruction Leaflet

Before using your Albuterol Inhaler, read...

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their insert labeling, then prepare and submit final printed copy.

cc: HFD-630
GJohnston/TPoux
ms: 3/28/90 (4329m)
DUP

Gordon Johnston

/S/

U 3/29/90

REVIEW OF PROFESSIONAL LABELING

ANDA - DRAFT

DATE OF REVIEW: 2/22/89

ANDA #:73-045

NAME OF FIRM: Superpharm

NAME OF DRUG: Trade:
Generic: Albuterol Inhalation Aerosol

DATE OF SUBMISSION: December 23, 1988

COMMENTS:

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

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 actuations per container.

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

I. Please submit a sample adaptor and container for our review.

J. Revise [✓] 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)
- C. See Insert Labeling (H) above.

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their labels and labeling, then prepare and submit final printed container labels and carton labeling.
3. Note to Chemist: Please contact me prior to issuing an action letter. Bio requirements are currently under review. Request for revised insert labeling is pending outcome of the Bio requirements.

Gordon Johnston

cc:
DUP
GJohnston/gp/2/23/89
1461g p-11&12

HJ 2/24

ND/S!
2/24/89

THIS REVIEW SUPERSEDES THE LABELING WORKSHEET
DATED October 27, 1995

APPROVAL SUMMARY

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

Date of Review: October 8, 1996

Date of Submission: September 20, 1996

Primary Reviewer: Carol Holquist

Secondary Reviewer: John Grace

ANDA Number: 73-045

Review Cycle: 3 - FPL INSERT

Applicant's Name [as seen on 356(h)]: Alpharma, U.S.
Pharmaceuticals Division

Manufacturer's Name (If different than applicant): CCL Industries
Limited

Established Name: Albuterol Inhalation Aerosol,
90 mcg/actuation

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: Satisfactorily submitted on December 2,
1994 (200 metered canister and refill canister).

Carton Labeling: Satisfactorily submitted on December 2,
1994 (1 x 200 metered canister and refill canister).

Professional Package Insert Labeling: September 20, 1996
(Rev. 8/96).

Patient Package Insert Labeling: September 20, 1996 (Rev.
8/96).

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Ventolin® Inhalation Aerosol

NDA Number: 18-473

NDA Drug Name: Ventolin® Inhalation Aerosol
NDA Firm: Glaxo Inc.

Date of Approval of NDA Insert and supplement #: February 2, 1994/S-022 with revisions from S/021 Approved July 20, 1993.

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance?
No

Basis of Approval for the Container Labels: Approved
Ventolin Container labels in file folder.

Basis of Approval for the Carton Labeling: Approved
Ventolin Carton labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
<i>PROPRIETARY NAME</i>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	

If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
<i>LABELING</i>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Error Prevention Analysis: LABELING (Continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	

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

FOR THE RECORD:

1. This review was based on the labeling of Ventolin® (Allen & Hanburys; Approved February 2, 1994; Revised July 1993).
2. Storage/Dispensing Recommendations

USP: Not the subject of a USP monograph.

NDA: Store between 15° and 30°C (59° and 86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.

ANDA: Store at CRT 15°-30°C (59°-86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.
3. The exclusivity for the indication "Prevention of Exercise-Induced Bronchospasm in Children Ages 4 to 11 Years", expired on July 20, 1996. The firm has amended the labeling to include this indication.

ISI
Primary Reviewer

10-9-96
Date

ISI
Team Leader
Labeling Review Branch

10/10/96
Date

cc:

ANDA 73-045
Dup/Division File
HFD-613/CHolquist/AVezza/JGrace (no cc)
10/8/96/firmsam/alpharma/ltrs&rev/73045AP.L
Review

REVIEW OF PROFESSIONAL LABELING #4

Original Amendment

DRAFT

DATE OF REVIEW: July 25, 1994

ANDA #: 73-045

NAME OF FIRM: A. L. Laboratories, Inc.

NAME OF DRUG: Albuterol Inhalation Aerosol, 90 mcg/Inhalation

DATE OF SUBMISSION: February 4, 1994

COMMENTS:

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 doctor. If symptoms get worse discontinue use and consult your doctor

immediately. Other inhaled medicines should be used only as prescribed by your doctor.

5. The storage recommendations and the "Contents Under Pressure" statement is on both side panels. Please delete this information from the left side panel and use that additional space to increase the size of the print and diagrams.

*has been revised
see Chem
letter 8/4/90
MG*

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 a majority of the patients
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.

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their 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.
3. For The Record:
 - a. Labeling review based on VENTOLIN labeling, approved July 20, 1993, revised June 1992.

- b. Exclusivity exist for the indication "PREVENTION OF EXERCISE-INDUCED BRONCHOSPASM IN CHILDREN AGES 4 TO 11 YEARS", which expires on July 20, 1996.

M. Gonitzke

cc:

ANDA 73-045

HFD-613/MGonitzke/JPhillips (no cc)

mpd/7/28/94; 73045FEB.94

Review

Final

ISI 7/28/94

ISI 8/2/94

REVIEW OF PROFESSIONAL LABELING

ORIG. AMENDMENT

DRAFT - Package Insert Labeling
Canister Label - Carton Labeling

DATE OF REVIEW: June 13, 1991

ANDA #: 73-045

NAME OF FIRM: Generics (UK) Limited
c/o Lachman Consulting Services

NAME OF DRUG: Generic: Albuterol Inhalation Aerosol,
0.09 mg/Actuation

DATE OF SUBMISSION: April 26, 1991

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.

*(note the 4/26/91 submission
supercedes the 7/5/90 and
the 11/19/90 submissions.
Our 7/12/91 letter
should have reference
to the formal
4/26/91
submission
space the
labeling
comments
to that
submission
of Miller
6/11/92)*

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.

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their label and labeling, then prepare and submit final printed copy.

Justina A. Molzon

/S/

6-18-91

cc:
HFD-638
JMolzon/YMille
np/6-18-91
73045R
REVIEW

/S/

7/6/19/91