

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75-111

CORRESPONDENCE



March 24, 1999

Office of Generic Drugs, HFD 600
Attn: Mr. Douglas Sporn
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 286
Rockville, Maryland 20855-2773

ANDA ORIG AMENDMENT

N/A/M

Re: **ANDA #75-111**
Ipratropium Bromide Inhalation Solution, 0.02%

MINOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR §314.96(a), Alpharma, U.S. Pharmaceuticals Division hereby submits an amendment to our pending abbreviated new drug application. Reference is made to the Agency's December 24, 1998 deficiency letter (attached) regarding our April 11, 1997 abbreviated new drug application for Ipratropium Bromide Inhalation Solution, 0.02%. The Agency's comments have been restated and Alpharma's response follows.

This application is deficient and, therefore, not approvable under 21 CFR 314.125(b) (13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging or holding of the drug product comply with current good manufacturing practice (cGMP) regulations.

We have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated new drug application.

Until such time as it can be demonstrated to the Agency that the cGMP-related issues associated with the Alpharma facility have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

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Alpharma USPD Inc.

Research & Development Center
Johns Hopkins Bayview Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Tel (410) 558-7250
Fax (410) 558-7258

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GENERIC DRUGS

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It is Alpharma's understanding that the Baltimore District Office of the FDA has issued notification to CDER that Alpharma's Baltimore, Maryland facility has now been found to be in compliance with current good manufacturing practice (cGMP) regulations. It is also Alpharma's understanding that the Baltimore District Office of the FDA has recommended approval for this pending abbreviated new drug application.

We trust that our responses fully address the Agency's concerns.

Sincerely,

Alpharma USPD Inc.

A handwritten signature in black ink, appearing to read "Ronald Bynum" with a stylized flourish at the end.

Ronald Bynum
Manager, Regulatory Affairs

RB/rb
Enclosures

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. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

R. Patel 12/22/11

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

October 16, 1998

Office of Generic Drugs, HFD 600
Attn: Mr. Douglas Sporn
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 286
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N / FA

Re: **ANDA #75-111**
Ipratropium Bromide Inhalation Solution, 0.02%

**FACSIMILE AMENDMENT TO A PENDING APPLICATION
RESPONSE TO MICROBIOLOGY DEFICIENCIES**

Dear Mr. Sporn:

Pursuant to 21 CFR §314.96(a), Alpharma, U.S. Pharmaceuticals Division hereby submits a facsimile amendment to our pending abbreviated new drug application. Reference is made to the Administration's letter of October 9, 1998 (attached), our abbreviated new drug application dated April 11, 1997 and our amendments dated February 19 and June 8, 1998. The Administration's comments have been restated and Alpharma's responses follow.

Microbiological Deficiencies:

1. **The intention of the media fill is to validate/qualify production conditions via process simulation, i.e., downtimes due to breaks, stoppages, repairs, etc. and to demonstrate that the process is always in control. This includes environmental reporting. The media fill should be a reflection of the duration of production time and the filled units that will occur as the result of a full production lot. The microbial limits that you have set for production should be maintained during the media fill. Environmental monitoring during the media fill is not for "information only". It is part of the validation of your process. If limits are exceeded, procedures for out-of-limit conditions should be initiated.**
 - a. **You should revise the media fill procedure to reflect the controls and standards established for production.**

Please be advised that the media fill procedure has been revised to reflect controls and standards for environmental monitoring established for production (pages 04-30). Please note that this revised SOP was

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GENERIC DRUGS

previously submitted as pages 4-30 of our 6/8/98 amendment. The previous revision of (G, date effective 12/19/97) was submitted as pages 079-104 of our 2/19/98 major amendment.

b. You should provide a current media fill including environmental monitoring with the above considerations.

Enclosed as pages 31-35 is a current media fill which includes environmental monitoring that reflects the controls and standards established for production. Please note that this media fill data was previously submitted as pages 32-36 of our 6/8/98 amendment.

2. Please indicate if the spore population, D values, etc. as provided by the manufacturer [SPORDEX®] were confirmed. Discrepancies in spore population and D values can occur.

The manufacturer's label claims were confirmed in accordance with Standard Operating Procedure for the Qualification of Biological Indicator's, Enclosed is a copy of SOP-5-43) and data for SPORDEX®, lot SS116A (pages 44-70). Please note that SS116A is the lot of biological indicators used in the experiments that validated the .cles.

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

Sincerely,
Alpharma, USPD


Ronald Bynum
Manager, Regulatory Affairs

RB/fm
Enclosures



Ipratropium Bromide Inhalation
Solution, 0.02%
ANDA 75-111

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

Ronald Bynum 10/16/98

Ronald Bynum
Manager, Regulatory Affairs

OCT 9 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-111

APPLICANT: ALPharma, USPD

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution

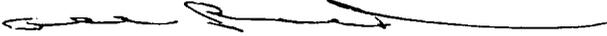
The deficiencies presented below represent FACSIMILE deficiencies.

Microbiology Deficiencies:

1. The intention of the media fill is to validate/qualify production conditions via process simulation, i.e., downtimes due to breaks, stoppages, repairs, etc. and to demonstrate that the aseptic process is always in control. This includes environmental reporting. The media fill should be a reflection of the duration of production time and the filled units that will occur as the result of a full production lot. The microbial limits that you have set for production should be maintained during the media fill. Environmental monitoring during the media fill is not for "information only". It is part of the validation of your process. If limits are exceeded, procedures for out-of-limit conditions should be initiated.
 - a. You should revise _____ to reflect the controls and standards established for production.
 - b. You should provide a current media fill including environmental monitoring with the above considerations.
2. Please indicate if the spore population, D values, etc. as provided by the manufacturer[SPORDEX^R] were confirmed. Discrepancies in spore population and D values can occur.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,


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

June 8, 1998

NDA ORIG AMENDMENT

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

N/AC

**Re: ANDA 75-111
Ipratropium Bromide Inhalation Solution, 0.02%**

AMENDMENT TO 2/19/98 MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR § 314.96(a), Alpharma, U.S. Pharmaceuticals Division hereby submits an amendment to our 2/19/98 major amendment to a pending abbreviated new drug application.

The Administration requested in Alpharma's [redacted] for [redacted] [redacted] Solution, 0.083%, (comment letter dated 3/27/98) that [redacted] [redacted]'s (Alpharma's proposed contract manufacturer), Standard Operating Procedure ([redacted] for the [redacted] of Media Fills be revised and media fill data be submitted. As [redacted] is relevant to this abbreviated new drug application, the requested information is being submitted at this time.

Please be advised that [redacted] has been revised to reflect controls and standards for environmental monitoring established for production. Additional revisions have also been implemented (attachment 1). The previous revision of [redacted] (effective 12/19/97) was submitted as pages 079-104 of our 2/19/98 major amendment.

Enclosed as attachment 2 is a media fill which includes environmental monitoring that reflects the controls and standards established for production.

Sincerely,


Ronald Bynum
Manager, Regulatory Affairs

RB:fm
Enclosures

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Ipratropium Bromide Inhalation
Solution, 0.02%
ANDA 75-111

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

Ronald Bynum 6/8/98

Ronald Bynum
Manager, Regulatory

*FPL needs
revisions
Call Log 4/17/98*

February 19, 1998

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

ORIG AMENDMENT
FPL
AC

Re: **ANDA 75-111**
Ipratropium Bromide Inhalation Solution, 0.02%

MAJOR AMENDMENT INCLUDING RESPONSE TO MICROBIOLOGY AND LABELING DEFICIENCIES

Dear Mr. Sporn:

Pursuant to 21 CFR § 314.96(a), Alpharma, U.S. Pharmaceuticals Division hereby submits a major amendment to our pending abbreviated new drug application. Reference is made to the Administration's facsimile dated September 22, 1997 regarding the above-referenced product application (attached). The Administration's comments have been restated and Alpharma's responses follow.

Chemistry Deficiencies

A. Deficiencies

1.

2.

...related substance whether chemically...

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GENERIC DRUGS

Page(s)

7

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

2/19/98

... in
... Attachment 13 "Performance of Rl

LABELING DEFICIENCIES:

General Comment: The description of the container closure system on page 508 of this submission, indicates an area available for labeling or engraving on the vial card. Please identify what will be engraved in this area.

The area indicated will be engraved with the following, "I FOR ORAL INHALATION ONLY Sterile I" as shown in the final printer's proof labeling of the unit dose ampule (page 117).

The unit dose ampule, foil wrap, carton, leaflet and insert labeling has been revised as requested by the Administration. We have added an additional package size of 120 ampules. Enclosed as attachment 14 are the following:

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

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

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

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

Sincerely,
Alpharma USPD Inc.


Ronald Bynum
Manager, Regulatory Affairs
RB:va:fm
Enclosures



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

Ronald Bynum 2/19/98

Ronald Bynum
Manager, Regulatory Affairs

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-111

APPLICANT: ALPharma, USPD

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution, 0.027,

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. of is inadequate. Please request them to respond to all outstanding deficiencies communicated in the recent FDA letter.
2. We have the following comments regarding the drug substance:
 - a. Your specification for total related substances of is excessive. We request a tighter specification. In addition, we request specifications for each individual related substance whether chemically identified or not.
 - b. Please revise your controls for Ipratropium Bromide drug substance to include test methods and specifications for melting point and heavy metals.
 - c. Please submit supporting analytical data for the qualification of your in-house Reference Standard (lot # IPRI494) including structure elucidation.
3. Please provide test results for USP <87> for Biological Reactivity Tests, In-Vitro for the used for the vial. USP <88> are alternatively acceptable.
4. Please revise your release and stability specifications of the drug product to include limits for individual unidentified impurities/degradants.
5. Please include an APHA test and specification for monitoring the color of the drug product for its release and stability. Alternatively, you may correlate your color test with the APHA scale.
6. Your specification for Tropic Acid for the stability of the drug product is excessive. Please tighten it.
7. Please revise your stability specifications for the drug product to include vial weight loss during shelf-life. Also, please submit your test method.
8. Please submit your revised release and stability specifications for the drug product and acceptance specifications for the drug substance to include revisions requested in this letter.

Microbiology Comments to be Provided to the Applicant

**ANDA: 75-111 APPLICANT: Alpharma,
U.S. Pharmaceuticals Division**

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution 0.02%

A. Microbiology Deficiencies:

1. The manufacturing area of your facility was not described in terms of the subject drug product. The rooms [filling rooms] intended to be use for manufacture of Ipratropium Bromide Inhalation Solution were not identified [Page 170]. The air cleanliness classes of these filling rooms and surrounding areas should be provided. Pressure differentials should also be clearly described.
2. The action level for bioburden in the bulk drug solution was stated to be [page 462]. The proposed upper limit is much too high. Limit specifications should be set using historical data. You should lower the action limit specification accordingly.
3. Describe the cycle parameters used to validate the production for the machine, mixing tanks and product transfer lines.
4. Describe the biological indicators (BI's) used in experiments that validated the production Include type of bacterium, vendor, viable count, lot number(s) used and heat resistance parameters [D value, Z value].
5. Submit a copy of your container/closure microbial integrity test procedure for review. A data summary of the experiment that demonstrated the microbial integrity of the 3.2 mL vials with twist-off caps should also be submitted.
6. The acceptance criterion employed in the pre-production process simulation tests, i.e., contamination rate less than was acceptable [pages 236-237]. However, the Division does not concur with the action levels [numbers of contaminated test units] required for media fill failure as found in Table 3 [page 238]. In principle, the number of contaminated test units for media fills should approach zero (0), regardless of fill size. The Division certainly considers this to be the case for an advanced manufacturing process, such as that excludes personnel from the filling area.

7. The results of environmental monitoring for the media fills described on page 216 should be submitted.
8. The results of Bacteriostasis/Fungistasis testing for the subject drug product should be submitted for review.

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

Sincerely yours,



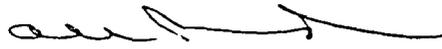
Rashmikant M. Patel, Ph.D.

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

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

1. The cGMP compliance of all 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 for methods validation will be requested at a later date once the testing issues have been resolved.
3. Please be advised that an approved supplement is needed to change your analytical methods submitted in this ANDA regardless of change that may happen in the European Pharmacopeia.
4. Please submit the currently available room temperature stability data for the exhibit batch. Please include data for all tests requested in this letter at the next station.
5. Microbiological and Labeling deficiencies will also need to be addressed in your reply.

Sincerely yours,

 9/19/27

2.
Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Microbiology Comments to be Provided to the Applicant

**ANDA: 75-111 APPLICANT: Alpharma,
U.S. Pharmaceuticals Division**

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution 0.02%

A. Microbiology Deficiencies:

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

Sincerely yours,



Rashmikant M. Patel, Ph.D.

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

Labeling review
completed
C. Hestquist 5/30/97

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April 11, 1997

APR 14 1997

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

GENERIC DRUGS

505(j)(2)(a)(ol)
Aurora Marie Hill Weikel
5/9/97

**Re: Abbreviated New Drug Application
Ipratropium Bromide Inhalation Solution, 0.02%**

Dear Mr. Sporn:

We are herewith submitting an Abbreviated New Drug Application pursuant to 21 CFR §314.94(a) and Section 505(j) of the Federal Food, Drug and Cosmetic Act for the drug product Ipratropium Bromide Inhalation Solution, 0.02%.

The abbreviated application is being submitted as follows:

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

Sincerely,



Vincent Andolina
Sr. Manager, Regulatory Affairs