CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75014

CORRESPONDENCE

ANDA 75-014

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

OCT 7 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 3, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Permethrin Lotion, 1%.

Reference is also made the to Agency's refuse to file letter of February 13, 1997, and the meeting held on March 26, 1997.

The Division of Bioequivalence has reviewed the June 4, 1997, data submitted regarding *ex vivo* studies for permethrin lotion 1%.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> The design of the study used is inadequate to establish bioequivalency.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

If appropriately designed, an *ex-vivo* study may be accepted. The Division of Bioequivalence is suggesting the following design:

1. The exposure method should mimic the *in vivo* situation.

2. The evaluation of the effect of permethrin should include nymphs and adults separately using a standardized louse colony or colonies.

3. Compare the dose-response curves (reproducible ldp lines - log-dose probit mortality curves, a standard method used to compare the toxicity of pesticides in insects) for test and reference products.

4. The evaluation time allowed for mortality of nymphs and adults should be for a duration longer than one hour (preferably 4 hours).

5. The effect of pre-treatment hair wash (dilution) on the effectiveness of the products should be compared.

6. Since permethrin is stable and quite lipophilic in nature, it may exhibit residual activity even after washing. Therefore, any differences in residual ovicidal or pediculicidal activity of the formulations should be determined.

Additional note:

The site of the *ex-vivo* study should be such that it complies with good clinical practices, and data submitted are verifiable. Pivotal study data for another Alpharma another product, permethrin cream, 5% (ANDA 74-806), was found to be non-verifiable.

If you have any questions regarding this issue, please contact Lizzie Sanchez, in the Division of Bioequivalence at (301) 827-5847.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions please call:

Saundra T. Middleton

Project Manager
(301) 827-5862

Sincerely yours,

/S/

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

ANDA 75-014

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

FEB 23 1999

Dear Sir:

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

Reference is also made to our "Refuse to File" letter dated October 7, 1997, and your amendments dated December 30, 1998 and February 9, 1999.

NAME OF DRUG: Permethrin Lotion, 1%

DATE OF APPLICATION: December 3, 1996

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 4, 1999

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

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

Should you have questions concerning this application contact:

Joe Buccine
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 75-014

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

FEB 13 1997

RECEIVED FEB 18 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 3, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Permethrin Lotion, 1%.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have included a change in the composition to include a significantly greater content of the inactive ingredients, protein hydrolysate and hydroxyethyl cellulose, than has been previously approved in a topical drug product [21 CFR 314.127(a)(8)(ii)(A)(6). Please reformulate your product.
>
> In addition, you request approval of a formulation other than the formulation used in your *in vivo* bioequivalence study. Please be advised that it is necessary to submit a new *in vivo* bioequivalence study to obtain approval of an alternate formulation. If you have any questions regarding this issue, please contact Lizzie Sanchez, in the Division of Bioequivalence at 301-594-2290.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, please evaluate the concentration of propylene glycol in your proposed formulation. The concentration of propylene glycol should be the same as that of the reference listed drug. Propylene glycol is known to be an absorption enhancer and may increase the absorption of the active ingredient.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions please call:

Cecelia Parise

Project Manager
(301) 594-0315

Sincerely yours,

/S/

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

ALPHARMA
U.S. Pharmaceuticals Division

Click for Filing
S. Middleton
2/23/99

December 30, 1998

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

Re: **ANDA #75-014**
Permethrin Lotion, 1%
RESPONSE TO REFUSE TO FILE LETTER

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application. This amendment consists of three volumes. Reference is made to the Agency's "Refuse To File Letter" of October 7, 1997 and to our drug application dated December 3, 1996.

In order to respond to the October 7, 1997 letter, the Agency's comments have been restated and our responses follow.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

The design of the study used is inadequate to establish bioequivalency.

Thus it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

If appropriately designed, an *ex-vivo* study may be accepted. The Division of Bioequivalence is suggesting the following design:

1. The exposure method should mimic the *in vivo* situation.

RECEIVED
JAN 0 4 1999
GENERIC DRUGS

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

2. **The evaluation of the effect of permethrin should include nymphs and adults separately using a standardized louse colony or colonies.**

3. **Compare the dose-response curves (reproducible ldp lines - log-dose probit mortality curves, a standard method used to compare the toxicity of pesticides in insects) for test and reference products.**

4. **The evaluation time allowed for mortality of nymphs and adults should be for a duration longer than one hour (preferably 4 hours).**

5. **The effect of pre-treatment hair wash (dilution) on the effectiveness of the products should be compared.**

6. **Since permethrin is stable and quite lipophilic in nature, it may exhibit residual activity even after washing. Therefore, any differences in residual ovicidal or pediculicidal activity of the formulations should be determined.**

Alpharma acknowledges the Agency's suggestions pertaining to an adequate design for an *ex-vivo* study. Upon evaluation of the Agency's concerns, Alpharma determined that the best approach for demonstrating bioequivalence would be to repeat the bioequivalence study for this drug product. Since the bioequivalence study was to be repeated, Alpharma also re-evaluated the Agency's previous concerns pertaining to the proposed drug product formulation that were expressed in the February 13, 1997 Refuse-To-File letter. Based on the re-evaluation of the formulation concerns, Alpharma revised its drug product formulation to be a quantitative match to the listed drug. This revised drug product formulation was then used to repeat the bioequivalence study.

Information pertaining to the revised drug product formulation and the repeated bioequivalence study are provided within this response. Within this amendment, we have identified when information has changed relative to the information previously submitted. In the instances where information has not changed, the information previously submitted in our December 3, 1996 ANDA and June 4, 1997 amendment remains applicable and is not resubmitted in this amendment. It should also be noted that the drug product names "Permethrin Lotion, 1%" and "Permethrin Creme Rinse 1%" are synonymous and have been used interchangeably throughout this amendment.

Additional note:

The site of the *ex-vivo* study should be such that it complies with good clinical practices, and data submitted are verifiable. Pivotal study data for

another Alpharma another product, permethrin cream, 5% (ANDA 74-806), was found to be non-verifiable.

Alpharma acknowledges that study sites should be in compliance with good clinical practices and the submitted data should be verifiable. It is worth noting that the study site for the other Alpharma drug product referenced above, ie., Permethrin Cream, 5%, ANDA #74-806, was inspected by FDA during August 1997 and the site was found to be in compliance with good laboratory practices and the data were found to be verifiable (page 002). In conjunction with these findings, ANDA #74-806 was approved by FDA on January 23, 1998.

We trust that the contents of this amendment will adequately address the Agency's concerns and we look forward to OGD filing the application pursuant to section 505(j) of the Act.

Pursuant to 21 CFR 314.96(b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA's Atlanta District Office.

Sincerely,
Alpharma USPD

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs

RB/rb
Enclosure

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ALPHARMA
U.S. Pharmaceuticals Division

September 29, 1999 **FACSIMILE AMENDMENT TO A PENDING APPLICATION**

CDER, FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Douglas Sporn, Director

Re: Permethrin Lotion 1%
ANDA #75-014

Dear Mr. Sporn:

Alpharma U.S. Pharmaceuticals Division hereby submits a Facsimile Amendment to our pending Abbreviated New Drug Application for Permethrin Lotion 1%. Reference is made to the Agency's letter dated September 24, 1999 regarding the above-referenced product application.

Alpharma has responded completely and comprehensively to each question posed by the Agency in the order that it was presented in the aforementioned letter.

For ease of reference, your questions or comments should be addressed to Martin Levy, Director of Regulatory Affairs at Alpharma. My contact telephone number is 410-558-7250 ext. 205 and my fax number is 410-558-7262.

Sincerely,
ALPHARMA USPD INC.

Martin Levy

Martin Levy, FBIRA
Director, Regulatory Affairs

ML:ckj

Enclosures

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Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

July 16, 1999 **FACSIMILE AMENDMENT TO A PENDING APPLICATION**

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn.: Douglas Sporn, Director

RE: **ANDA #75-014**
Permethrin Lotion, 1%

Dear Mr. Sporn:

Alpharma U.S. Pharmaceuticals Division hereby submits a Facsimile Amendment to our December 3, 1996 abbreviated new drug application.

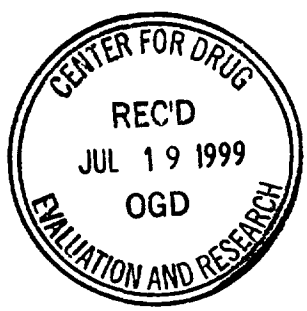
This amendment responds to the Agency's communication of June 17, 1999. The applicant has responded, completely and comprehensively, to the Agency questions in the order that they were asked.

For ease of reference, please contact Martin Levy, Director of Regulatory Affairs should you have any additional questions or comments concerning this file. I can be reached at 410-558-7250 ext. 205 or by fax at 410-558-7262.

Yours sincerely,
ALPHARMA USPD INC.

Martin Levy

Martin Levy, FBIRA
Director, Regulatory Affairs



ML:rb
Enclosures

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Alpharma USPD Inc.
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Johns Hopkins Bayview Campus
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Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

February 29, 2000 MINOR AMENDMENT TO A PENDING APPLICATION

FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Douglas Sporn, Director

N/A 4

RE: ANDA 75-014
Permethrin Lotion, 1%

Dear Mr. Sporn:

In response to the December 20, 1999 minor action letter concerning certain aspects of our container/closure system used for this product, Alpharma is pleased to forward our responses.

First, we would like to correct a misimpression that Paul Bank's letter of December 1st may have left with certain Agency officials. It is clear that the fluorination process creates a "coating-like" layer of fluorine ions to a depth of 0.2 microns [personal communication Fluoro-Seal]. It is not a process that produces a new plastic or material. Therefore, we did not previously submit information to "qualify this new resin" as no new resin is created. Mr. Bank's comment that fluorinated HDPE can be recycled as HDPE is consistent with this understanding.

In addition to the fact that the fluorination process does not, in our vendor's opinion, create a new resin, the acceptability of our container is supported by evidence that fluorinated HDPE bottles are already used by liquid drug manufacturers regulated by the Agency. We have identified Block Drug's Phazyme® Infant Drops and Pfizer's RID® Shampoo (a naturally derived pediculicide) as two such products. We are enclosing a letter from Block Drug supporting this understanding. Although we could not obtain a similar letter from Pfizer, Alpharma conducted a study, "Bottle Comparison for Permethrin Lotion and Maximum Strength RID Drug Products" as scientific evidence that our bottle is identical to the RID® bottle.

Both of the aforementioned products are OTC monographed products. A history of safe use as a container for RID® Shampoo, a liquid drug product chemically related to Permethrin Lotion, supports the acceptability of our identical container. Some fluorinated bottles of RID shampoo have been sold in the United States in 1999 data) and a total of bottles have been sold in the United States since 1995. The OTC regulations requires OTC monograph products to meet the following condition:

> The product container and container components meet the requirements of §211.94 [of the GMP regulations]. 21 C.F.R. §330.1(f)

The GMP regulations (§211.94) in turn require product containers to meet standards for reactivity, absorption, protection and so forth. Thus, although the RID container may not have been approved

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The Johns Hopkins Bayview Center
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through an NDA or ANDA, it is directly regulated by the FDA, and a history of safe use and acceptability for RID should be deemed adequate evidence to support use with the closely related drug Permethrin Lotion.

The suitability of our container is further supported by data showing that it protects the drug product, is compatible with the drug product, and is safe for use. We have provided additional confirmatory data in this submission. Significantly, our study of the level of residual fluoride detected in room temperature stability samples of our drug product shows that our container is acceptable under the Agency's indirect food additive approval for fluorinated polyethylene food-contact articles. 21 C.F.R. §177.1615. This approach to demonstrating the safety of the container is directly suggested by the Agency's container/closure guidance (May 1999). Supportive data from physicochemical and biological reactivity testing is also provided in this submission.

In terms of the lot to lot variability in the fluorination process, we attach a letter from Mr. Paul Banks of February 28, 2000 which notes that there is a quality assurance program in force at . that assures lot to lot consistency.

These data, coupled with the preexisting use of an identical container for a chemically related drug product regulated and accepted by the Agency, provide a more than adequate basis to approve our container for our drug product.

With regard to widespread use of use fluorinated bottle by other manufacturers, the container/closure guidance (May 1999) specifically says, "A packaging system found acceptable for one product is not automatically assumed to be appropriate for another." Other drug manufacturers will have to support their specific use of their container with appropriate evidence.

Should you have any questions on the content of this letter, please do not hesitate to contact me at (410) 277-1742.

Yours sincerely,
ALPHARMA USPD INC.

Martin Levy, FBIRA
Director, Regulatory Affairs

ALPHARMA
U.S. Pharmaceuticals Division

December 1, 1999 **TELEPHONE AMENDMENT TO A PENDING APPLICATION**

FOOD AND DRUG ADMNINISTRATION
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Douglas Sporn, Director

FA

RE: ANDA 75-014
Permethrin Lotion, 1%

Dear Mr. Sporn:

In response to the November 30 inquiry by Cpt. Joe Buccine and Dr. Paul Schwartz concerning certain aspects of our container/closure system used for this product, Alpharma is pleased to forward our responses.

Specifically, we have attached two attachments to this letter that answers their questions completely and comprehensively. Attachment one is a letter from a representative of (the vendor that applies the fluorination to the HDPE bottle) which address the questions of the Agency whilst Attachment two is a study conducted by Alpharma that investigates the concentration of ionic fluoride in the drug product. Please be aware that L410075 was a packaging lot that was not fluorinated and L604076 was fluorinated. We show that the ionic concentration is not detectable in the drug product, and therefore this process has not affected drug quality.

Alpharma wishes to withdraw the Packaging Interchangeability Protocol which appears in Section XIV (5) [page 14054] of our submission.

Should you have any questions on the content of this letter, please do not hesitate to contact me at (410) 558-7250 extension 205.

Yours sincerely,
ALPHARMA USPD INC.

Martin Levy, FBIRA
Director, Regulatory Affairs

DEC 02 1999

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

October 21, 1999 **TELEPHONE AMENDMENT TO A PENDING APPLICATION**

FOOD AND DRUG ADMNINISTRATION
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Douglas Sporn, Director

NDA ORIG AMENDMENT
N/FA

RE: ANDA 75-014
Permethrin Lotion, 1%

Dear Mr. Sporn:

In response to the October 21 inquiry by Cpt. Joe Buiccine concerning comments from the Philadelphia District Laboratory, Alpharma is pleased to forward our responses.

Should you have any questions on the content of this letter, please do not hesitate to contact me at (410) 558-7250 extension 205.

Yours sincerely,
ALPHARMA USPD INC.

Martin Levy, FBIRA
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 22 1999
DGD

Alpharma USPD Inc.
Research & Development Center
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Baltimore, MD 21224
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ALPHARMA
U.S. Pharmaceuticals Division

Permethrin Lotion, 1%
ANDA # 75-014
Alpharma USPD Inc.

October 7, 1999 **TELEPHONE AMENDMENT TO A PENDING APPLICATION**

CDER, FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Douglas Sporn, Director

FA

Re: Permethrin Lotion 1%
ANDA #75-014

Dear Mr. Sporn:

Reference is made to the October 6, 1999 telecommunication between myself and Lillie Golson pertaining to Alpharma U.S. Pharmaceuticals Division's facsimile amendment dated 9/24/99 submitted to our pending Abbreviated New Drug Application for Permethrin Lotion 1%.

As requested by the Agency, we are submitting 12 copies of printer proofs for the container and the cartons (1 x 59 mL and 2 x 59 mL).

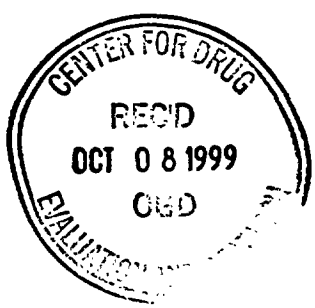
For ease of reference, your questions or comments should be addressed to Martin Levy, Director of Regulatory Affairs, at Alpharma. My contact telephone number is 410-558-7250 ext. 205 and my fax number is 410-558-7262.

Sincerely,
ALPHARMA USPD INC.

Martin Levy

Martin Levy, FBIRA
Director, Regulatory Affairs
ML:ckj

Enclosures



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Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

October 15, 1999 **TELEPHONE AMENDMENT TO A PENDING APPLICATION**

CDER, FOOD AND DRUG ADMINISTRATION
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Douglas Sporn, Director

NDA ORIG AMENDMENT
N/FA

Re: Permethrin Lotion 1%
ANDA #75-014

Dear Mr. Sporn:

Reference is made to the October 15, 1999 telecommunication between myself and Lillie Golson pertaining to Alpharma U.S. Pharmaceuticals Division's facsimile amendment dated 9/24/99 submitted to our pending Abbreviated New Drug Application for Permethrin Lotion 1%.

As requested by the Agency, we are submitting 12 copies of printer proofs for the professional labeling.

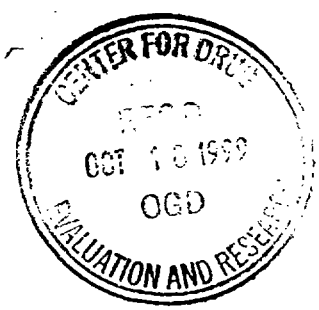
For ease of reference, your questions or comments should be addressed to Martin Levy, Director of Regulatory Affairs, at Alpharma. My contact telephone number is 410-558-7250 ext. 205 and my fax number is 410-558-7262.

Sincerely,
ALPHARMA USPD INC.

Martin Levy

Martin Levy, FBIRA
Director, Regulatory Affairs
ML:ckj

Enclosures



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Baltimore, MD 21224
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ALPHARMA
U.S. Pharmaceuticals Division

October 21, 1999 **TELEPHONE AMENDMENT TO A PENDING APPLICATION**

FOOD AND DRUG ADMNINISTRATION
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Douglas Sporn, Director

NDA ORIG AMENDMENT
N/FA

RE: ANDA 75-014
Permethrin Lotion, 1%

Dear Mr. Sporn:

In response to the October 21 inquiry by Cpt. Joe Buiccine concerning comments from the Philadelphia District Laboratory, Alpharma is pleased to forward our responses.

Should you have any questions on the content of this letter, please do not hesitate to contact me at (410) 558-7250 extension 205.

Yours sincerely,
ALPHARMA USPD INC.

Martin Levy, FBIRA
Director, Regulatory Affairs

OCT 22 1999

Alpharma USPD Inc.

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

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

ALPHARMA
U.S. Pharmaceuticals Division

June 4, 1997

ORIG AMENDMENT
N/A
BIOAVAILABILITY

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

Re: **ANDA #75-014**
Permethrin Lotion, 1%
RESPONSE TO REFUSE TO FILE LETTER

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application. This amendment consists of one volume. Reference is made to the Administration's "Refuse To File Letter" of February 13, 1997 and to our drug application dated December 3, 1996. Reference is also made to our meeting of March 26, 1997 with representatives from the Office of Generic Drugs.

Before we respond to the questions in the February 13, 1997 letter, it is important to provide clarification about the formulation revision in relation to the *in vivo* clinical study. Alpharma provides the following explanation for the changes initiated in this drug product prior to submission of the ANDA. An *in vivo* equivalency study with a formulation containing % cetyl alcohol and the innovator's product containing % cetyl alcohol was conducted (pages 06 052 to 06 291 of our December 3, 1996 ANDA submission). The study demonstrated equivalency between the two drug products with regard to safety and efficacy.

Subsequent to the equivalency study, Alpharma determined that a % cetyl alcohol formulation was superior to the % cetyl alcohol formulation in maintaining long term chemical stability of the drug product.

Alpharma revised its formulation to match the % cetyl alcohol content in the innovator drug product and changed its container to a fluorinated bottle in order to achieve long term stability of the drug product.

RECEIVED
JUN 0 6 1997
GENERIC DRUGS

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

In order to link the *in vivo* clinical study data from the % cetyl alcohol formulation to the % cetyl alcohol formulation, Alpharma conducted an ex vivo (in vitro) bridging equivalency study (pages 06 292 to 06 308 of our December 3, 1996 ANDA submission). The ex vivo (in vitro) bridging study was conducted on patients selected from a population in the same geographical location so as to provide subjects similar to those used in the *in vivo* equivalency study. The ex vivo (in vitro) bridging study utilized the Alpharma drug product formulation with % cetyl alcohol, the innovator drug product which also contains % cetyl alcohol, and the Alpharma drug product formulation with % cetyl alcohol. The ex vivo (in vitro) bridging study confirmed similar efficacy for the Alpharma drug product formulation containing % cetyl alcohol and the innovator drug product, thereby linking the % cetyl alcohol formulation to the *in vivo* clinical study by means of comparative data to the innovator drug product.

It is important to note that the sites of action of this topical drug product are the lice and their eggs, both of which are external to the patient.

Despite the change in cetyl alcohol concentration from %, quantitative differences between the test and reference drug products remain. These differences were listed in the "Comparative Quantitative Composition Statement" that was previously provided as page 07 005 of our December 3, 1996 ANDA submission. Further comparison of the inactive ingredients was listed and characterized in the "Permethrin Creme Rinse, 1% Q1/Q2 AND IIG Comparison With Reference Listed Drug" table that was previously provided as pages 07 009 to 07 011.

During the March 26, 1997 meeting with OGD, a question was raised as to the timing of receipt of information relative to the quantitative analysis of the reference listed drug product. We have prepared a chronology of events pertaining to the development of our drug product and this report is enclosed as pages 02-06. The chronology report details when decisions were made and provides the rationale for those decisions.

In order to respond to the February 13, 1997 letter, the Administration's comments have been restated and our responses follow.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> **You have included a change in the composition to include a significantly greater content of the inactive ingredients, protein hydrolysate and hydroxyethyl cellulose, than has been previously approved in a topical drug product [21 CFR 314.127(a)(8)(ii)(A)(6). Please reformulate your product.**

21 CFR 314.94(a)(9)(v) allows an applicant to seek approval of a topical "drug product that differs from the reference listed drug, provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product."

The December 24, 1996 letter from Mr. Douglas Sporn (Director, OGD, CDER, FDA) to all applicants indicates that if the level of an inactive ingredient in the reference listed drug is not listed in the CDER Inactive Ingredient Guide (IIG), "the sponsor may also refer to other sources of information, such as other approved topical products where quantitative levels are known, recognized literature references or information from the ingredient manufacturer." (APPLICATION PROCESS ISSUES section, Refusal to File Issues subsection, B. Inactive Ingredient Issues sub-subsection, 2. Quantitative Statement sub-sub-subsection, pages 10-11 of the December 24, 1996 letter).

Thus, both the regulations and current OGD policy allow for use of inactive ingredients at levels other than that used in the reference listed drug, providing that information supporting the safe use of the inactive ingredient at the proposed level is provided.

Pages 07 007 to 07 011 of our December 3, 1996 ANDA submission provided comparative inactive ingredient information for the reference listed drug and our proposed drug product. Information from the IIG and other sources were provided to demonstrate safety at the proposed levels for the inactive ingredients in the test drug product.

In addition, we are now submitting an evaluation of the safety of hydroxyethyl cellulose and hydrolyzed animal protein for the levels in our proposed drug product (pages 07-29). The safety report was compiled by toxicological consulting firm. The safety report concludes that the proposed levels of hydroxyethyl cellulose and hydrolyzed animal protein in our drug product pose "a *de minimus* toxicological risk" to the patient. Therefore, the quantitative differences between the test and reference listed drug products do not impact or will not affect the safety profile of the test drug product. Please note that this same report also discusses the use of propylene glycol, in response to the final concern expressed in the February 13, 1997 Refuse To File Letter. A copy of several of the literature references and additional information is provided for review (pages 30-75).

In addition, you request approval of a formulation other than the formulation used in your *in vivo* bioequivalence study. Please be advised that it is necessary to submit a new *in vivo* bioequivalence study to obtain approval of an alternate formulation. If ... at 301-594-2290.

Pages 06 002 to 06 010 of our December 3, 1996 ANDA submission provided drug product information and comparative information for both the *in vivo* and ex vivo (in vitro) bridging bio studies (in which the proposed drug product formulation contained a cetyl alcohol concentration of % and %, respectively). We have prepared an additional explanation for the change in formulation and a comparison of the *in vivo* and the ex vivo (in vitro) bridging study (pages 76-80). The conclusion of the report is that whether the proposed drug product contains % cetyl alcohol or % cetyl alcohol, its pediculicidal and ovicidal activities are as good as or better than those of the reference listed drug product.

Please note that complete information on the drug product batch containing % cetyl alcohol, that was used in the *in vivo* clinical study, was submitted as pages 22 001 to 22 142 of our December 3, 1996 application. This information included raw material records, executed drug product batch records, drug product batch certificate of analysis, and stability data.

We maintain that for topical drug products, *in vivo* studies are not the only models available for bioequivalency determination. Alternate methodologies, such as the ex vivo (in vitro) bridging study, are appropriate for determining bioequivalency, and/or as in this case, an ex vivo (in vitro) study can be used as a bridging study to the *in vivo* study.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Based on the regulations, current OGD policy, our March 26, 1997 meeting with OGD, and this amendment, we request that our December 3, 1996 application be filed as an abbreviated new drug application within the meaning of Section 505(j) of the ACT.

In addition, please evaluate the concentration of propylene glycol in your proposed formulation. The concentration of propylene glycol should be the same as that of the reference listed drug. Propylene glycol is known to be an absorption enhancer and may increase the absorption of the active ingredient.

As mentioned above, both the regulations and current OGD policy allow for use of inactive ingredients at levels other than that used in the reference listed drug, providing that information supporting the safe use of the inactive ingredient at the proposed level is provided.

Pages 07 007 to 07 011 of our December 3, 1996 ANDA submission provided comparative inactive ingredient information for the reference listed drug and our proposed drug product. Information from the IIG was provided to demonstrate safety of propylene glycol at the proposed level in the test drug product.

In addition, we are now submitting an evaluation of the penetration enhancing capability and safety of propylene glycol for the level in our proposed drug product (pages 07-29). This report was compiled by toxicological consulting firm. The report concludes that the proposed level of propylene glycol in our drug product will not enhance penetration of permethrin or the other ingredients of the proposed drug product. Since concentrations of greater than % are required for propylene glycol to act as a penetration enhancer, the use of % propylene glycol in the test drug product will not affect the penetration of permethrin into the body. Please note that this same report also discusses the safety of hydroxyethyl cellulose and hydrolyzed animal protein, in response to the first concern expressed in the February 13, 1997 Refuse To File Letter. Additional literature references and a brief summary for the penetration enhacing capability of propylene glycol are provided for review (pages 81-84).

In conclusion, we believe that the data provided in this amendment provide an adequate characterization of the differences in inactive ingredients relative to the reference listed drug product and supports the fact that those differences do not affect the safety of the proposed drug product. In addition, Alpharma wishes to re-emphasize that the alternate testing methodologies employed for this application should be evaluated in the context of the review of the application and not dismissed prior to rigorous scientific review and debate. Alpharma believes that the ex vivo (in vitro) bridging study proposed and conducted to bridge the results of our *in vivo* study to the minor formulation revision has merit and should be accepted and evaluated by the agency.

We trust the contents of this amendment will adequately address the agency's concerns and we look forward to OGD filing the application pursuant to section 505(j) of the Act.

Pursuant to 21 CFR 314.96(b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA's Atlanta District Office.

Sincerely,
Alpharma

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs

RB/rb
Enclosure
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ALPHARMA
U.S. Pharmaceuticals Division

June 4, 1997

Mr. Ballard H. Graham
District Director
Food and Drug Administration
60 Eighth Street NE
Atlanta, GA 30309

RE: ANDA #75-014
Permethrin Lotion, 1%

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Graham:

In accordance with 21 CFR 314.96 (b), enclosed is a copy of the June 4, 1997 amendment to the application. Alpharma certifies that this field copy is a true copy of the technical section contained in the archival and review copies of the amendment to the application.

Sincerely,

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs

RB/rb

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

June 4, 1997

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Ms. Lizzie Sanchez
HFD-617
Metro Park North II
7500 Standish Place, Room E115
Rockville, Maryland 20855-2773

Re: ANDA #75-014
Permethrin Lotion, 1%

Dear Ms. Sanchez,

Per your request of March 26, 1997, Alpharma is providing a copy of the transparencies that Alpharma utilized during the March 26, 1997 meeting with representatives of the Office of Generic Drugs. The meeting was convened to discuss the Agency's February 13, 1997 Refuse To File letter for Alpharma's application for Permethrin Lotion, 1% (ANDA #75-014).

Sincerely,

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs
enclosure

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JUN 0 5 1997
GENERIC DRUGS

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Research & Development Center
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Baltimore, MD 21224
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Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

NEW CORRESP

NC

March 13, 1997

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

Re: **Permethrin Lotion, 1%**
ANDA #75-014

Dear Mr. Sporn:

This letter is to provide notification that Alpharma USPD hereby authorizes SRA International, Inc. to represent us as a consultant before the Food and Drug Administration in matters related to Permethrin Lotion, 1%; ANDA #75-014.

Sincerely,

Ronald Bynum

Ronald Bynum
Sr. Manager, Regulatory Affairs

RB:rb

MAR 17 1997

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ALPHARMA
U.S. Pharmaceuticals Division

December 3, 1996

Mr. Douglas Sporn, Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7200 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **Abbreviated New Drug Application**
Permethrin Creme Rinse 1%

DEC 0 5 1996

Dear Mr. Sporn:

Alpharma, U.S. Pharmaceuticals Division of Lincolnton, North Carolina[1] is 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 Permethrin Creme Rinse 1%.

The abbreviated application is being submitted as follows:

1) **Archival Copy** (Blue Folder) - consisting of two volumes which contains items required for an ANDA per 21 CFR § 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 USPD Inc. hereby certifies that a field copy that contains (a) a true copy of the technical section required by 21 CFR § 314.94(a)(9), (b) a copy of the 356h form, and (c) certification that this true copy of the technical section is the same as that contained in the archival and review copies, has been sent simultaneously to the Atlanta District Office.

[1]Please note, NASKA Pharmacal, Co., Inc. Lincolnton, NC, was acquired by Barre-National Inc. in March 1993. Barre-National's corporate name was officially changed to Alpharma, U.S. Pharmaceuticals Division in June 1996.

Research & Development Center
The Johns Hopkins Bayview Campus, 333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel (410) 558-7250 Fax (410) 558-7258

ALPHARMA™
U.S. Pharmaceuticals Division

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).

This ANDA contains the two additional copies of the methods validation section (Section XVI) which are required for drug products not found in the United States Pharmacopeia.

Sincerely,
Alpharma

Deborah Miran
Senior Director, Regulatory Affairs

DM:ah
Enclosures

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