CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-307

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 7, 2001 Number of Pages (including cover sheet) - 1

TO: Mary Williams, Associate Director, Regulatory Affairs
COMPANY: Schering-Plough HealthCare Products
FAX #: 908-679-1741

MESSAGE: Regarding our facsimile transmision of December 3, 2001, please commit to the following revised Post Marketing Commitment # 2 for NDA 21-307, Lotrimin Ultra butenafine hydrochloride Cream 1%.

2. Conduct a study to evaluate the efficacy of this drug for tinea corporis in the 2 - 12 year old pediatric population, especially since the dermatophyte species responsible may vary from adults. Alternatively, information may be submitted that demonstrates that the dermatophyte species responsible for tinea corporis in the 2 - 12 year old pediatric population does not vary from adults. If this information is demonstrated, the need for an efficacy study could be waived.

Protocol Submission:	Within 3 months of the date of this letter submit the protocol and alternative information for Agency review and approval.
Study Start:	Within 9 months of the date of this letter initiate the study, if the FDA concludes that the alternative information is not convincing.
Final Report Submission:	Within 19 months of the date of this letter submit the final report.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

and

FROM: Daniel P. Keravich, R.Ph., M.B.A., Regulatory Project Manager
PHONE #: 301-827-2248
FAX #: 301-827-2316

Schering-Plough
HealthCare Products

Schering-Plough Corporation
Three Oak Way
PO Box 603
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Telephone (908) 679-1640
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December 7, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Response to FDA Transmission

Subject: **New Drug Application #21-307**
Butenafine HCl Cream, 1%
Post Marketing Commitment

Dear Dr. Wilkin:

This is in response to the facsimile transmission received from the Agency this afternoon regarding minor changes in the Post Marketing Commitments that Schering-Plough HealthCare Products (SPHCP) had made on December 3, 2001 for the subject NDA. The recommended revisions affected commitment #2 on the efficacy of butenafine HCl cream for the treatment of tinea corporis in the 2 – 12 year old pediatric population.

SPHCP agrees with the proposed changes and commits to the revised Post Marketing Commitment #2 as described in your above correspondence and reiterated below.

2. Conduct a study to evaluate the efficacy of this drug for tinea corporis in the 2 – 12 year old pediatric population, especially since the dermatophyte species responsible may vary from adults. Alternatively, information may be submitted that demonstrates that the dermatophyte species responsible for tinea corporis in the 2 – 12 year old pediatric population does not vary from adults. If this information is demonstrated, the need for an efficacy study could be waived.

Protocol Submission:	Within 3 months of the date of the NDA approval letter, SPHCP will submit the protocol and alternative information for Agency review and approval.
Study Start:	Within 9 months of the date of the NDA approval letter, SPHCP will initiate the study, if the FDA concludes that the alternative information is not convincing.
Final Report Submission:	Within 19 months of the date of the NDA approval letter, SPHCP will submit the final report.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

Facsimile to Cmdr. Cross
Duplicate copies to the NDA file
Desk copy to CMDR. Cross.

Mary Williams
Schering-Plough HealthCare Products
Three Oak Way
Berkeley Heights, NJ 07922

Phone # 908-679-1952
Fax # 908-679-1741

Schering-Plough HealthCare Products

Confidential Fax -- Please deliver quickly

To:	**Frank Cross, Jr., MA, CDR** **Div. of Dermatologic and Dental Drug Products**	**From:**	**Mary Williams** **Assoc. Dir. RA**
Fax:	(301) 827-2075	**Pages:**	2 + Cover page
Phone:	(301) 827-2063	**Date:**	12/7/01
Subjec	Butenafine HCl Cream, 1%: NDA 21-307	**CC:**	

Dear Comdr. Cross:

Please find the attached copy of the letter being sent concurrently to the NDA file regarding minor revisions to Post Marketing Commitment #2 for tinea corporis. Please don't hesitate to contact me if you have any questions regarding this matter.

Sincerely,

Mary Williams

Mary Williams
Assoc. Director Regulatory Affairs

Schering-Plough
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December 3, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Response to FDA Transmission

Subject: **New Drug Application #21- 307**
Butenafine HCl Cream, 1%
Post Marketing Commitment

Dear Dr. Wilkin:

This is in response to the Agency's facsimile transmission received this afternoon regarding certain Post Marketing Commitments for the subject NDA. The commitments would require Schering-Plough HealthCare Products (SPHCP) to conduct a study(s) on the use of butenafine HCl cream, 1% in the treatment of tinea corporis in the 2 – 12 year old pediatric population.

Accordingly, SPHCP commits to conduct the study(s) as described in your correspondence and reiterated below.

1. Conduct a study to evaluate the safety of this drug for tinea corporis in the 2 – 12 year old pediatric population. This study should include pharmacokinetic sampling (systemic absorption data under maximal use conditions) and a comprehensive evaluation of local intolerance. Any additional information regarding local effects in children may be submitted, if available.

Protocol Submission:	Within 3 months of the date of the NDA approval letter, SPHCP will submit the protocol for Agency review and approval and any additional information regarding local effects in children.
Study Start:	Within 6 months of the date of the NDA approval letter, SPHCP will initiate the study.
Final Report Submission:	Within 16 months of the date of the NDA approval letter, SPHCP will submit the final report.

2. Conduct a study to evaluate the efficacy of this drug for tinea corporis in the 2 – 12 year old pediatric population, especially since the dermatophyte species responsible may vary from adults. Alternatively, information may be submitted to support the assertion that the dermatophyte species responsible for tinea corporis in the 2 – 12 year old pediatric population does not vary from adults.

Protocol Submission:	Within 3 months of the date of the NDA approval letter, SPHCP will submit the protocol or alternative information for Agency review and approval.
Study Start:	Within 6 months of the date of the NDA approval letter, SPHCP will initiate the study.
Final Report Submission:	Within 16 months of the date of the NDA approval letter, SPHCP will submit the final report.

At this time, the labeling for the Lotrimin® Ultra™ Cream (butenafine HCl cream, 1%) will remain as submitted in the final printed labeling provided in the October 5, 2001 Resubmission of the NDA. If we wish to label the OTC butenafine HCl cream, 1% for the treatment of tinea corporis in children ages 2-12 years at a future date, we will request a meeting with FDA to discuss the details of the requirements. We acknowledge that the Agency has indicated the need for both efficacy data and data demonstrating that parents/ guardians can distinguish tinea corporis from other dermatologic conditions in their children, especially conditions that might require treatment with an antibiotic, should we pursue an OTC labeled indication.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

Mark Gelbert

Mark Gelbert, Ph.D., JD
Vice President, Scientific Affairs

Facsimile to Cmdr. Cross
Duplicate copies to the NDA file
Desk copy to CMDR. Cross.

Schering-Plough
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N-000/MR

NDA SUPPL AMENDMENT

November 5, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

FDA Request for Desk Copies

Subject: New Drug Application #21- 307
Butenafine HCl Cream, 1%

Dear Dr. Wilkin:

Enclosed, please find an identical copy of the correspondence and information being concurrently submitted to Ms. Sandy Childs (FDA Project Manager). These desk copies had been requested by Comdr. Frank Cross in preparation for the scheduled November 20, 2001 teleconference to discuss a tinea corporis study in a pediatric population. However, because Schering-Plough included a literary article in this submission that had not previously been provided to the NDA, Comdr. Cross asked that we also submit an official copy to the file.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

Filed in duplicate
17 desk copies to Ms. Sandy Childs

ORIGINAL

Schering-Plough
HealthCare Products

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October 5, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RESUBMISSION

Subject: **New Drug Application #21- 307**
Butenafine HCl Cream, 1%
Amendment in Response to Approvable Letter

Dear Dr. Wilkin:

Reference is made to your July 27, 2001 approvable letter for the subject new drug application. Schering-Plough HealthCare Products (SPHCP) is herein resubmitting the application and addressing all of the deficiencies listed in your approvable letter in the enclosed amendment.

For ease of review, each of the items described in the approvable letter is listed below, followed by SPHCP's response in italics.

1) During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved.

   On August 24, 2001, the butenafine HCl [redacted] listed in the application, [redacted] responded to the observations made by FDA during their inspection. SPHCP has been notified that the FDA has completed their review of the [redacted] response/status report and has found it satisfactory. In addition, the FDA has reclassified the facility as acceptable and has recommended approval of pending applications.

2) Also, you should propose a protocol to satisfy a Post Marketing Commitment to evaluate the safety and efficacy of tinea corporis in the 12 year old and under pediatric population, especially since the dermatophyte species responsible may vary from adults.

   A draft protocol to evaluate the safety and efficacy of butenafine HCl in the treatment of tinea corporis in children 2 years up to 12 years old is provided in Attachment 1. Please note: on September 26, 2001, SPHCP requested a teleconference with the appropriate FDA personnel to gain a fuller understanding of the Agency's request.

3) In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the immediate container and outer carton labels).

   Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

   20 paper copies of the final printed labeling, ten of which are individually mounted on heavy weight paper, are provided in the Appendix (Volumes 2 and 3) to this submission. This labeling is identical in content to the labeling enclosed in the approvable letter.

4) We remind you of your postmarketing study commitment in your submission dated July 25, 2001. This commitment is listed below.

   Conduct a study to test consumers' ability to differentiate the Lotrimin AF labeling from the Lotrimin Ultra labeling in terms of distinguishing the different active ingredients.

Protocol Submission:	Within 1 month of the date of this letter submit the protocol for Agency review and approval.
Study Start:	Within 3 months of the date of this letter initiate the study.
Final Report Submission:	Within 6 months of the date of this letter submit the final report.

   As stated in our August 3, 2001 response to the approvable letter, SPHCP had previously agreed to the timing of this study from the date of NDA approval, not the date of the approvable letter. In a subsequent telephone conversation, Comdr. Frank Cross agreed that this was an Agency oversight, and that the NDA approval date would be used as the start date for the consumer study commitment.

5) Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug.

   The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

   1. Describe in detail any significant changes or findings in the safety profile.

      There are no significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   There are no new safety data on the studies to support the proposed indications (tinea pedis, tinea corporis, and tinea cruris) that were referenced in the subject Rx-to-OTC switch application.

   A separate interdigital tinea pedis clinical study (IND #[redacted] Serial #061) to evaluate the rate of recurrence with the use of the approved butenafine cream 1% formula is not completed and the data are still blinded. FDA will be notified of any serious and unexpected adverse experience associated with the use of the drug in this study in a written IND safety report, as well as in a 15-day Alert Report to the NDA (21 CFR § 312.32(c)(1) and § 314.80(e)(1)). FDA will also be notified by telephone or by facsimile of any unexpected fatal or life-threatening experience associated with the use of the drug in this study no later than 7 calendar days after receipt of the information (21 CFR § 312.32(c)(2). Finally, reports of clinical experience pertinent to safety will be provided in the Annual Report to the NDA (21 CFR § 314.81(l), (vi)).

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

   Currently SPHCP is involved in clinical trials for two indications other than the proposed indication for butenafine HCl. One of the indications is the [redacted] (IND # [redacted]). The second indication being studied is the [redacted] (IND # [redacted]). The studies for these indications are not complete and the data is still blinded. FDA will be notified of any adverse event associated with the use of the drug in these clinical studies as described above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

   There are no newly completed studies.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

   *The above referenced clinical studies are ongoing and unblinded adverse event data are not available. However, the following **blinded** data/ information is provided in Attachment 2:*

   (IND #

   - *Tables 1.1 Listing of patients who died during a study. (Note: no patient died during any of the studies.)*
   - *Table 1.2 Listing of patients who did not complete a study because of an adverse event*
   - *Table 1.3 Listing of serious adverse events*

   (IND #

   - *Table 2.1 Listing of patients who died during a study.*
   - *Case report form for each patient who died during the study.*
   - *Table 2.2 Listing of patients who did not complete a study because of an adverse event*
   - *Table 2.3 Listing of serious adverse events*

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

   There is no new information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other counties.

   A summary of worldwide experience on the safety of this drug is provided in Attachment 3. An updated estimate of use for butenafine HCl drug marketed in other counties is contained in "Periodic Safety Update Report" (PSUR) included in Attachment 3.

7. Provide English translations of current approved foreign labeling not previously submitted.

   To the best of our knowledge, there are no new foreign countries that marketed this product over-the-counter. On October 25, 2000, SPHCP submitted a translated copy of the butenafine HCl labeling from Canada which is the only foreign country included in the 1988 guideline for content and format of the Clinical/ Statistical sections of an NDA that markets butenafine HCl as an over-the-counter product.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you require any additional information, please don't hesitate to contact Ms. Mary Williams at (908) 679-1952. Thank you.

Sincerely,

Mark Gelbert

Mark Gelbert, Ph.D., JD
Vice President, Scientific Affairs

Attachment
Volume 1: filed in duplicate
Volumes 2 and 3: Appendix for FPL , 1 copy each
Desk copy of Volume 1 to Comdr. Frank Cross

Schering-Plough
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September 26, 2001

DUPLICATE

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

MR

NDA ORIG AMENDMENT

Request for Meeting

RECEIVED
SEP 2 7 2001
MEGA/CDER

Subject: **New Drug Application #21-307**
Butenafine HCl Cream, 1%
Approvable Letter

Dear Dr. Wilkin:

Reference is made to your July 27, 2001 approvable letter for the subject new drug application.

As allowed under 21 CFR § 314.102 (d), Schering-Plough HealthCare Products (SPHCP) requests a telephone conference to discuss certain criteria listed by the Agency in the approvable letter. Specifically, SPHCP wishes to discuss the Agency's request for a proposed "protocol to satisfy a Post Marketing Commitment to evaluate the safety and efficacy of tinea corporis in the 12 year old and under pediatric population." Details on the anticipated sponsor attendees and the questions for discussion are attached.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

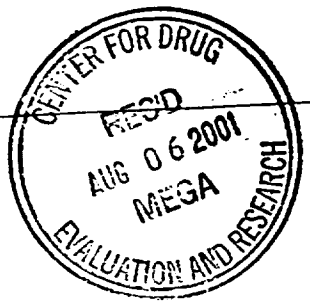
Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

Filed in duplicate
Facsimile desk copy to CMDR. Cross

NEW CORRES



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August 3, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Intent to File an Amendment

Subject: **New Drug Application #21- 307**
Butenafine HCl Cream, 1%
Response to Approvable Letter

Dear Dr. Wilkin:

Reference is made to your July 27, 2001 approvable letter for the subject new drug application. As required under 21 CFR § 314.110, Schering-Plough HealthCare Products (SPHCP) is hereby notifying you of our intent to file an amendment to the application that will respond to all of the deficiencies listed in your letter.

In addition, as allowed under 21 CFR § 314.102 (d), we intend to request an informal meeting or telephone conference to discuss the Agency's request for a Post Marketing Commitment to evaluate the safety and efficacy of tinea corporis in the 12 year old and under pediatric population. SPHCP requests further clarification of this request via the telephone conference before agreeing to this commitment.

Finally, please note that the outline of the timing in your letter does not agree with that specified in our July 25, 2001 commitment to conduct a Postmarketing Study on the consumers' ability to differentiate the Lotrimin AF labeling from the Lotrimin Ultra labeling in terms of distinguishing the different active ingredients. Specifically, we had agreed to the timing of this study from the date of NDA *approval*, whereas the timing specified in your letter is from the date of the *approvable* letter. Because this is a postmarketing study, and marketing cannot begin until approval of the NDA, we assume this is an Agency oversight, and will use the NDA approval date as the start date for the consumer study commitment.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

ORIGINA

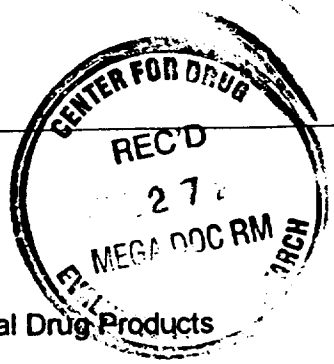
If you require any additional information, please don't hesitate to contact Ms. Mary Williams at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams for M.G.

Mark Gelbert, Ph.D., JD
Vice President, Scientific Affairs

Filed in duplicate
Facsimile desk copy to CMDR. Cross



Schering-Plough HealthCare Products

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July 25, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Response to FDA Transmission

Subject: **New Drug Application #21- 307**
Butenafine HCl Cream, 1%
Post Marketing Commitment

Dear Dr. Wilkin:

This is in response to the Agency's facsimile transmission received this morning regarding a Post Marketing Commitment for the subject NDA. The commitment would require Schering-Plough HealthCare Products (SPHCP) to "conduct a study to test consumers' ability to differentiate the Lotrimin AF® labeling from the Lotrimin Ultra™ labeling in terms of distinguishing the different active ingredients."

Accordingly, SPHCP commits to conduct the above study. As further discussed, the timing of this commitment is as follows:

Protocol Submission:	Within 1 month of the NDA approval, SPHCP will submit the protocol for Agency review and approval.
Study Start:	Within 3 months of NDA approval, SPHCP will initiate the study.
Final Report Submission:	Within 6 months of NDA approval, SPHCP will submit the final report.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

Mary E. Williams
Associate Director Regulatory Affairs

Sent via e-mail
Duplicate copies to the NDA file
Desk copy to CMDR. Cross.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: July 25, 2001 Number of Pages (including cover sheet) - 1

TO: Mary Williams, Associate Director, Regulatory Affairs
COMPANY: Schering-Plough HealthCare Products
FAX #: 908-679-1741

MESSAGE: Please commit to the following Post Marketing Commitment for NDA 21-307, Lotrimin Ultra (butenafine hydrochloride) Cream, 1%.

Conduct a study to test consumers' ability to differentiate the Lotrimin AF labeling from the Lotrimin Ultra labeling in terms of distinguishing the different active ingredients

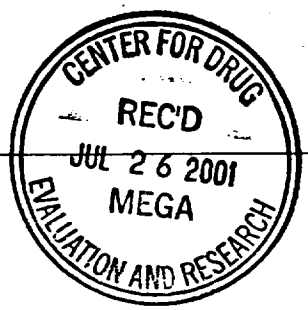
Protocol Submission:	Within 1 month of the date of this letter submit the protocol for Agency review and approval.
Study Start:	Within 3 months of the date of this letter initiate the study.
Final Report Submission:	Within 6 months submit the final report.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

and

FROM: Daniel P. Keravich, R.Ph., M.B.A., Regulatory Project Manager
PHONE #: 301-827-2248
FAX #: 301-827-2316



Schering-Plough
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Fax (908) 679-1840

July 25, 2001

Frank Cross, Jr., MA, CDR, Sr. Regulatory Management Officer
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-540, Room # N 229
9201 Corporate Blvd.
Rockville, Maryland 20850

DESK COPY
Labeling for all package sizes

Subject: **New Drug Application #21-307**
Butenafine HCl Cream, 1%

Dear Comdr. Cross:

Enclosed, please find your desk copy of the labeling amendment that is being concurrently submitted to the subject NDA. This amendment provides a copy of the labeling (tubes and cartons) for each of the package sizes included in the subject NDA, with the exception of the 2-gram package size.

If you require any additional information, or have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E Williams

Mary E. Williams
Associate Director Regulatory Affairs

Attachment
disk

Schering-Plough
HealthCare Products

Schering-Plough Corporation
Three Oak Way
PO Box 603
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July 25, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Labeling for all package sizes

Subject: **New Drug Application #21- 307**
Butenafine HCl Cream, 1%
Labeling Amendment

Dear Dr. Wilkin:

Please find the attached copy of labeling (tubes and cartons) for each of the package sizes included in the subject NDA, with the exception of the 2-gram package size. (Note: as discussed previously, the labeling for the 2-gram package is not available at this time and will be submitted in a post marketing labeling supplement at a future date.)

The attached labeling meets all of the format and content requirements for over-the-counter (OTC) drug product labeling as set forth in 21 CFR § 201.66. In addition, this labeling incorporates all of the changes requested in the Agency's July 23, 2001 facsimile transmission and is identical to that included in our response to that facsimile, with the following minor exceptions:

- On all tubes: the bullets for "adults and children 12 years and older" and "children under 12 years" under the heading ***Directions*** are no longer in a bold font. This is consistent with the Drug Facts labeling on the cartons.

- On the 12-gram tube: the statement "All rights reserved" has been removed from the copyright text because of space constraints.

- On all cartons: the "recyclable carton" symbol and statement have been added to the bottom panel of the carton.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

Sent via e-mail
Duplicate copies to the NDA file
Disk
Desk copy to CMDR. Cross.

31 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: July 23, 2001 Number of Pages (including cover sheet) - 18

TO: Mary Williams, Associate Director, Regulatory Affairs
COMPANY: Schering-Plough HealthCare Products
FAX #: 908-679-1741

MESSAGE: Please find attached to this facsimile transmission draft labeling for NDA 21-307, Lotrimin Ultra (butenafine hydrochloride) Cream, 1%. To facilitate your review, please note the following:

1. Your proposed Tradename, Lotrimin Ultra (butenafine hydrochloride) Cream, 1%, is acceptable.

2. On the Back Panel of the proposed Carton Labeling for Athlete's Foot Cream:

   a. Under "Directions", retention of the instructions to "...apply to affected skin between and around the toes..." is acceptable.

   b. Under "Directions", for athlete's foot between the toes:" the next sentence should read: "apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks or as directed by a doctor."

3. The website referenced in the labeling should direct consumers to both Lotrimin AF and Lotrimin Ultra.

4. On the proposed labeling, the size of the statement of identity should be reasonably related to the size of the most prominent printed material on the proposed product labeling, in accordance with 21CFR 201.61(c).

5. As previously discussed, alternative wording for "new ingredient", for the "Flag the Label" banner, should be submitted for Agency review.

6. Please submit labeling for all product sizes intended for marketing at this time. Please include a statement that the labeling for each product size is the same with the exception of the differences in sizes.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

and

FROM: Daniel P. Keravich, R.Ph., M.B.A., Regulatory Project Manager
PHONE #: 301-827-2248
FAX #: 301-827-2316

17 pages redacted from this section of the approval package consisted of draft labeling

ORIG AMENDMENT
BL

Schering-Plough
HealthCare Products

Schering-Plough Corporation
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PO Box 603
Berkeley Heights, NJ 07922-0603
Telephone (908) 679-1640
Fax (908) 679-1840

July 23, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Response to FDA Transmission

Subject: New Drug Application #21- 307
Butenafine HCl Cream, 1%
Labeling Amendment

Dear Dr. Wilkin:

This is in response to the Agency's facsimile transmission received this afternoon regarding draft labeling for the subject NDA. Schering-Plough HealthCare Products (SPHCP) agrees with all of the proposed changes to the labeling as described in the facsimile. Specifically, the following Agency recommendations have been incorporated into the labeling:

- On the back panel of the proposed carton labeling for Athlete's Foot Cream, the phrase "or as directed by a doctor" has been added under "Directions".

- The prominence of the statement of identity on the principal display panel has been enhanced.

In addition, we agree that the website referenced in the labeling will direct consumers to both Lotrimin AF® and Lotrimin® Ultra™ products.

A copy of the draft carton labeling with the above revisions is attached for your review. If these changes are satisfactory, identical carton and tube labeling for all of the package sizes (i.e., 12, 15, 24, and 30 gram) will be sent to the Agency by end of day Wednesday, July 25, 2001. Please note: the labeling for the small 2 gram package size is not available at this time. As discussed, we will provide the labeling copy for this small package in a supplement to the NDA at a future time.

DUPLICATE

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director, Regulatory Affairs

Sent via e-mail
Submitted in duplicate to the NDA

2 pages redacted from this section of the approval package consisted of draft labeling

ORIG AMENDMENT
BC

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July 19, 2001

Jonathan Wilkin, M.D., Director
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Office of Drug Evaluation V
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Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Deletion of Control Site

Subject: **New Drug Application #21- 307**
Butenafine HCl Cream, 1%
CMC Amendment

Dear Dr. Wilkin:

This Chemistry, Manufacturing and Controls (CMC) amendment is being made to delete Bertek Pharmaceuticals Inc. ———————————————) as a control site for ——— testing in the subject NDA (originally added in an amendment on 11/22/00). Accordingly, a NDA replacement page is attached for the Sites of Manufacturing, Packaging, and Control that does not include Bertek ———

In accordance with 21 CFR 314.70(a) Schering-Plough HealthCare Products certifies that a copy of this supplement is being sent to FDA's New Jersey District Office.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

DUPLICATE

Attachment/Duplicate
Desk copy: Comdr. F. Cross

Schering-Plough
HealthCare Products

Schering-Plough Corporation
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Fax (908) 679-1840

July 18, 2001

Frank Cross, Jr., MA, CDR, Sr. Regulatory Management Officer
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-540, Room # N 229
9201 Corporate Blvd.
Rockville, Maryland 20850

DESK COPY
Safety Update Report Addendum

Subject: **New Drug Application #21-307**
Butenafine HCl Cream, 1%

Dear Comdr. Cross:

Enclosed, please find your desk copy of the addendum to the Safety Update Report that is being concurrently submitted to the subject NDA.

If you require any additional information, or have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams
Associate Director Regulatory Affairs

Attachment

Redacted 144

pages of trade

secret and/or

confidential

commercial

information

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July 18, 2001

Jonathan Wilkin, M.D., Director
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Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Safety Update Report
Addendum

Subject: **New Drug Application #21- 307**
Butenafine HCl Cream, 1%

Dear Dr. Wilkin:

Enclosed, please find an addendum to our January 31, 2001 Safety Update Report (SUR) to provide information from the Toxic Exposure Surveillance System (TESS) compiled by the American Association of Poison Control Center (AAPCC). As explained in our SUR, information from AAPCC for the year 2000 was not available until after March/April 2001.

Schering-Plough HealthCare Products (SPHCP) reviewed the enclosed TESS report and a summary of our findings follows this letter. Four adverse reactions were reported, all after accidental *ingestion* of butenafine HCl cream. An 81 year old female experienced nausea and headache; a 51 year old male experienced nausea; and an 18 month old child experienced vomiting. All experiences were considered to be non-serious. This report documents the benign safety profile of butenafine cream 1%.

Please note, we have not yet received the Japanese Periodic Safety Update Report (PSUR) for July 1, 2000 to December 31, 2000. Any new adverse event data for butenafine HCl covered in this report will be submitted to the subject NDA upon receipt.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this information, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director, Regulatory Affairs

attachment/ duplicate
Desk copy: Comdr. Frank Cross

NEW CORRESP NC

Schering-Plough
HealthCare Products

Mark Gelbert, PhD, JD
Vice President
Scientific Affairs

Schering-Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276
Telephone (908) 604 -1640
Fax (908) 604 -1840

July 12, 2001

Frank Cross, Jr. MA, CDR, Sr. Regulatory Management Officer
Division of Dermatologic and Dental Drug Products
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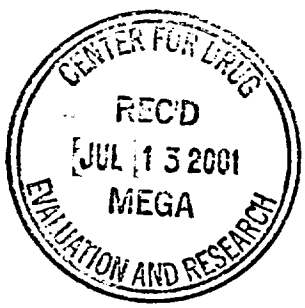
9201 Corporate Blvd.
Rockville, Maryland 20850



Subject: **New Drug Application #21-307**
Butenafine HCl Cream, 1%
Brand Name Options

Dear Comdr. Cross:

On Monday, July 9, representatives from Schering-Plough HealthCare Products met with FDA via telephone to discuss the proposed brand name for the subject NDA product. Enclosed, as requested, is a color rendition of the Principle Display Panel for the proposed product, Lotrimin[redacted]. In addition, also enclosed is a color rendition comparing the proposed PDP to the current Lotrimin AF PDP.

We believe that the two labels are dramatically different and will not result in confusion for the consumer in choosing an appropriate Athlete's Foot treatment. Along with the obvious graphic differences, other distinguishing features of the proposed PDP are as follows:

a. The active ingredient, butenafine HCl cream 1%, is prominently identified directly under the brand name.

b. A "Flag the Label" banner on the principal display panel indicates a "new ingredient" and is readily apparent.

c. The brand name for this product is differentiated from the existing Lotrimin® cream product by way of the new suffix, font style and graphics.

d. The labeling on the PDP indicates that this product "cures most athlete's foot between the toes."

DUPLICATE

To further minimize any confusion, the active ingredient is the first item described on the back panel of the carton in the new Drug Facts format provided to you earlier.

In addition to the Lotrimin [redacted] brand name, Schering-Plough has considered other suffixes to be used with the Lotrimin name for this product. Based on review of existing trademarks and other Marketing considerations, we would also be comfortable marketing this product with the following other brand names:

Lotrimin [redacted]
Lotrimin [redacted]
Lotrimin Ultra

Lotrimin [redacted] continues to be our first choice. The new dosing options are a benefit to the consumer. The brand name was chosen to communicate to the consumer an improved product offering. Identifying other brand name alternatives suitable for this product would require additional research and time.

We look forward to discussing this matter, along with other labeling issues, at our teleconference on July 19.

Sincerely,

Mark Gelbert

Mark Gelbert, PhD, JD
Vice President, Scientific Affairs

Attachment
Duplicate Copies (7)

2 pages redacted from this section of the approval package consisted of draft labeling

Schering-Plough
HealthCare Products

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June 8, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

Subject: New Drug Application #21- 307
Butenafine HCl Cream, 1%
Labeling Amendment

Dear Dr. Wilkin:

Revised labeling for the subject product is enclosed. Changes to this labeling were made in response to the Agency's comments received on March 2, 2001. In addition, the directions for use were modified to include the "once a day for 4 weeks" treatment regimen as suggested by the Agency at the March 22, 2001 meeting to discuss appropriate OTC treatment regimens.

The following information is provided in support of this amendment:

Attachment 1	A detailed list and explanation of the differences between the attached proposed labeling and the recommended labeling received from the Agency on March 2, 2001
Attachment 2	Schering-Plough's proposed labeling with the differences annotated, followed by a copy of the Agency's March 2, 2001 labeling recommendations
Attachment 3	A mocked up version of the Drug Facts labeling for the athlete's foot and jock itch cartons
Attachment 4	A disk copy of both the annotated labeling (Word 97) and Drug Facts labeling (Adobe PDF)

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

Attachment
Duplicate
Desk copy: Comdr. F. Cross

3 pages redacted from this section of the approval package consisted of draft labeling

Schering-Plough
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June 8, 2001

Frank Cross, Jr., MA, CDR, Sr. Regulatory Management Officer
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-540, Room # N 229
9201 Corporate Blvd.
Rockville, Maryland 20850

DESK COPY
Labeling Amendment

Subject: **New Drug Application #21-307**
Butenafine HCl Cream, 1%

Dear Comdr. Cross:

Enclosed, please find your desk copy of the labeling amendment that is being concurrently submitted to the subject NDA. Changes to this labeling were made in response to the Agency's comments received on March 2, 2001 and at the March 22, 2001 meeting to discuss appropriate OTC treatment regimens.

If you require any additional information, or have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

Attachment

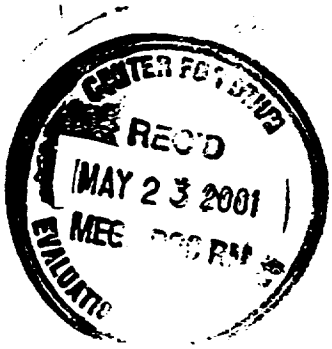
NEW CORRES:
NC

Schering-Plough
HealthCare Products

Mark Gelbert, PhD, JD
Vice President
Scientific Affairs

Schering-Plough Corporation
Three Oak Way
PO Box 603
Berkeley Heights, NJ 07922-0603
Telephone (908) 679-1640
Fax (908) 679-1640

May 22, 2001



Frank Cross, Jr. MA, CDR, Sr. Regulatory Management Officer
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-540, Room # N 229
9201 Corporate Blvd.
Rockville, Maryland 20850

Subject: **New Drug Application #21-307**
Butenafine HCl Cream, 1%
Rationale for Lotrimin [redacted] Brand Name

Dear Comdr. Cross:

Enclosed, as requested, please find three copies of our rationale for use of the Lotrimin [redacted] brand name on the butenafine HCl cream, 1% product that is subject of this Rx-OTC switch NDA. For commercial reasons we are withdrawing the brand name [redacted] for consideration for this product application.

As indicated in the enclosed rationale, Schering-Plough HealthCare Products does not agree with the FDA's decision that use of the Lotrimin [redacted] brand name on this product would result in consumer confusion that would lead to a significant safety issue. For this reason, we have decided not to submit additional brand name options at this time.

We look forward to your review and decision on this matter.

Sincerely,

Mark Gelbert

Mark Gelbert, PhD, JD
Vice President, Scientific Affairs

Attachment
Duplicate Copies (2)

DUPLICATE

Rationale for Using the Lotrimin® Brand Name for the OTC Butenafine HCl 1% Cream Product.

Summary

FDA has raised an issue with using Lotrimin[redacted] as a brand name for the switch of butenafine HCl 1% cream for the treatment of athlete's foot. FDA has communicated to SPHCP its concern that there could be potential safety issues with use of the existing brand name (*e.g.*, a consumer who is allergic to butenafine may use the product not realizing it contains butenafine). FDA has also communicated to SPHCP that, for this reason, the Office of Postmarketing and Drug Risk Assessment (OPDRA) and the NDA review teams do not agree to the use of the submitted brand name and that it would not be included in the switch approval.

SPHCP asks the FDA to reconsider this point of view. Specifically, we are submitting this paper to support our belief that:

1. There is no demonstrated safety issue (e.g. contact allergic dermatitis) based on a complete review of the butenafine safety database.

2. The proposed labeling incorporates multiple signals to the consumer to minimize or eliminate any potential for confusion.

3. A number of examples of products exist in the market place that are similar to the proposed product and brand name, demonstrating FDA's acceptance to the use of brand names in this manner.

4. Trademark law and FDA precedent support the proposed brand name for this product.

Each of these reasons for justifying the use of the proposed brand name are further detailed below.

1. Potential Safety Concerns Based on Consumer Confusion

There is no demonstrated safety issue (*e.g.*, contact allergic dermatitis) based on a complete review of the butenafine clinical study database. More adverse events were seen in the vehicle treated subjects than the butenafine treated subjects. No subject withdrew from a butenafine study due to an adverse event associated with butenafine cream 1%. All dermal safety studies located in NDA 20-524 further establish the excellent safety profile, including no evidence of delayed contact sensitization. The spontaneous reports of adverse reactions during the Rx use of topical butenafine cream likewise demonstrate this excellent safety profile. The likelihood a consumer would experience a significant or serious allergic reaction to a butenafine 1% cream product is

exceptionally minimal. A complete review of this safety data can be found in the Integrated Summary of Safety for NDA 20-524.

2. Proposed Labeling

The proposed product labeling for the Lotrimin [redacted] butenafine product will minimize any potential for confusion with respect to brand name and active ingredient. As stipulated in the new OTC Drug Labeling final rule, and directed in the CHPA "Voluntary Codes and Guidelines," the proposed labeling incorporates the following features to minimize any potential for confusion:

a. The active ingredient, butenafine HCl 1%, is prominently identified on the proposed principle display panel (PDP) directly under the brand name.

b. The active ingredient is the first item described on the back panel of the carton in the new Drug Facts format.

c. A "Flag the Label" banner on the principal display panel indicating a new ingredient will be displayed for at least 6 months after market introduction.

d. The brand name for this product is further differentiated from existing Lotrimin® products by way of the new suffix.

e. While not in final form at this time, the package graphics for this new product will be distinctly different from the existing Lotrimin cream product.

With regard to the first two points above, FDA's own position reported in the Over-The-Counter Human Drugs; Labeling Requirements; Final Rule [Federal Register: March 17, 1999 (Volume 64, Number 51) Page 13253] supports the adequacy of this format to minimize consumer confusion. In creating a standard "Drug Facts" format for all OTC drug product labels, the agency stated that a standardized appearance and standardized content would help consumers locate and read important health and safety information and allow quick and effective product comparisons, thereby helping consumers to select the most appropriate product. Specifically related to potential confusion among similarly branded products, the FDA stated:

> This final rule requires the listing of active ingredients as the very first information within a clearly defined panel, immediately below a prominent title. This location will enable consumers to quickly and systematically compare ingredients within products for similar uses. In addition, because the respective purposes will be listed next to each active ingredient, consumers will know why the ingredient is in the product. Regardless of placement on the PDP, such uniform and prominent placement will help to ensure proper product selection, especially for product line extensions. [Page 13260]