3. Recent Examples in the Market

There are a number of similar examples in the market place in which the same brand name, with appropriate suffixes, are used for different active ingredients. In these cases, existing brand names currently on the market with OTC Monograph ingredients were used with recently "switched" active ingredients. The following recent similar examples in the market demonstrate FDA's acceptance of the extension of OTC brand names using new switch ingredients:

a. Terbinafine, an antifungal active ingredient for athlete's foot that was approved as an OTC product in March 1999 under the prescription brand name Lamisil®, was also launched under the Desenex® brand name in May 2000. The Desenex brand name has traditionally been and currently is marketed with undecolenic acid, miconazole nitrate and clotrimazole active ingredients.

b. Tioconazole, an antifungal ingredient introduced as Vagistat-1® in February 1997 for OTC treatment of vaginal yeast infections, was also launched in June 1999 under the Monistat® brand name, which continues to be used for marketing similar products containing the active ingredient miconazole nitrate.

c. Famotidine, an H2 receptor antagonist, was launched under the Pepcid® brand name in 1995. Later in 1997, this ingredient was also marketed under the Mylanta® brand name, traditionally and currently used to market aluminum and magnesium hydroxide, and calcium carbonate antacids. In this case, a systemic ingredient with a completely different mode of action was marketed under the same brand name (Mylanta) that is also marketed with a completely different pharmacologic class of compounds (antacids).

As we understand, these changes were made with notification to the FDA in respective NDA Annual Reports and apparently without FDA action. Although each situation presents unique facts, the above examples present identical issues to those of our own butenafine product. These examples indicate that issues of potential consumer confusion between products of similar brand names can be effectively dealt with, and that there is an acceptable level of safety if confusion results even in situations where systemic actives are involved. In order to assure a "level playing field," FDA should permit the use of the proposed Lotrimin name for the approved butenafine product.

4. Current Trademark Law

It is well established under trademark law and FDA precedent that the use of the brand name Lotrimin[redacted] appropriate. FDA may not prohibit the use of an extended brand name unless it is inherently misleading and no other measure (such as clarification in the labeling) will eliminate consumer confusion. The extreme remedy of forbidding

the use of a trademark is appropriate only where gross confusion among consumers would be experienced if the use of the mark were permitted. As discussed above, no demonstrated safety issued exists with the use of the proposed brand name, and the proposed labeling further aids the consumer in choosing the appropriate product.

A more detailed discussion on brand name line extensions and trademark law is presented in the attached excerpt from the written comments of the Consumer Healthcare Products Association submitted to FDA on August 25, 2000 as part of the Part 15 meeting held that summer on Rx-OTC Switches (Docket No. 00N-1256).

APPEARS THIS WAY
ON ORIGINAL

Attachment 1

Excerpt from the Consumer Healthcare Products Association Written Comments for the Part 15 Meeting on Rx-OTC Switches (June 29-30, 2000) Submitted to FDA on August 25, 2000 Docket No. 00N-1256

A. Brand Name Line Extensions

FDA requested comment on the use of brand name line extensions, and inquired in particular about the possibility of consumer confusion when the active ingredients generally associated with a brand are not present in some of the brand's extended product line. 65 Fed. Reg. at 24705. As explained below, brand name line extensions provide accurate and useful information to consumers. Moreover, the use of brand name line extensions is essential for manufacturers in developing useful new products for consumers. Finally, FDA may not prohibit the use of an extended brand name unless it is inherently misleading and no other measure (such as clarification in the labeling) will eliminate consumer confusion. Prohibiting the use of a brand name on a product in an extended product line is tantamount to trademark excision, which is ordinarily reserved for situations where use of the brand name would be so misleading as to constitute an outright lie.

1. Brand Name Line Extensions Provide Accurate and Material Information to Consumers and are Essential for the Continued Availability of New OTC Drug Products.

The function of a trademark or brand name is twofold: to identify to consumers the source of a product, and to secure for the manufacturer a return on its investment in research, development, and advertising, by differentiating its product from other products.

Brand name line extensions are useful to consumers. Consumers confronted with many products offering similar benefits need and seek criteria for narrowing the field of products available to the single product they will ultimately select. A brand name line extension conveys the message that the product on which the brand name appears is available from the same company as an already-marketed product with which the consumer may be familiar. This accurate message assists the purchasing decision by identifying the source of a product. It allows the consumer to locate a family of products in which he or she has trust, and to choose from among them the one most appropriate to a current need. In short, brand line extensions provide information to consumers that is both accurate and useful to the purchasing decision.

Brand name line extensions are also critical to the market success of OTC drug products. Brand names are the principal repository of the good will that leads to repeat purchases of products. They are also the principal mechanism by which a company distinguishes its product from that of others. See, e.g., *American Steel Foundries* v.

Comm'r of Patents, 269 U.S. 372 (1925); *Estate of Beckwith* v. *Comm'r of Patents*, 252 U.S. 538 (1919). Use of an established company trademark on a second company product identifies the source of the product and communicates to consumers a particular standard of quality.

The inherent value of brand names is augmented by the fact that they are costly to create. The value of a brand name is only as significant as the images it inspires in the minds of consumers. These images are hard to fashion in a powerful and memorable way, and the start-up costs of producing a successful brand name are high. A company often invests significant sums in advertising the safety, effectiveness, and quality of a product. The company similarly invests in its product development and manufacturing operations to ensure that those advertising claims are supported in practice. Brand names thus become extremely valuable business assets.

A limit on line extensions would raise the costs of introducing new products, thereby reducing competition and ultimately increasing consumer prices. Such a limitation also would restrict consumer choice because the expense of establishing new brand names could reduce the number of new products introduced to the market.

2. FDA May Not Preclude the Use of Brand Name Line Extensions on OTC Drug Products.

FDA's authority over a company's use of its trademark stems from the statutory provision deeming a drug to be misbranded if its labeling is false or misleading and from the related provision authorizing FDA to refuse to approve an NDA proposing labeling that is false or misleading. 21 U.S.C. §§ 352(a) and 355(d)(7). The legislative history of the latter provision makes it clear that a product is misbranded in this way only if there are "objective facts of record which make the proposed labeling demonstrably false or demonstrably misleading." See 108 *Cong. Rec.* 21066 (1962). Similarly, under the Federal Trade Commission Act, use of a trademark can be prohibited only if additional labeling will not clarify the confusion. See, e.g., *FTC* v. *Royal Milling Co.*, 288 U.S. 212, 217 (1932) (trade names are misleading where purchasers are deceived into purchasing an article which they do not wish or intend to buy, and which they might or might not buy if correctly informed as to its origin).

The First Amendment requires the same conclusion. It has been clear since at least the early 1980s that product labeling is commercial speech entitled to the protection of the First Amendment. See *Bolger* v. *Young Drug Prods. Corp.*, 463 U.S. 60, 67-68 (1983); *Pearson* v. *Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999) (applying First Amendment and striking FDA regulation that governed health claims on the labels of dietary supplements). It is also well settled that trademarks are commercial speech. See *Friedman* v. *Rogers*, 440 U.S. 1, 11 (1979) (adoption of a symbol as a trademark is a form of commercial speech); J. Thomas McCarthy, "Important Trends in Trademark and Unfair Competition During the Decade of the 1970s," 71 Trademark Rep. 93, 119 (1981) ("[A] company's trademark is the most important element of commercial speech . . . ."); Marla J. Caplan, Comment, "Antidilution Statutes and the First Amendment," 21 S.W.U. L. Rev. 1139, 1163 (1992).

Commercial speech that is neither misleading nor illegal may be regulated or prohibited only if (1) the asserted government interest is substantial, (2) the regulation directly advances the government interest, and (3) the fit between the means and the ends is reasonable. *Central Hudson Gas & Elec. Corp.* v. *Public Serv. Comm'n*, 447 U.S. 557 (1980). The fit between means and ends is per se unreasonable if the government chooses suppression when a disclaimer would adequately serve its interest. See *Pearson*, 164 F.3d at 656-57. Moreover, the courts have tended to apply the First Amendment strictly when government seeks to regulate a company's right to use its mark. See, e.g., *Berkey Photo* v. *Eastman Kodak*, 603 F.2d 263 (2d Cir. 1979), *cert. denied*, 444 U.S. 1093 (1980) (reversing trial court decree that Kodak sell color print paper without its backprint at the option of the purchaser).

Line extensions are not inherently misleading. The *Central Hudson* Court explained that speech is inherently misleading only if it is "more likely to deceive the public than to inform it." 447 U.S. at 563. Line extensions, by way of contrast, reduce customer confusion by providing accurate information that helpfully categorizes products by source. They provide patients and physicians with helpful information, by allowing them to associate a new product with a known manufacturer or distributor. Because line extensions are not inherently misleading, the FDA may not prohibit them unless it can articulate a substantial government interest in doing so, demonstrate that preventing them directly advances that government interest, and show that some sort of explanatory information in the labeling would not serve its interest. *Cf. Washington Legal Foundation* v. *Friedman*, 13 F. Supp.2d 51, 72-74 (D.D.C. 1998), *appeal dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000); *see also Nutritional Health Alliance* v. *Shalala*, 953 F. Supp. 526 (S.D.N.Y. 1997).

FDA has suggested it may have an interest in preventing the customer confusion that may result if products in the same line use different active ingredients. However, the Agency's own regulations require the inclusion of sufficient information to ensure complete and accurate consumer understanding of all items purchased. OTC drug products must be labeled with their ingredients, indications, and directions for use. 21 C.F.R. §§ 201.5, 201.10, 201.66. Thus FDA regulations already ensure that consumers know precisely what is being purchased. Indeed, in the final rule on OTC labeling, FDA required active ingredients to be listed first in the "Drug Facts" panel, remarking that this placement "will help to ensure proper product selection, especially for product line extensions." 64 *Fed. Reg.* 13254, 13260 (March 17, 1999). Accordingly, under the *Central Hudson* test, FDA may not prohibit the use of brand names in OTC product line extensions.

The recent spate of federal court decisions rejecting FDA's attempts to suppress truthful commercial speech suggests the Agency should tread lightly in the area of brand name line extensions. These cases have confirmed the fundamental proposition -- that is definitive in this area — that FDA may not prohibit truthful speech simply to protect consumers from confusion, when further speech will remedy any possible confusion.[1] In *Pearson*, for instance, FDA argued "that it is never obligated to utilize the disclaimer

approach, because the commercial speech doctrine does not embody a preference for disclosure over outright suppression." 164 F.3d at 657. The Court of Appeals unequivocally rejected this argument: "Our understanding of the doctrine is otherwise." *Id.* Quoting the Supreme Court, the Court of Appeals wrote that "'the preferred remedy is more disclosure, rather than less.'" *Id.*, *quoting Bates* v. *State Bar of Arizona*, 433 U.S. 350, 376 (1977). Indeed, in "recent cases, the [Supreme] Court has reaffirmed this principle, repeatedly pointing to disclaimers as constitutionally preferable to outright suppression." *Id.* at 657. See also *Washington Legal Foundation*, 13 F. Supp.2d at 72-74 (describing "Supreme Court's preference for combating potentially problematic speech with more speech," rejecting Guidance Document restrictions on off-label speech, and noting "the most obvious alternative [which] is full, complete, and unambiguous disclosure by the manufacturer"); *Western States Medical Center* v. *Shalala*, 69 F. Supp.2d 1288 (D. Nev. 1999), *appeal pending*, No. 99-17424 (9th Cir.).

3. Trademark Excision is Permissible Only when Use of the Brand Name is Tantamount to a Lie.

Longstanding FDA policy permits trademark excision only when qualifying language would not adequately correct likely consumer misperceptions. Twenty years ago, FDA proposed a rule providing that a change in the formulation of a drug would not require the excision of a trade name, if the change did not significantly alter the product's use or active ingredients. The proposed rule was not adopted, due to administrative backlog, but the Notice of Proposed Rulemaking in question made it quite clear that the agency recognized this was already its existing policy and the rule announced by the courts. FDA stated that "It is the policy of the Food and Drug Administration, in accordance with principles laid down in the courts, to require excision of a brand name only where nothing less than excision would eliminate the possibility of deception, and to permit retention of a brand name where either permanent qualification of the name or prominent public disclosure of the change in the product for a significant period of time is sufficient to inform the public of the change in the product or its use." 39 Fed. Reg. 11298 (March 27, 1974).

Cases in which excision have been found appropriate present extreme circumstances where the brand name was so misleading as to constitute an outright lie. See, e.g., *FTC* v. *Algoma Lumber*, 291 U.S. 67 (1934) (sustaining FTC determination that no method short of trade name excision would protect the public from being misled into purchasing "yellow pine" that was advertised as the superior and more expensive "California White Pine"); *Indiana Quartered Oak* v. *FTC*, 26 F.2d 340 (2d Cir. 1928) (finding excision the only appropriate remedy where "Philippine Mahogany" wood was not mahogany). In these instances, "white pine" was not white pine, and "mahogany" was not mahogany. No amount of clarification could render these brand names non-misleading. Compare *Jacob Siegel* v. *FTC*, 327 U.S. 608, 613 (1946) ("[T]he policy of the law to protect [trade names] as assets of a business indicates that their destruction 'should not be ordered if less drastic means will accomplish the same result.'"). These cases have no application to line extensions: while a trade name may be associated with products containing a particular ingredient, the trade name is not the active ingredient

name, and it is not inherently misleading to use the same trade name for a variety of products, each accurately labeled with its active ingredients.

In sum, the courts permit excision only when a brand name rises to the level of a lie. There is no way that brand name extensions on OTC drug product lines could be deemed to rise to this level; to the contrary, they accurately convey useful information about the source of a product, as described above. FDA prohibition of a brand name line extension would violate the food and drug law, FDA policy, and the First Amendment.

APPEARS THIS WAY
ON ORIGINAL

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

BMHRS B2

Schering-Plough HealthCare Products

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May 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
4201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

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

Subject: **Additional Information**
Revised Table for March 22, 2001 Briefing Package

Dear Dr. Wilkin:

Information that addresses the requests made by the Agency at our March 22, 2001 meeting is enclosed. These requests were captured in FDA's minutes of the meeting and are highlighted below.

Request: *A tabular representation of those patients studied in the four week/ q.d., dosage regimen which had patients having onychomycosis listed as having an adverse event. Ideally, if post-hoc analysis is done to exclude onychomycosis patients, such patients should also be excluded.*

Response: A review of the databases for this information revealed there were no patients having onychomycosis listed as having an adverse event in the four week/ q.d. dosage regimen pivotal studies.

Request: *Table 2S (Attachment 3, page 2 of 14 of the March 14, 2001 Meeting Briefing Package) should be revised and submitted to the Agency for its review.*

Response: Table 2S (redefined criteria for "Effective Treatment") has been revised to include the additional information discussed at the meeting. In order to accommodate all of the information in a clear manner, the table has been broken into the following six tables:

1. Patients with concurrent onychomycosis excluded (active treatment)
2. Patients with concurrent onychomycosis excluded (vehicle treatment)
3. Patients with concurrent onychomycosis only (active treatment)
4. Patients with concurrent onychomycosis only (vehicle treatment)
5. All patients (active treatment)
6. All patients (vehicle treatment)

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

trust this information satisfies your requests from our March 22, 2001 meeting. If you e any questions regarding this matter, please don't hesitate to contact me at (908) -1952. Thank you.

cerely,

Mary E. Williams

ary E. Williams
ssociate Director Regulatory Affairs

ttachment
uplicate
esk copy: Comdr. F. Cross

6

Schering-Plough HealthCare Products

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rch 14, 2001

athan Wilkin, M.D., Director
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01 Corporate Blvd., HFD-540
ckville, Maryland 20850

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

ubject: Briefing Document: Meeting of March 22, 2001

ear Dr. Wilkin:

Enclosed, please find three copies of the Briefing Document for the meeting scheduled on March 22, 2001, to discuss the appropriateness of an OTC one-week treatment regimen for the subject product. The Briefing Document contains the following information:

1. Meeting agenda and participants
2. History and summary of the rationale for the OTC one-week treatment regimen
3. Supplement to "A Comparative Review of Penederm Protocols"
4. Key Issues and Questions
5. Appendix: "A Comparative Review of Penederm Protocols." (Included in original application on 9/28/00.)

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) 679-1703. Thank you.

Sincerely,

Mary E. Williams for M.G.

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

Triplicate
Attachment with 1 SAS data disk
12 Desk Copies with 1 SAS data disk: Comdr. F. Cross

ORIGINAL

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March 8, 2001

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

New Drug Application #21- 307
Butenafine HCl Cream, 1%
NDA [illegible] AMENDMENT

pw

Subject: Additional Information Regarding the Waiver from Pediatric Data Requirements

Dear Dr. Wilkin:

On February 21, 2001, Schering-Plough HealthCare Products (SPHCP) received a request from Comdr. Frank Cross (Sr. Regulatory Management Officer, FDA) for additional information to support a waiver from certain pediatric data requirements.

As part of the new drug application submitted on September 28, 2000, SPHCP had requested a partial waiver from the pediatric requirements for data to assess the safety and effectiveness of butenafine HCl cream, 1% for the treatment of athlete's foot, jock itch, and ringworm in children under the age of 12 years. (Note: the subject product is approved for use in children 12 years and older.) As allowed under 21 CFR § 314.55(c)(3), SPHCP justified this request based on the knowledge that the subject product (1) does not represent a meaningful therapeutic benefit over existing treatments for children 2 to 12 years of age, and (2) it is not likely to be used in a substantial number of pediatric patients under the age of 2 because of the low incidence of athlete's foot, jock itch, and ringworm in that age group.

Subsequently, the FDA Medical Review Officer directed Comdr. Cross to obtain the following information from SPHCP to support the request for a waiver from the pediatric data requirements for children under the age of 12:

1. The number and percent of prescriptions written for butenafine HCl cream, 1% (Mentax® Cream) for children under the age of 12. This information should be broken out for each indication.

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2. Information on the incidence of tinea corporis (ringworm) in children under the age of 12 years.

3. Information to support the low incidence of antifungal infections (tinea pedis, tinea corporis, and tinea cruris) in children under the age of 2 years.

Each of these items is addressed below.

1. Information on the prescriptions written for butenafine HCl cream, 1% (Mentax® Cream) was obtained from "IMS HEALTH, National Disease and Therapeutic Index – Drug – Moving Annual Total Ending January 2001." This information covers the number and percentage of Mentax prescriptions written from 1997 (when the product was first marketed) to January 2001, for each indication. The data is broken out into three age groups: adults; children ages 13 to 19 years of age; and children under the age of 12 years.

   Of the ——— prescriptions written since 1997 for Mentax Cream, ———) of these were for children under the age of 12 years (——— % of the total scripts). The largest percent of these prescriptions for children under the age of 12 years was for *pityriasis versicolor* (—— %), followed by *tinea capitis* —— %). Of the approved indications, only —— % of the prescriptions for children under the age of 12 years were for *tinea corporis* (ringworm) and —— % were for *tinea pedis* (athlete's foot). There were no prescriptions for children under the age of 12 years written for *tinea cruris* (jock itch). A copy of the complete information is provided in Attachment 1.

2. An extensive literature search was conducted for information on the incidence of tinea corporis (ringworm) in children under the age of 12 years. Although numerous articles addressed the treatment of tinea corporis in children, there was little information on the incidence in the general population. One of the largest studies reported in the literature was conducted in Londrina, Brazil[1] (original and translated copy provided in Attachment 2) which provided information on a prospective study of 6,000 children under the age of 12 years with dermatoses. Approximately 59% of these children were between 0 to 5 years of age; 36% were between 6 to 10 years of age; and 5% were between 11 to 12 years of age. In the total population of 6,000 children, the incidence of tinea corporis was 1.5%, the incidence of tinea pedis was 0.28% and the incidence of tinea cruris was 0.08%. Given the propensity of dermatophytoses in tropical climates, the percentage of tinea corporis in the US is predicted to be no more than that seen in the above study.

---

[1] Lotrivaldo Minelli, Helder Jose Minelli, "Dermatosis in children: statistical study of 6,000 cases" Anais Brasileiros de Dermatologia (Jan/ Feb 1992)

3. An extensive literature search was also conducted for information to support the low incidence of antifungal infections (tinea pedis, tinea corporis, and tinea cruris) in children under the age of 2 years. Little information was found for this age group because patients less than two years of age were rarely discussed in the literature.

   While the Brazilian 6000-patient prospective study discussed above did not break out incidence of tinea corporis, pedis and cruris in the age groups studied, it is important to note that more than half of the children studied (approximately 59%) were between 0 to 5 years of age. Therefore the total percent of incidence for tinea corporis, pedis, and cruris reported in this study can also be used to predict a low incidence in children under the age of 2 years.

We trust this information is adequate to address your concerns. Should we find any additional significant information, we will promptly provide it to the Agency.

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
Triplicate
2 Desk copies: Comdr. F. 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: March 2, 2001 Number of Pages (including cover sheet) - 9

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

MESSAGE: Draft labeling for NDA 21-307, TRADENAME (butenafine hydrochloride) Cream, 1%, is attached to this facsimile transmission.

Thank you.

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

DRAFT

Labeling Comments:

1. With regard to the Drug Facts Panel, please submit a foot diagram that clearly demonstrates to the consumer when the product is to be applied between the toes.

2. Please decrease the font size of the TRADENAME and increase the font size of the established name so that the established name has more prominence.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

ORIG AMENDMENT

B1

Schering-Plough
HealthCare Products

Schering-Plough Corporation
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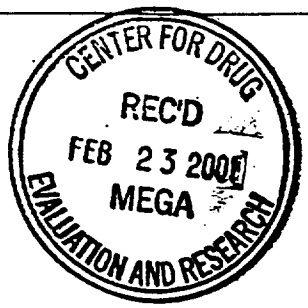

February 21, 2001

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

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

Subject: **Labeling Amendment**
Proposed Trade Names

Dear Dr. Wilkin:

Schering-Plough HealthCare Products (SPHCP) is herein providing a list of potential trade names for the butenafine HCl antifungal cream product that is the subject of the Rx-to-OTC switch new drug application (NDA # 21-307) currently under review.

It is our intention to market this product under two of our existing brand names for athlete's foot and jock itch products, i.e., Lotrimin ® and [ ]®. A qualifying suffix is to be added to these brand names to distinguish the butenafine HCl product from other topical antifungals marketed under these brand names. A list of proposed trade names including suffixes for the Lotrimin brand is attached in descending order of our preference, as well as the one desired trade name and suffix for the [ ] brand.

Please be advised that while the FDA Office of Postmarketing and Drug Risk Assessment (OPDRA) is reviewing the proposed trade names, SPHCP will be concurrently conducting a trademark search, as well as additional market research. We will combine the information we gain from these activities with the feedback we receive from the Agency before deciding on the final trade names for marketing.

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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, 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
Duplicate
Desk copy: Comdr. F. Cross

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

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January 31, 2001

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

Safety Update Report

NDA [illegible]

SU

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

Dear Dr. Wilkin:

The enclosed safety update report is being submitted to the pending subject application per 21 CFR 314.50(d)(5)(vi)(b).

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

Desk copy: Comdr. Frank Cross
attachment/ duplicate

Redacted 15

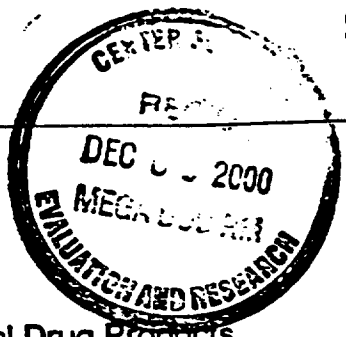
pages of trade

secret and/or

confidential

commercial

information



Schering-Plough
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December 7, 2000

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:

During the preparation of mocked up OTC labeling for the subject product (being concurrently submitted as a desk copy to Comdr. Frank Cross), several changes were made to the text for the jock itch product. Accordingly, Schering-Plough HealthCare Products is herein submitting an amendment to the subject NDA to provide the revised labeling text on the attached pages and enclosed disk (Word 97 format).

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, 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

Enclosures
Duplicate
Desk copy: F. Cross

Schering-Plough
HealthCare Proc

Schering-Plough Corporation
Three Oak Way
PO Box 603
Berkeley Heights, NJ 07922-0
Telephone (908) 679-1640
Fax (908) 679-1840

November 22, 2000

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

Bc

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

Dear Dr. Wilkin:

Following the Agency's meeting to discuss the acceptability of the subject NDA for filing, Schering-Plough HealthCare Products (SPHCP) received a request for additional information and clarification of certain items from Comdr. Frank Cross (Sr. Regulatory Management Officer) on November 11, 2000. These items are addressed below.

1. On page 3 016, Vol. 1.1 of the new drug application, SPHCP stated that "The identity, strength, quality, and purity of the drug product will be maintained for OTC use" and "...the CMC information for the subject new drug application will remain the same as that previously approved in NDA 20-524...and NDA 20-663...."

   SPHCP herein clarifies that the drug substance and drug product specified in the subject NDA (#21-307) are the same as in the approved referenced NDAs (# 20-524 and # 20-663). In addition, to the best of our knowledge the drug product formulation specified in NDA 21-307 is the same as the formulation used in the pivotal clinical trials to support the approved NDAs. (Note: benzyl alcohol was added as an additional preservative subsequent to the pivotal *tinea pedis* studies.)

2. The most current information available at the time of the NDA submission was provided from the following safety databases: World Health Organization (WHO); the American Association of Poison Control Center's Toxic Exposure Surveillance System (TESS); data from the FDA's AERS system; and the

ORIGINA

Japanese Worldwide Post-Marketing Surveillance Data of Mentax Cream and Gel (butenafine HCl) ——— Japan. Updated information from these databases will be provided in the required Safety Update Report to the NDA four months from the date of the original application submission, i.e., January 28, 2001.

3. As stated in the introduction to the annotated labeling (Volume 1.1 (i), page 3 003), the *text* for the proposed labeling was drafted in accordance with 21 CFR § 201.66 "Format and Content Requirements for OTC Drug Product Labeling." This draft labeling was intended for review of the content, not the format. At the Agency's request, SPHCP is in the process of preparing "mocked-up" labeling in the required format and will submit in an amendment to the application the week of December 3, 2000.

4. A request was made that a statement of readiness for inspection be provided for the sites listed in our NDA. This information was provided for the drug product in Volume 1.1, page 1 006, following the Form FDA 356h as "Timing for Site Inspection: January 2001." When informed of the projected timing, the Agency expressed concern that the sites were not immediately ready for inspection, which could result in a delay of the NDA approval.

   In a follow-up conversation with the Agency, it was agreed that SPHCP would work with the field office to determine an inspection date acceptable to the field office. If SPHCP was unable to meet that date, the SPHCP Memphis control site for ——— testing would be withdrawn from the NDA and resubmitted later in a post approval supplement. In addition, it was agreed that SPHCP could reinstate Bertek as a control site as part of this amendment to the application. Accordingly, a NDA replacement page is enclosed for the Sites of Manufacturing, Packaging and Control that includes additional control sites.

5. The Agency expressed concern that SPHCP was using the approved 2 gram physician sample package to bracket the new 12 gram package size, since the stability data generated for a sample package is typically less than that for a marketed package. SPHCP informed the Agency that stability data had been provided for the 2 gram package size in the original application, as well as in a packaging supplement (#S-004) on 7/1/99. A subsequent SPHCP review of Bertek CMC information also confirmed that stability data for the 2 gram package were included in a supplement for extension of expiry dating (#S-002) on 12/16/96, as well as in the 1997, 1998, 1999 Annual Reports.

   Finally, at the request of the Agency, a stability commitment statement for all marketed package sizes is 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 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

Desk Copy: Mr. Frank Cross

Schering-Plough
HealthCare Products

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October 25, 2000

NDA ORIG AMENDMENT

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

BL

Subject: New Drug Application #21-307
Butenafine HCl Cream, 1%
Amendment to Foreign Marketing Information

Dear Dr. Wilkin:

A copy of the labeling for the butenafine HCl cream, 1% product marketed over-the-counter (OTC) in Canada is herein provided.

A list of foreign countries where butenafine HCl is marketed was provided in the Foreign Marketing History section of Volume 1.1 in the September 28, 2000 Rx-to-OTC switch application. On October 13, 2000, Cdr. Frank Cross, Sr. Regulatory Management Officer, requested that Schering-Plough submit a translated copy of the butenafine HCl labeling for foreign countries where it is marketed OTC. This request was based on the 1988 guideline for content and format of the Clinical/ Statistical sections of an NDA, which states that this type of information should be provided for a product marketed in European countries, Canada, ———————— , and/ or Japan. To the best of our knowledge, Canada is the only listed country included in the guideline 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).

ORIGINAL

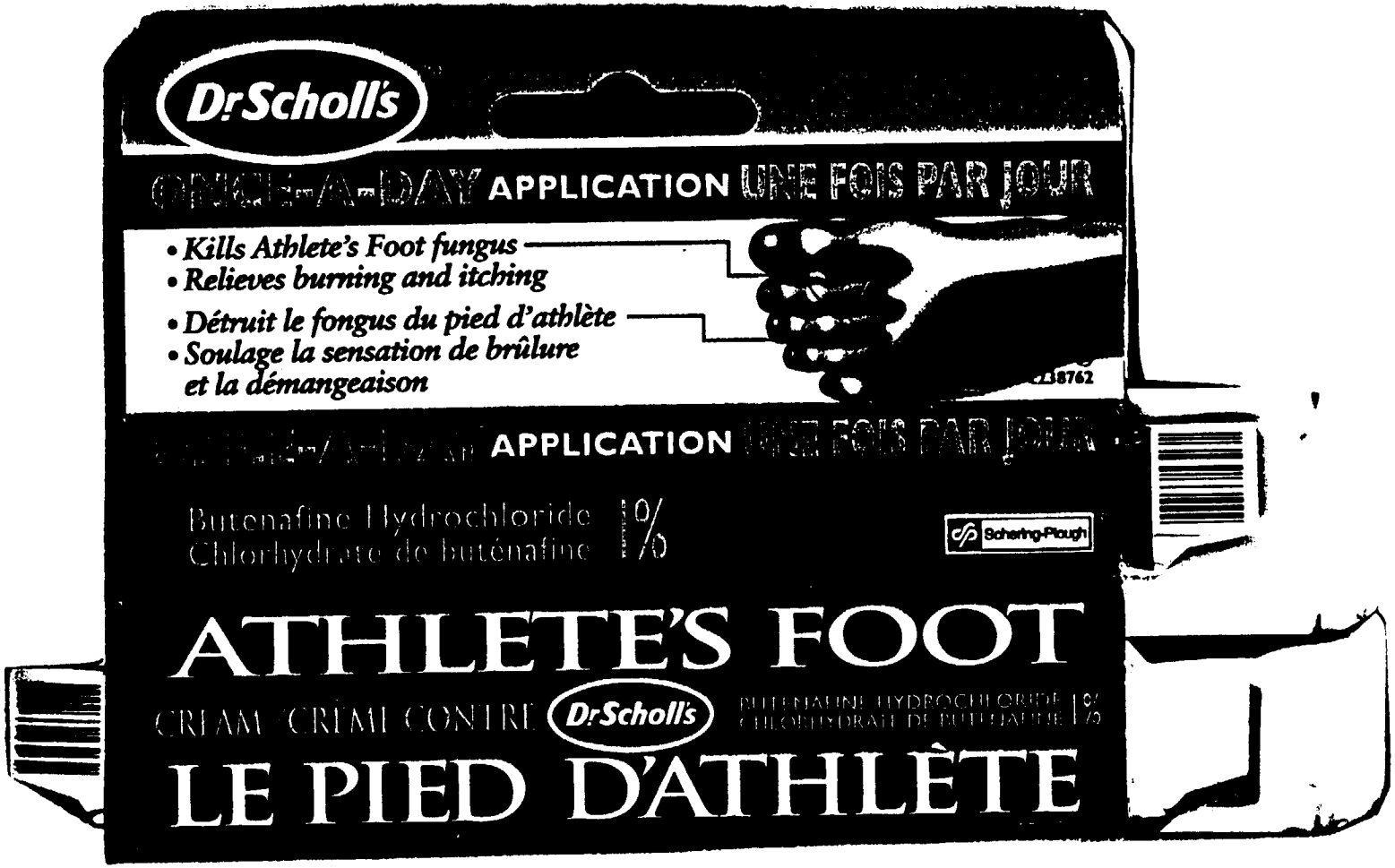
If you have any questions regarding this matter, please don't hesitate to contact me at (908) 679-1952. Thank you.

Sincerely,

Mary E. Williams

Mary Williams
Associate Director, Regulatory Affairs

Filed in duplicate
Desk copy: Mr. Frank Cross


Dr.Scholl's
APPLICATION UNE FOIS PAR JOUR
• Kills Athlete's Foot fungus
• Relieves burning and itching
• Détruit le fongus du pied d'athlète
• Soulage la sensation de brûlure et la démangeaison
APPLICATION
Butenafine Hydrochloride 1%
Chlorhydrate de buténafine 1%
Schering-Plough
ATHLETE'S FOOT
CREAM CRÈME CONTRE Dr.Scholl's
LE PIED D'ATHLÈTE

NDA 21-307

OCT 20 2000

Schering Plough Health Care Products
Attention: Mark Gelbert, Ph.D., JD
Vice President, Scientific Affairs
3 Oak Way
Berkeley Heights, NJ 07922

Dear Dr. Gelbert:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Butenafine Hydrochloride Cream, 1%

Review Priority Classification: Standard (S)

Date of Application: September 28, 2000

Date of Receipt: September 29, 2000

Our Reference Number: NDA 21-307

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 28, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 29, 2001 and the secondary user fee goal date will be September 29, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with

the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Frank H. Cross, Jr., Project Manager, at (301) 827-2020.

Sincerely,

/S/ 10/19/00

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 21-307
HFD-540/Div. Files
HFD-540/F.H.Cross
S.Walker
M.Okun
W.DeCamp
A.Jacobs

DISTRICT OFFICE

Drafted by: /smc/October 4, 2000
filename: N21307AC

ACKNOWLEDGEMENT (AC)

Schering-Plough
HealthCare Products

Schering-Plough Corporation
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October 19, 2000

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

NEW CORRESP
NC

Subject: **New Drug Application #21-307**
Butenafine HCl Cream, 1%
Revised 356h Form

Dear Dr. Wilkin:

A revised Form FDA 356h is enclosed that replaces the form provided in the original Rx-to-OTC switch NDA for the subject product on September 28, 2000. The revision to this form involves a change in the "Type of Submission" from an efficacy supplement to an original application, resulting in a change in the User fee payment. Other than the date of signature, no other changes have been made to this form.

The change in the "Type of Submission" is the result of a telephone conversation between Schering-Plough Healthcare Products (SPHCP) and Cdr. Frank Cross, Sr. Regulatory Management Officer, FDA on October 13, 2000. Cdr. Cross informed us that, based on his conversation with Mr. Michael Jones from the User Fee office, SPHCP had filed the subject application incorrectly, i.e. as an efficacy supplement for a "Type 6" NDA, requiring one half of the full User Fee payment. Since the switch application involves three indications *(tinea pedis, tinea corporis,* and *tinea cruris*), Cdr. Cross stated that there are only two possible options for filing. They are: (1) three separate efficacy supplements, (one for each of the three indications), requiring ½ User Fee payment for each supplement; or (2) an *original* application (not a "Type 6" NDA) for all three indications, requiring a full User Fee payment.

Because SPHCP had previously discussed the User Fee requirements with Ms. Beverly Friedman from the User Fee office on August 18, 2000, and these filing options had not been mentioned, Mr. Cross contacted Ms. Friedman and conferenced her on the call with SPHCP. Ms. Friedman agreed with the directions Cdr. Cross had given SPHCP regarding the filing options, and stated she had not been aware that the switch application involved more than one indication.

DUPLICATE

After further discussion, it was agreed that the FDA Form 356h would be revised to indicate that the switch application was an original application for three indications, and that the User Fee Cover Sheet would not require revision. In addition, since a full User Fee payment was now owed, the additional amount of $142,870 should be submitted as soon as possible. It was also agreed that, since SPHCP had submitted in good faith what they believed to be the complete User Fee payment at the time of the original filing, the PDUFA date would not change, i.e., September 29, 2000 would remain as the start date for the review clock, and SPHCP would not be required to pay the higher FY 2001 fees implemented on October 1, 2000.

SPHCP disagrees with this FDA decision on User Fees and reserves the right to appeal this decision at a later date. The three indications subject to this NDA are all similar tinea fungal infections of different parts of the body. These indications are already approved for the prescription drug product, and the review of each indication for OTC status does not present significantly different safety issues from the initial review to require multiple User Fees.

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 contact Ms. Mary Williams at (908) 679-1952. Thank you.

Sincerely,

Mark Gelbert

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

Attachment
Filed in duplicate

Schering-Plough
HealthCare Products

Schering-Plough Corporation
Three Oak Way
PO Box 603
Berkeley Heights, NJ 07922-0603
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Fax (908) 679-1840

NDA ORIG AMENDMENT

October 13, 2000

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

BL

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

Dear Dr. Wilkin:

Non-annotated labeling for the butenafine HCl cream, 1% is herein provided on the attached pages and enclosed disk (Word 97 format) at the request of Cdr. Frank Cross, Sr. Regulatory Management Officer. Please note, an annotated version of the identical labeling was provided in Volume 1.1 of the September 28, 2000 Rx-to-OTC switch application for the subject 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 have any questions regarding this matter, please 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

ORIGINAL

Filed in duplicate
Enclosure: 2 disks
Desk copy letter: Mr. Frank Cross

Schering-Plough
HealthCare Products

Schering-Plough Corporation
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Fax (908) 679-1840

October 12, 2000

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

NEW CORRESP

N C

Subject: **General Correspondence**
Butenafine HCl Cream, 1%
NDA #21-307

Dear Dr. Wilkin:

A copy of a recent correspondence to Mr. Frank Cross (Sr. Regulatory Management Officer, FDA) is herein provided to the subject new drug application. The purpose of this correspondence was to inform Mr. Cross of the timing for arrival of the butenafine HCl cream, 1% Rx-to-OTC switch application. In addition, we acknowledged Mr. Cross's recommendation for a pre-NDA meeting to discuss content and format of this Rx-to-OTC switch application prior to its submission.

As explained to Mr. Cross, various reasons factored into our decision to submit the application at this time, and we have relied on the information received from FDA pertaining to this application at our November 22, 1999 pre-NDA meeting.

If you have any questions regarding this matter please don't hesitate to contact me at (908) 679-1703. Thank you.

Sincerely,

Mark Gelbert

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

Desk copy: Mr. Frank Cross

Schering-Plough
HealthCare Products

Mark Gelbert, PhD, JD
Vice President
Scientific Affairs

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September 29, 2000

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
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Subject: NDA #21-307
Butenafine HCl Cream, 1%
Rx-to-OTC Switch

Dear Frank:

This is to inform you that Schering-Plough HealthCare Products (SPHCP) has decided to submit the subject NDA for the Rx-to-OTC switch of butenafine HCl cream 1%. The application should arrive at FDA this week. Various business reasons factored into our decision to submit the application at this time.

I am aware that you have recommended to us that we should schedule a pre-NDA meeting between SPHCP and FDA to discuss the format and content of the submission. We respectfully decline this offer, as we will rely on the information we received from the FDA pertaining to this application at our November 22, 1999 meeting.

We continue to appreciate your support as Sr. Regulatory Management Officer on this project and other future projects.

Respectfully,

Mark Gelbert

Mark Gelbert
Vice President
Scientific Affairs

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

Schering-Plough
HealthCare Products

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September 28, 2000

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%
Rx-to-OTC Switch

Dear Dr. Wilkin:

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations Section 314.50, Schering-Plough HealthCare Products (SPHCP) herewith submits a new drug application (NDA) ("Type 6") for the switch from prescription status to over-the-counter (OTC) marketing of butenafine hydrochloride cream, 1% for the treatment of athlete's foot, jock itch, and ringworm.

Information concerning the safety and efficacy of butenafine HCl cream, 1% for these indications was previously submitted to the Agency by Bertek Pharmaceuticals Inc.[1] in the investigational new drug application (IND) and the two new drug applications (NDA) listed below. As authorized in the August 24, 2000 letter from Bertek to FDA (copy enclosed), the information contained in the following Bertek IND and NDAs is herewith incorporated by reference into the subject switch application:

- IND [redacted]
- NDA 20-524
- NDA 20-663

Reference is also made to a pre-NDA meeting held on November 22, 1999, with representatives from the Division of Dermatologic and Dental Drug Products (DDDDP), the Division of Over-the Counter Drug Products (DOTDP), Bertek, and SPHCP to discuss the requirements for the switch application. (A copy of the FDA and the SPHCP minutes of the meeting follow this application cover letter for your reference. Note: the

[1] The company name was changed to Bertek Pharmaceuticals Inc. from Penederm Inc on May 19, 1999; a copy of the notification to FDA on August 3, 1999 follows this application cover letter.

SPHCP minutes have not been previously submitted due to the timing of the Bertek letter (August 24, 2000) authorizing FDA and SPHCP to interact directly.)

During the 11/22/99 meeting, the appropriateness of the one-week b.i.d. dosing regimen for treatment of athlete's foot in the over-the-counter setting was discussed with the Agency. Questions were raised concerning an apparent difference in efficacy between the approved one-week b.i.d. dosing regimen and the approved four-week q.d. dosing regimen.

To further examine the comparative efficacy of these two dosing regimens, a supplementary statistical analysis was commissioned by SPHCP. The results of this comparative review of the one-week and four-week regimens showed that it is not possible to demonstrate superiority of one regimen over the other based on the available clinical trials. A copy of the full text of this supplementary analysis is provided in the Application Summary Volume (item viii), and at the end of the Clinical Data Section and the Statistical Section of this application.

In addition to the information contained in the above referenced Bertek IND and NDAs, the following information is herein submitted in support of the subject switch application:

- A complete **Application Summary** consisting of:

  (1) annotated labeling,
  (2) updated foreign marketing history,
  (3) new Chemistry, Manufacturing, and Controls (CMC) information concerning the deletion of certain control sites and the addition of two new "bracketed" package sizes.
  (4) copies of original Bertek NDA pages for items that have not changed,
  (5) combined reports when appropriate for the six pivotal studies contained in the referenced NDAs, and

  (Note: copies of the original Bertek NDA numbered pages have been labeled with their NDA # and date of submission for identification.)

- An updated **Chemistry, Manufacturing, and Controls** section which:

  (1) references the existing approved CMC information,
  (2) provides new CMC information concerning the deletion of certain sites and the addition of two new "bracketed" package sizes, and
  (3) provides a new Environmental Assessment for the OTC marketing of butenafine HCl cream, 1%.

- Identical **Clinical Data** and **Statistical Sections** which include:

  (1) an updated Integrated Summary of Effectiveness and an updated Integrated Summary of Safety that combines the discussions of the data from the six pivotal studies contained in the referenced Bertek NDAs,
  (2) the recent comparative review of the studies for one-week b.i.d. and four-week q.d. dosing regimens, and
  (3) copies of the original Clinical Study Reports for the six pivotal studies.

The following additional information is also enclosed:

(1) An Appendix containing the source documents for post marketing safety information is provided with the Clinical Data.
(2) A copy of the annotated labeling is provided on a disk in the Archival Copy of the Application Summary, as well as in the Review Copy of the Application Summary provided with the Clinical Data Volume.
(3) A copy of the SAS data disks used in the supplementary analysis for the one-week dosing studies is enclosed in the Archival and Review copies of the Statistical Data volumes for the reviewer's reference.

(Note: for the reviewer's convenience, a copy of the indices for Bertek's NDA 20-524, NDA 20-524/ S-001, and NDA 20-663 are provided in Attachment 1, Volume 1.1.)

The above information is provided in the following volumes:

Section	Archival Copy Volume Number(s)	Review Copy Volume Number(s)
Application Summary	1.1	(Provided for Each Section)
Chemistry, Manufacturing and Controls	1.2	1.1, 1.2
Clinical Data	1.3, 1.4, 1,5	1.1, 1.3, 1.4, 1.5
Statistical Data	1.6	1.1 , 1.6
Total Number of Volumes	6	8

In addition, four desk copies of the Application Summary (Volume 1) are included for distribution to the FDA reviewers by the Project Manager.

Per 21 CFR § 314.55(c)(2), Schering-Plough HealthCare Products herewith requests a waiver from the requirements for data to assess the safety and effectiveness of butenafine HCl cream, 1% for the treatment of athlete's foot, jock itch, and ringworm in children under the age of 12 years. The justification for this partial waiver of the requirements is based on the knowledge that butenafine HCl cream, 1% does not represent a meaningful therapeutic benefit over existing treatments (e.g., OTC Monograph Topical Antifungal products) for children 2 years up to 12 years of age. In addition, butenafine HCl cream, 1% is not likely to be used in a substantial number of pediatric patients under the age of two because of the low incidence of the above indications in that age group.

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

Desk Copy: Mr. Frank Cross - Application Summary Volume (4 copies)