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September 5, 2002

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned submits this petition on behalf of Paddock Laboratories, Inc. ("Paddock"), pursuant to 21 C.F.R. § 10.30.

A. Action Requested

Paddock respectfully requests that the Commissioner of Food and Drugs take the following actions:

- Immediately (i) advise the sponsors of the products listed below that the products are unapproved and misbranded new drug products that may not lawfully be distributed in U.S. interstate commerce, *and* (ii) request that the sponsors recall all such unapproved and misbranded products that have been distributed:

<u>SPONSOR</u>	<u>UNAPPROVED PRODUCTS</u>
Upsher-Smith Laboratories, Inc.	AmLactin® 12% Moisturizing Lotion AmLactin® 12% Moisturizing Cream AmLactin® AP Anti-Itch Moisturizing Cream
Clay-Park Laboratories, Inc.	Ammonium Lactate Lotion 12%
SDR Pharmaceuticals, Inc.	LACTREX™ 12% Moisturizing Cream

- Promptly pursue enforcement action (*e.g.*, seizure or injunction) against Upsher-Smith, Clay-Park, and SDR if those companies do not cease distribution of and recall the identified unlawful products; and

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- Pursue comparable action against any similar, unapproved ammonium lactate 12% lotion or cream product that has been, or may be, distributed in interstate commerce without an approved new drug application (“NDA”) or abbreviated new drug application (“ANDA”).

Paddock previously brought the identified products to the Food and Drug Administration’s (“FDA”) attention. The agency advised that it would review the matter (*see* Attachment 1); however, we are unaware of any enforcement action to date. Significantly, in May and June 2002, FDA approved two ANDAs for ammonium lactate 12% lotion and cream, rendering enforcement action against the unlawfully marketed products even more timely and appropriate.

B. Statement of Grounds

The products identified in Section A of this petition are “new drug” products that may be marketed only pursuant to an approved NDA or ANDA. None of the identified products is subject to such an approval, nor do they comply with important marketing restrictions applicable to FDA-approved ammonium lactate 12% products for the intended uses (*e.g.*, prescription dispensing to ensure safe and effective application).

The products also are misbranded, as they fail to bear adequate directions for use, and are not exempt from that requirement. The products fail to bear required label statements, such as “Rx only.” Certain products also bear misleading comparative claims.

1. Ammonium Lactate 12% Lotion And Cream For Relevant Uses Are “New Drugs” Restricted To Prescription Use

FDA has determined that ammonium lactate 12% lotion and ammonium lactate 12% cream intended for the treatment of dry, scaly skin (xerosis) and ichthyosis vulgaris¹ are “new drug” products requiring marketing pre-approval and prescription dispensing restriction.

¹ *See, e.g.*, The Merck Manual of Diagnosis and Therapy Section 10, Chapter 121 (defining ichthyosis as “dry skin” and describing “xerosis” as “the mildest form of ichthyosis” marked by “mild to moderate itching”); *see also* Merriam-Webster Medical Dictionary (defining xerosis as “abnormal dryness of a body part or tissue (as the skin...)” and ichthyosis as “any of several congenital diseases of hereditary origin characterized by rough, thick, and scaly skin”).

Labeling Claims

Labeling claims for the Upsher-Smith, Clay-Park, and SDR products place these products squarely within the definition of a “drug” (21 U.S.C. § 321(g)), as they indicate the products are for use in the “cure, mitigation, treatment, or prevention of disease” or “to affect the structure or any function of the body.”

As set forth in Attachments 2 and 3, product claims range from explicit disease-related statements, for example:

[LACTREX™ is intended f]or treatment of moderate to severe dry skin resulting from xerosis, eczema, ichthyosis, complications of diabetes or other chronic conditions. Contains the same active ingredient (12% ammonium lactate) that is found in prescription products for severe dry skin.... [See Attachment 2]²

to more subtle structure/function claims, for example:

Some moisturizers just work on the surface of the skin. AmLactin® 12% Moisturizing Lotion and Cream hydrate your skin, allowing it to retain moisture better. [See Attachment 3]

Subjects [treated with AmLactin® AP therapy] had statistically significant improvement in skin surface hydration by day 3 with further improvement at day 7. Subjects also reported statistically significant improvement in dry skin and itch on day 1 with continued improvement through day 7. [Footnotes omitted; see Attachment 3].

Whether in scientific or simple language, all of these claims reveal the same intended use and purported therapeutic benefit: *i.e.*, use of ammonium lactate 12% lotion or cream as a skin humectant to alleviate the symptoms of ichthyosis vulgaris and xerosis.

In a 1998 Warning Letter to Upsher-Smith Laboratories, FDA deemed indicated uses almost identical to those presented here to render AmLactin® an unapproved new drug product. Comparison of current product claims and those deemed objectionable in 1998 confirms the comparability of indicated uses. See Attachments 4 (Warning Letter to

² The referenced indications, of course, include the precise indications for which Squibb's Lac-Hydrin®, Paddock's LAClotion™, and Clay-Park's ammonium lactate 12% cream have been NDA- or ANDA-approved.

Mr. Kenneth L. Evenstad, President of Upsher-Smith Laboratories, Inc. (August 5, 1998)) and 5 (comparison of product claims).³

Formulation

The formulations of the Upsher-Smith, Clay-Park, and SDR products further establish that these products are “new drugs” within the meaning of the Federal Food, Drug, and Cosmetic Act. FDA has stated that 12% ammonium lactate is a “formulation which is known to act as a keratolytic agent on the skin” and it is “commonly associated with treatment of the conditions” for which four prescription drug products are currently approved. See Warning Letter to Upsher-Smith Laboratories, Inc. (Attachment 4) at 2.

Attachment 6 provides a qualitative comparison of the components in FDA-approved ammonium lactate 12% lotions and creams versus the Upsher-Smith, Clay-Park, and SDR products. It is self-evident that the latter products have been formulated to closely match and substitute for the FDA-approved products in terms of active and inactive ingredients and other key product characteristics, such as pH.

Target Audience

A key marketing audience for the products at issue is physicians who treat dermatological conditions and who might otherwise prescribe prescription ammonium lactate 12% cream or lotion to their patients. Promotional materials urge physicians, for example, “for patients with rough, dry skin ... [r]ecommend AmLactin 12% Moisturizing Lotion and Cream” (Attachment 3). The price of the purported over-the-counter drug also is clearly targeted to health professionals: “reduce the potential for patient irritation.” *Id.*

Paddock has verified that at least Upsher-Smith details its AmLactin® family of products to physicians and pharmacists. The company also exhibits its products at professional meetings, such as recent meetings of the American Academy of Dermatology, American Association of Diabetes Educators, American Society of Health-System Pharmacists, and National Association of Chain Drug Stores. SDR was actively promoting LACTREX™ to physicians at the most recent annual meeting of the American Academy of Dermatology.

Both Upsher-Smith and SDR Pharmaceuticals distribute “professional sample” packages of their products (*see* copies of sample labeling in Attachments 2 and 3), which present a distinct prescription drug-like trade dress.

³ It is clear that Upsher-Smith softened its product claims following FDA’s 1998 Warning Letter. It is equally clear, however, that the intended use of the product and its mechanism of action remain the same as before.

“New Drug” Status

Upsher-Smith, Clay-Park, and SDR may designate their products as non-prescription drug products that do not require FDA approval; however, their subjective claims of intent are not determinative. FDA may find actual therapeutic intent and determine regulatory status on the basis of objective evidence, including circumstances surrounding distribution of the article, and knowledge about probable use in the marketplace. 21 C.F.R. § 201.128; *see National Nutritional Foods Ass’n v. Mathews*, 557 F.2d 325 (2d Cir. 1977); *United States v. Undetermined Quantities of an Article of Drug, Labeled as “Exachol”*, 716 F. Supp. 787 (S.D.N.Y. 1989); *United States v. An Article ... Consisting of 216 Individually Cartoned Bottles ... Labeled in Part: “Sudden Change”*, 409 F.2d 734 (2d Cir. 1969).

It is evident that the objectionable ammonium lactate 12% products are recognized as substitutes for FDA-approved, prescription ammonium lactate 12% lotion and cream. *See, e.g.*, Attachment 7 (on-line dermatology website (www.dermadoctor.com) describes AmLactin® 12% Moisturizing Lotion as “equivalent to other prescription lactic acid moisturizing agents. Great for seriously dry skin conditions like eczema, ichthyoses, psoriasis and keratosis pilaris.”).

FDA has determined that ammonium lactate 12% lotion and cream are “new drugs” requiring approval pursuant to an NDA or ANDA before they may be marketed in U.S. commerce. 21 U.S.C. §§ 321(p), 355. FDA expressly considered this issue and advised in 1998 that the agency was unaware of any scientific evidence that ammonium lactate 12% cream or lotion is generally recognized as safe and effective to cure, mitigate, treat, or prevent xerosis or ichthyosis vulgaris, or to affect a structure or function of the body. *See* Warning Letter to Upsher-Smith Laboratories, Inc. (Attachment 4) at 2. We have no reason to expect that FDA would conclude differently at the present time.

To date, FDA has approved four drug applications for ammonium lactate 12% lotion and cream for the referenced indications:

- Westwood-Squibb’s Lac-Hydrin® 12% Lotion (NDA # 19-155) was approved in 1985;
- Westwood-Squibb’s Lac-Hydrin® 12% Cream (NDA # 20-508) was approved in 1996;
- Clay-Park secured approval of the first bioequivalent ammonium lactate 12% cream in May 2002 (ANDA # 75-744); and
- Paddock Laboratories secured approval of LAClotion™, the first bioequivalent ammonium lactate 12% lotion in June 2002 (ANDA # 75-575).

The just-issued ANDA approvals reaffirm that FDA considers ammonium lactate 12% products for the relevant indications to be new drugs subject to the definition of 21 U.S.C.

§ 321(p), the approval requirements 21 U.S.C. § 355, and the prescription dispensing restriction of 21 U.S.C. § 353(b).

We are mystified that Clay-Park -- which has just obtained ANDA approval of its ammonium lactate 12% *cream* -- may continue to market an ammonium lactate 12% *lotion* product without comparable regulatory approval. At a minimum, the Clay-Park 12% lotion was available for purchase from a wholesaler as of July 18, 2002. Like the cream, however, Clay-Park's lotion product requires approval under an ANDA before it may lawfully be marketed in the U.S.

2. The Upsher-Smith, Clay-Park, and SDR Products Are Misbranded

The Upsher-Smith, Clay-Park, and SDR products are misbranded because they lack adequate directions for use. The products are subject to the provisions of 21 U.S.C. § 353(b)(1) and are not exempt from § 352(f)(1) in that the labeling fails to bear information required by regulation 21 C.F.R. § 201.100 (outlining adequate directions for use under which a practitioner licensed by law can use a drug safely and for the purposes for which it is intended, including indications, effects, dosages, routes, methods, frequency and duration of administration, relevant hazards, contraindications, side effects, and precautions).

Promotional materials for the products at issue lack fair balance and requisite qualifying information. For example, materials promoting AmLactin® 12% Lotion and Cream make positive product claims concerning efficacy and reduced skin and mental irritation. Yet there is no qualifying information to balance the claims, as required by 21 C.F.R. § 201.100.

The Upsher-Smith and SDR products also bear misleading label claims. For example:

- Upsher-Smith promotes the results of a study of AmLactin® AP that has not been verified to have clinical validity (*see* Attachment 3). An IBS Skicon-200 impedance meter was used to measure high-frequency conductance of the skin and support claims of improved skin hydration. We are not aware that this methodology has been determined an appropriate method of demonstrating bioavailability or equivalence to approved ammonium lactate products.
- SDR expressly claims equivalence to the approved product Lac-Hydrin®, based upon measurement of capacitance and Transepidermal Water Loss ("TEWL") (*see* Attachment 2). However, this methodology has been affirmatively rejected by FDA as a means of establishing equivalence between ammonium lactate products. *See* Letter from J. Woodcock to J. Scager re: Docket No. 95P-0379/CP1 at 2 (May 22, 2002). SDR's claims of bioequivalence thus may mislead healthcare practitioners or consumers

(who currently may obtain LACTREX™ without healthcare provider oversight) and suggest a level of regulatory approbation and supervision that does not in fact exist.

3. Fundamental Fairness Requires That FDA Take Regulatory Action

There is no reason that FDA should permit continued marketing of unapproved ammonium lactate 12% lotion and cream products subject to this letter. There are four FDA-approved products in the marketplace. Upsher-Smith, Clay-Park, and SDR have had fair warning (since at least 1998) that FDA regards the products at issue as new drugs, subject to applicable regulatory requirements. FDA may not authorize the marketing of an unapproved new drug in the absence of an approved NDA or ANDA. See Hoffman-LaRoche v. Weinberger, 425 F. Supp. 890 (D.D.C. 1975). This is not a situation in which there is any arguable medical necessity to permit continued marketing of unapproved new drug products until such time as FDA can evaluate appropriate drug applications and determine whether the covered products are safe, effective, and properly manufactured and labeled.

Upsher-Smith's, Clay-Park's, and SDR's unlawful distribution of their products, and misrepresentations as to safety and effectiveness, also raise important questions of fundamental fairness and threaten real economic harm to competitor companies that are playing by the rules. Paddock Laboratories, for example, has expended significant time and resources to conduct clinical studies and other activities to support FDA approval of its 12% ammonium lactate lotion. On a post-marketing basis, it is complying with on-going FDA-related obligations. Apart from potential safety and effectiveness questions that surround use of the unapproved ammonium lactate drug products, it is simply wrong to let the competitors continue with their current obvious and serious violations in the face of such legitimate industry investment.

C. Environmental Impact

As provided in 21 C.F.R. § 25.31, neither an environmental assessment nor an environmental impact statement is required.

D. Economic Impact

As provided in 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

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E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to us which are unfavorable to the petition.

Sincerely,

KING & SPALDING

By: 
Christina M. Markus

Attachments

cc: William Nychis, Acting Director
Division of Drug Labeling and
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(w/attach.)