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January 10, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 02P-0401/CP1

Dear Sir/Madam:

On behalf of Upsher-Smith Laboratories, Inc. (Upsher-Smith), the undersigned submit these comments on the September 5, 2002, citizen petition filed by King & Spalding on behalf of Paddock Laboratories, Inc. (hereinafter the "Paddock Citizen Petition").

The Paddock Citizen Petition requests that the Food and Drug Administration (FDA) take action against Upsher-Smith, Clay-Park Laboratories, Inc. (Clay-Park), and SDR Pharmaceuticals, Inc. (SDR) for marketing "unapproved and misbranded new drug products." The petition alleges that the companies' products[1] are unapproved and misbranded drugs because, among other reasons, they contain 12% ammonium lactate, the same ingredient found in Paddock Laboratories, Inc.'s (Paddock's) recently FDA-approved

[1] The Paddock Citizen Petition alleges that Clay-Park's Ammonium Lactate Lotion 12%, SDR's Lactrex™ 12% Moisturizing Cream, and Upsher-Smith's AmLactin® 12% Moisturizing Lotion and Cream, and AmLactin AP Anti-Itch Moisturizing Cream products are unapproved and misbranded new drug products.

02P-0401

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LAClotion 12% Lotion prescription drug product, which is indicated for the treatment of ichthyosis vulgaris and xerosis.

FDA should deny the Paddock Citizen Petition. As discussed in more detail below, the AmLactin 12% Moisturizing Lotion and Cream products are lawfully marketed cosmetics, and AmLactin AP Moisturizing Cream is a lawfully marketed over-the-counter (OTC) drug and cosmetic product under the Federal Food, Drug, and Cosmetic Act (FDC Act). Therefore, there is no basis for FDA to take any regulatory action against these products.

I. AmLactin 12% Moisturizing Lotion and Cream Products Are Lawful Cosmetics

A. AmLactin 12% Moisturizing Lotion and Cream Products Bear Lawful Cosmetic Claims

Upsher-Smith's AmLactin 12% Moisturizing Lotion and Cream products are lawfully marketed cosmetics under the FDC Act. As noted in the Paddock Citizen Petition, the claims made for the products in labeling include the following:

> 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.

Paddock Citizen Petition at 3; see also AmLactin 12% Moisturizing Lotion and Cream brochure (Attachment 1). Similar claims are made for these products on their immediate container labels and in other labeling:

> AmLactin® 12% Moisturizing Cream Moisturizes and Softens Rough, Dry Skin. (Attachment 2.)
>
> AmLactin® 12% Moisturizing Lotion Moisturizes and Softens Rough, Dry Skin. (Attachment 3.)
>
> 12% Lactic Acid – Promotes natural moisture retention. (Attachment 4.)

> 12% Lactic Acid – An effective naturally occurring humectant. (Attachment 5.)
>
> . . . AmLactin® 12% breaks through the roughness to restore lost moisture and soften the skin. (Attachment 6.)
>
> For Patients with Rough, Dry Skin – Break Through the Roughness To Restore Moisture and Bring Relief. (Attachment 7.)

The Paddock Citizen Petition asserts that the claims made for AmLactin 12% Moisturizing Lotion and Cream products are "structure/function" claims and that the claims, "[w]hether in scientific or simple language, . . . 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." Paddock Citizen Petition at 3.

The above claims for the AmLactin 12% Moisturizing Lotion and Cream products are not "structure/function" claims, which would create drug status for the products. Rather, the claims are lawful cosmetic claims. The FDC Act defines "cosmetic," in pertinent part, as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance." FDC Act § 201(i)(1); 21 U.S.C. § 321(i)(1). Products intended to moisturize or hydrate the skin fall under the definition of "cosmetic" since they beautify and alter the appearance of the skin by making it feel smoother and less dry. See FDA, Cosmetics and U.S. Law (Apr. 28, 2000) ("Included in [the FDC Act] definition [of cosmetic] are products such as skin moisturizers."), at http://www.cfsan.fda.gov/~dms/cosuslaw.html (Attachment 8).

Furthermore, numerous other cosmetic products bear moisturizing and hydrating claims, and FDA has not objected to such claims. See, e.g., label of Cetaphil® Moisturizing Cream (Attachment 9) ("Cetaphil® Moisturizing Cream was formulated specifically for chronic dry, sensitive skin. Contains a superior system of extra-strength emollients and humectants, clinically proven to bind water to the skin and prevent moisture loss. Provides long-lasting relief to even severe dry skin."); label of Neutrogena® Hand Cream (Attachment 10) ("Concentrated relief for dry chapped hands."). If FDA adopts the theory proposed by the Paddock Citizen Petition – i.e., that moisturizing and hydration claims are "structure/function" claims – then numerous other cosmetic products making the same claims will be subject to regulation as drugs.

Furthermore, in no way do the AmLactin 12% Moisturizing Lotion and Cream product claims suggest that the products are intended to alleviate ichthyosis vulgaris and xerosis.[2] None of the labeling for the products mentions ichthyosis vulgaris or xerosis, and one cannot infer from the claims in the labeling that the products are intended to treat these diseases.

Ichthyosis is defined as "dry skin" that "ranges from mild but annoying dryness to severe dryness with scales and flaking that becomes disfiguring." The Merck Manual of Diagnosis and Therapy 831 (Mark H. Beers, M.D. & Robert Berkow, M.D. eds., 17th ed. 1999). "Xeroderma," or xerosis, is defined as "the mildest form of ichthyosis" that "usually occurs on the lower legs of middle-aged or older patients." Id. Although one of the symptoms of ichthyosis vulgaris and xerosis is dry skin, this symptom is a condition that many people have without these diseases. For example, dry skin can be caused by the weather or exposure to chemical cleaning agents on the hands. Thus, dry skin is not associated solely with ichthyosis vulgaris or xerosis, and dry skin caused by factors other than these diseases can be alleviated by the use of cosmetic moisturizing lotions and creams.

If FDA adopts the theory proposed by the Paddock Citizen Petition – i.e., that in addition to being structure/function claims, moisturizing and hydration claims are implied claims to treat ichthyosis vulgaris or xerosis – then, again, numerous other cosmetic products making the same claims will be subject to regulation as drugs.

B. The Products' Formulations Do Not Create Drug Status

The AmLactin 12% Moisturizing Lotion and Cream products each contain 12% lactic acid, which is an alpha-hydroxy acid and a naturally occurring humectant for the skin. Alpha-hydroxy acids are present in numerous cosmetic products, and lactic acid itself is well-known for its cosmetic moisturizing properties. See Cosmetic, Toiletry, and Fragrance Association (CTFA), International Cosmetic Ingredient Dictionary and

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[2] SDR's Lactrex 12% Moisturizing Cream, however, does bear in its labeling claims regarding the product's effectiveness in the treatment of ichthyosis vulgaris and xerosis. As noted in the Paddock Citizen Petition, SDR's website promotes Lactrex "[f]or [the] treatment of moderate to severe dry skin resulting from xerosis, eczema, [and] ichthyosis." See Paddock Citizen Petition at 3; see Attachment 11.

Handbook 860 (Renae Canterbery Pepe et al. eds., 9th ed. 2002) (hereinafter "Cosmetic Ingredient Dictionary") (listing lactic acid as an exfoliant, humectant, and pH adjuster); see also 67 Fed. Reg. 71,577 (Dec. 2, 2002) (FDA Draft Guidance for Industry on Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients) ("The predominant AHAs present in cosmetic products are glycolic and lactic acid.").

Contrary to what the Paddock Citizen Petition asserts, the inclusion of 12% lactic acid in the AmLactin 12% Moisturizing Lotion and Cream products does not cause the products to be unapproved new drugs. A product can be a drug or cosmetic, depending on the product's intended use. See, e.g. United States v. Articles of Drug for Veterinary Use, 50 F.3d 497, 500 (8th Cir. 1995) ("[W]hether a product is a drug depends on the intended application.") (quoting United States v. Pro-Ag, Inc., 796 F. Supp. 1219, 1224 (D. Minn. 1991), aff'd, 968 F.2d 681 (8th Cir. 1992)). A manufacturer's claims as to a product's use determines the product's intended use. See Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998) ("[N]o court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDC Act] absent manufacturer claims as to that product's use.") (internal quotation marks omitted) (quoting Coyne Beahm, Inc. v. FDA, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997)); see also Action on Smoking and Health v. Harris, 655 F.2d 236, 238-39 (D.C. Cir. 1980) (stating that it is an accepted "matter of statutory interpretation" that a manufacturer's representations determine a product's intended use).

For example, some cosmetics contain a sunscreen active drug ingredient to function as a sunscreen – that is, to absorb, reflect, or scatter the harmful burning rays of the sun – and other cosmetic products contain a sunscreen ingredient "for nontherapeutic, nonphysiologic uses (e.g., as a color additive or to protect the color of [a] product)." 21 C.F.R. § 700.35(a). Whether a cosmetic product containing a sunscreen ingredient will be regulated as a cosmetic or a combination cosmetic-drug depends on the intended use of, or claims made for, the product.[3]

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[3] The Paddock Citizen Petition alleges that "[i]t is evident that the objectionable ammonium lactate 12% products are recognized as substitutes for FDA-approved, prescription ammonium lactate 12% lotion and cream." Paddock Citizen Petition at 5. The petition then quotes the following text from dermadoctor.com, an on-line dermatology website: "[AmLactin® 12% Moisturizing Lotion is] equivalent to other prescription lactic acid moisturizing agents. Great for seriously dry skin conditions like eczema, ichthyoses, psoriasis and keratosis pilaris.'" However,

Similarly, numerous cosmetics contain the ingredients cocoa butter, lanolin, mineral oil, and petrolatum, which can function cosmetically as skin conditioning agents, see CTFA, Cosmetic Ingredient Dictionary at 868, 994, 1230, 1705, and which can function therapeutically as OTC skin protectant active drug ingredients, 21 C.F.R. § 346.14(a)(2), (6)-(8). Thus, there is nothing inherently illegal in including in a cosmetic product 12% lactic acid provided that the ingredient is intended to function as a cosmetic.

C. The Target Audience for AmLactin 12% Moisturizing Lotion and Cream Products Does Not Create Drug Status for the Products

The Paddock Citizen Petition asserts that Upsher-Smith's marketing of AmLactin 12% Moisturizing Lotion and Cream products to physicians further demonstrates the company's intent to market the products as substitutes for prescription ammonium lactate products. See Paddock Citizen Petition at 4. However, numerous non-drug products are marketed to physicians, and the mere marketing of products to physicians does not create drug status for products.

It is well-known that dermatologists receive "professional samples" of various cosmetic products, from anti-wrinkle cosmetic creams to moisturizing lotions.[4] These products are also featured at professional dermatological meetings.[5] The manufacturers of these cosmetics market their products to physicians so that the physicians will recommend the products to patients for the products' cosmetic uses, whether that be to combat the appearance of the signs of aging or to moisturize dry skin. Similarly, companies market various dietary supplements and medical foods to physicians so that the physicians will recommend the products to patients – not so that the products will replace appropriate drug

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Upsher-Smith does not run the dermadoctor.com website, and Upsher-Smith does not sell AmLactin products directly to the website operators.

4 Attached are copies of labels of cosmetic samples that Upsher-Smith obtained from dermatologists' offices. Presumably company representatives left these samples with the dermatologists. See Attachment 12.

5 At the upcoming American Academy of Dermatology annual meeting, numerous cosmetic companies will undoubtedly display their cosmetic products. See Attachment 13.

products. In sum, the mere marketing of the AmLactin products to physicians, or labeling the products as "professional samples," does not create drug status for the products.

II. AmLactin AP Moisturizing Cream Is a Lawful OTC Drug and Cosmetic Product

In contrast to the two AmLactin cosmetic products, AmLactin AP Moisturizing Cream is both (1) a lawful cosmetic and (2) an OTC external analgesic drug product that substantially conforms with FDA's tentative final monograph (TFM) for external analgesics. See 48 Fed. Reg. 5852, 5867 (Feb. 8, 1983) (Proposed 21 C.F.R. Part 348). AmLactin AP Moisturizing Cream contains 1% pramoxine HCL and is indicated for the temporary relief of "itching associated with dry skin and other minor skin irritations."[6] Attachment 14. The labeling for the product bears similar claims, such as:

> 1% Pramoxine HCL – Temporarily relieves itching. (Attachment 4.)
>
> 12% Lactic Acid – Promotes natural moisture retention. (Attachment 4.)

As noted in the Paddock Citizen Petition, the labeling for AmLactin AP Moisturizing Cream also describes the product's effectiveness in a study on subjects with a history of dry, itchy skin:

> Subjects [treated with AmLactin AP] had statistically significant improvement in skin surface hydration by day 3 with further improvement by day 7. Subjects also reported statistically significant improvement in dry skin and itch on day 1 with continued improvement through day 7.

Attachment 15 (footnotes omitted); see also Paddock Citizen Petition at 3.[7]

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[6] FDA has tentatively concluded that 1% pramoxine HCL, a Category I ingredient in the OTC TFM for external analgesics, is a generally recognized as safe and effective external analgesic drug. See 48 Fed. Reg. at 5865.

[7] The Paddock Citizen Petition asserts that Upsher-Smith's promotion of the results of this study is misleading (and therefore misbrands the product) because the results have "not been verified to have clinical validity." Paddock Citizen Petition at 6. The petition maintains that the use of an IBS Skicon-200 impedence meter "to

The above indications and claims comport with the indications permitted in the TFM for OTC external analgesic drug products containing the active ingredient pramoxine HCL. The TFM for OTC external analgesic drugs permits the following indications for products containing pramoxine HCL:

> "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," or "minor skin irritations.")).

48 Fed. Reg. at 5868 (Proposed 21 C.F.R. § 348.50(b)(2)).

That the AmLactin AP Moisturizing Cream product is indicated to temporarily relieve itching "associated with dry skin," which is not mentioned in the TFM, does not cause the product to be an unapproved new drug. An OTC drug product may bear "alternative truthful and nonmisleading statements describing only those indications for use that have been established" in a monograph. 21 C.F.R. § 330.1(c)(2). Further, FDA has acknowledged that the external analgesic TFM does not list all causes of itching and that OTC antipruritic drugs can provide temporary relief for causes of itching that are not listed in the TMF. See 48 Fed. Reg. at 5863 ("The agency agrees with the comment that products containing antipruritic ingredients should be allowed to use the indication 'For the temporary relief [of] itching' without listing examples of causes of itching. Such labeling would be clearly recognizable and meaningful to a consumer who was experiencing itching without knowing the cause.").

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measure high-frequency conductance of the skin and support claims of improved skin hydration" is not known to be "an appropriate method of demonstrating bioavailability or equivalence to approved ammonium lactate products." Id. However, the purpose of the study was not to demonstrate AmLactin AP's bioavailability or equivalence to approved ammonium lactate products; rather, the study was intended to determine whether AmLactin AP reduces itch and hydrates the skin compared to no treatment. Furthermore, the IBS Skicon-200 impedence meter is a well-accepted instrument to use to measure skin hydration in cosmetic products.

Further, for the reasons provided in section I.A above, the claims for AmLactin AP Moisturizing Cream do not suggest that the product treats ichthyosis vulgaris or xerosis. Moreover, the product's formulation does not cause it to be an unapproved new drug; the product is properly formulated as an OTC external analgesic drug and cosmetic product. Finally, as noted in section I.C above, companies market all kinds of products to physicians – both prescription and nonprescription drugs as well as cosmetics and foods. Marketing AmLactin AP Moisturizing Cream to dermatologists does not imply that the product is intended to treat ichthyosis vulgaris or xerosis.

III. AmLactin 12% Moisturizing Lotion and Cream Products and the AmLactin AP Moisturizing Cream Product Are Not Misbranded

The Paddock Citizen Petition alleges that Upsher-Smith's AmLactin products are misbranded because they fail to bear adequate directions for use and "lack fair balance and requisite qualifying information." Paddock Citizen Petition at 6. Because the AmLactin 12% Moisturizing Lotion and Cream products are cosmetics and not prescription drugs, these products are not required to bear adequate directions for use, and their promotional materials are not subject to FDA's fair balance standard for prescription drug advertising. See 21 U.S.C. § 502(f)(1) (requiring adequate directions of use for drugs); 21 C.F.R. § 202.1 (requiring fair balance in the advertisement of prescription drugs).[8]

Furthermore, the AmLactin AP Moisturizing Cream product does bear adequate directions for use, as specified in the TFM for OTC external analgesic products. See Attachment 14; see also 48 Fed. Reg. at 5869 (Proposed § 348.50(d)). The promotional

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[8] In arguing that the promotional materials for AmLactin 12% Moisturizing Lotion and Cream products lack fair balance, the Paddock Citizen Petition states that one of the "positive product claims" for the products is that they reduce "mental irritation." Paddock Citizen Petition at 6. The Paddock Citizen Petition misquoted the claim and took it out of context, however. The claim, which is actually "patient irritation," is simply a play on words as can be seen from the context of the brochure. It refers to the cost of the product – not to any claim of product performance. See Attachment 4 ("AmLactin 12% Moisturizing Lotion and Cream . . . Fragrance-Free Formulation – Reduces the potential for skin irritation[, and] Economic Pricing – Reduces the potential for patient irritation.").

materials for the AmLactin AP Moisturizing Cream are not subject to FDA's fair balance requirement for prescription drug advertising because, like AmLactin 12% Moisturizing Lotion and Cream products, AmLactin AP Moisturizing Cream is not a prescription drug.

* * * *

In sum, FDA should deny the Paddock Citizen Petition because Upsher-Smith's AmLactin 12% Moisturizing Lotion and Cream products are lawful cosmetics and the AmLactin AP Moisturizing Cream product is a lawful cosmetic and OTC drug product under the FDC Act.

Sincerely,

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Cassandra A. Soltis
Counsel for Upsher-Smith

RAD/CAS/vam
Attachments