

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2000P-1378]

Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance document entitled “Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients.” The guidance recommends content for a labeling statement for cosmetic products containing alpha hydroxy acids (AHAs) as ingredients. This action was prompted by a citizen petition filed by the Cosmetic, Toiletry, and Fragrance Association, which requested that FDA issue a regulation establishing labeling requirements relating to sun protection with use of cosmetic products containing AHAs.

DATES: You may submit written or electronic comments on the guidance document at any time.

ADDRESSES: Submit written requests for single copies of the guidance document to the Office of Cosmetics and Colors, Center for Food Safety and Applied Nutrition (HFS-100), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835. Include a self-addressed adhesive label to assist that office in processing your request or include a fax number to which the guidance document may be sent.

Submit written comments on the guidance document to the Division of Dockets Management (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Julie N. Barrows, Center for Food Safety and Applied Nutrition (HFS-125), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835, 301-436-1344.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance document entitled “Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients.”

On December 2, 2002 (67 FR 71577), FDA announced the availability of the draft version of this guidance document in the **Federal Register**.

II. Comments on Draft Guidance

FDA has evaluated the seven comments received in response to the draft guidance recommending “Sunburn Alert” labeling on cosmetic products that contain AHAs as ingredients.

One comment from a nurse’s association fully supported the AHA labeling statement. The comment stated that the inclusion of the “Sunburn Alert” on skin care products containing AHAs is an important step in empowering health providers and consumers with valuable information about how to protect their skin while using these products.

Three comments stated that the guidance should apply only to products intended to function as an exfoliant. For example, the comments suggested that

the guidance should not apply to products containing citric acid when it is used for adjusting the hydrogen-ion concentration (pH) in shampoos and other products.

Limiting the recommended labeling statement to products with exfoliation claims may leave out products that FDA believes should bear the labeling statement. FDA's surveys indicated that approximately half of the products on the market that contain an AHA as an ingredient have an intended use as an exfoliant, as determined by the presence of exfoliant claims in the product labeling. Even some salon products containing high levels of AHAs did not contain exfoliation claims in the labeling. FDA has no data suggesting that citric acid has less of an effect on the skin than glycolic acid or lactic acid, the predominant AHAs present in cosmetic products, regardless of its intended use. FDA has not modified the guidance in response to these comments.

Two comments requested that FDA provide an exemption from the AHA labeling statement for products that exceed an appropriately high pH level.

Percutaneous absorption studies suggest that topically applied AHAs in any cosmetic product may be absorbed by the skin to some extent, depending on product formulation, pH, and contact time (Refs. 1 and 2). The studies measured absorption of glycolic acid, lactic acid, and other AHAs by human skin at pH 3 and pH 7 using various product formulations. Although much greater absorption was observed at pH 3, substantial absorption was observed at pH 7. FDA has not modified the guidance in response to these comments.

Three comments requested that FDA provide an exemption from the AHA labeling statement for cosmetic products containing low concentrations of AHAs. One comment suggested that products containing AHA ingredients at

concentrations of 1 percent or less should be exempted. The comments did not provide any data to support their request.

The evidence reviewed so far by FDA suggests that topical application of a cosmetic product containing an AHA as an ingredient at any concentration may increase skin sensitivity to the sun and the possibility of sunburn. FDA analyzed approximately 100 cosmetic products containing AHAs as ingredients and found concentrations of AHAs ranging from 0.01 percent to 67 percent (Ref. 3). Most of the analyzed products with very low levels of some AHAs also contained higher levels of other AHAs. One product for which FDA received five adverse experience reports (e.g., skin irritation, burning) contained only 0.3 percent α -hydroxydecanoic acid and 0.4 percent α -hydroxyoctanoic acid, for a total of 0.7 percent AHAs, suggesting that AHAs may be associated with adverse reactions even at these low concentrations. FDA has not modified the guidance in response to these comments.

FDA recognizes that an AHA can be present in a cosmetic product as an incidental ingredient. As defined in § 701.3(l) (21 CFR 701.3(l)), incidental ingredients are ingredients that are present in a cosmetic at insignificant levels and that have no technical or functional effect in the cosmetic. Incidental ingredients are not required to be declared in the ingredient lists on cosmetic labels. Therefore, if an AHA were used only as an incidental ingredient in a cosmetic product, its presence would not require declaration on the label. The agency finds that providing for a “Sunburn Alert” labeling statement on a cosmetic product in which the only use of an AHA was as an incidental ingredient would have very limited utility in protecting the consumer. Moreover, the presence of the “Sunburn Alert” labeling statement could be confusing to consumers because the ingredient label would not declare the

presence of an AHA. Therefore, FDA has modified the guidance to state that the agency's recommendation for the AHA labeling statement does not apply to products in which an AHA is present as an incidental ingredient, as defined in § 701.3(l).

Three comments noted that AHA ingredients are used in a wide range of products as pH adjusters, chelating agents, fragrance ingredients, humectants, and skin conditioning agents and asserted that AHAs present in a product for these uses could not be reasonably anticipated to cause increased susceptibility to sunburn. An example given was citric acid. Two of the comments requested that the guidance apply only to AHA-containing cosmetic products used on areas of the body normally susceptible to sunburn.

The comments addressed a range of intended uses for AHAs in cosmetic products, as well as identified many different types of products that contain AHAs as ingredients, but did not provide data to support their request. The percutaneous absorption studies discussed previously suggest that topically applied AHAs in any cosmetic product, regardless of intended use, may be absorbed by the skin, including the skin on the scalp or under the arms. The draft guidance did not address the possibility of unintentional topical application of AHAs to parts of the skin or mucous membrane that are exposed to the sun. Therefore, FDA has modified the guidance to state that FDA recommends "Sunburn Alert" labeling for cosmetic products that contain an AHA as an ingredient and that are intended for application to areas of the body that may result in unintentional application to the skin or mucous membrane that are exposed to the sun.

FDA recognizes that AHAs can be present in cosmetic products that are applied to areas of the body that are not sun exposed. Such products include

mouthwashes, breath fresheners, and douches. Therefore, FDA has modified the guidance to state that the guidance does not apply to cosmetic products that contain an AHA as an ingredient and that are intended for application to non-sun exposed areas of the body.

Three comments recommended modified labeling statements for AHA-containing products that also contain a sunscreen. The comments stated that the AHA labeling statement may not be appropriate for products containing sunscreens and may be confusing to consumers. One comment suggested that inclusion of a sunscreen at an appropriate level might serve as a basis for not recommending the AHA labeling statement. Two comments proposed that the AHA labeling statement for products containing a sunscreen should be shortened to address only the need to use a sunscreen for 7 days after use of the AHA product is discontinued.

When an AHA is present in a product that is labeled to contain a sunscreen, that product meets the definition of a drug-cosmetic. Such products must comply with the requirements for drugs and cosmetics, including applicable over-the-counter sunscreen drug product regulations. FDA has modified the guidance to state that the recommended AHA labeling statement does not apply to drug-cosmetic products that contain an AHA as an ingredient and also are labeled to contain a sunscreen for sunburn protection. FDA intends to address labeling for such products in a future document.

Three comments requested changes to FDA's recommended AHA labeling statement. Two comments urged FDA to reconsider identifying AHAs in the labeling statement because the presence of an AHA ingredient does not always result in increased sun sensitivity or likelihood of sunburn. Another comment stated that FDA's AHA labeling statement is quite long, especially for labeling

cosmetic products packaged in small containers. The comment submitted a statement that is about three-fourths the length of FDA's recommended statement.

In the AHA guidance, FDA discusses research on effective labeling statements. The research suggests that an effective labeling statement would begin with a signal phrase, identify the subject of the statement, identify the consequences of not heeding the statement, and provide instructions on what to do (or not do) to avoid these consequences. Removal of any of these elements may significantly decrease the effectiveness of the statement. Therefore, FDA finds that all of the recommendations in the "Sunburn Alert" are important components of information for an AHA labeling statement.

FDA's current thinking on sun protection is that a total program to reduce harmful effects from the sun would include limiting sun exposure, wearing protective clothing, and using sunscreens. Therefore, in accordance with this current thinking on sun protection, the agency has modified the "Sunburn Alert" labeling statement that we recommended in our draft guidance to add the words "wear protective clothing" to the list of actions that may be taken to reduce the possibility of sunburn when using cosmetic products that contain an AHA as an ingredient.

FDA recognizes that there is limited labeling space on cosmetic products packaged in small containers and has modified the guidance to clarify that it recommends that the AHA labeling statement appear prominently and conspicuously once in the labeling of a cosmetic product.

One comment recommended that a "Sunburn Alert" labeling statement be extended to products containing poly hydroxy acid and/or beta hydroxy acid. The comment noted that these compounds are exfoliants with the same

increased skin sensitivity concern as that for AHAs. The comment did not define the term “poly hydroxy acid” and did not provide data to support its recommendation to extend a “Sunburn Alert” labeling statement to products containing poly hydroxy acid and/or beta hydroxy acid. FDA does not have data on the effect of topical use of these compounds on the skin. Therefore, FDA finds that there is currently no basis to recommend that the “Sunburn Alert” statement appear in the labeling of cosmetics that contain the compounds discussed in this comment. FDA has not modified the guidance in response to this comment.

Finally, two comments on the draft guidance requested that FDA provide an exemption from the AHA labeling statement for properly formulated cosmetic products when the manufacturer or distributor has competent and reliable scientific evidence demonstrating that the product containing an AHA at any level of concentration and pH does not increase sun sensitivity or the likelihood of sunburn. To support its contention, one comment provided documentation of a study of the effects of ultraviolet (UV) radiation on skin pre-treated with lactic acid.

In its report (Ref. 4), published in 1998, the Cosmetic Ingredient Review (CIR) Expert Panel reported the following conclusion:

Based on the available information included in this report, the CIR Expert Panel concludes that Glycolic and Lactic Acid, their common salts and their simple esters, are safe for use in cosmetic products at concentrations ≤ 10 percent, at final formulation pH ≥ 3.5 , when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations ≤ 30 percent, at final formulation pH ≥ 3.0 , in products designed for brief, discontinuous use followed by thorough rinsing from

the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection. * * *

FDA reviewed the study submitted in the second comment and determined that the study used less sensitive methods than did the studies reviewed for the guidance (Ref. 5). For example, the study reported that exposure of control sites (i.e., sites without topical treatment with AHA-containing test samples) to 1 minimal erythema dose (MED) of UV radiation resulted in sunburn cell formation in only 4 out of 18 subjects. However, in the studies that FDA reviewed for the guidance and that used sunburn cell formation as an indicator of UV radiation-induced damage, exposure of control sites to 1 MED of UV radiation resulted in sunburn cell formation in 71 out of 72 subjects. (The MED is the minimum level of UV radiation needed to cause skin redness and has to be measured for each subject.)

FDA has modified the guidance to state that it may be possible in the future to formulate a cosmetic product that contains an AHA as an ingredient and that does not increase the sensitivity of skin to the sun. However, FDA is not aware of the current existence of such a product.

Based on evidence reviewed so far, FDA concludes that topically applied cosmetic products containing AHAs as ingredients may increase skin sensitivity to the sun while the products are used and for up to a week after use is stopped, and that this increased skin sensitivity to the sun may increase the possibility of sunburn. FDA does not know the extent of consumer awareness of the potential for increased skin sensitivity to the sun from the topical use of AHA-containing cosmetic products. The agency is publishing this guidance to help assure consumer awareness of this potential and to

educate manufacturers to help ensure that their labeling is not false or misleading.

Publication of this guidance is an interim measure while FDA continues to review the data on the effects of AHA-containing products on skin sensitivity to UV radiation, including a photocarcinogenicity study by the National Toxicology Program's Center for Phototoxicology and recent studies published in peer-reviewed journals. FDA invites comments to continue to inform FDA of new studies when they become available.

FDA is issuing this guidance as a level 1 guidance consistent with FDA's good guidance practices regulation (21 CFR 10.115). This guidance represents the agency's current thinking on the labeling of topically applied cosmetic products that contain an AHA as an ingredient. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if the approach satisfies the requirements of applicable statutes and regulations.

III. Comments on Guidance

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IV. Electronic Access

Copies of this guidance also are available on the Internet at <http://www/cfsan.fda.gov/~dms/guidance.html>.

V. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Sah, A., S. Mukherjee and R. R. Wickett, "An In Vitro Study of the Effects of Formulation Variables and Product Structure on Percutaneous Absorption of Lactic Acid," *Journal of Cosmetic Science*, vol. 49, pp. 257–273, 1998.

2. Kraeling, M. E. K. and R. L. Bronaugh, "In Vitro Percutaneous Absorption of Alpha Hydroxy Acids in Human Skin," *Journal of the Society of Cosmetic Chemists*, vol. 48, pp. 187–197, 1997.

3. Yates, R. L. and D. C. Havery, "Determination of Phenol, Resorcinol, Salicylic Acid and α -Hydroxy Acids in Cosmetic Products and Salon Preparations," *Journal of Cosmetic Science*, vol. 50, pp. 315–325, 1999.

4. Andersen, F. A., ed., "Final Report on the Safety Assessment of Glycolic Acid, Ammonium, Calcium, Potassium, and Sodium Glycolates, Methyl, Ethyl, Propyl, and Butyl Glycolates, and Lactic Acid, Ammonium, Calcium, Potassium, Sodium, and TEA-Lactates, Methyl, Ethyl, Isopropyl, and Butyl Lactates, and Lauryl, Myristyl, and Cetyl Lactates," *International Journal of Toxicology*, vol. 17, supplement 1, pp. 1–241, 1998.

5. Wamer, W., Office of Cosmetics and Colors, CFSAN, Review of Documents from Access Business Group: Aupperlee, D., et al., "The Effects of UV Light on Skin Pre-Treated With Alpha Hydroxy Acid Moisturizers," and Thomas J. Stevens and Associates, "The Effects of Repetitive Cutaneous Application of Test Materials Containing Alpha Hydroxy Acid on the Sensitivity of Skin to Ultraviolet (UV) Light," July 1, 2003.

Dated: December 29, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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