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Guidance for Industry

Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients

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U.S. Department of Health and Human Services
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Cosmetics Labeling

Guidance for Industry[(1)]

Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients

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I. Introduction

FDA has considered evidence that suggests that topically applied cosmetic products containing alpha hydroxy acids (AHAs) as ingredients may increase the sensitivity of skin 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. The purpose of this guidance is to educate consumers about the potential for increased skin sensitivity to the sun from the topical use of cosmetics containing AHAs as ingredients and to educate manufacturers to help ensure that their labeling for cosmetic products containing AHAs as ingredients is not false or misleading. As an interim measure, while FDA continues to review the data on AHAs to address the potential for this increased skin sensitivity to the sun, FDA is recommending that the labeling of a cosmetic product that contains an AHA as an ingredient and that is topically applied to the skin or mucous membrane bear a statement that conveys the following information. The information in the AHA labeling statement is consistent with FDA's current thinking on sun protection.

> Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards.

Alpha hydroxy acids are organic acids with a hydroxyl group on the carbon adjacent to the carboxylic acid group. The predominant AHAs present in cosmetic products are glycolic acid and lactic acid. Other AHAs used in cosmetic products include citric acid, α-hydroxyoctanoic acid, and α-hydroxydecanoic acid (Reference 1).

Starting in 1994, the Cosmetic, Toiletry, and Fragrance Association's Cosmetic Ingredient Review Expert Panel, FDA's AHA Review Committee, and FDA reviewed the safety of topically applied

AHAs in cosmetic products (References 2 through 4). The reviewers evaluated human clinical studies that investigated the effects of ultraviolet (UV) radiation on the skin after exposure to AHAs. The studies demonstrated that topically applied AHAs increase skin sensitivity to UV radiation during application and that this increased skin sensitivity to UV radiation diminishes after discontinuing application for a week.

Sensitivity to UV radiation is the main reason for the skin's sensitivity to the sun (Reference 5). Short-term exposure to the sun may cause sunburn and chronic long-term exposure to the sun may increase risk of premature skin aging (Reference 5). Experimental and epidemiological studies have demonstrated that prolonged exposure to the UV radiation in sunlight is a primary risk factor for certain types of skin cancer (References 6 through 8).

The human clinical studies reviewed by the Cosmetic Ingredient Review Expert Panel, FDA's AHA Review Committee, and FDA provided data for the effects of UV radiation on the skin after short-term (up to 12 weeks) topical exposure to AHAs. The evidence from the clinical studies suggests that increased skin sensitivity to UV radiation may increase the possibility of sunburn for consumers. Adverse experience reports by consumers of increased sunburn after AHA use support this conclusion (Reference 2). The increased skin sensitivity to UV radiation also may result in other harmful effects to the skin, but the data currently available to FDA's Center for Food Safety and Applied Nutrition (CFSAN) are still inconclusive on this point at this time.

This guidance applies to cosmetic products that contain an AHA as an ingredient and that are intended for topical application to the skin or mucous membrane. Most AHAs used as cosmetic ingredients are formulated into products that are intended for topical application to the skin or mucous membrane.

Certain products may not be intended for topical application of AHAs to parts of the skin or mucous membrane that are exposed to the sun, but such application may be unintentional (e.g., shampoos, deodorants). This guidance also applies to 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 topical application to the skin or mucous membrane that are exposed to the sun.

However, AHAs can be present in cosmetic products that are applied to areas of the body that are not sun exposed (e.g., mouthwashes, breath fresheners, and douches). This 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.

AHAs can be present in products that also are labeled to contain a sunscreen. This guidance does not apply to drug-cosmetic products that contain an AHA as an ingredient and also are labeled to contain a sunscreen for sun protection. FDA intends to address labeling for such products in a future document.

AHAs can be present in cosmetic products as incidental ingredients. As defined in section 701.3(l) of the Code of Federal Regulations (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 the labels of cosmetic packages. This guidance does not apply to cosmetic products that contain an AHA as an incidental ingredient.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but

not required.

II. AHAs in Cosmetic Products

Since the early 1990's, there has been a proliferation of cosmetic products containing AHAs as ingredients available commercially and in salons (Reference 2). AHAs have been formulated into skin products, make-up, hair products, nail products, bath products, colognes, and suntan preparations. Most products containing AHAs as ingredients are "leave on" products that are intended for daily use on the skin or mucous membrane or are "discontinuous use" products that are intended to be applied to the skin for a short period of time (e.g., less than an hour) followed by thorough rinsing. Salon products are usually discontinuous use products.

In 1992, in its Voluntary Cosmetics Registration Program, FDA received the first four registrations of new lines of cosmetic products containing glycolic acid as an ingredient (Reference 2) (note that the information obtained through the program is an incomplete market history as the data are reported voluntarily). By 1997, the registrations of cosmetic product lines containing glycolic acid increased to forty-two, as glycolic acid and lactic acid were added to previously marketed lines of products.

From 1992 to 1996 and from 1999 to 2000, FDA conducted two market surveys of skin care products containing AHAs as ingredients and found that the predominant AHAs present in the products were glycolic acid and lactic acid (References 1 and 2). Other AHAs found were citric acid, α-hydroxyoctanoic acid, and α-hydroxydecanoic acid (Reference 1).

Between 1989 and 1991, FDA received five reports from consumers that described adverse dermatologic experiences from a line of cosmetic skin care products that were labeled as containing AHAs, including glycolic acid (Reference 2). The reported adverse experiences were similar and included pigmentary changes, burning, and swelling. FDA issued a warning letter to the manufacturer on May 13, 1992, and the products were withdrawn from the market. Although FDA analyses found that the products did not contain an AHA, but rather phenol and resorcinol, through this FDA became aware of the increasing use of AHAs as ingredients in cosmetic products. Between 1992 and 1993, FDA received 10 reports of adverse dermatologic experiences with products that were determined by FDA to contain AHAs. In 1994, the number of reports increased to 32. FDA received a total of 114 adverse dermatologic experience reports for AHA-containing skin care products between 1992 and February 2004, with the maximum number in 1994. The reported adverse experiences include burning (45), dermatitis or rash (35), swelling (29), pigmentary changes (15), blisters or welts (14), skin peeling (13), itching (12), irritation or tenderness (8), chemical burns (6), and increased sunburn (3).

III. Citizen Petition from the Cosmetic, Toiletry, and Fragrance Association

The Cosmetic, Toiletry, and Fragrance Association (CTFA) submitted a citizen petition, dated June 29, 2000, assigned FDA Docket No. 2000P-1378/CP1, which advocated sun protection labeling for cosmetic products containing AHAs as ingredients. The petition noted that at that time, products containing AHAs represented a significant portion of the $6 billion domestic United States skin care market; approximately 1500 stock-keeping units of skin care products contained AHAs.

In the petition, CTFA requested that FDA issue a regulation under 21 U.S.C. 362(a) establishing labeling requirements related to sun protection with use of certain cosmetic products containing AHAs as ingredients. The petition proposed the following regulation for 21 CFR Part 701-Cosmetic Labeling:

> The label and labeling of a cosmetic product that contains an alpha hydroxy acid

> ingredient that is intended to function as an exfoliant shall bear the following prominent and conspicuous statement:
>
> "Sun Alert: Because this product may make your skin more sensitive to the sun, be certain you have adequate sunscreen protection while using this product and for a week after you discontinue use."

IV. Safety Reviews of AHAs

CTFA's Cosmetic Ingredient Review (CIR) Expert Panel, FDA's AHA Review Committee, and FDA reviewed the safety of topically applied AHAs used as ingredients in cosmetic products (References 2 through 4). The reviewers evaluated human clinical studies that investigated the effects of UV radiation on the skin after exposure to glycolic acid and lactic acid, as well as salts and esters prepared from glycolic or lactic acids. The salts and esters included ammonium, calcium, potassium, and sodium glycolates; methyl, ethyl, propyl, and butyl glycolates; ammonium, calcium, potassium, sodium, and triethanolamine (TEA) lactates; methyl, ethyl, isopropyl, and butyl lactates; and lauryl, myristyl, and cetyl lactates.

The human clinical studies measured sunburn cell (SBC) formation and change in the minimal erythema dose (MED). SBCs are apoptotic skin cells that are produced in response to UV radiation, primarily UVB, and the MED is the minimal amount of UV radiation needed to cause the skin to redden (References 2 and 5). Both skin responses, SBC formation and erythema (skin reddening), are characteristic of sunburn (Reference 5). The studies also measured UV-induced cyclopyrimidine dimer (CPD) formation, which is a type of DNA damage.

CTFA's CIR Expert Panel concluded from human clinical studies that AHAs in cosmetic products increase skin sensitivity to UV radiation (UVB or solar-simulating radiation), as measured by SBC formation, which was found on average to increase, and as measured by change in the MED, which was found on average to decrease (Reference 3). In its final report, published in 1998 (Reference 3), the 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%, 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%, 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's AHA Review Committee, which met on February 12, 1997, and May 6, 1997, agreed that the evidence suggests that topical application of AHAs increases skin sensitivity to UV radiation, as measured by increased SBC formation and decreased MED (Reference 4). The Committee noted that in the human clinical studies they reviewed, a small proportion of people showed an amplified effect on increased SBC formation or decreased MED.

FDA has evaluated the CTFA citizen petition and the safety reviews of topical application of AHAs by the CIR Expert Panel and the AHA Review Committee. FDA also has reviewed in detail six human clinical studies that provide data for assessing increased skin sensitivity to UV radiation produced by

use of topically applied cosmetic products containing AHAs (Reference 2). Five of the studies measured increased SBC formation and/or decreased MED. The sixth study measured increased CPD formation. The studies used solar-simulating radiation and/or UVB radiation for determining baseline MEDs and for determining changes in MED and SBC or CPD formation. Although the studies investigated the effects of glycolic acid, FDA believes that the effects of other types of AHAs used in cosmetic products may be the same.

The human clinical studies that measured increased SBC formation or decreased MED found that topical application of glycolic acid at concentrations as low as 4% and for as short a duration as four days can alter the skin's response to UV radiation. Furthermore, the skin's enhanced sensitivity to UV radiation continues during exposure to glycolic acid of up to 12 weeks. Thus, the studies suggest that there is no compensatory mechanism by which the skin moderates the effects of an AHA on sensitivity to UV radiation. The studies also found that increased skin sensitivity to UV radiation no longer is evident one week after discontinuing topical application of glycolic acid. This suggests that AHA-induced sensitivity to UV radiation is reversible. However, further studies are required to determine how the length of time of AHA use affects the time required for reversal of AHA-induced effects. Skin sensitivity to UV radiation, measured as UV-induced CPD formation, may increase after four weeks of topical application of glycolic acid. However, the increase found (8%) is not statistically significant and suggests that further studies are required to determine the effects of AHA exposure on UV-induced CPD formation. Finally, the addition of sunscreens to cosmetic products containing AHAs, under some conditions of use, may affect skin sensitivity to UV radiation.

In most of the studies reviewed, a subset of subjects appeared to be more susceptible to the effects of glycolic acid on UV-induced increased SBC formation and decreased MED. This suggests that some individuals are more responsive than others to AHA-induced increased skin sensitivity to UV radiation. However, the studies did not identify any basis for identifying this subset of sensitive individuals, as a wide range of skin types was implicated.

The human clinical studies provided data for the effects of UV radiation on the skin after short-term (up to 12 weeks) topical exposure to AHAs. The evidence from the clinical studies suggests that increased skin sensitivity to UV radiation may increase the possibility of sunburn for consumers. Adverse experience reports by consumers of increased sunburn after AHA use support this conclusion (Reference 2). The increased skin sensitivity to UV radiation also may result in other harmful effects to the skin, but the data currently available to CFSAN are inconclusive on this point.

FDA's National Center for Toxicological Research (NCTR) is currently investigating the effects of long-term exposure to AHAs, in a photocarcinogenicity study by the National Toxicology Program's Center for Phototoxicology (Reference 2). The purpose of the NCTR study is to allow quantitative determination of the effect AHA treatment (glycolic acid) has on the induction of mouse skin cancer (SKH-1 hairless mouse) by simulated solar radiation.

V. "Sunburn Alert" AHA Labeling Statement

In its citizen petition, CTFA requested that the labeling statement informing consumers about measures to take when using certain cosmetic products containing AHAs as ingredients should say:

> Sun Alert: Because this product may make your skin more sensitive to the sun, be certain you have adequate sunscreen protection while using this product and for a week after you discontinue use.

FDA has reviewed information on the elements of effective labeling statements (Reference 2). This information indicates 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 significantly decreases the perceived effectiveness of the statement.

Based on this information, FDA has developed an alternate recommended statement and encourages manufacturers to use the following labeling statement for cosmetic products containing AHAs as ingredients:

> Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards.

FDA's basis for its recommended labeling is as follows.

First, FDA suggests a change in the signal phrase in the recommended AHA labeling statement from "Sun Alert" to "Sunburn Alert." Clinical studies indicate that increased skin sensitivity to the sun from topical application of AHA-containing cosmetic products increases the possibility of sunburn for consumers. Therefore, FDA's suggested signal phrase helps consumers recognize that the intent of the AHA labeling statement is to alert them to this increased possibility of sunburn.

Second, FDA believes that the recommended AHA labeling statement should identify to consumers the subject of the statement, which is the AHA ingredient contained in the cosmetic product. Therefore, FDA is including the phrase "This product contains an alpha hydroxy acid (AHA)" in its recommended statement.

Third, FDA believes that the recommended AHA labeling statement should tell consumers about the consequences of not heeding the statement, which are that use of cosmetic products containing AHAs as ingredients may increase their skin's sensitivity to the sun and that this increased skin sensitivity to the sun may increase the possibility of sunburn. Therefore, FDA is including the phrase "may increase your skin's sensitivity to the sun and particularly the possibility of sunburn" in its recommended statement.

Fourth, FDA believes that the recommended AHA labeling statement should provide instructions on what consumers can do to avoid these consequences, i.e., how to reduce the possibility of sunburn. The CTFA petition requested that the AHA labeling statement recommend the use of "adequate sunscreen protection" and cited the conclusion of the CIR Expert Panel review of AHAs (Reference 3) as support for its recommended labeling statement. The Expert Panel's conclusion, however, recommends "daily use of sun protection" without specifying what kind of sun protection should be used. FDA concurs with the conclusion of the Expert Panel and therefore is recommending the language "use a sunscreen, wear protective clothing, and limit sun exposure" to suggest actions to implement the Expert Panel's recommendation of "daily use of sun protection."

FDA published a final monograph (21 CFR part 352) on over-the-counter (OTC) sunscreen drug products in the *Federal Register* of May 21, 1999 (64 FR 27666). In this monograph, the agency recommended the following optional "Sun alert" in the labeling of OTC sunscreen drug products:

> Sun alert: Limiting sun exposure, wearing protective clothing, and using sunscreens may

reduce the risks of skin aging, skin cancer, and other harmful effects of the sun.

In the *Federal Register* of December 31, 2001 (66 FR 67485), the agency stayed the sunscreen monograph and stated its intention to publish a proposed rule to amend 21 CFR part 352 in order to develop a comprehensive sunscreen monograph that addresses formulation, labeling, and testing requirements for both UVA and UVB radiation protection. However, FDA's current thinking on sun protection continues to be 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 recommends that the "Sunburn Alert" labeling statement include the words "wear protective clothing" in 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.

Sunscreens are effective for reducing the possibility of sunburn, but sunscreens come off. An important limitation for sunscreens is the need for their frequent application for continued effective sun protection. Therefore, in addition to using sunscreens, consumers also should be mindful of wearing protective clothing and limiting sun exposure. The agency believes that it is important to emphasize all of these steps-using a sunscreen, wearing protective clothing, and limiting sun exposure-together as part of an overall program for reducing the possibility of sunburn when using cosmetic products containing AHAs as ingredients. FDA's recommended AHA labeling statement conveys all of this information to consumers when using cosmetic products containing AHAs as ingredients.

Finally, FDA recommends that the AHA labeling statement include the phrase "for a week afterwards," to indicate how long the user is advised to take the recommended actions for sun protection.

VI. Function of "Sunburn Alert" AHA Labeling Statement

In its citizen petition, CTFA requested that FDA establish labeling requirements that inform consumers about measures to take when using certain cosmetic products containing AHAs. FDA has reviewed the petition and other information about labeling statements on cosmetic products containing AHAs as ingredients and labeling statements on other consumer products. FDA also has considered information on consumer awareness of increased skin sensitivity from use of cosmetic products containing AHAs as ingredients.

Labeling statements on consumer products are often used for communicating product safety information (Reference 2). The function of a labeling statement depends on the information environment in which a statement will be perceived and the content of the statement. Labeling statements for product safety are used to convey new information to consumers who are unaware of an identified risk associated with a product and also to remind consumers who are aware of the risk of the recommended precaution.

Examples of labeling statements used for communicating product safety information include FDA's required warning labeling statement on iron-containing dietary supplements and drugs (21 CFR 101.17(e) and 21 CFR 310.518), the U.S. Department of Agriculture's required safe handling labeling statement on retail raw meat and poultry products (9 CFR 317.2(l)), and FDA's required safe handling labeling statement on cartons of shell eggs (21 CFR 101.17(h)).

Consumers use cosmetic products to maintain or improve the appearance of the body. Focus group research suggests that consumers generally believe cosmetic products are safe for their intended uses and that consumers are not aware of possible risks associated with use of cosmetic products (Reference 2). FDA does not know the extent of consumer awareness of increased skin sensitivity to the sun from

the use of cosmetic products containing AHAs as ingredients. In the March-April and May-June 1998 issues of its magazine, *FDA Consumer*, FDA recommended precautions that consumers should take when using an AHA-containing product, including using an effective sunscreen (Reference 2). The information also is available on FDA's website at http://www.cfsan.fda.gov/. However, in November 2004, as an example, only about 0.006% of U.S. households visited this website for information on AHAs.

FDA has not observed that the effect of AHAs on increased skin sensitivity to the sun has been widely publicized in the media or popular press, unlike the effect of AHAs on skin irritation (Reference 2). (In the early 1990s, consumers frequently experienced skin irritation from using AHA-containing cosmetic products. This concern was widely publicized to consumers and was addressed by manufacturers reformulating their products (Reference 3).)

To help assure consumer awareness of the potential for increased skin sensitivity to the sun from topical use of cosmetic products containing AHAs as ingredients, FDA recommends that such products bear information on their labeling such as the "Sunburn Alert" that helps convey information about the need for sun protection to avoid sunburn. FDA expects that a labeling statement such as the recommended "Sunburn Alert" will be a source of new information about sun protection for most consumers, as well as a reminder of FDA's recommended precautions for consumers who are already aware of the need to use sun protection when using these products (Reference 2).

VII. Requested Restriction of CTFA's Alert Statement to Exfoliant Use

In its citizen petition, CTFA proposed that the regulation establishing labeling requirements for cosmetic products containing an AHA as an ingredient be restricted to products that are intended to function as an exfoliant.

FDA has traditionally determined intended use for a product from statements in the product's labeling and promotional materials. Between 1992 and 2000, FDA personnel evaluated products containing AHAs and compiled surveys of label claims made for the products (Reference 2). Consumer products were purchased from retail stores and FDA inspectors collected salon products. FDA's surveys found that AHAs are added to cosmetic products with the intention of achieving many different effects. Claims made for such products included, for example, moisturizing, cleansing, softening, smoothing, and skin protection.

FDA's surveys found that, in 64 consumer products, exfoliation claims were the most common and were made on 50% of the products. In 33 salon products, exfoliation claims also were the most common and were made on 64% of the products. The surveys suggest that approximately half of the AHA-containing products on the market have an intended use as an exfoliant, as determined by the presence of "exfoliant" claims on the product labeling. Even some salon products containing high levels of AHAs did not specify "exfoliation" as an intended use.

It is the presence of AHAs in a product, rather than the claims made for certain uses, that may increase the possibility of sunburn. Limiting the recommended AHA labeling statement to products with exfoliation claims may leave out as many as half the products that FDA believes should bear the labeling statement. Therefore, FDA recommends a statement such as the "Sunburn Alert" be included in the labeling for any cosmetic product containing an AHA as an ingredient.

VIII. Use Conditions for "Sunburn Alert" AHA Labeling Statement

FDA recommends that the "Sunburn Alert" AHA labeling statement appear prominently and conspicuously once in the labeling of a cosmetic product.

To provide guidance to manufacturers on when FDA recommends that products should bear "Sunburn Alert" labeling, the agency has identified the following use conditions:

1. The product contains an AHA as an ingredient (other than as an incidental ingredient as defined in 21 CFR 701.3(l)).

FDA recommends "Sunburn Alert" labeling for cosmetic products containing an AHA as an ingredient. FDA does not recommend "Sunburn Alert" labeling for cosmetic products containing an AHA only as an incidental ingredient, as defined in 21 CFR 701.3(l).

2. The product is intended for topical application to the skin or mucous membrane that are exposed to the sun or 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. The product may be a "leave on" product that is intended to remain on the skin or mucous membrane or it may be a "discontinuous use" product that is intended to be left on the skin for a short period of time (less than an hour) followed by thorough rinsing.

FDA recommends "Sunburn Alert" labeling for cosmetic products that are intended for topical application to the skin or mucous membrane that are exposed to the sun. FDA also recommends "Sunburn Alert" labeling for cosmetic products that are intended for application to areas of the body that may result in unintentional topical application to the skin or mucous membrane that are exposed to the sun. This 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.

3. The product contains an AHA as an ingredient and does not also contain a sunscreen for sun protection.

This guidance does not apply to drug-cosmetic products that contain an AHA as an ingredient and also are labeled to contain a sunscreen for sun protection. FDA intends to address labeling for such products in a future document.

IX. Statutory Basis

21 U.S.C. 362(a) provides that a cosmetic is misbranded if its labeling is false or misleading in any particular. 21 U.S.C. 321(n) amplifies what is meant by "misleading." This section states that in determining whether labeling is misleading, the law takes into account the extent to which the labeling fails to reveal facts material to results which may occur from the use of the product as it is labeled or customarily used (*see also* 21 CFR 1.21).

Based on evidence reviewed so far (including safety reviews conducted by the CIR Expert Panel, the AHA Review Committee, and FDA), FDA currently believes 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 believes that this conclusion may be a material fact that manufacturers should disclose to users under 21 U.S.C. 362(a), 21 U.S.C. 321(n), and 21 CFR 1.21. Accordingly, FDA believes that if manufacturers inform users of cosmetic products containing AHAs as ingredients about the potential for increased skin sensitivity to the sun and particularly the

possibility of sunburn, and what steps a user may take to avoid such consequences, this will help avoid the potential that the products are misbranded under 21 U.S.C. 362(a) and 21 U.S.C. 321(n).

X. Significance of Guidance

CTFA's citizen petition requested that FDA issue a regulation in part 701 of the CFR (21 CFR Part 701-Cosmetic Labeling) establishing a sun alert labeling statement for cosmetic products containing AHAs as ingredients. FDA is issuing this guidance entitled "Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients" rather than a regulation.

FDA is issuing this guidance pending the results of the NCTR photocarcinogenicity study because the agency believes interim action is warranted to recommend that manufacturers label topically applied cosmetic products that contain AHAs as ingredients to alert consumers of the need to use sun protection when using these products.

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.

After assessing the results of the NCTR photocarcinogenicity study and the effectiveness of the guidance, the agency intends to determine if additional agency action is appropriate.

XI. Electronic Access

Copies of this guidance are available on FDA's website at http://www.cfsan.fda.gov/guidance.html. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

XII. References

1. 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.
2. Barrows, Julie N., Memorandum to the Administrative File, "Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients," Office of Cosmetics and Colors, CFSAN, FDA, September 12, 2002.
3. 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.
4. FDA, Memoranda of Meetings of AHA Review Committee, May 6, 1997, and February 12, 1997, and index of reviewed information.
5. Hawk, J. L. M., Ed., "Photodermatology," Arnold Publishers, Chapters 4, 6, and 7, pp. 43-52 and 69-102, 1999.
6. DeGruijl, F. R., J. B. VanDerMeer, and J. C. VanDerLeun, "Dose-Time Dependency of Tumor Formation by Chronic UV Exposure," Photochemistry and Photobiology, vol. 37, pp. 53-62, 1983.
7. Strickland, P. T., et al., "Quantitative Carcinogenesis in Man: Solar Ultraviolet B Dose Dependence of Skin Cancer in Maryland Watermen," Journal of the National Cancer Institute,

vol. 81, pp. 1910-1913, 1989.

8. Forbes, P. D., et al., "Simulated Stratospheric Ozone Depletion and Increased Ultraviolet Radiation: Effects on Photocarcinogenesis in Hairless Mice," Cancer Research, vol. 42, pp. 2796-2803, 1982.

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(1)This guidance has been prepared by the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition (CFSAN) at the U.S. Food and Drug Administration.

The draft version of this document, "Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients," was issued by FDA on December 2, 2002.