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November 1, 1982

Dockets Management Branch, (HFA-305)
Food and Drug Administration
Room 4-62
5600 Fishers Lane
Rockville, Maryland 20857

Re: Comments of Nicholas Laboratories,
Inc. on Tentative Final Monograph
for Skin Bleaching Drug Products
for Over-the-Counter Human Use;
Docket No. 78N-0065

Dear Sir:

On September 3, 1982, the Food and Drug Administration ("FDA") published a notice of proposed rulemaking entitled "Skin Bleaching Drug Products for Over-the-Counter Use; Tentative Final Monograph" ("proposal") at 47 Fed. Reg. 39108. The proposal invited the submission of written comments by November 2, 1982. These comments are submitted in response to that invitation.

Nicholas Laboratories, Inc. (formerly Nicholas Products, Ltd.) ("Nicholas") is a manufacturer and distributor of hydroquinone products which would be affected by this monograph. Nicholas has previously submitted data and information to the Advisory Review Panel on OTC Miscellaneous External Drug Products in connection with this proceeding. On February 1, 1979, Nicholas, through its counsel, submitted written comments to the FDA on the Agency's proposed monograph ("February 1979 comments").

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Nicholas, through its undersigned counsel, respectfully requests the agency to consider the following comments on the tentative final monograph:

1. The terms "skin color toning [insert dosage form, e.g., cream, lotion, or ointment]," "skin fade [insert dosage form]," and skin depigmenting [insert dosage form]" should at the very least be added as allowable alternative statements of identity under 21 CFR §358.50(a).

In its February 1979 comments, Nicholas expressed its opinion that the term "skin bleaching" does not accurately describe the function of the products covered by the monograph and that terms such as "skin color toning" agent and "skin depigmenting" agent are more appropriate.

In the proposal, the agency suggests the terms "skin bleaching" agent and "skin lightener" as appropriate statements of identity, based upon the undocumented belief by the Agency that "consumers are familiar with [these] terms." The Agency rejects the term "skin color toning" agent, despite the evidence in the record that this historically widely-used term is familiar to the consumer, especially the Black consumer, and accurately describes the intended action of the products. The proposal to disallow the latter term is apparently based upon the Agency's concern that the phrase fails "to describe clearly the pharmacological action" of the product because according to the Agency's rationale, the word "tone" may suggest "a shading of

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skin color" or "a direct action on the skin such as improvement in skin elasticity or resiliency." This ignores the fact that the word "tone" is qualified by the word "color," thereby eliminating any possibility that the use of the word "tone" creates confusion as to the intended action.

Additionally, it should be noted that FDA's regulations require merely that the statement of identity be "descriptive of general pharmacological category(ies) or principal intended actions; . . . 21 CFR §201.61(b). The "principal intended action" of these products, as historically used by Black and other consumers, is to provide an even skin color tone by lightening darkened patches of skin. The term "skin color toning" agent is therefore an appropriate, truthful, non-misleading statement of identity which describes the "principal intended action" of these products and should be adopted as an "allowable alternative."

The proposal (at p. 39117) correctly finds that these products are appropriately indicated "For the gradual fading of dark pigment" (emphasis added). Consistent with this finding, the Agency should also find that the terms "skin fade" [insert dosage form] and "skin depigmenting" [insert dosage form] are appropriate alternate statements of identity for the products. Both of these terms accurately and succinctly describe the pharmacological action of these products. In this regard, the

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Agency's proposed rejection of the term "skin depigmenting" agent is based merely on its assertion that depigmentation is not "a word that is understood by the ordinary lay consumer under customary conditions of purchase and use." 47 Fed. Reg. 39111. The Agency has stated no basis in the record for this belief, and indeed none exists. See Almay, Inc. v. Califano, 569 F.2d 674, 682-83 (D.C. Cir. 1978) (invalidating as arbitrary and capricious FDA regulations defining "hypoallergenic" cosmetics because of lack of record support for the definition).

Moreover, the limitation of the statement of identity to the terms "skin bleaching" and "skin lightener" could result in considerable misunderstanding among consumers, including Black consumers who purchase over 50 percent of these products. These persons may not use such products because of a fear of having their skin permanently "bleached," i.e., whitened, ^{*}/ or excessively "lightened," as opposed to having their skin color tone evened. And, as demonstrated in Nicholas' February 1979 comments, an informal survey of Black female consumers indicated that of four possible statements describing the intended function of these products "skin bleaching" was most often rated "most offensive," while "skin color toner" was most often rated "least offensive."

^{*}/ It is Nicholas' experience that consumers associate the term "bleaching" with "whitening," probably because the term is customarily used in connection with laundry bleaches.

2. The Agency's attempt to prescribe exclusive labeling is inappropriate, untimely, and ill-advised.

- a. The Exclusivity Policy

It appears from the proposal that the Agency is proceeding to implement its so-called "Exclusivity Policy" by prescribing certain narrow and restrictive language to the exclusion of other truthful, descriptive and non-misleading language. Nicholas submits that the adoption of the Exclusivity Policy for skin depigmenting products constitutes bad policy and is legally and factually unsupportable. (See the record compiled during the September 29, 1982 hearing before Commissioner Hayes on the Exclusivity Policy as it applies to all OTC drug products). This is particularly so in the case of depigmenting products because they are intended to be used by different ethnic and racial groups who historically have used, and become familiar with, different terms to describe the intended action and uses of depigmenting products. In any event because the Exclusivity Policy as a whole is under reconsideration by the Agency, it would be ill-advised and inappropriate for the Agency to take any action on proposed labeling claims until a decision is reached on the future of the Policy.

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- b. The application of the "Exclusivity Policy" to prohibit truthful and non-misleading label statements such as "Even skin tone by lightening darkened areas" is unsupported and inappropriate.

Many consumers, especially Blacks, use depigmenting agents on hyperpigmented areas of skin to produce an "even" skin color tone. As applied to these products, the statement "Even skin tone by lightening darkened areas" is truthful, non-misleading, and well understood by a substantial portion, if not all, of the consuming public.

The Agency, however, proposes that the term "tone" and the concept of making skin color "even" not be acceptable for inclusion in the indications for an OTC skin depigmenting drug product. By application of the "Exclusivity Policy" the use of this term and concept in the indications section or elsewhere on the label is apparently to be prohibited. Such a prohibition is unsupported and inappropriate.

As its sole basis for rejecting the term "tone," the Agency states that two of the various dictionary meanings of "tone" are "apt to be confused when applied to products for use on the skin: 'color quality or value' and 'healthy elasticity'" and therefore concludes "that substantial confusion can be prevented by excluding the word 'tone' from the labeling . . ." 47 Fed. Reg. 39111. Assuming arguendo that an unqualified reference to "skin tone" might create confusion as to the intended use, this

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is clearly not the case when appropriate qualifiers are used such as "Even skin tone by lightening darkened areas." The use of the term "tone" in the context of this statement obviously relates to color quality, not to skin elasticity. Accordingly, the Agency's proposed prohibition of the word "tone" is unfounded and has no basis of support in the record.

The Agency rejects the concept of making skin color "even" on the following basis:

Statements that refer to making skin color "even" are not acceptable because they imply that skin bleaching agents have a selective action on concentrations of pigment and would produce even color if applied indiscriminately to wide areas of skin. In fact, an effective skin bleaching agent would exert its action on all pigment so that the result of indiscriminate application would be a lightening of the color of the total area, not just the portions in which the pigment is concentrated.

47 Fed. Reg. 39111. The Agency's concern is completely unfounded. First, there is no support in the record for the conclusion that depigmenting agents exert their action on all pigment. Rather, Arndt and Fitzpatrick ^{*/} state that the effectiveness of hydroquinone, the only Category I depigmenting agent, appeared to depend on the type of melanosis. This

^{*/} Arndt, Kenneth and Fitzpatrick, T. B. "Topical Use of Hydroquinone as a Depigmenting Agent," Journal of the American Medical Association. 194:965-967, 1965.

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indicates that hydroquinone does not exert its effect equally on all pigment. Moreover, even if it were assumed that hydroquinone exerts its action on all pigment, the directions for use incorporated in the monograph explicitly indicate that the product is to be applied only to "affected," i.e., darkened, areas, and not indiscriminately to wide areas of skin. Thus, when used as directed, these products will indeed "Even skin tone by lightening darkened areas." The Agency's concern that a product may not work as intended if used contrary to clear label directions is no basis to prohibit a truthful statement of the product's effect when used as directed.

Prohibition of the term "tone" and the concept of making skin color "even" based solely on an undocumented belief that "substantial confusion" will result, that a depigmenting agent exerts its action on all pigment, and that the products will be misused by indiscriminate application to wide areas of skin would be arbitrary, capricious, and without an adequate foundation in law and fact. Similarly, there is no evidence in the administrative record which would support an Agency decision prohibiting the use of any term not specifically endorsed and recited in the monograph. In the absence of adequate support in the administrative record that such alternate terms are false or misleading in some particular, the automatic prohibition on the use of all such terms can only be characterized as arbitrary and capricious. See *Almay, Inc. v. Califano*, supra.

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Based upon the evidence of record, use of the indication "even skin tone by lightening darkened areas" should be explicitly permitted by its incorporation within 21 CFR §358.50(b)(1). At the very least, FDA should not prohibit the use of this or other similarly truthful, non-misleading labeling statements under the Exclusivity Policy or on any other basis.

3. There is nothing in the record to support the required label statement "Lightening effect of this product may not be noticeable when used on very dark skin."

The statement "lightening effect of this product may not be noticeable when used on very dark skin" is without foundation and potentially confusing to consumers who may mistakenly construe it to mean that the product will not lighten areas of darkened skin.

The Agency acknowledges that data support the lightening effect of hydroquinone on dark skin in certain animal models, but alleges that literature references indicate that the lightening effect in humans may not be noticeable on very dark skin. The references cited by the Agency, however, simply do not support this conclusion. The articles by Spencer ^{*/} compare the depigmenting action of hydroquinone on hyperpigmented areas of white males with the effect on normal pigmentation of Black

^{*/} Spencer, M. C. "Topical Use of Hydroquinone for Depigmentation," Journal of the American Medical Association, 194:962-964, 1965; Spencer, M. C. "Hydroquinone Bleaching," Archives of Dermatology, 84:131-134, 1961.

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males. The ordinary use of hydroquinone, however, is for lightening hyperpigmented areas, not normally pigmented areas. Consequently, the Spencer articles do not support or justify the required statement. The article by Arndt and Fitzpatrick provides no support at all for the required statement, notwithstanding the Agency's reliance upon it. Indeed, the authors specifically state:

Twelve percent of the patients were Negroes; no difference was noted between their skin reaction and that of Caucasians. */

Affirmatively requiring a label statement for which there is no support in the record is clearly arbitrary and capricious. See Almay, Inc. v. Califano, supra.

4. The statement "Children under 12 years of age: do not use unless directed by a doctor" is unnecessary and should be removed in view of the required warning statement: "Do not use on children under 12 years of age unless directed by a doctor."

Nicholas has no objection to the required warning statement, but submits that the requirement that the same information appear in the "Directions" is unnecessarily redundant. The Agency's mere belief that "this information should be presented in both sections" is legally inadequate to support the double requirement.

*/ Arndt and Fitzpatrick, supra at 965.

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5. The statements required at 21 CFR §358.50(d)(2) and (3) should be revised to distinguish adequately the procedures which should be observed when using a depigmenting product which contains a sunscreen agent and one which does not.

The statements required in the tentative final monograph at 21 CFR §358.50(d)(2) and (3) are confusing, verbose, and fail to distinguish adequately the difference between products which contain a sunscreen and those which do not.

It is recommended that these subsections be revised to read:

- (2) For products containing the ingredient identified in 352.10

"When using this product protect treated areas from the sun to maximize effect. After treatment is completed protect skin from sun to prevent darkening from reoccurring."

- (3) For products containing any combination identified in §358.20.

"After treatment is completed protect skin from sun to prevent darkening from reoccurring."

This revision will help to differentiate between single ingredient hydroquinone products and products containing hydroquinone combined with sunscreen agents. As the Agency states:

[C]onsumers should be informed of the difference between products containing a sunscreen and those not containing a sunscreen.

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47 Fed. Reg. 39115. The revision will also reduce the possibility that consumers will mistakenly interpret the statement in §358.50(d)(3) as recommending that a separate sunscreen agent be used concurrently with the combination product.

Respectfully submitted,


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