

Plough, Inc.

MEMPHIS, TENN. 38151

February 1, 1979

Office of the Hearing Clerk (HFA-305)
Food and Drug Administration
Room 4-65
5600 Fishers Lane
Rockville, Maryland 20852

Re: Docket No. 78N-0065
Establishment of a Monograph; Notice of Proposed
Rulemaking, Skin Bleaching Drug Products for Over-
the-Counter Human Use 43 Fed. Reg. 51546
November 3, 1978⁷

Dear Sir:

The above referenced Proposal was published in the Federal Register on November 3, 1978 and contained the findings and conclusions of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Panel).

PLOUGH, INC. is a manufacturer and distributor of hydroquinone-containing products sold over-the-counter (OTC) and is both interested in, and would be affected by, this proposed rule.

PLOUGH, INC. is also an active member of the Proprietary Association, a trade association which intends to submit comments on the above Proposal. By reference, the comments of the Proprietary Association are incorporated herein for consideration by the Commissioner of Food and Drugs (Commissioner), in addition to the comments submitted below by PLOUGH, INC.

INTRODUCTION

Throughout the preamble and the proposed rule, hydroquinone and, therefore, hydroquinone-containing products are treated exclusively as drugs. It must be understood and appreciated that while these products do function as drugs they are viewed by the consumer to be cosmetic products and are

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employed for cosmetic effect, specifically, to beautify the skin by creating an even skin color. This conclusion is based on long years of marketing experience.

Many of the following comments reflect a concern that both the nomenclature and labeling requirements set forth in the proposed rule do not consider that the subject products are viewed by the consumer as cosmetics. It is suggested that the modifications recommended hereinafter be adopted because much of the nomenclature and labeling requirements, while possibly appropriate for a drug product, are inappropriate for products which are understood by the consumer to be cosmetics.

I.

Statement of Identity Should be Modified to Replace the Words "Skin Bleaching Agent" With More Appropriate Terms. (Proposed 358.50 (a))

The specific designation of hydroquinone-containing products as "skin bleaching agents" to the exclusion of other terminology, it is felt, would be objectionable and misleading to many consumers. Particularly, black users of these products do not desire bleaching of the skin but rather lightening of hyperpigmented areas. Implications of a whitening or bleaching effect imparts a negative and possibly misleading connotation. In addition, scientific investigations to elucidate the nature of the depigmenting effects by hydroquinone¹, showed that these effects are achieved largely by interference with complete pigment formation rather than a true bleaching effect as the proposed statement of identity suggests.

For the reasons above, it is recommended that the term "skin bleaching agent" in the proposed statement of identity be replaced with one of the more meaningful following statements:

- 1) Skin toner
- 2) Skin lightener

It is further recommended that interested parties, including manufacturers, be permitted to use other accurate, appropriate terminology meaningful to the consumer.

1. Jimbrow, K., Obata, H., Pathak, M., and Fitzpatrick, T.B.: "Mechanisms of Depigmentation by Hydroquinone", Journal of Investigative Dermatology, 62:436-449, 1974.

II.

The Indications at Proposed 358.50 (b) are Unduly Limiting and Should be Expanded to Include Additional, Meaningful Terms.

While the term "lightens dark pigment in the skin" is accurate in describing the intended action of these products, this phrase is not the only appropriate indication. Therefore, this section should be expanded to better communicate the uses of the product to the consumer. Many users purchase hydroquinone-containing products to achieve an "evening" or fading effect to blend areas of darker pigmentation into an overall improved skin appearance. It is recommended that the following be added at Proposed 358.50 (b):

- 1) Helps fade away dark spots
- 2) Evens skin tone
- 3) Helps achieve an even-toned complexion
- 4) For fading hyperpigmented areas of the skin
- 5) Lightens skin tone

III.

The Warning at Proposed 358.50 (c)(1)(i):

"WARNING: Sun exposure should be avoided indefinitely by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin in order to prevent darkening from reoccurring"

is Misleading and Unduly Alarming to the Consumer.

Although the Panel has expressed concern regarding the response of treated skin to sunlight and the redarkening which may occur, we are unaware of any reasonable basis for the inordinate attention proposed for this warning. Incorporation of this warning within the labeling of these products will have a strong tendency to mislead consumers in the belief that sunlight is contraindicated when using hydroquinone products. Such a warning, particularly one highlighted in such a remarkable manner, is likely to create the impression that a hazard is somehow associated with exposure to sunlight. Obviously, this is not the case, and no safety issue has been raised with products containing 1.5 to 2% hydroquinone when used in the presence of sunlight. Many people will have difficulty and will be inconvenienced in an attempt to avoid sunlight. Consumers who

use such products are quite aware of the temporary skin lightening effects of these products and would expect some redarkening with sufficient sun exposure. The Panel has placed importance on this issue, apparently, due in large part to the so-called Meirowsky effect (long wave-lengths of ultraviolet light darkening melanin already present in the skin presumably by a rapid photo-oxidative process). No evidence has been presented which indicates this unique increased response of hydroquinone-lightened skin occurs after exposure to sunlight. Most investigators have concluded that hydroquinone works by inhibiting melanogenesis and not by an effect on already existing melanin in situ. In all probability repigmentation occurs normally, i.e., by stimulation of melanogenesis by ultraviolet light. The evidence suggests that many users will experience an acceptable degree of depigmentation in spite of normal intermittent sun exposure.

For these reasons, it is submitted that this proposed warning is misleading and unduly alarming and should be deleted from Proposed 358.50 (c)(1)(i).

IV.

The Proposed Warning at 358.50 (c)(iv),

"If no improvement is seen after two months of treatment, use of this product should be discontinued"

is Unnecessary and Should not be Required.

Although such a limitation might be appropriate for products containing higher concentrations of hydroquinone, evidence reviewed by the Panel does not support such a limitation for products containing hydroquinone at 1.5 to 2.0%.

A clinical investigation by Arndt and Fitzpatrick² with 2% hydroquinone cream determined that use of such products for periods of up to three months resulted in negligible side effects. The Panel has also affirmed this finding by a determination of the safety of topically applied products at a level of 1.5 to 2.0% hydroquinone. This clinical investigation and the Panel's report failed to support any rationale

2. Arndt, K.A. and Fitzpatrick, T.B., "Topical Use of Hydroquinone as a Depigmenting Agent", JAMA 194:965-967, 1965.

for limiting the use of this product in the event no improvement is seen within two months. These authors³ found a wide variation of responses in a group of fifty-six patients with initial onset of depigmenting effects ranging from as early as three weeks to as long as three months. Consumers understand the temporary and transient effect of these products and continued use will be self-limiting dependent upon results obtained. Results will depend on the degree of compliance with the directions for use, and one can expect discontinuance well within two months should no improvement be seen after such a period of daily application.

V.

The Proposed Warning at 358.50 (c)(v), "Not Recommended for Children Under 12 Years of Age" is not Needed.

There is no evidence to suggest that use of this product by persons under the age of twelve is associated with risk factors of any significant degree or such use would differ in any appreciable way from its use by older individuals. No evidence to support the proposed age limitation or rationale for this warning has been presented by the Panel. Although the purchasers and consumers of these products are generally above twelve years of age, it may be desirable to allow use in individuals under twelve with adult supervision. Further, while it would be inappropriate to encourage unlimited and unsupervised use by children, we recommend that this restriction of use should be included in the directions for use section rather than in the warning section. The proposed directions for use limitations should be sufficient. Therefore, the proposed warning above is redundant and not needed.

VI.

It is Suggested that the Proposed Warning at 358.50 (c)(vi),

"Depigmentation (Lightening) Effect of this Product may not be Noticeable When Used on Very Dark Skin",

is Unwarranted and Should be Deleted.

3. Arndt, K.A. and Fitzpatrick, T.B, JAMA 194:965-967, 1965.

As with all drug products, there is no guarantee that the desired results will be achieved in all individuals nor is this an absolute expectation on the part of the consumer. This proposed warning does not take into account the very large differences in response to hydroquinone products which have been documented in the medical literature⁴. Variability in use patterns and whether the product is conscientiously applied will have an effect on the results obtained. It can also be anticipated that there will be some confusion on the part of consumers as to what constitutes very dark skin and certain individuals would be dissuaded from use of these products. A significant number of darkly pigmented individuals will desire to treat skin areas or spots of hyperpigmentation and it is reasonable to expect an observable effect with longer term use in many of these individuals.

VII.

The Warning Proposed at 358.50 (c)(2) for Combination Products,

"This Product Will Bleach Skin and is not for
use for the Prevention of Sunburn"

is Unwarranted and Should not be Required.

In those instances where a Category I sunscreen is included in the formulation, in combination with hydroquinone, the consumer will benefit from a reduction of exposure to ultraviolet light. In its discussion of the use of such combination products, the Panel has seen fit to disallow the proposed Category I sunburn prevention claim. It is recommended that the Commissioner recognize that the absence of this labeling claim is sufficient to limit the use of these products as sunburn preventatives. For these reasons it is requested that the above warning not be required.

In summary, it is requested that the Commissioner consider the above comments relating to the statement of identity of hydroquinone products. It is requested that this class of OTC drugs be identified with alternate but accurate and meaningful terminology as specified in Comment No. I.

4. Arndt, K.A. and Fitzpatrick, T.B, JAMA 194:965-967, 1965.

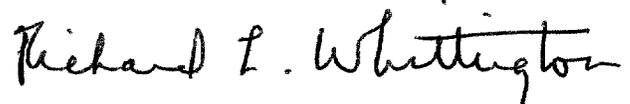
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It is also emphasized that due to the attitude of the users of this class of products that the indications for use be expanded to better communicate their appropriate uses as specified within these comments.

It is noted that for single active ingredient products there are six separate proposed warning statements and one additional proposed warning statement for combination products identified at proposed 358.20. Where a minimum of concern for safe use exists, which we suggest is the case with hydroquinone products, an effort should be made to limit unnecessary warnings in this section to promote effective communication with the consumer.

PLOUGH, INC. appreciates the opportunity to submit these comments and hopes that the Food and Drug Administration will find them useful.

Sincerely,



Richard L. Whittington
Manager of Regulatory Services

RLW/md

Submitted in Quadruplicate