



January 24, 1979

Office of the Hearing Clerk (HFA-305)
Food and Drug Administration
Room 4-65
5600 Fishers Lane
Rockville, Maryland 20857

RE: Establishment of a Monograph; Notice of Proposed Rulemaking, Skin Bleaching Drug Products for Over-the-Counter Human Use ((43 Federal Register 51546 (November 3, 1978)) (Docket No. 78N-0065).

Dear Sir:

The above-referenced proposal was published in the FEDERAL REGISTER (Fed. Reg.) on November 3, 1978, together with the findings and conclusions of the Advisory Review Panel on OTC Miscellaneous External Drug Products (the Panel) convened for the purpose of evaluating skin bleaching drug products.

The Paul B. Elder Company is the manufacturer and the Thomas C. Elder, Inc. is the distributor (Elder), of skin bleaching drug products sold over-the-counter (OTC). Elder is both interested in, and would be affected by, this proposed rule.

Elder submits the following comments and recommendations for consideration by the Commissioner of Food and Drugs.

I.

IT IS RECOMMENDED THAT THE PROPOSED SECTION 21 CFR 358.10 BE EXPANDED TO INCLUDE PRODUCTS THAT CONTAIN HYDROQUINONE WITHIN THE DOSAGE LIMITS 1.5 TO 4.0 PERCENT.

As part of its review, the Panel was charged to evaluate data and information on the safety and effectiveness of OTC skin bleaching products. The Panel concluded that only hydroquinone should be classified as a Category I Active Ingredient, and that hydroquinone is safe and effective for OTC use as a skin bleaching drug product as specified in the dosage and labeling sections of the proposed regulation.

The Panel reviewed chronic toxicity studies in the rat (Stern, G.S., S. Lang, N.R. Brewer, and A.J. Carlson, Federation Proceedings, 9:121-122, 1950), a clinical study involving ingestion of hydroquinone (Lang, S., N.R. Brewer, and A.J. Carlson, "Chronic Studies of Effect of Hydroquinone on Man," Federation Proceedings, 9:74, 1950) and a study of 35 cases of hydroquinone damage to the dermis of South African women (Findley, G.H., J.G.L. Morrison, and I.W. Simson, "Exogenous Ochronosis and Pigmented Colloid Milium from Hydroquinone Bleaching Cream," British Journal of Dermatology, 93:613-622, 1975). Following this review the Panel concluded that "prolonged use of high concentrations (5 percent or more) of hydroquinone with exposure to the sun may produce disfiguring effects. These effects have not been reported at lower concentrations." (refer to 43 Fed. Reg. 51549).

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Spencer, who is credited with first reporting the use of hydroquinone as a bleaching agent, applied concentrations of 1%, 4%, and 7% of hydroquinone in a vanishing cream base to a clinical population comprised of 142 white and 6 Negro male subjects for a period of two months.¹ Several bilateral applications were made on the hands and forearms twice daily, seven days weekly. No significant reactions occurred. No sensitization developed.

In another clinical study,² Spencer observed that in the use of hydroquinone formulations in concentrations of 2% and 3%, no sensitivity reactions developed. This study involved the treatment of freckles and lentigines on the hands of 94 middle-aged and older white men and 43 Negro men of the same age group with normal skin. Twice daily applications of ointments were made for three months. Several patients, in contrast, became sensitized when an ointment containing hydroquinone in 5% concentration was used under the same conditions.

In summary, after review of all information bearing on the question of safety, the Panel concluded (in part) that "...neither the eye damage reported with industrial exposure nor the skin damage reported with prolonged use of 5 percent creams has ever been reported with concentrations below 5 percent." (Refer to 43 Fed. Reg. 51551).

Elder has had two products containing hydroquinone in 4% concentration on the market for many years. The first of these, ELDOPAQUE FORTE[®], was launched in December, 1969. During this time over 900,000 sample and regular 1/2 oz. tubes of ELDOPAQUE FORTE have been made and distributed. ELDOQUIN FORTE[®] was introduced in April, 1972, and more than 850,000 sample, 1/4 oz., 1/2 oz. and 1 oz. tubes of this product have been made and distributed. We have examined our Patient Complaint Files for these two products, and certify that Elder has never received a patient complaint involving the side reactions and sensitization phenomena described in the medical literature and documented in 43 Fed. Reg. 51546 that accompany the use of hydroquinone preparations with concentrations of 5% or more.

In conclusion, the Panel has found that hydroquinone preparations with concentrations less than 5% are safe for use and do not cause eye or skin damage. The long experience on the market place of Elder, with two established skin bleaching products (ELDOQUIN FORTE and ELDOPAQUE FORTE) incorporating hydroquinone in 4% concentration, supports this finding by the Panel. Therefore, Elder recommends that Proposed Regulation 21 CFR 358.10 be amended to read as follows:

358.10 Skin bleaching active ingredient.

The active ingredient of the product consists of the following when used within the dosage limits established: Hydroquinone 1.5 to 4.0 percent.

1. Spencer, M.C., Archives of Dermatology, 84: 131-134, 1961.
2. Spencer, M.C., Journal of the American Medical Association, 194: 962-964, 1965.

II.

IT IS RECOMMENDED THAT THE PROPOSED SECTION 21 CFR 358.20 BE EXPANDED TO INCLUDE HYDROQUINONE FORMULATIONS IN A BASE OPAQUE TO ULTRAVIOLET RADIATION.

The Proposed Section 21 CFR 358.20 approves combinations of hydroquinone, as identified in Proposed Section 21 CFR 358.10, with any generally recognized safe and effective sunscreen active ingredient identified in 21 CFR 352.10.

Proposed Regulation 21 CFR 352 - Sunscreen Products for Over-the-Counter Human Use was developed by another Advisory Review Panel that considered only products for which the sunscreen indication is the primary claim. It did not consider non-transparent opaque bases such as are used in cosmetic formulations.

Dr. Thomas B. Fitzpatrick and his co-authors of the text "Dermatology in General Medicine", McGraw-Hill, Inc., 1971, Library of Congress Catalog Card No. 75-142967 07-021195-7, page 1027, state that "For patients with chronic photosensitivity diseases, it is desirable to add a light-scattering and reflecting agent in combination with a light absorber (e.g. titanium dioxide, talc and zinc oxide) in a hydrophilic ointment."

Based upon this rationale Elder developed ELDOPAQUE[®] and ELDOPAQUE FORTE[®], 2% and 4% hydroquinone formulations, respectively, that utilize a hydrophilic opaque base containing 10% talc as a light scattering and reflecting agent. As indicated earlier, these products have been established on the market place for many years.

Therefore, we recommend that Proposed Regulation 21 CFR, 358.20 be expanded to include generally recognized light scattering and reflecting agents in combination with hydroquinone.

III.

IT SHOULD BE MANDATED AFFIRMATIVELY THAT ANY SKIN-BLEACHING PRODUCT FOR OTC HUMAN USE THAT CONTAINS HYDROQUINONE AS BLEACHING AGENT BE STABILIZED.

Spencer, in his original investigations of hydroquinone as a skin bleaching agent (see Footnotes 1 and 2, page 2), noted that hydroquinone is readily oxidized to colored oxidation products in ointments, and that once this agent is oxidized, its effectiveness as a depigmenting agent is negligible. In a clinical study on white adult males, Spencer commented that the proportion of patients in whom depigmentation developed from treatment with stabilized hydroquinone was greater, e.g. 28 of 41, when the 2% ointment was used compared to the proportion, e.g. 31 of 53 when unstabilized hydroquinone was used.

The Panel has noted these observations of Spencer (43 Fed. Reg. 51552) and pointed out that "the ease of oxidation of hydroquinone is an important factor in reducing its effectiveness as a skin-lightening agent."

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We recommend that the Proposed Regulation 21 CFR 358, Subpart A-Skin Bleaching Drug Products, be amended to require that any bleaching product that meets the conditions of this regulation, and is thus classified as an OTC skin bleaching drug product that contains Hydroquinone, be required to have a stabilizer in the product that will retard the oxidation of hydroquinone.

The opportunity to have been permitted to present these comments is appreciated. They are submitted in quadruplicate.

Sincerely,



Richard N. Hurd, Ph.D.
Vice President of Technical Affairs
PAUL B. ELDER COMPANY

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submitted in quadruplicate