December 19, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 1978N-0065, RIN No. 0910-AF53

Dear Sirs,

My comments are directed towards the proposed rulemaking to ban the use of hydroquinone in skin treatment products. Very recent information, including papers published during or after the proposed rulemaking, should be considered before denying the benefits of hydroquinone to the public.

Hydroquinone is widely regarded as the most effective treatment for hyperpigmentation. The economic and social costs of hyperpigmentation should not be minimized. Nordlund et al., 2006 (enclosed), review studies by Balkrishnan et al. of 2004 and 2005 that report that treatment of hyperpigmentation improves the quality of life of patients. In a landmark study of the cost of skin diseases, Bickers et al. 2006 (enclosed) considered the direct and indirect cost of several conditions including vitiligo, a condition closely related to hyperpigmentation. In vitiligo there is an absence, not excess of pigmentation. They estimate the direct costs for the 1.5 million people with vitiligo to be $175 million, and the indirect cost due to lost productivity, which includes time away from work seeking medical care for one's self or child, to be $55 million. Hyperpigmentation affects far more people and the losses should be at least equal to and probably greater than vitiligo.

The safety profile of hydroquinone has been recently reviewed by Nordlund et al., 2006 (enclosed). They reviewed 73 publications in the literature. The relevant points made by these dermatologists are:

- Hydroquinone has been manufactured and used for over 50 years and no cases of skin cancer or internal malignancy related to the topical application of hydroquinone have been reported. The weakness of the carcinogenicity data in animals has not allowed any U.S. or foreign scientific agency to conclude that hydroquinone is a carcinogen.

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205 buffalo avenue
freeport, ny 11520
phone:516.868.9026
fax:516.868.9143
www.agiderm.com

- Hydroquinone is a natural component of foods and 0.2 mg may be ingested in a simple meal. It is found in foods such as blueberries, tea and red wine which are associated with reduced, not increased, cancer risk.

- Occupational exposure to hydroquinone is likewise associated with a reduction in premature deaths compared to control groups.

- The chronic adverse effect of onchronosis is highlighted in reports from South Africa, but cases in the U.S. are uncommon. This is likely because formulations of hydroquinone in the U.S., as well as the associated use of sunscreens, and even incorporation of sunscreens in hydroquinone products, differ significantly from those in South Africa.

The proposed mechanism for the mutagenicity of hydroquinone is that it is a metabolite of benzene. The recent study by Gaskell et al., 2005 (enclosed) demonstrates that the frequency of DNA adducts produced by *in vitro* treatment of DNA with hydroquinone is more than an order of magnitude less than that produced by either benzene or its major metabolite para-benzoquinone. In addition, the mutation spectrum produced by either benzene or para-benzoquinone differs significantly from the spectrum produced by hydroquinone. The authors call into question the assumption of association between benzene mutagenicity and hydroquinone. They suggest that the hydroquinone effects in this *in vitro* system may be due to oxidation. The relevance of these findings to skin with a system of antioxidants should be further investigated.

A very recent study by Topping et al. 2007 (enclosed) examined the acute and subchronic toxicity of hydroquinone, using currently accepted GLP-compliant study guidelines not used in prior studies. At acute dermal application to rabbits of 2000 mg/kg, no adverse neurobehavioral effects were observed and all application sites appeared normal. In the subchronic toxicity study, hydroquinone was administered to rats in the water for 13 weeks. Tremors and convulsions were observed to be dose-dependent and were described as transient, with no evidence of subchronic neurotoxicity. In addition, no nephrotoxicity was found, in contrast to observations in other rat strains. No other treatment-related changes were observed at gross necropsy. Much of the hydroquinone toxicity literature is dated, and these findings suggest that newer studies are warranted.

Restricting access to hydroquinone, or eliminating it from the marketplace, will not reduce the demand for OTC skin lightening products. The effect of such action, as has been seen in Japan, will be to drive consumers to purchase less

effective and much less characterized botanical and chemical lighteners. The ineffectiveness of these substitutes causes very short product cycles as "new" lightening candidates are rapidly introduced, making scientific study and responsible regulation of any one entity very difficult.

Hydroquinone is an effective drug that has been safely used in the United States for the past fifty years. The other drugs for treating hyperpigmentation without hydroquinone are less effectve and much less is known about their safety. The proposed rulemaking will not benefit the public.

Sincerely,

Daniel B. Yarosh, Ph.D.

Daniel B. Yarosh, Ph.D.
President and Chairman

enclosed: D.R. Bickers et al. The Burden of Skin Diseases: 2004. J. Am. Acad. Dermatol. 55:490-500, 2006.

J.J. Nordlund, P.E. Grimes, J.P. Ortonne. The Safety of Hydroquinone. J. Eur. Acad. Dermatol. Venerol. 20:781-787, 2006.

M. Gaskell et al. Genotoxicity of the benezene metabolites *par*-benzoquinone and hydroquinone. Chem.-Bio. Interact. 153-154:267-270, 2005.

D. Topping et al. Hydroquinone: Acute and subchronic toxicity studies with emphasis on neurobehavioral and nephrotoxic effects. Food Chem. Toxicol. 45:70-78, 2007.

Cc: Marsha Wertzberger, Arent Fox