



# American Academy of Dermatology Association

Physicians Dedicated to Excellence in Dermatology™

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December 27, 2006

Andrew C. von Eschenbach, MD  
Commissioner of Food and Drugs  
U.S. Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857-0001

RE: Docket No. 1978N-0065 -- RIN 0910-AF53 -- Skin Bleaching Drug Products for Over-the-Counter Human Use; Proposed Rule

Dear Commissioner von Eschenbach:

The American Academy of Dermatology Association (the Academy), representing 15,000 dermatologists, opposes the U.S. Food and Drug Administration's (FDA) proposed rule that would establish that over-the-counter (OTC) skin bleaching drug products containing hydroquinone are not generally recognized as safe and effective (GRASE) and are misbranded. Additionally, the Academy does not support the FDA's intent to consider all skin bleaching drug products, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (ANDA) for continued marketing.

As stated in the Federal Register of August 29, 2006, the FDA's proposed rule change is based on new evidence of carcinogenicity in rats and mice to OTC skin bleaching products containing hydroquinone. The FDA states that it cannot rule out the potential carcinogenic risk from topically applied hydroquinone in humans. In addition, the FDA cites hydroquinone as having been shown to cause disfiguring effects (ochronosis) after use of concentrations as low as 1 percent to 2 percent. Based on these data, the FDA has tentatively concluded that there is no benefit of OTC skin bleaching drug products to physical health that would justify the continued marketing of these products.

The FDA states that for OTC skin bleaching drug products, the sole intended benefit would be to improve the user's appearance by bleaching the skin. Consequently, the benefits of these products, for an otherwise healthy target population, appear low and the risks not minimal. Hence, OTC hydroquinone products are no longer recognized by the FDA as safe and effective and their use cannot be justified. The FDA proposes that hydroquinone in skin bleaching drug products should be restricted to prescription use only, and users of such products should be closely monitored under medical supervision.

The Academy strongly opposes the proposed rule changes for the following reasons:

- Millions of patients each year are affected by dyschromias including melasma, post-inflammatory hyperpigmentation, solar lentigines, and uneven skin tone.

The National Ambulatory Care Survey data identifies about three million dermatologist's office visits for the treatment of dyschromias.<sup>1</sup> There are several million additional cases that are unreported as these individuals do not see a physician for evaluation and treatment of their dyschromias but utilize over-the-counter products.<sup>2</sup> Dyschromias are recognized cutaneous diseases with significant patient morbidity. The FDA is mistaken in its view that these disorders affect appearance only.

- Restricting skin bleaching drug products to prescription use only would eliminate a safe, effective, readily accessible and affordable treatment for millions of dyschromias patients.
- Requiring an ANDA for continued marketing of all prescription hydroquinone products, would likely result in the withdrawal of all but one of the 75 skin bleaching drug products currently marketed with concentrations greater than 2-percent. Small entities that manufacture these hydroquinone products would be unable to support the costs associated with an ANDA thus necessitating withdrawal of their products. This would have deleterious effects on dyschromias patients.
- Dyschromias disproportionately affects minority patient populations including African Americans, Latinos, and Asians and the removal of safe, effective, readily accessible and affordable treatment would pose an unnecessary burden on populations for whom health disparities abound.
- Dyschromias of greater severity, which also disproportionately affect minority patients, necessitate treatment with prescription hydroquinone products. Requiring an ANDA would severely limit the availability and most likely the affordability of an effective prescription treatment for this population.
- Exogenous ochronosis is a remarkably uncommon disorder among patients in the United States and removing OTC skin bleaching drug products will not have a significant impact on the number of cases of exogenous ochronosis that may occur each year.
- The actual risk to humans from the use of hydroquinone has yet to be fully determined. Evidence of carcinogenicity related to high oral doses of hydroquinone in the mouse and rat species cannot necessarily be extrapolated to the human species.
- Carcinogenicity in humans is not supported by any case reports of renal or hepatic neoplasms or leukemia in individuals with normal use of hydroquinone over a 50 year span or for those individuals with excessive hydroquinone exposures including industrial workers.

The Academy is dedicated to achieving the highest quality of dermatologic care for everyone. Our members diagnose and treat cutaneous diseases including the dyschromias, melasma, post inflammatory hyperpigmentation, solar lentigines and uneven skin tone. These are commonly occurring disorders for which patients seek evaluation and treatment. In the United States, The National Ambulatory Care Survey (NACS) conducted by the National Center for Health Statistics monitors physician patient visits and provides primary diagnosis by race and ethnicity for various specialties including dermatology.<sup>1</sup>

**DYSCHROMIA**

White race	2,087,079
Black race	413,013
Asian race	205,910
Native Hawaiian and other Pacific islanders	27,157
Hispanic or Latino	135,991

As physicians who treat on a daily basis the millions of patients with dyschromias, we disagree with the position that these disorders are only cosmetic in nature and only affect the appearance of the skin. Quite the contrary, dyschromias can be severely disfiguring and can have severe adverse psychological and emotional effects for affected individuals.<sup>3, 4</sup> There are three life domains that are most adversely affected by melasma: social life, recreation/leisure and emotional well-being. These three areas of life were the same that patients believed would improve the most if they no longer were affected by the disease. In summary, dyschromias are recognized medical disorders the severity and importance of which should not be trivialized.

Dyschromias occur in many individuals who are unable to visit a dermatologist for treatment. Self treatment with over-the-counter products is often the first and preferred method of treatment by patients. Many factors account for this preference and include costs associated with a dermatology office visit and prescription medications, the unavailability of timely dermatology appointments, and the inability of patients to leave their place of employment for dermatology appointments. Therefore, restricting skin bleaching drug products to prescription use only would eliminate safe, effective, readily accessible and affordable treatment for millions of dyschromias patients. These Americans would then go without treatment.

Dyschromias also occur commonly in minority populations and are often within the top 10 diagnoses among those patients when seen in private or clinic dermatologic practices. For example, the dyschromias, melasma and hyperpigmentation were reported in 8.2% and 6.0% respectively of 1,000 Latino patients treated in a dermatology private practice.<sup>5</sup> Pigmentary disorders (dyschromias) were the third most common dermatoses reported in a predominantly African American private practice in Washington, DC.<sup>6</sup> The FDA's proposed rule would disproportionately impact racial and ethnic groups and add to already significant health disparities for these groups. The most significant barriers to dermatologic care are the following:<sup>7</sup>

- Availability of financial resources;
- Time constraints;
- Use of folk medicine or home remedies; and
- Lack of knowledge about skin cancer.

Statistics compiled by the Alliance for Health Reform for 2002 revealed that 20.2% of African Americans and 32.4% of Hispanics/Latinos were uninsured vs.11.7% of Caucasians.<sup>8</sup> In 2001, 50% of Hispanics/Latinos, African Americans, and Native Americans were considered poor (\$28,256 annual income) vs. 25% of Caucasians. These very patients will be the most affected by the removal of over-the-counter skin bleaching drug products containing hydroquinone.

The Academy emphasizes that exogenous ochronosis is a remarkably uncommon disorder among our patients in the United States. Exogenous ochronosis is a cutaneous disorder characterized by a blue, grey, or black discoloration at the site of application of chemicals to the skin. This disfiguring disorder has been described after the use of a variety of topical agents including hydroquinone, mercury, resorcinol, phenol, and picric acid.

Exogenous ochronosis secondary to hydroquinone was first described by Findlay et al in South Africa.<sup>9</sup> In this original group of patients, hydroquinone containing creams in concentrations of 5% or more applied to areas of hyperpigmentation for an average of 3 years resulted in exogenous ochronosis. No systemic effects were reported. Despite legislation in South Africa to limit concentration of hydroquinone in OTC skin lightening products to 2%, exogenous ochronosis continues to be a condition quite unique to the African and South African populations. An epidemiologic study of exogenous ochronosis by Hardwick in South Africa revealed a prevalence rate of 69% among users of skin lighteners.<sup>10</sup> In 1990, Weiss reported a prevalence of exogenous ochronosis of 65% among black South African women who had used skin lightening products containing hydroquinone.<sup>11</sup>

There have been several proposed hypotheses to explain the exceedingly high prevalence of exogenous ochronosis in the black South African population which include the following:<sup>9, 12</sup>

- High concentrations of hydroquinone in the range of 6-percent to 8-percent contained in skin lightening agents before 1984;
- The inclusion of multiple agents in skin lightening creams including mercury containing compounds (an ochronotic agent) and t-butyl alcohol;
- The use of anti-acne agents containing resorcinol (an ochronotic agent);
- The frequent use of the combination of resorcinol and hydroquinone for more rapid skin lightening; and
- The hydroalcoholic acid vehicle in South African hydroquinone products which increases skin penetration of HQ,

In marked contrast, in the United States, exogenous ochronosis has been and remains a remarkably uncommon cutaneous disorder. The FDA proposal states that, “Exogenous ochronosis was not extensively reported in the United States or the United Kingdom as a result of using OTC skin drug products containing 2-percent hydroquinone until after publication of the TFM for these drug products in 1982”. The FDA docket then goes on to describe 16 cases of exogenous ochronosis (one case involved an African woman with a 10-year history of hydroquinone use) which leaves 15 case reports in American patients. Industry estimates are of at least 10 million users of hydroquinone containing products in the past 40 years. Fifteen case reports of exogenous ochronosis supports the fact that this disease entity occurs infrequently in the United States.

In 2001, Levin and Maibach published an update on clinical features, causative agents and treatment options of exogenous ochronosis.<sup>13</sup> These authors reviewed the literature on exogenous ochronosis by examining articles from Medline from 1966 to 2000 as well as Science Citation Index from 1967 to 2000 and manual searches for additional references. There were 28 reported cases of

exogenous ochronosis in the US from 1983 to 2000. The majority of cases occurred in Black females using 2% hydroquinone for two months to 30 years.

In addition to the hypotheses previously stated to explain the high prevalence of exogenous ochronosis in black South Africans as compared to Americans, there are several crucial differences between the populations, the manner in which they use the hydroquinone products and the actual product themselves that may account for these differences. These differences which are discussed in a 2003 article by Mahe et al who surveyed 425 women from Dakar, Senegal on their use of bleaching products are highlighted below:<sup>14</sup>

- 117 different brands of bleaching products were used by the African women;
- 89% of African women used hydroquinone products with a concentration ranging from 4-percent to 8.7-percent;
- 70% of African women used corticosteroids of whom 93% used class 1 steroids;
- 10% of African women used mercury iodide containing products;
- 17% of African women used caustic agents (hydrogen peroxide, salicylic acid, soap);
- 13% of African women used products unknown ingredients (chemical analysis was unable to identify the ingredients);
- 80% of African women used two or more bleaching products simultaneously;
- 92% of African women applied bleaching products to their total body surface either once or twice daily; and
- 52.7% of African women used bleaching products for a median of 4 years (range: 1 month to 35 years).

In contrast, America women utilize hydroquinone products to lighten only specific areas of hyperpigmentation and not to lighten or alter their overall complexion. They are not exposed to year round intense sunlight as are women living on the African continent. American women rarely use hydroquinone products for prolonged periods of time and utilize over-the-counter products containing 2-percent hydroquinone that are governed by the FDA monograph on skin lightening products, which are formulated in a cream vehicle. Importantly, they rarely use multiple skin lightening products and in particular do not use products containing corticosteroids, mercury, caustic agents, or resorcinol.

Finally, exogenous ochronosis is a disorder that has been successfully treated in recent years with laser therapy and microdermabrasion.<sup>15,16</sup> Significant lightening of the pigmented skin areas was achieved in two patients with the Q-switched Alexandrite laser without scarring or textural changes. Decreased dermal pigmentation was observed on histologic examination of treated skin specimens. Likewise, dermabrasion was successfully employed to remove ochronotic deposits.

Understanding that exogenous ochronosis is a remarkably uncommon disorder among patients in the United States it is obvious that removing over-the-counter hydroquinone containing products

will not have a significant impact on the number of cases of exogenous ochronosis that may occur each year. Therefore, physician monitoring of both the hydroquinone and the patient is unnecessary.

The actual risk to humans from the use of hydroquinone products has yet to be fully determined. Hydroquinone is a ubiquitous molecule, found in the environment, plants and foods as either hydroquinone or as the metabolite, arbutin. Foods and drinks containing hydroquinone in variable levels include cranberries, blueberries and pears, coffee, tea and red wine as well as rice, onions and wheat (including wheat germ and bread). Estimates of blood and plasma levels of hydroquinone have been done after the ingestion of hydroquinone containing meals. For example, a breakfast consisting of coffee, wheat cereal and a slice of wheat bread is estimated to contain 214 ug of hydroquinone/arbutin.<sup>17</sup> In humans, small quantities of hydroquinone are detectable in the blood at levels of 0.038 +/- 0.018 ug/g and urinary excretion at 115.4 +/- 109.7 ug/h.<sup>17</sup>

Human ingestion of hydroquinone in large amounts certainly does not support an association with carcinogenicity. Two study subjects ingested 500 mg of HQ orally for 5 months.<sup>18</sup> No renal or bone marrow cancers or abnormalities were reported. In another study, 17 subjects ingested 300 mg of hydroquinone daily for 3 to 5 months. Again, no renal or blood abnormalities were reported.<sup>18</sup>

Occupational exposure to high levels of hydroquinone occurs in workers in film development, lithography and in chemical processing plants. If hydroquinone is carcinogenic to humans, surveys of these workers would reveal higher prevalence of carcinomas, which is not supported by the literature. A survey of 478 film processor workers did not demonstrate increased cancer prevalence as compared to workers in other occupations.<sup>19</sup> A study of lithographers exposed to both hydroquinone and other chemicals showed a higher incidence of melanoma (2 cases as compared to the expected 1.5 cases).<sup>20</sup> A study of 9,000 chemical plant employees producing hydroquinone and other chemicals revealed lower numbers of premature deaths in the employees as compared to occupational control subjects and the general population.<sup>21</sup> Finally, a study of 858 employees who manufactured hydroquinone and were exposed to airborne hydroquinone at variable amounts for over 13 years revealed no excess incidence of blood dyscrasias, leukemia, kidney or liver cancer.<sup>22</sup> In the occupationally exposed group, there was a significantly lower rate of death from cancers and total mortality from all causes as compared to the general population and to industrial controls. The Academy therefore asserts that there is insufficient epidemiological data to support the argument that hydroquinone is carcinogenic in humans.

The FDA sites evidence of carcinogenicity in male and female rats as well as in female mice as evidence for potential carcinogenic risk from hydroquinone in humans. The evidence is outlined as follows:

- Male F344/N rats: marked increases in tubular cell adenomas of the kidney;
- Female F344/N rats: increases in mononuclear cell leukemia;
- Female B6C3F1 mice: increases in hepatocellular neoplasms, mainly adenomas
- Female and male B6C3F1 mice: Thyroid follicular cell hyperplasia; and
- Male B6C3F1 mice: Anisokaryosis, multinucleated hepatocytes, and basophilic foci of the liver.

DeCaprio performed an extensive review of the carcinogenicity of hydroquinone in both the rat and mouse model.<sup>23</sup> DeCaprio points out that renal adenomas in the male F344 rat fed hydroquinone are unique to this specific rat species, strain and sex. He postulated that the mechanism of tumorigenesis in male F344 rats by hydroquinone, involved an interaction between renal tubule toxicity and chronic progressive nephropathy that is characteristic of all aged male rats of this species. Furthermore, renal toxicity was dependent upon the route of administration, occurring in association with oral and not topical administration, and the age of the animal. Mouse adenomas and mononuclear cell leukemia have been reported in the female F344 rat following hydroquinone exposure. Again, bone marrow and hematologic effects are characteristic of only parenteral administration of hydroquinone in these animal models. In studies of hepatic adenomas in B6C3F1 mice results were inconsistent in the incidence rates for hepatic adenomas. In summary, it is unlikely that these animal data can be translated into any meaningful carcinogenicity data in the human species.

The Academy hopes that these comments on the FDA's proposed rule changes have provided valuable information and perspective which will allow the FDA to make a fair and reasoned decision regarding the future of over-the-counter and prescription hydroquinone containing products in the United States. Furthermore, the Academy trusts that the FDA now understands that:

- Dyschromias are important cutaneous disorders with significant patient morbidity;
- Dyschromias affect millions of Americans including those from under-representative minority groups including African Americans, Latinos, and Asians;
- Treatments for dyschromias, whether self-treatment by patients with over-the-counter hydroquinones or by dermatologists with prescription hydroquinone, should not be denied to the American population;
- Eliminating safe, effective, readily accessible and affordable over-the-counter hydroquinone products is injurious to millions of dyschromias patients particularly those from under-representative minority groups who are less likely to see a dermatologists for treatment;
- Requiring an ANDA for all prescription hydroquinone products would severely limit treatment for more severe dyschromias;
- In marked contrast to the African experience, in the United States, exogenous ochronosis is a remarkably uncommon adverse event from the use of hydroquinone containing products, and the exceedingly low risk does not support removal from the market; and
- The association of cancer in humans from the use of hydroquinone is unproven and existing animal data do not support removal of these products from the market.

The FDA has underestimated the benefit of over-the-counter and prescription hydroquinone treatment to the physical health of dyschromias patients. While the Academy welcomes additional and ongoing safety data for hydroquinone from manufacturers, a review of current data demonstrates that the benefits of these treatments are high and the risks minimal. Withdrawing over-the-counter and limiting prescription hydroquinone treatment will have deleterious effects for dyschromias patients. The action is in many respects punitive in nature for dyschromias patients and is potentially inequitable for patients of various minority groups. Accordingly, the Academy

recommends no change in the status of either over-the-counter or prescription hydroquinone containing products. Finally, the Academy is committed to working with the FDA regarding this issue and welcomes future discussions.

Thank you for considering the views of the Academy. Please do not hesitate in contacting Vera LeBrun in our Washington Office at [vlebrun@aad.org](mailto:vlebrun@aad.org) or 202-842-3555 if you or your staff has questions arising from our comments.

Sincerely,



Stephen P. Stone, MD, FAAD  
President

SPS/vel

cc: Diane R. Baker, MD, FAAD, President-elect  
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