

## LETTER TO THE EDITOR

### Hydroquinone and the FDA—The Debate?

Recently you may have received e-mails, telephone calls, letters, or read articles stating that within the next few months, hydroquinone—our workhorse bleaching cream—will be banned in the US. Point of clarification, on August 29, 2006 the US Food and Drug Administration (FDA) published a monograph in the United States Federal Register proposing that all hydroquinone products, which have not been approved through the New Drug Application process, will be considered misbranded and therefore banned. This “proposed rule” allowed anyone to submit comments to the FDA by a specified date (in this case December 27, 2006—later extended 30 days) before the “final rule” is published. Once the final rule is published in the Federal Register, manufacturers will have 30 days to remove noncompliant hydroquinone products from the marketplace or risk seizure, fines, and possibly imprisonment.

The following is the history behind the proposed ban. Prior to 1962, the year Congress passed the Kefauver Harris Amendment, drugs sold over the counter (OTC) were assumed to be not only safe but also effective. The congressional amendment granted the FDA the authority to review the entire OTC drug market—thousands of products. As a result of the review spanning over 40 years, hydroquinone was one of many products receiving the “GRASE” (generally recognized as safe and effective) designation. In the 1980s, reports of exogenous ochronosis secondary to hydroquinone use by South African Blacks appeared in the medical literature. A large proportion of these reports describe subjects that had applied high concentrations (6%-8.5%) of hydroquinone-containing products (hydroalcoholic solutions, some with mercury and/or resorcinol) over extensive body surfaces, several times a day, for years and even decades. The FDA met with US hydroquinone manufacturers; agreements were made to supply the FDA with studies supporting hydroquinone’s safety. The FDA states it never received the data. In the interim, the FDA’s National Toxicology Program (NTP) completed a pharmacologic-toxicology profile on hydroquinone. The results were reviewed by both the FDA and its Cancer Assessment Committee, and hydroquinone was classified as having “some evidence of carcinogenicity.”

We have received a list of nongovernment-sponsored pharmacology/toxicology studies from the consumer health care industry that were not included in the FDA’s proposed rule. They may not have been aware of their existence when the rule was written. It is important to understand that when these animal studies are performed large amounts of the drug product (far exceeding human dosages) are administered systemically and dermally in order to obtain worse case scenario information. To the best of our knowledge, there have been no cases of cancer associated with cutaneous application of hydroquinone.

The FDA states that due to the reports of “disfiguring ochronosis,” toxicology risks, and lack of economic impact (the economic impact of banning hydroquinone to the manufacturers could not have been that great or they would have completed the safety studies) the rule is proposed.

We have reviewed all the exogenous ochronosis cases cited in the Federal Register document, along with the currently available English medical literature. It comes as no surprise that the use of hydroquinone by the American consumer is very different from that of their African counterparts in frequency, duration, amount applied, and concentration/formulation. We found less than 25 reported cases of hydroquinone-associated ochronosis in the US over the past 25 years. Certainly, there may be unreported cases; however, conservative use of the data suggests that there would be one case of exogenous ochronosis for every 300 to 450 million units of hydroquinone sold in the US. Nonpublished *manufacturing* data from the hydroquinone producers would decrease the incidence further. The clinical and histological descriptions of the large patient numbers in the African “series” demonstrate a much more aggressive disease than in the rare US cases. Furthermore, the exogenous ochronosis reported in US patients responded to treatment.

The pharmacology data is a concern; we would not want our patients or the American consumer to use drugs whose benefits are outweighed by the risks. The FDA’s evaluation of the results was that there was “some evidence of carcinogenicity.” “Some evidence” is not a strong enough indictment to necessitate banning a drug for which there are no acceptable, readily available, affordable, and safe alternatives for so many Americans.

On behalf of the Dermatology Section of the National Medical Association, we included in our response to the FDA a request that in consideration of their “mission” they: 1) consider the cases of exogenous ochronosis reported in the US—not Africa, 2) review all of the available pharmacology/toxicology data on hydroquinone, and 3) use their resources to obtain epidemiologic human data to fully answer the safety questions.

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