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Nonprescription Drug
Manufacturers Association
1150 Connecticut Avenue, N.W.
Washington, D.C. 20036

RE: Docket No. 78N-0065
Comments RPT 4 and RPT 5

Dear Dr. Soller:

This letter is in response to: (1) Your submissions dated January 4, 1994, filed as Comment No. RPT 4 and January 22, 1996, filed as Comment No. RPT 5 in Docket No. 78N-0065, (2) the recommendations made by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) at the public meeting held on December 4, 1996 (copy enclosed), (3) the Ochronosis Recall Survey (submitted as part of RPT 4), and (4) the voluntary labeling guidelines submitted to FDA by the Nonprescription Drug Manufacturers Association's (NDMA) Hydroquinone Task Group at the May 20, 1992 feedback meeting.

I. Data Submissions and CAC Recommendations

At the May 1992 feedback meeting, NDMA presented a research program to further evaluate hydroquinone's carcinogenic potential based on the hypothesis that the renal cell adenomas seen in the oral bioassay studies performed by the National Toxicology Program (1989) and Shibata et al. (1991) were due to the unusual sensitivity of male Fischer 344 rats to hydroquinone. On January 4, 1994, NDMA submitted the report "An Update on Chronic Health Effects Testing for Hydroquinone." This report provided results of completed studies, including preliminary results for on-going studies, and an outline of studies in the planning phase. NDMA further updated this report in their January 22, 1996 submission.

We have evaluated the studies submitted with these submissions and conclude that the available data are insufficient to rule out the potential carcinogenic risk from topically applied hydroquinone. At the December 4, 1996, public meeting, the CAC

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concluded with this conclusion and recommended that additional studies be performed to assess the safety of skin bleaching drug products containing 2 percent hydroquinone. Because hydroquinone is applied topically and absorbed systemically, hydroquinone must be assessed for both topical and systemic tumorigenicity. A dermal carcinogenicity study, conducted in an appropriate model with functioning melanocytes, must be performed on hydroquinone to assess both its topical and systemic tumorigenicity. This study should be performed in one animal species, such as a suitable mouse strain that contains active melanocytes. The test article should be 2 percent hydroquinone in a vehicle comparable to the formulation bases for the over-the-counter (OTC) skin bleaching drug products currently available. The protocol for this study should be submitted to the agency for review by the CDER Office of Drug Evaluation V and CAC.

In addition, we request that the following studies be performed: (1) In vivo dermal bioavailability, pharmacokinetic, and metabolism studies between humans and the animal species chosen for the dermal bioassay study, and (2) a standard tissue distribution study in pregnant animals (to determine potential genetic damage in the fetus). This additional information should provide important, necessary data concerning the human carcinogenic potential of these products.

II. Ochronosis Recall Survey

The ochronosis recall survey was developed by the NDMA Hydroquinone Task Group in collaboration with the American Academy of Dermatology (AAD) Committee on Therapeutics and is a result of a request made by the Division of OTC Drug Products at the May 20, 1992 feedback meeting. The survey consisted of a questionnaire mailed out to 6,500 practicing AAD dermatologists for the purpose of determining the occurrence of hydroquinone-associated exogenous ochronosis during the lifetime of their practices.

Thirty-two percent (2,108) of the dermatologists responded with an estimated cumulative practice of 44 million patients. The median length of practice per dermatologist was 12 years (range 1 to 46 plus years). Eighty-nine percent of the respondents stated that they had seen no cases of exogenous ochronosis in their career. Two hundred and twenty-two dermatologists reported that they had diagnosed one or more cases of exogenous ochronosis (total = 512 cases). More than half of the cases (296) were reported by the respondents as due to hydroquinone or OTC skin bleaching drug products. Of these cases, 46 were reportedly associated with 2 percent hydroquinone skin bleaching products.

Fifty-two to fifty-seven percent of the respondents stated that they were the only attending physician on the case. Although physicians reported the availability of medical records in 40 percent of exogenous ochronosis cases, virtually no physicians reviewed their records before answering the survey. One hundred and thirty physicians stated that they had obtained biopsies for definitive diagnosis in some or all of their cases. There was no independent review or confirmation of these reported cases.

We have the following comments concerning the survey:

(1) A long list of differential diagnoses (post-inflammatory hyperpigmentation, argyria, hemochromatosis, Addison's disease, porphyria, pellagra, and endogenous ochronosis) exists for this condition. Without a more detailed past medical history of each individual patient and their concomitant medications, any suspected diagnoses can be challenged.

(2) Thirty-two percent is a relatively low response rate to the survey.

(3) Possible reporting bias cannot be excluded from the survey results. The accuracy of the recall can be questioned, especially if records for this condition are not maintained (some respondents reported they were in practice for 40 plus years).

(4) Medical record availability is limited. Medical records were only available for 40 percent of the cases and no physicians reviewed their records before answering the survey.

(5) Although 130 physicians stated that they had obtained biopsies, no confirmations or reviews of the biopsies were conducted.

(6) It is uncertain how many of these cases are duplicative, as only 52 to 57 percent of the respondents stated that they were the only attending physician on the cases.

(7) A dermatologist knowledgeable about this condition may discontinue the use of the drug in the patient early on. Thus, because full symptomatology may never develop, total prevalence may be under reported.

(8) Hyperpigmentation is a frequent complaint of the patient population using these products and mis-diagnoses may occur.

The results of this survey suggest that exogenous ochronosis may occur in association with use of skin bleaching drug products containing hydroquinone. Unfortunately, the survey does not provide sufficient information to accurately determine the number of confirmed cases of exogenous ochronosis or the number of cases associated with the use of two percent hydroquinone. Thus, the incidence of exogenous ochronosis from the use of two percent hydroquinone-containing skin bleaching drug products cannot be established.

The survey does indicate that the development of exogenous ochronosis occurs from the use of these products. Therefore, due to the potential for OTC skin bleaching drug products to cause exogenous ochronosis in some people, and the fact that exogenous ochronosis is cosmetically disfiguring, the Division believes that consumers should be alerted to the potential risk of developing exogenous ochronosis in the labeling of OTC skin bleaching drug products containing two percent hydroquinone (see recommendations below).

III. Voluntary Labeling Guidelines

At the May 20, 1992 feedback meeting, NDMA submitted voluntary labeling guidelines for OTC skin bleaching drug products. These guidelines represent a combination of labeling proposed by the FDA in the tentative final monograph for OTC skin bleaching drug products (47 FR 39108, September 3, 1982), and labeling proposed by NDMA's Hydroquinone Task Group.

As discussed above, we believe that a warning on the label of OTC skin bleaching drug products is necessary to alert consumers to the possibility of developing exogenous ochronosis. We believe that the new language proposed by the task group (i.e., "Some users of this product may experience a mild irritation or temporary darkening. If skin irritation becomes severe or darkening persists, stop use and consult a physician.") does not adequately convey the risk. If consumers believe that the darkening they are experiencing is only temporary, they may continue to use the product until more severe effects occur. In addition, we believe that darkening and skin irritation warnings should be separated. Consumers should be alerted on the label to the potential risk of exogenous ochronosis and to seek appropriate action if the condition occurs. We recommend the following language be used under the Warnings subheading, "When using this product" "■ mild irritation may occur" and the following language be used under the Warnings subheading "Stop use and ask a doctor if" "■ a gradual blue-black darkening of the skin occurs" "■ irritation becomes severe."

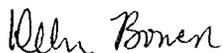
A considerable amount of data have been generated on hydroquinone since the publication of the tentative final monograph in 1982. Based on the review of these data, the agency cannot rule out hydroquinone's potential to be a topical or systemic carcinogen in humans. In addition, the systemic absorption of hydroquinone in humans has been reported in the literature and by NDMA. In the FEDERAL REGISTER of December 3, 1982 (47 FR 54750), FDA amended its drug labeling policy to include a general warning statement for pregnant or nursing women who use OTC drugs intended for systemic absorption. In light of the new data generated on hydroquinone and the fact that hydroquinone is systemically absorbed, we believe that the following general pregnancy warning should be included under the heading "Warnings": "If pregnant or breast-feeding, ask a health professional before use."

The above labeling changes have been provided in a current labeling format. We request that manufacturers of affected products implement these labeling changes within 12 months.

We are interested in your feedback and request that you provide us with an implementation schedule within 60 to 90 days. This schedule should include time frames for protocol development, protocol submission, study initiation and completion, and analysis of data.

We appreciate your cooperation in these matters and look forward to further dialogue in the future.

Sincerely yours,



Debra L. Bowen
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Enclosure