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## CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

*Formerly Nonprescription Drug Manufacturers Association*

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April 13, 1999

Debra L. Bowen, M.D.  
Acting Director  
Division of OTC Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Re: Docket No. 78N-0065

Dear Dr. Bowen:

In response to your letter dated December 7, 1998, the Hydroquinone Task Group of the Consumer Healthcare Products Association (CHPA; formerly the Nonprescription Drug Manufacturers Association) provides here an implementation schedule for additional safety studies of hydroquinone, the active ingredient in over-the-counter (OTC) skin discoloration fade creams. FDA has requested the following studies:

1. Dermal carcinogenicity study in an appropriate animal model with functioning melanocytes;
2. In vivo studies to obtain bioavailability, pharmacokinetic, and metabolism data from dermal applications in humans and the species used in the dermal carcinogenicity study (#1 above);
3. Tissue distribution study in pregnant animals.

This letter also responds to FDA's request in the December 7, 1998 letter for particular additions and changes in label warning statements on OTC drug products containing hydroquinone.

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### Research Program

The available data and longstanding clinical experience with 2% hydroquinone products support the continued OTC availability of hydroquinone as a skin discoloration lightener as research is undertaken to confirm further the ingredient's safety profile. The CHPA Task Group plans to conduct a study in which 2% hydroquinone is applied daily for 2 years to the skin of B6C3F1 mice, which have pigmented skin. The study's purpose is to evaluate the carcinogenic potential of topically applied hydroquinone. The study protocol has been developed and is currently being reviewed by companies who will sponsor the project.

The dose levels for the 2-year study will be determined in a 4-week dermal range-finding toxicity study with hydroquinone at three concentrations applied to the dorsal skin of B6C3F1 mice. The hydroquinone will be administered in oil-in-water emulsion creams with a formulation that is similar to marketed skin discoloration fade creams, and the vehicle will be used as the control article in each of the studies.

Considerable bioavailability, pharmacokinetic, and metabolism data are available for hydroquinone in humans and various animal species. The CHPA Hydroquinone Task Group is planning to conduct an additional study within the next 6 months to obtain more data on the absorption, metabolism, and excretion of dermally applied <sup>14</sup>C-labeled hydroquinone in humans (male volunteers). We are currently considering what similar data are needed for B6C3F1 mice, as well as when to conduct any additional studies that may be necessary. Those studies would be completed during the time the dermal carcinogenicity study is being conducted, perhaps as part of the 4-week range-finding study.

FDA asked that a study also be conducted with hydroquinone in pregnant animals. The CHPA Hydroquinone Task Group is currently reviewing a study synopsis for a tissue distribution and mass balance study with pregnant rats given topical applications of <sup>14</sup>C-hydroquinone. We

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expect to develop a protocol and prepare to conduct the study within the same time frame as the carcinogenicity study.

The hydroquinone research program schedule is primarily determined by the time required for the 2-year carcinogenicity study, including the preceding range-finding study. The projected dates for the carcinogenicity study are as follows:

May 1999	Submit draft protocols for FDA review
August 1999	Initiate 4-week range-finding study
November 1999	Submit revised 2-year study protocol to FDA
January 2000	Initiate the 2-year study
January 2002	Conduct terminal sacrifice and necropsy

This schedule allows for estimated FDA review times. Meeting the schedule, of course, depends on the actual length of review times and the occurrence of no unforeseen events that cause unavoidable delay. The histopathologic evaluation, quality assurance audits, and report preparation, review, and finalization will take approximately 1 year after the terminal sacrifice.

The other studies requested by FDA have considerably shorter durations than the 2-year carcinogenicity study and can therefore be finished while the carcinogenicity study is in progress.

#### Changes in Labeling

For several years, members of the CHPA Hydroquinone Task Group have been following voluntary labeling guidelines that were submitted to FDA at a May 20, 1992 feedback meeting. Your December 7, 1998 letter contains FDA recommendations for several additions and other changes in label warning statements on OTC drug products with the active ingredient hydroquinone.

Task group members intend to incorporate the FDA recommendations in product labeling at least

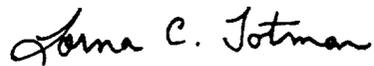
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by December 12, 1999. Some products already have revised labeling. We plan to submit updated voluntary labeling guidelines to FDA within the next few months that will show the requested changes.

Please let me know if you have additional comments or need clarification on our hydroquinone research plans or the voluntary labeling program.

On behalf of the CHPA Hydroquinone Task Group,

Sincerely,



Lorna C. Totman, Ph.D., DABT  
Director of Scientific Affairs

cc: FDA Dockets Management Branch (three copies)

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