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VIA FACSIMILE AND U.S. MAIL

April 5, 2002

Dr. Joan Denton
Director
Office of Environmental Health
Hazard Assessment
P.O. Box 4010
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Re: Lovastatin

Dear Joan:

As you know, OEHHA has placed lovastatin, also known as MEVACOR®, on the candidate list for future review by the Proposition 65 Carcinogen Identification Committee ("CIC"). Lovastatin is a well-established aid in lowering cholesterol among patients at risk for atherosclerotic coronary artery disease, the leading cause of mortality in California and the United States. The AFCAPS study of over 6500 participants demonstrated lovastatin's effectiveness in significantly reducing the incidence of various adverse events, including first acute major coronary events (rr = 0.63), myocardial infarction (rr = 0.60), unstable angina (rr = 0.68), and other events (rr $\leq$ 0.75). Downs, JR, et al. (JAMA 1998). Merck & Co. has applied to market lovastatin over-the-counter. Lovastatin is one of six "statins" (also known as HMG-CoA reductase inhibitors) that have been approved by FDA.

When OEHHA was evaluating whether to place lovastatin on the candidate list, Merck stressed that it would be critical for public health and competitive fairness to present all statins to the CIC at the same time. OEHHA responded that it was "exploring" the option of treating the statin drugs as a class of related compounds. OEHHA's most recent list of chemicals to be evaluated for prioritization, released just a few months ago, contained groupings of pharmaceuticals, such as dihydropyridine calcium channel blockers and nucleoside analogues. In discussing these groupings with Val Siebal, I have learned that OEHHA also decided to group the statin drugs together in the tracking database.

In light of these developments, Merck reiterates its request that if OEHHA considers it necessary to present one statin to the Carcinogen Identification Committee for review, OEHHA present all the statins to the CIC for review at the same time. This simultaneous evaluation of all the statins is warranted for at least the following reasons:

- Examining lovastatin by itself will not advance the public health goals of Proposition 65, and risks damaging public health by disseminating incomplete information. If the CIC were to find that lovastatin has been clearly shown to be a carcinogen, a conclusion Merck strongly opposes, statin users and providers likely would misinterpret California's action as a signal that lovastatin presents a unique risk of cancer not presented by the other statins. This misimpression would undermine the central purpose of Proposition 65 -- providing consumers meaningful information to assist them in making better-informed health decisions.

- OEHHA has stated in the final data summary for lovastatin that "a number of other HMG-CoA reductase inhibitors . . . have also been shown to cause liver, lung or forestomach tumors in rodents," and has signaled an intent to present structure-activity and structure-function information on all statins to the CIC for its consideration of lovastatin. In this light, it would appear far more efficient for the CIC to consider all of the statins together rather than to undertake duplicative reviews of the same mechanistic information. Similarly, presenting all the statins to the CIC at the same time would save staff time for OEHHA by avoiding duplicative hazard identification documents and would enable the staff and the CIC to have a more complete understanding of the carcinogenicity data.

- FDA has treated the statins as a class for labeling purposes, and the CIC should act in harmony with this practice by reviewing the statins simultaneously – FDA's history of class labeling increases the risk that any differential labeling which may result from the CIC's isolated review of lovastatin would be misperceived as reflecting a comparative analysis of all statins.

- Simple fairness dictates that all statins should be evaluated together, if they need to be evaluated by the CIC.

Very truly yours,

Gary M. Roberts