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November 16, 2007

The Honorable Andrew von Eschenbach, M.D.
Commissioner, Food and Drug Administration
5600 Fishers Lane
Room 14-71
Rockville, MD 20857

Dear Dr. von Eschenbach,

We are writing to request that the FDA undertake or commission a review of the adverse event profile and long-term safety of the cholesterol-lowering drugs known as "statins." We believe such review should involve a formal systematic analysis of existing studies and a benefit-risk analysis targeted primarily at the "primary-prevention" population. In addition, we would urge that such a review include a request to manufacturers for adverse reaction and long-term safety data on all drugs containing a statin. We would urge the agency to undertake this review and report the results of this analysis to the physician community and the public in a timely manner, ideally within 18 months.

As you know, statins are among the most widely prescribed drugs in the U.S. One in 10 adults currently takes a statin and one in four people over age 65 do. Moreover, the number of people taking statin drugs has expanded dramatically in recent years and is poised to continue growing in the years ahead as the population ages and the approved clinical indications for statins expands. Most recently, statin use has grown sharply among people with type 2 diabetes, and one recent study adds to evidence that statins may be beneficial for many if not most of the estimated 19 million people in the U.S. with chronic kidney disease.[1] In addition, statin use by Medicare Part D enrollees increased 7 percent in 2006, attributable to new drug coverage gained by millions of seniors.[2]

It's possible that 25 to 30 million people in the U.S. could be taking a statin every day by 2010, up from about 20 million today.[3]

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[1] Agarwal, R., "Effects of Statins on Renal Function," *Mayo Clinic Proceedings*, 82(11):1381-1390 (November 2007).
[2] The Pink Sheet (August 20, 2007), page 24.
[3] "Trends in Serum Lipids and Lipoproteins of Adults, 1960-2002," *Journal of the American Medical Association* (October 12, 2005),Vol. 294:1773-1781. See also: *The Bottle Report*, (Vol. 93) Bear Stearns Research (October 15, 2007).

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Our concern about the adverse effects and long-term safety of statins is prompted by the greatly expanded use of these medicines and the following developments and factors:

(1) It is now well established that people with heart disease, and especially those who have had a first heart attack or stroke, benefit from a greater LDL reduction than was appreciated five years ago. This has resulted in wider use of higher doses of statins, to drive LDL below 100, in the secondary prevention setting. It has also resulted in the greater use of the 80mg dose of some statins. It is highly likely that the clinical benefit of higher doses and lower LDL levels *in this group* is well worth the higher risk of adverse events such as myopathies, muscle soreness and inflammation, peripheral neuropathy, liver failure, and rhabdomyolysis. Still, we believe that because of the widespread nature of this emerging clinical practice, a formal assessment of the current side effect and safety experience is now warranted.

(2) Many clinicians appear to have extended the "push LDL lower" approach to those who have no diagnosis of heart disease and no prior coronary events but who have risk factors – i.e. the primary prevention setting. Recent studies indicate that between half and two-thirds of new statin prescriptions are for people who do not have heart disease. While the benefit of statins and LDL lowering is increasingly clear for this group,[4] the benefit/risk balance of high doses (even 40mg compared to 20mg) is much less firmly established and likely highly individualistic.[5] As one observer recently wrote: "no primary prevention trial provides information about events below an LDL cholesterol of about 90 mg/dl, and none of the trials address the issue in adults in their early to middle years."[6] In addition, it has come to our attention that the full data sets on adverse events from several of the important statin primary prevention trials have never been publicly released.[7] We believe that a formal assessment of the current state of the evidence on side effects and long-term safety in the primary prevention population would be a highly valuable undertaking.

(3) Merck has reapplied to the FDA to market an over-the-counter version of Mevacor (lovastatin) at 20mg. On December 13, two FDA advisory committees (Nonprescription Drugs and Endocrine and Metabolic Drugs) will hear evidence from Merck and possibly others to support this application. We believe strongly that the agency needs updated and

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[4] Ford, I. et al, "Long-term Follow-up of the West of Scotland Coronary Prevention Study," *NEJM* 357;15, pages 1477-1486 (October 11, 2007).

[5] An analysis of statin trials conducted in 2003 found that 71 primary prevention patients with cardiovascular risk factors would have to be treated with a statin for three to five years to prevent one heart attack or stroke. *Therapeutics Letter – Evidence Based drug Therapy*. (May/June 2003), Therapeutics Initiative, University of British Columbia Dept of Pharmacology and Therapeutics. See also: Ward, S. et al , "A Systematic Review and Economic Evaluation of Statins for the Prevention of Coronary Events," *Health Technology Assessment* 2007 - Vol. 11;14) (April 2007. UK National Health Service.

[6] Domanski, M., "Primary Prevention of Coronary Artery Disease," *NEJM* 357;15, pages 1543-1545

[7] Personal communication from Maryann Napoli at the Center for Medical Consumers, New York, referencing the work of Jim Wright et al. at the University of British Columbia.

thorough data on the adverse effects and long-term safety of statins in the context of this new application. The benefit-risk balance of an over-the-counter (or possibly a behind-the-counter) statin deserves the closest possible scrutiny.

(4) Some doctors may have grown complacent about the adverse effects of statins. A study published in the August 2007 issue of the journal *Drug Safety* (Vol. 30; 8, pages 669-675) has raised such concerns. It probed the experiences of 650 adults who were statin users and reported making complaints to their doctors about side effects they believed were associated with the drugs. The authors say that the majority of the symptoms were indeed acknowledged potential side effects of statins. The patients reported a high level of physician dismissal of, or non-committal responses to, the complaints. For example, among patients reporting muscle weakness and pain to their doctors, 29 percent of the doctors agreed that this could be linked to the statin, 47 percent dismissed a possible link, and 24 percent were non-committal.

(5) Some evidence suggests that women and men have different responses to statins yet most of the clinical trials have either predominately been in men or lumped men and women together in assessment of benefits, outcomes and risks.[8] We believe a full gender sub-analysis of statin adverse event data is warranted.

(6) Studies indicate that about one in 20 people who take a statin experience "minor muscle pain" over a year's time.[9] We have concerns about whether all those episodes are so minor. Anecdotally, they seem not to be if some social networking and statin-related Web sites are to be believed. In addition, we believe that many statin users need a better explanation of the risk of minor muscle pain, and guidance about when it reaches a level that exceeds minor. We also urge data analysis and perhaps future studies to clarify whether there is a cumulative risk of muscle pain, weakness and/or soreness, and peripheral neuropathy, after years of taking a statin and whether this risk increases with age.

(7) More people today, and especially seniors, are taking multiple medicines for multiple chronic diseases. There is a paucity of data in general on the potential adverse interactions of these medicines. With statin use so prevalent and growing, we urge more targeted analyses of aggregate data on people who take statins together with several other medicines over long periods.

Finally, we make this request because it has been our observation that many consumers are confused about the side effects and long-term safety of many widely used drugs today; statins are prominent among these. In two separate initiatives we have had underway for three years – *Consumer Reports Best Buy Drugs*™ (a public education project) and *Prescription for Change* (an advocacy campaign), we have heard from

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[8] Walsh, J. & Pignone, M., "Drug Treatment of Hyperlipidemia in Women," *JAMA*: 291;18. pages 2243-2252 (May 12, 2004)

[9] "Statin Safety – A Perspective" (May 2006), Bandolier (www.bandolier.com). Downloaded August 31, 2007

thousands of consumers about prescription drug issues. Safety and side effects are an ever-present concern. Recent polls and surveys yield similar findings.

In light of this mounting concern and in the context of recent legislation giving the FDA enhanced authority to compel data to be gathered on drug safety, we believe the agency would be performing a critical public service to assess the statin evidence and provide clear guidance to both physicians and consumers.

Let us be clear: the outcome of the review we request is probably more likely to reassure doctors and the public about the safety of statins than to reveal a level of problems that could change clinical practice or the labeling of the drugs. But the fact is we don't know.

Thank you for considering this matter. We would be pleased to supply any additional material to support this request or to answer any questions you or FDA staff might have on the issue.

Sincerely,

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Consumers Union

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Managing Editor
Consumer Reports Best Buy Drugs™
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cc: Paul Seligman, M.D., Dir., Office of Safety Policy & Communications