DEPARTMENT OF HEALTH & HUMAN SERVICES

MAR 4 2005

Food and Drug Administration
Rockville MD 20857

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Re: Docket Nos. 2002P-0243/CP1 and 2002P-0244/CP1

Dear Mr. Emord, Mr. Goodman, and Dr. Whitaker:

This letter responds to your two petitions dated May 24, 2002, and supplement dated November 29, 2004, regarding HMG-CoA reductase inhibitors (statins) and coenzyme Q10 (CoQ10 or CoQ). One petition (Boxed Warning Petition)[1] asks that the Food and Drug Administration (FDA or the Agency) require the labeling of all approved statins to include a boxed warning that (in part) (1) discusses what you refer to as "risks" associated with statin-induced[2] deficiency of CoQ10 (i.e., impairment of myocardial function, liver dysfunction, and myopathies); and (2) recommends CoQ10 supplementation with all statins. The other petition (MedGuide Petition)[3] requests that we declare statin-induced deficiency of CoQ10 a "serious and significant concern," and order the distribution of Medication Guides for all approved statins. Your supplement, among other things, references the National Cholesterol Education Program's recommendations for cholesterol management, which you claim will increase statin use. Your supplement also mentions what you characterize as "warnings" regarding decreased CoQ10 levels that appear on product monographs of all statin drugs sold in Canada. For the reasons discussed below, your petitions and supplement are denied.

I. DECISION SUMMARY

The boxed warning that you request is not warranted because the currently available, scientific evidence does not support the inclusion of that information under the applicable legal standard. Specifically, there is no reasonable evidence upon which to conclude that statin-induced decreases in CoQ levels are associated with impairment of myocardial function, liver dysfunction, or myopathies. Nor is there reasonable evidence upon which to conclude that CoQ supplementation with statin therapy is associated with decreased risk, prevention, or mitigation of such adverse events.[4] In addition, the Medication

[1] Docket No. 2002P-0244.
[2] You use the term "statin-induced" to refer to decreases in CoQ levels that are sometimes observed in patients treated with statins. Although we note that the correct characterization of this observation would be "statin-associated" decreases in CoQ levels, we also use the term "statin-induced" in this response to avoid distracting the reader.
[3] Docket No. 2002P-0243.
[4] Although FDA regulations (21 CFR 314.80(a)) use the term "adverse drug experience," we use the lay term "adverse event" in this response.

2002P-0243

PDN 1

Guides, such as those you describe, are not warranted. The Agency has determined that statin-induced decreases in CoQ levels *do not*, as you suggest, pose a serious and significant public health concern requiring distribution of FDA-approved patient information (with warnings to that effect and recommendations on CoQ supplementation).

II. BACKGROUND

Below we set forth some general background information. Section II.A provides some general information on statins. Section II.B describes the biochemical function of CoQ.

A. Statins

Statins, or HMG-CoA reductase inhibitors, are lipid-altering drugs that inhibit the enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is involved in the biosynthesis of cholesterol. The mean cholesterol reduction achieved with these drugs ranges from 15 to 65%. The Agency has approved new drug applications (NDAs) for seven statins (listed below in Table 1).

Table 1

Statin Tradename/Manufacturer	Non-proprietary Name	Original Date of FDA Approval
Mevacor/Merck*	lovastatin	1987
Pravachol/Bristol-Myers Squibb	pravastatin	1991
Zocor/Merck	simvastatin	1991
Lescol and Lescol XL/Novartis	fluvastatin	1993
Lipitor/Pfizer	atorvastatin	1996
Baycol/Bayer**	cerivastatin	1997
Crestor/Astra-Zeneca	rosuvastatin	2003

*Generics available for lovastatin; lovastatin is also marketed in combination with niaspan as Advicor and as an extended-release formulation as Altoprev.
**Withdrawn from worldwide markets in August 2001.

All of these FDA-approved statins are prescription drugs. All currently approved statins are indicated for patients with a variety of lipid abnormalities including familial and non-familial forms of hypercholesterolemia and mixed dyslipidemias (elevated cholesterol

and triglyceride). Several FDA-approved statins are also indicated for the reduction of risk of cardiovascular mortality and morbidity.

In general, statins are well tolerated; however, rare, serious side effects have been reported with their use, including rhabdomyolysis and liver enzyme elevations. Rhabdomyolysis is severe muscle damage that may precipitate kidney failure and death.[5] Incidence of rhabdomyolysis is estimated to be between 0.03 and 0.05% (Thompson PD et al. Statin associated myopathy. *JAMA* 2003; 289(13):1681-1690).

Increases in liver enzyme levels have also been observed with all drugs in this class. Rarely do these result in serious clinical consequences. Recent analyses of large controlled clinical trial databases and postmarketing adverse event reports suggest that the risk of liver toxicity associated with statin use is similar to the background rate of liver disease in the general population, which is approximately 1 per 1,000,000 person-years (Graham DJ et al. Incidence of idiopathic acute liver failure and hospitalized liver injury in patients treated with troglitazone. *Am J Gastroenterol* 2003; 98(1):175-179).

These more serious adverse events associated with statin use already appear under the Warnings and Precautions section of the approved labeling. Statin labeling currently contains specific sections for muscle toxicity (e.g., myopathy) and liver dysfunction under the Warnings section. None of the currently approved statins have Medication Guides.[6]

B. Biochemical Function of CoQ10

Although a complete discussion of the role of CoQ in cellular/metabolic processes is beyond the scope of this response, we set forth below a brief summary of the role of CoQ in such processes.

The most well-recognized function of CoQ is as an electron carrier involved in cellular energy production. The metabolism and oxidation of glucose and lipids generate adenosine triphosphate (ATP), an energy source involved in a multitude of physiologic functions in the organism, including muscle contraction. Energy metabolism (in the presence of oxygen) involves the conversion of one molecule of glucose and free fatty acids (from lipids) to carbon dioxide and water and 32 molecules of ATP. The entire process involves several enzymatic reactions and a series of complex chemical reactions taking place in both the cytosol and mitochondria with the bulk of energy production occurring in the mitochondria. It is within the mitochondria that CoQ contributes to the production of ATP.

A less well-understood function of CoQ is its role as an antioxidant. CoQ is located in the mitochondrial inner membrane and in all membranes throughout the cell, primarily in

[5] Rhabdomyolysis is generally considered to be an extreme form of myopathy.
[6] A list of current Medication Guides can be found at: http://www.fda.gov/cder/Offices/ODS/labeling.htm.

its reduced state as ubiquinol, where it has the potential to act as a primary scavenger of free radicals. The antioxidant effects of CoQ, if any, and their potential impact on the course of atherosclerosis and other diseases have not been elucidated.

III. DISCUSSION

In support of your two petitions, you submitted more than 50 references, including laboratory data, position papers, animal studies, and clinical investigations.[7] We reviewed not only the references submitted, but we also surveyed the literature independently. As discussed in more detail below, based on our review of the currently available, relevant scientific evidence and our experience and expertise, we find that the clinical significance, if any, of statin-associated decreases in CoQ levels is unknown. Likewise, we find there is insufficient evidence at this time to support the purported benefits of CoQ supplementation with statin therapy.[8]

Our review of clinical studies was particularly important in reaching these conclusions. That is, we expect clinical studies to be more relevant than those done in animals. We do not include in this response an analysis of our conclusions regarding all of the references submitted. For example, we do not provide an analysis of the animal studies submitted because such studies have little predictive value for statin use in humans when assessing the claims you make in support of your petitions. In animal studies it is not uncommon to employ higher doses than those typically used in studies done in humans. Data from human studies are more directly applicable to the clinical use of a drug than data from animal studies. Some of the clinical studies we reviewed are summarized in Appendix A.

Many of these (and other) clinical studies that we reviewed were observational, uncontrolled, controlled and non-randomized in design, or of short duration. Such study designs introduce biases and confounders. Accordingly, they do not provide adequate evidence to support your requests.

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[7] You cite Dr. Langsjoen's scientific report, which in turn relies on many of these sources (Exhibit A of the Boxed Warning Petition and MedGuide Petition). Both petitions are based on substantially the same data and information, although they contain two different requests for Agency action. In addition, both petitions are based on three main premises (Boxed Warning Petition at 4-6; MedGuide Petition at 4-6): (1) that statin therapy reduces CoQ levels; (2) that this CoQ "deficiency" is associated with several "risks," including impairment in myocardial function, increased risk of myopathy, and liver dysfunction; and (3) that supplementing statin treatment with 100 to 200 mg of CoQ daily would "prevent and/or reverse the dangers of CoQ10 depletion effects of statins."

[8] We note, as do you, that Dr. Whitaker "recommends the use of CoQ10 as a dietary supplement and also licenses the use [*sic*] of his name and likeness in connection with manufacturing and sale of . . . dietary supplements, including CoQ10" (Boxed Warning Petition at 2; MedGuide Petition at 2).

A. Request for Boxed Warning

Congress charged the Agency with ensuring that prescription drugs are "safe and effective" and not misbranded.[9]

You ask that we require the following warning to be included in the labeling for all statins (Boxed Warning Petition at 1):

> Warning:
> HMG CoA reductase inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q_{10}, required for energy production. A deficiency of coenzyme Q_{10} is associated with impairment of myocardial function, with liver dysfunction and with myopathies (including cardiomyopathy and congestive heart failure). All Patients taking HMG CoA reductase inhibitors should therefore be advised to take 100 to 200 mg per day of supplemental coenzyme Q_{10}.

We find that the currently available relevant scientific evidence, when considered in accordance with the applicable statutes and regulations, does not warrant requiring statin prescription drug labeling to include the above-referenced boxed warning at this time.[10]

FDA regulations include specific provisions regarding Warnings for prescription drug labeling. Specifically, these regulations provide that the "Warnings" section of the labeling "shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. *The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.*" (21 CFR 201.57(e)) (emphasis added). In addition, the Agency may require that "[s]pecial problems, particularly those that may lead to death or serious injury," be placed in a "prominently displayed box" (id.). The regulations further provide that "[t]he boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data" (id.). Moreover, the Agency

[9] See sections 503, 505(b)-(d), 301(a), (b), (k), 502(a), (f), (j) of the Act.

[10] To obtain FDA approval for a prescription drug, an applicant must submit an NDA. Section 505(b) of the Act. The NDA must include adequate tests to show safe use under, and substantial evidence of effectiveness for, the "conditions of use prescribed, recommended, or suggested in the proposed labeling." Section 505(d) of the Act. Consequently, the evaluation of a drug's safety and effectiveness is inextricably intertwined with its labeling. FDA's decision on appropriate labeling is based on the evidence submitted by an applicant, as well as the Agency's review of other relevant information. When FDA concludes that a prescription drug is both safe and effective under the conditions of use prescribed, recommended, or suggested in proposed labeling, the Agency approves the NDA, including the appropriate product labeling. After approval, the Agency continues to monitor information bearing on the safety and effectiveness of the drug and, where appropriate, works with the sponsor to update the labeling. We note, as have many courts, that "The FDA is the agency charged with implementing the [Act]. [The Agency's] judgments as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of the FDA's expertise" (See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3rd Cir. 1995)).

has stated that "to ensure the significance of boxed warnings in drug labeling, they are permitted in labeling only when specifically required by FDA."[11]

First and foremost, the prescription drug labeling for statins already includes in the Warnings section information on muscle toxicity (e.g., myopathy) and liver dysfunction.[12] These warnings are present in the current labeling because there is reasonable evidence upon which we can conclude that there is an association between statin use and these adverse events (i.e., muscle toxicity and liver dysfunction). In other words, the relevant scientific evidence supports inclusion of that information under the standard set forth in FDA regulations.

However, the available evidence does not support the warning statements you request. Specifically, there is no reasonable evidence upon which we can conclude that statin-induced decreases in CoQ levels are associated with impairment of myocardial function (including cardiomyopathy and congestive heart failure), liver dysfunction, and myopathies (e.g., rhabdomyolysis). Further, there is no reasonable evidence upon which we can conclude that CoQ supplementation (with statin therapy) is associated with decreased risk, prevention, or mitigation of such adverse events. Accordingly, your proposed warning statements are not warranted.[13]

Additionally, based on our examination of the materials described above, we also conclude that a boxed warning is not warranted. Because FDA regulations emphasize that boxed warnings ordinarily will be based on clinical data, our assessment of the clinical data you presented is particularly important. Although serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data (21 CFR 201.57(e)), the warning you advocate does not relate to animal toxicity. Below we explain in greater detail our evaluation of the clinical data you presented and explain why the data are inadequate to support your request. Our discussion focuses on studies you cited that looked at clinically relevant endpoints with respect to your claims. For example, we discuss clinical studies that examined the association of reduced CoQ levels and reduced myocardial function or an increased incidence of myopathy. Studies you cited that merely show an association between statin use and reduced levels of CoQ in the

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[11] See final rule on *Prescription Drug Advertising; Content and Format for Labeling of Human Prescription Drugs* (44 FR 37434, 37448; June 26, 1979).

[12] You appear to acknowledge this point in stating that "current prescribing information for the various statin drugs contains some general information regarding" certain risks (MedGuide Petition at 4; Boxed Warning Petition at 4). However, the latter part of your statement — that "there are no specific warnings. . . . available for physicians and patients in the prescribing information" — is not completely accurate (MedGuide Petition at 4; Boxed Warning Petition at 4). The Warnings section gives specific instructions for some statins that have known drug interactions and recommends dosing limits.

[13] Our response focuses primarily on the last two sentences of the boxed warning. Because we have concluded that the second and third statements in the boxed warning are not warranted, we also conclude that the first sentence, "HMG CoA reductase inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q_{10}, required for energy production," is also not warranted in the Warnings section of the labeling. Current statin labeling includes statements about the mechanism of action by which statins exert their therapeutic effect.

blood[14] do not provide reasonable evidence of an association with a "serious hazard with a drug" as required by FDA regulations. As explained more fully below, we believe that evidence that statins lower CoQ levels in the blood is less relevant than the association of statins and CoQ levels in tissue, because tissue is the site where the serious hazards you claim would occur.

1. CoQ Levels and Myocardial Function

Two clinical articles cited in support of your petitions evaluated the cardiac consequences of statin-induced CoQ reductions and CoQ supplementation with statin therapy. These articles (i.e., Studies 1 and 2 in Appendix A), along with others submitted with your petitions, provide evidence for the reduction of blood CoQ levels associated with statin therapy. These studies are uncontrolled, non-randomized, conducted in too few patients, or are anecdotal reports. We cannot conclude that these studies, together with other studies we reviewed, constitute sufficient evidence that statin-associated decreases in blood CoQ levels are associated with impairment of myocardial function. Likewise, these articles do not support your claim that CoQ supplementation with statin therapy is associated with decreased risk, prevention, or mitigation of impairment of myocardial function. Each of the articles is discussed in turn below.

a. Folkers K et al. Lovastatin decreases coenzyme Q levels in humans. Proc. Natl. Acad. Sci. 1990; 87:8931-8934.

This article summarizes the findings from two clinical study reports. In the first study, case reports of five patients with cardiomyopathy are presented. In all five anecdotal cases, patients with congestive heart failure (CHF) showed increases in CoQ levels and ejection fraction (a measure of heart function) following CoQ supplementation that were then reduced with the initiation of statin therapy. In some instances, reduction in statin dose along with administration of CoQ improved laboratory and clinical status. However, these anecdotes do not constitute sufficient evidence either of a role of CoQ deficiency in depressed cardiac function or of an effect of CoQ supplementation to ameliorate that function. This observational report cannot rule out the possibility that other interventions (e.g., treatment with diuretics or established heart failure therapies) contributed to improved clinical status. Conversely, a deterioration in clinical status may be the result of worsening cardiac ischemia, changes in the patients' salt and volume intake, or other triggers for worsening heart failure.

In the second study, a 43-year old healthy volunteer underwent baseline evaluation of serum CoQ levels, cardiac function, and cholesterol levels, and had these procedures repeated at three other time points while receiving, in sequence, lovastatin 40 mg/day for 29 days, lovastatin 40 mg/day plus CoQ 200 mg/day for 6 days, or CoQ 200 mg/day for 5

[14] We note that the term blood includes plasma and serum. Although the various sources to which you cite use different terms (*i.e.*, blood, plasma, or serum) to reflect the study methodology employed, we sometimes refer to the terms collectively as "blood."

days. Although this study found that supplementation with CoQ increased CoQ levels and was associated with improved cardiac parameters, this study was an uncontrolled, single-patient investigation. Therefore, it does not provide reasonable evidence to support your claim regarding the purported adverse consequences of statin-induced decreases in CoQ levels or of the benefits of supplementation.

b. Miyake Y. et al. Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. ArzneimForsch Drug Research 1999;49(I):324-329.

Citing this article, you state that that the potential adverse events associated with statins, most notably cardiomyopathy, are associated with statin-induced CoQ10 depletion, and that CoQ10 supplementation should be recommended to offset this depletion (Boxed Warning Petition at 5; MedGuide Petition at 5). This article documented an observational, non-randomized study of healthy volunteers, diabetics, and patients with familial hypercholesterolemia (FH), evaluating the serum CoQ levels across the different populations and the effect of statin therapy on CoQ levels on a subset of patients treated with a statin. None of the patients in this study had overt heart failure, other heart disease, or electrocardiograpahic abnormalities at baseline.

From this study, the authors concluded that in both normocholesterolemic type 2 diabetics who are not on statin therapy and type 2 diabetics treated with a statin have reduced CoQ levels and this finding may be associated with "subclinical diabetic cardiomyopathy." We note that the term "subclinical diabetic cardiomyopathy" is not defined by any sensitive measure of cardiac function (e.g., exercise tolerance, left ventricular ejection fraction).

This study reported a significant reduction in serum CoQ levels in 8 hypercholesterolemic diabetic patients treated with simvastatin daily for 4 weeks. Mean CoQ levels in hypercholesterolemic diabetic patients were higher at baseline (prior to statin therapy) than normocholesterolemic diabetic patients. Although not a conclusion of the study's authors, this finding supports a view that blood CoQ levels reflect circulating LDL-C (low density lipoprotein-cholesterol) concentration because the LDL-C particle is a major carrier of CoQ in the blood.[15] Reductions in CoQ levels associated with statin therapy may therefore be the result of LDL-C reduction in the blood. It is interesting to note that in this study, two severely hypercholesterolemic patients had their cholesterol levels reduced with LDL-apheresis rather than statin therapy. A session of LDL-apheresis decreased CoQ levels in concert with the reduction in cholesterol levels suggesting that the mere removal of LDL-C from the bloodstream will lower CoQ levels.

This article went on to further suggest that CoQ supplementation may be beneficial in patients with "subclinical diabetic cardiomyopathy" who are treated with statins. This

[15] Elmbery PG et al. Discharge of newly synthesized dolichol and ubiquinone with lipoproteins to rat liver perfusate and to the bile. *Lipids.* 1989; 25:93-99.

conclusion was based on a decrease in the cardiothoracic ratio (CTR) in Type 2 diabetic patients who received 6 months of CoQ supplementation while on statin therapy. Again, we emphasize that this study did not assess cardiac function based on a reliable or sensitive test (e.g., cardiac doppler, left ventriculogram, exercise tolerance test). Instead, this study used the CTR, which provides an estimate of heart size but provides no information on heart function. While the CTR may be a crude measure used by physicians evaluating chest x-rays, this is not a reliable measure of clinical benefit nor a diagnostic tool for heart failure or cardiomyopathy.

In conclusion, this study shows a reduction in CoQ levels in Type 2 diabetic patients receiving statin therapy; however, reductions in CoQ levels were also observed in patients who had LDL-C reduction through apheresis. Finally, while the study reported that CoQ supplementation increases CoQ levels in patients who are receiving statin therapy, this study did not provide sufficient evidence that this supplementation is associated with prevention, mitigation, or decreased risk of cardiomyopathy.

Your petition also suggests there is potential harm associated with statin therapy in patients with congestive heart failure (CHF) (MedGuide Petition at 2-5, Boxed Warning Petition at 2,4). You asserted that many statin clinical trials excluded such patients and would therefore obscure such a finding in the large clinical outcome trials.

While severe CHF patients may have been excluded from such trials due to ethical reasons, several investigators have evaluated the heart failure trials and analyzed subgroups of patients receiving statins. One such analysis evaluated the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study of patients with severe heart failure (New York Heart Association Class IIIB or IV with EF < 30%). These investigators noted that statin therapy was associated with a 48% lower risk of death.[16] In a prospective study of 551 heart failure (EF ≤ 40%) patients referred to a single center, survival without the urgent need for heart transplantation was evaluated between patients on statin therapy and those not on statin therapy. This study found improved survival without a need for heart transplantation after 1-year follow-up in 81% of statin-treated patients compared to 63% of patients not receiving statin therapy ($p<0.001$).[17] Clinical studies specifically evaluating the benefit of statin therapy in CHF patients are ongoing. One such study, the GISSI-HF trial, has a planned enrollment of 7,000 CHF patients randomized to rosuvastatin 10 mg daily or placebo daily. This trial will specifically evaluate cardiovascular mortality and morbidity.[18]

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[16] Mozaffarian D et al. Statin therapy is associated with lower morality among patients with severe heart failure. *Am J Cardiol.* 2004 May 1;93(9):1124-1129.

[17] Horwich TB et al. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. *J Am Coll Cardiol.* 2004 Feb 18;43(4):642-648.

[18] This is public information. (See Tavazzi L et al. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *Eur J Heart Fail.* 2004 Aug;6 (5):635-641.)

In summary, there is currently insufficient evidence in the published literature or the scientific community for us to reasonably conclude that statins (or statin-induced decreases in CoQ levels) exacerbate or cause congestive heart failure. It is not uncommon for patients to whom statins are administered to have CHF as a pre-existing condition. We also cannot conclude, based on the relevant evidence, that CoQ supplementation with statin therapy is associated with decreased risk, prevention, or mitigation of CHF. Nonetheless, we will continue to closely monitor adverse events for the possibility that statin therapy is associated with CHF.

2. CoQ Levels and Myopathy

Most of the clinical studies reviewed by the Agency (including those described in Appendix A) reported, in association with statin therapy, a reduction in CoQ levels in blood, as opposed to a reduction in CoQ levels in tissue. This distinction is important because you describe clinical adverse events related to CoQ deficiency affecting the muscle tissue (e.g., cardiac muscle tissue). However, you did not provide sufficient evidence to suggest a consistent, predictable effect of statins leading to depletion of tissue (e.g., muscle tissue) CoQ levels. We cannot reasonably conclude that statins deplete **muscle tissue** CoQ levels in certain individuals, nor do you provide sufficient evidence upon which we can reasonably conclude that there is an association between purported statin-induced depletion of CoQ levels in muscle tissue and (among other things) the myopathic effects sometimes seen with these drugs. Finally, you have provided no clinical evidence that CoQ supplementation with statin therapy is associated with decreased risk, prevention, or mitigation of myopathy.

You submitted two studies (i.e., Studies 5 and 6 in Appendix A) relating to the effects of statin therapy on muscle tissue CoQ levels. You assert, based on these and many of the other studies you submitted, that depletion of CoQ10 can increase the risk of statin-induced myopathies in some patients (Boxed Warning Petition at 4-5).

The evidence does not support such a determination. Although these two studies provide evidence to suggest that statin therapy is associated with a reduction in *blood* CoQ levels, they do not show that statin therapy is associated with a reduction in *tissue* CoQ levels. Neither of the studies explored the purported relationship between decreases in CoQ levels and myopathy, nor did they investigate the purported benefits of CoQ supplementation. Each of the studies is discussed below.

a. Laaksonen R. et al. Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. Clin Pharmacol Ther 1995;57:62-66.

This was a controlled study in 20 hypercholesterolemic patients treated with simvastatin to assess the effects of drug treatment on blood and tissue CoQ levels. Fifteen healthy, normocholesterolemic patients were evaluated in a control group. All hypercholesterolemic patients had blood and muscle (quadriceps femoris) samples

obtained before and after the initiation of simvastatin 20 mg daily for 4 weeks. Blood and muscle biopsies were also obtained in the control group simultaneously with the collection of pretreatment samples in the hypercholesterolemic patient group.

It is important to note that although the authors reported a reduction in blood CoQ levels, it appears that there was a statistically significant **increase** in muscle tissue CoQ levels. This finding calls into question the role of statin-induced reduction of blood CoQ levels on muscle tissue injury when there is no corresponding reduction in tissue CoQ levels.

Further, this study did not include myopathy as an endpoint, nor did it assess symptoms of muscle injury (e.g., inquire about muscle aches and pain in study subjects). In addition, this study did not include any CoQ supplementation.

b. Laaksonen R. et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. Am J Cardiol 1996;77:851-854.

This study evaluated the effects of 6 months of simvastatin 20 mg daily therapy on blood and tissue CoQ levels. It enrolled 19 hypercholesterolemic patients, with 15 healthy normocholesterolemic patients serving as a control group. Eight patients in the control group consented to a muscle biopsy at baseline and at 6 months. The hypercholesterolemic patients had blood and muscle samples obtained at baseline, 1 month and 6 months post-statin therapy.

This study does not show a mean reduction in muscle tissue CoQ levels after 6 months of statin therapy despite decreases in blood CoQ levels. This study did not include myopathy as an endpoint, nor did the study include any CoQ supplementation.

3. CoQ Levels and Liver Dysfunction

You have presented no evidence that decreases in CoQ levels are associated with liver dysfunction. None of the clinical studies we reviewed (including those in Appendix A) evaluated liver enzyme levels as an endpoint. During study treatment, no cases of transaminitis were reported in any treatment group. Further, none of the clinical studies you submitted were designed to evaluate the effect of CoQ supplementation on reducing the incidence of liver transaminase elevations. Therefore, you have not provided evidence to support your claim that CoQ supplementation is associated with decreased risk, prevention, or mitigation of liver dysfunction. To properly evaluate whether the incidence of liver dysfunction would be lowered by CoQ supplementation, a clinical trial in which statin-treated patients were randomized to receive CoQ supplementation or no supplementation would be needed. To our knowledge, no such study has been done. The currently available, relevant scientific evidence does not support the inclusion of this information in the warnings section of the labeling.

B. Request for Medication Guides

You request that we require Medication Guides for all approved statins, discussing what you regard as risks associated with statin-induced reductions in CoQ levels and recommending CoQ10 supplementation with statin therapy. Currently, statins do not have Medication Guides. Based on the information you submitted in your petitions and supplement, other relevant information reviewed, and the Agency's experience and expertise, we do not believe that the Medication Guides you propose are warranted.

Part 208 of the Code of Federal Regulations (21 CFR 208.1–208.26) sets forth requirements for Medication Guides for human prescription drug products, including biological products, that the Agency determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information. The purpose of Medication Guides, as specified by regulation, "is to provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products" (21 CFR 208.1(b)). Under section 208.1(c), Medication Guides will be required if FDA determines that at least one of three factors described in the regulation has been met. Although we have discussed at length above that the currently available scientific evidence does not support your requests for labeling changes, we nonetheless summarize below the applicability of each factor described in the regulation to your request for Medication Guides.

> Factor (1): The drug product is one for which patient labeling could help prevent serious adverse effects.

First, as discussed above, there is no reasonable evidence to show that there are serious adverse effects associated with statin-induced decreases in CoQ levels and therefore the patient labeling you request is not warranted. Second, even assuming arguendo we thought there were serious adverse effects associated with statin-induced decreases in CoQ levels, we cannot conclude that CoQ supplementation should be recommended as a known "risk control strategy" or "preventative measure" against such adverse events because the scientific evidence, as discussed above, does not support that conclusion either.[19]

> Factor (2): The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.[20]

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[19] The Agency stated in the preamble to the final rule on *Prescription Drug Labeling Medication Guide Requirements* (63 FR 66378, December 1, 1998) (Medication Guide Final Rule) that drugs potentially falling into this category are those "cases in which there is a known 'risk control strategy'" or "where easily taken preventative measures can prevent harm" (Medication Guide Final Rule at 66388).

[20] The Agency stated that drugs potentially meeting this criterion would be those in which "the risk of a drug is relatively great, greater than a patient would anticipate given the relatively benign condition being treated . . . [or] where understanding the adverse effects is a critical choice among alternative treatments with different safety and effectiveness profiles. . . (Medication Guide Final Rule at 66388).

As a class, statins have been established to effectively lower cholesterol levels which can further reduce the risk of cardiovascular mortality and morbidity. The clinical benefits of lowering cholesterol with statins have been established in multiple, independent clinical studies across a broad range of baseline cholesterol levels. The Agency has reviewed many of these studies, including seven that provided controlled data in over 50,000 patients for an average of 5 years. These studies consistently demonstrated a 20 to 30% reduction in risk of having heart attacks (fatal and nonfatal), unstable angina, stroke, and other clinical manifestations of arteriosclerosis. The benefits of statin therapy for treating serious conditions are well established.

In these same trials, the incidence of rhabdomyolysis and clinically significant increases in liver enzymes remains low. Across all studies the rate of rhabdomyolysis ranged from 0 to 0.05%. The incidence of clinically significant liver enzyme elevations was 0.3 to 2.3% with no reports of drug-induced hepatic failure. Given the rarity of such events, these risks do not outweigh the established benefits of statin therapy or convince us that patient labeling in the form of a Medication Guide is warranted. The professional labeling already contains specific sections describing serious adverse events (see section II.A). Further, as discussed at length, there is no reasonable evidence upon which we can conclude that these adverse events (or others) are associated with statin-induced decreases in CoQ levels. Accordingly, this specific information should not be included in statin labeling to influence patients' decisions to use, or to continue to use, statins.

> Factor (3): The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.[21]

As discussed at length above, there is no reasonable evidence to show that CoQ supplementation is associated with decreased risk, prevention, or mitigation of the adverse events to which you refer — let alone evidence to show that CoQ supplementation is essential to the effectiveness of statin therapy. Clinical studies establishing the cholesterol-lowering effects of statins have not required the co-administration of CoQ, nor have clinical study outcomes established the benefits of statins only in the presence of CoQ supplementation.

The Agency has determined, after considering these three factors, that Medication Guides such as those you describe are not necessary to patients' safe and effective use of statins. Our decision is supported by the Agency's view that such labeling should be reserved for human prescription drug "products of serious and significant concern" (Medication Guide Final Rule at 66379).

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[21] The Agency stated that drugs potentially falling under this category are those for which "nonadherence could compromise patients' health by interfering with effectiveness" (Medication Guide Final Rule at 66388).

C. Additional Issues

Your Boxed Warning Petition, MedGuide Petition, and Supplement contain certain arguments that you claim provide additional support for your requests. These arguments include quotes from patents, guidelines for cholesterol management, adverse events associated with statins, adverse events for other drugs, and labeling in Canada. We do not agree that these arguments provide adequate support for your requests and below we address each of these issues in greater detail.

1. Patent Claims Relating to CoQ10 and Statins

You assert that "in apparent recognition of the dangers associated with statin-induced CoQ depletion, Merck has obtained patents to combine CoQ10 with its statin drugs" (MedGuide Petition at 5; Boxed Warning Petition at 5). You point to Merck's statements, in patent 4,929,437 ("patent '437") and patent 4,933,165 ("patent '165"), as "underscor[ing] the critical" need for FDA to require certain Warning statements and Medication Guides (MedGuide Petition at 5; Boxed Warning Petition at 5).

FDA standards for labeling changes are different from those that must be satisfied for approval of patent applications by the United States Patent and Trademark Office.[22] Nonetheless, we note that the patent statements you quote do not, on their face, support your requests for labeling changes.[23] You include in your petitions the following quote from the '437 patent: "The most serious reported adverse effects of lovastatin, a commercially available HMG-CoA reductase inhibitor, are myopathy and asymptomatic but marked and persistent increases in liver transaminases . . . [CoQ10] is . . . an essential co-factor in the generation of metabolic energy and may be important in liver function" (MedGuide Petition at 5 quoting '437 patent; Boxed Warning Petition at 5 quoting '437 patent).[24]

These statements do not support your requests. The first statement notes that adverse events associated with lovastatin are myopathy and asymptomatic but marked and persistent increases in liver transaminases. The lovastatin labeling currently includes myopathy under the Warnings and Precautions sections, and liver dysfunction under the Warnings section. The inclusion of these adverse events reflects the fact that there is reasonable evidence of an association between lovastatin and these adverse events — and does not, as you claim, reflect an association between statin-induced decreases in CoQ levels and such adverse events. As previously indicated, the currently available, relevant

[22] The standards for approval of patent applications are set forth in 35 U.S.C. 101, 102, 103, and 112.
[23] Our response should not be construed as commenting in any way on the validity of the claims in the patents to which you refer.
[24] Your juxtaposition of the quotes on adverse events and CoQ10 is odd because in the patent itself these sentences appear in different paragraphs pertaining to different issues.

scientific evidence simply does not support your requests for labeling changes under FDA regulations.[25]

2. Recommendations of the National Cholesterol Education Program

You assert that the National Cholesterol Education Program's (NCEP) recommendations for changes to the 2001 Adult Treatment Panel III (ATP III) guidelines for cholesterol management[26] will increase statin use (Supplement at 5-8). You state that these changes "mean that millions more Americans now fall in the category of those for whom statin treatment may be recommended" (Supplement at 6).

We note that NCEP's recommendations are based on recent reports of several large controlled, clinical outcomes studies showing clinical benefit of statins in patients who are at very high risk for a cardiovascular event such as patients with acute coronary syndromes or who have multiple risk factors for cardiovascular disease (e.g., diabetes, hypertension, and peripheral arterial disease).[27] The amount of statin use, however, is not relevant to your requests. The currently available, relevant scientific evidence, as discussed above, does not support the labeling changes you request. Therefore, it is inappropriate at this time to require statin labeling to include that information.

3. Adverse Events Relating to Statins

You state that the *Physician's Desk Reference* (*PDR*) estimates that 0.5% to 2.3% of patients who use statins experience adverse events (including myopathies) (MedGuide Petition at 6; Boxed Warning Petition at 5-6; Supplement at 6). You extrapolate that incidence to "the universe of patients now treated with statins," which you state is approximately 25,000,000 people worldwide (MedGuide Petition at 6; Boxed Warning Petition at 5-6; Supplement at 6). You therefore conclude that an estimated 125,000 to

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[25] You also include in your petition the following quote from the '165 patent: "[CoQ10 supplementation] would be of considerable benefit to counteract the myopathy observed in a small amount of patients. Since CoQ10 is of benefit in congestive heart failure patients, the combination with [statins] should be of value in such patients who also have the added risk of high cholesterol levels" (MedGuide Petition at 5 quoting '165 patent; Boxed Warning Petition at 5 quoting '165 patent). Your petitions do not accurately reflect the first statement as set forth in the '165 patent. The statement in the '165 patent actually reads as follows: "Although cholesterol-lowering therapy through the use of HMG-CoA reductase inhibitors is generally free of side reactions, it would be of considerable benefit to counteract the myopathy observed in a small amount of patients." (emphasis added). This statement does not, as you claim in your petition, assert that "CoQ10 supplementation" would be of considerable benefit to counteract the myopathy observed in a small amount of patients. Merck's statement is merely a general comment that counteracting the observed myopathy would be beneficial. The second statement that you quote (i.e., asserting that the use of statins in combination with CoQ "should" be of value in certain patients) is speculative in nature and does not support your requests.

[26] In 2004, the NCEP recommended changes to professional practice guidelines on cholesterol management, including more intensive statin drug treatment and initiating statin therapy for those with a high risk of heart disease.

[27] Grundy SM et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004; 110:227-239.

575,000 patients can be expected to experience such adverse events (MedGuide Petition at 6; Boxed Warning Petition at 5-6; Supplement at 6).

It is not clear from your petitions and the *PDR* how you derived the incidence rate of 0.5%-2.3%. It is also unclear whether this rate is intended to correspond to all adverse events, or only certain events. All the statin labels include tables listing the adverse experiences observed in controlled clinical trials that may contain events with incidence rates falling within this range. It should be noted, however, that placebo-treated patients also have adverse experiences occurring at similar incidence rates. Nonetheless, we note that you only assert that statin-induced decreases in CoQ levels are associated with three adverse events in particular — impairment of myocardial function, liver dysfunction, and myopathies. These three adverse events constitute only a subset of the overall adverse event profile for statins. In fact, the incidence of these specific adverse events is significantly lower (e.g., between 0.03 and 0.05% for rhabdomyolysis,[28] and approximating the background rate of liver disease, 1 per 1,000,000 person-years[29]) than the range you cite as *PDR* estimates.

4. Comparison of Statins With Other Drugs

You mention two examples of drugs for which we required Warnings and/or Medication Guides post-approval, mifepristone and antidepressants (Supplement at 7). You state that the estimated risk of serious bleeding that occurs with mifepristone is about 1%. You also state that the labeling change for antidepressants was based on studies showing an increased risk of suicidality of 2% over the risk in patients receiving placebo (Supplement at 7). You state that 0.5% to 2.3% of patients who use statins experience adverse effects, that this incidence rate is similar to that for mifepristone and antidepressants, and that we should therefore grant your requests for labeling changes (Supplement at 7).

Decisions about the most appropriate way to include safety information in labeling are not made simply by comparing the relative incidences between drugs or by using some arbitrary incidence threshold. Instead, FDA takes several factors into account, including the patient population, the severity of the adverse event, and whether it can be monitored by the patients or physicians. As discussed above, all statin approved labeling includes detailed discussions on serious adverse events under the Warnings and Precautions sections of labeling. In addition, the currently available, relevant scientific evidence, as discussed at length elsewhere in this response, does not support your requests. We also note, as mentioned in the section above, that you appear to aggregate the incidence of adverse events; however, the adverse events at issue in your petition (i.e., impairment of myocardial function, liver dysfunction, and myopathies) have a significantly lower incidence rate than that cited as *PDR* estimates in your petition.

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[28] Thompson PD et al. Statin associated myopathy. *JAMA* 2003; 289(13):1681-1690.

[29] Graham DJ et al. Incidence of idiopathic acute liver failure and hospitalized liver injury in patients treated with troglitazone. *Am J Gastroenterol* 2003; 98(1):175-179.

5. Labeling of Statins in Canada

You state that certain "warnings" about decreased levels of CoQ now appear on product monographs (labeling) of all statin drugs sold in Canada (Supplement at 3).[30] You state that this shows that the Canadian government has recognized the existence of "reasonable evidence of an association of a serious hazard with a drug" and this should put FDA on notice and encourage the Agency to grant your petitions (Supplement at 3-4).

FDA regularly monitors foreign regulatory activity regarding the safety of drug products marketed in the United States and makes decisions based on all of the information available to us, including both foreign and domestic data. Although other countries have different regulatory provisions for reviewing adverse events for drug products and for making risk-benefit evaluations, some of the excerpts from Canadian statin drug labeling referenced in your petition support the Agency's conclusions rather than your conclusions. As we noted elsewhere, there is some evidence to suggest that statin therapy may be associated with decreased CoQ levels in blood (i.e., circulating CoQ levels), but there is insufficient evidence of an association with decreased CoQ levels in tissue. We cannot conclude, nor does Health Canada (the Canadian equivalent of FDA), that statin-induced decreases in CoQ levels have any clinical significance.

For example, Canadian Zocor labeling provides that "Significant decreases in circulating [CoQ] levels in patients treated with [Zocor] and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of [CoQ] has not been established. . . ."[31] The Canadian Mevacor labeling contains substantially the same statements as those contained in the Canadian Zocor labeling. The Canadian Lipitor and Crestor labeling are similar to the Canadian Zocor and Mevacor labeling in this regard, but they also includes the following sentence: "It has been reported that a decrease in myocardial [CoQ] levels could lead to impaired cardiac function in patients with borderline congestive heart failure. . . ."[32] This labeling does not conclude that there is *reasonable evidence of an association* between statin-induced decreases in CoQ levels and cardiac function in patients with borderline congestive heart failure. It only states that it has been reported. As discussed in Section III.A.1, it is not uncommon for patients to whom statins are administered to have CHF as a pre-existing condition. Some studies suggest that statin therapy has a beneficial effect on CHF. Although we will continue to monitor information that has an effect on our risk-benefit determinations, the inclusion of this information is not warranted based on the current, relevant scientific data.

Because there is no reasonable evidence of an association between statin-induced decreases in CoQ levels and the adverse events referenced in your petition, the inclusion of this information in the warnings section of the labeling is not warranted under FDA

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[30] You characterize as "warnings" the excerpts from Canadian statin drug labeling for certain drugs (Supplement at 3-4). However, these statements actually appear in the Precautions section, not the Warnings section, for each of those drugs (Supplement Exhibits A, B, C, and E).
[31] Supplement at 4.
[32] Supplement at 3.

regulations. In addition, the fact that the Canadian statin labeling does not recommend CoQ supplementation with statin therapy is consistent with the Agency's conclusions. Likewise, we conclude that the currently available, relevant scientific evidence does not support the inclusion of recommendations regarding CoQ supplementation with statin therapy in the warnings section of the labeling as specified in your petition.

IV. CONCLUSION

After a thorough review of the information submitted and currently available, relevant scientific evidence, we conclude that there is no reasonable evidence that statin-induced decreases in CoQ levels are associated with impairment of myocardial function, liver dysfunction or myopathies. Nor can we conclude that there is reasonable evidence that CoQ supplementation with statins is associated with decreased risk, prevention, or mitigation of such adverse events. Accordingly, the requested boxed warning is not warranted because the scientific data does not support the inclusion of such a warning under the applicable legal standard. The current statin labeling already includes the serious and rare side effects of statin therapy, namely, muscle toxicity and liver dysfunction. We have also determined (based on current, relevant scientific information) that Medication Guides such as those you describe are not warranted. Nonetheless, we continue to give careful consideration to any relevant information that bears on the safe and effective use of statins.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

Appendix A

Table 2. Clinical Studies of Statin Effects on Coenzyme Q levels

Study	Study Design	Statin/dose/duration	Results (as summarized by study author(s))
1. Folkers et al. *Proc Natl Acad Sci* 1990;87:8931-8934	uncontrolled case reports of 5 patients with cardiomyopathy and 1 healthy volunteer	lovastatin/20-40 mg/varying duration of treatment	association of lowered CoQ levels and cardiac function with lovastatin treatment observed supplementation with CoQ increased CoQ levels and was associated with improved cardiac parameters
2. Watts et al. *J Clin Pathol* 1993;46:1055-1057	observational study in A. 20 hyperlipidemic treated with diet/simvastatin B. 22 hyperlipidemic patients treated with diet alone C. 20 normal controls	simvastatin median dose of 20 mg range 10-80 mg mean duration of 15 months	lower CoQ levels observed in Group A vs. Groups B and C but no baseline measure available for Group A patients
3. Ghirlanda et al. *J Clin Pharmacol* 1993;33(3): 226-229	Group A – 10 healthy volunteers treated with pravastatin or simvastatin Group B – 30 hypercholesterolemic patients treated with pbo, simvastatin, or pravastatin	simvastatin or pravastatin 20 mg daily healthy volunteers treated for 1 month, hypercholesterolemic patients treated for 3 months	both healthy and hypercholesterolemic patients treated with statins had reductions in plasma CoQ levels from baseline in the range of –26 to –54% pbo treated patients had reduction of –17% from baseline in plasma CoQ levels
4. Bargossi et al. *Int J Clin Lab Res* 1994;24(3):171-176	randomization of 34 hypercholesterolemic patients to: simvastatin + diet simvastatin + diet + CoQ supplement 100 mg/day	simvastatin 20 mg daily for 3 months	reductions in plasma CoQ levels noted in the simvastatin alone group of –22 to –28% whereas plasma levels increased in group supplemented with CoQ (~14%) without affecting the hypocholesterolemic properties of simvastatin
5. Laaksonen et al. *Clin Pharmacol Ther* 1995;57(1):62-66	20 hypercholesterolemic males treated with simvastatin 15 healthy males served as controls	simvastatin 20 mg daily for 4 weeks	simvastatin resulted in a 32% reduction in serum CoQ levels from baseline but no reduction in muscle CoQ concentrations

6. Laaksonen et al. *Am J Cardiol* 1996;77(10):851-854	19 hypercholesterolemic males treated with simvastatin 15 healthy males served as controls	simvastatin 20 mg daily for 6 months	simvastatin resulted in a 25% reduction in serum CoQ levels from baseline but no reductions in muscle CoQ concentrations
7. De Pinieux et al. *Br J Clin Pharmacol* 1996;42(3):333-337	40 hypercholesterolemic patients treated with a statin 20 hypercholesterolemic patients treated with a fibrate 20 hypercholesterolemic patients not receiving any treatment 20 healthy controls	simvastatin (n=28) pravastatin (n=8) fluvastatin (n=4) ciprofibrate (9) fenofibrate (n=8) gemfibrozil (n=3) dose and duration of therapy not provided	low CoQ levels in statin and healthy control groups elevated lactate:pyruvate ratios in statin>fibrate>untreated> healthy control group
8. Palomaki et al. *FEBS Lett*	CHD patients with hyperlipidemia enrolled in a DB, crossover trial	lovastatin 20 mg to 60 mg, force titration over 6 wk period	lovastatin therapy associated with reduced CoQ levels and increased oxidizability of LDL-C but study did not have a concomitant pbo group but rather a crossover design with all subjects treated first with lovastatin then crossover to placebo
9. Mortensen et al. *Mol Aspects Med* 1997;18 Suppl:S137-44	randomized, double-blind active control study of 45 hypercholesterolemic patients	lovastatin 20, 40, 80 mg prava 10, 20, 40 mg daily force-titration q 6 wks for total 18 wk treatment duration	dose-related reductions in CoQ levels noted in both statin groups
10. Palomaki et al. *J Lipid Res* 1998 July;39(7):1430-1437	randomized, double-blind, cross-over study of 19 CHD patients	lovastatin 20, 40, 60 mg daily in weekly force-titration scheme coenzyme Q supplementation or placebo	reductions in ubiquinol in lovastatin only groups. CoQ supplementation increased ubiquinol levels without affecting lipid-lowering effects of lovastatin
11. Miyake et al. *Arzneimittelforschung* 1999 Apr;49(4):324-9	Nonrandomized, observational study of: a. 20 healthy volunteers b. 97 Type 2 DM patients -44 did not receive statins -53 received statins c. 2 familial hypercholesterolemic patients	pravastatin 10 or 20 mg/day simvastatin 5 mg/day 2 FH patients received LDL apheresis	mean serum CoQ levels lower in the 97 DM patients vs. 20 controls mean serum CoQ levels in statin treated DM group (n=53) lower than 20 controls but was higher than the untreated DM patients (n=44) FH pts undergoing LDL apheresis also had reductions in CoQ levels.

12. de Lorgeril et al. *J Cardiovasc Pharmacol* 1999 Mar;33(3):473-8	randomized, double-blind, active control study in patients w/ previous QWMI to detect differences in left ventricular function (LV fxn) in patients treated with statin (n=32) or fibrate (n=32)	simvastatin 20 mg daily fenofibrate 200 mg daily duration of study = 12 wks	reductions in serum CoQ levels observed in simvastatin group vs. fenofibrate group no deleterious effect observed with simvastatin or fenofibrate on LV fxn as assessed by radionuclide imaging
13. Bleske et al. *Am Heart J* 2001 Aug;142(2):E2	open-label, randomized, crossover study in 12 healthy subjects to evaluate the effects of 2 statins on CoQ levels	pravastatin 20 mg daily for 4 wks atorvastatin 10 mg daily for 4 wks 4-8 wk washout period between treatments	both groups demonstrated significant reductions in mean TC and LDL-C. Reductions in mean CoQ levels observed that were not statistically significant
14. Jula et al. *JAMA* 2002 Feb 6;287(5)598-605	randomized, double-blind, cross-over study in healthy hypercholesterolemic patients to assess effects of simvastatin and diet on lipids, insulin, and antioxidant levels	simvastatin 20 mg daily for 12 wks	simvastatin reduced serum ubiquinol levels by 22%