

November 29, 2004

VIA UPS OVERNIGHT

VIA E-MAIL: d.commissioner@fda.hhs.gov

VIA FACSIMILE: (301) 443-3100

Lester M. Crawford
Acting Commissioner
U. S. Food and Drug Administration
5600 Fishers Lane, HF-1
Room 1471
Rockville, MD 20857-0001

Re: Citizen Petition, Docket No. 02P-0244

Dear Dr. Crawford:

We represent Dr. Julian M. Whitaker and the Whitaker Health Freedom Foundation. On May 24, 2004, Dr. Whitaker filed a citizen petition alerting the agency to the fact that the statin drugs have a deleterious side effect: blockage of coenzyme Q10 (the coenzyme essential for energy production in all major muscles, including the heart). Dr. Whitaker urged the agency to act immediately to include a label statement on all statin drugs warning the medical community and the public that use of the statins depletes coenzyme Q10 levels and can induce rhabdomyolysis and myopathies, including cardiomyopathy. The condition can be reversed with oral ingestion of coenzyme Q10.

Now, two and a half years later, FDA has still done nothing. That despite the fact that the National Cholesterol Education Program's recommendation to increase use of the statins places tens of thousands of new Americans at risk of these potentially life-threatening myopathies. We call on you to act immediately to require use of the warning recommended in Dr. Whitaker's petition. The crisis that may well befall the American public due to agency inaction could surpass in significance the crisis created by agency inaction on Vioxx® adverse effects.

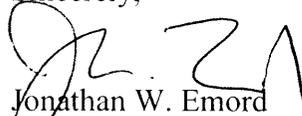
Today Dr. Whitaker is filing a supplement to the original citizen petition. That supplement informs FDA, *inter alia*, that Health Canada has acted to compel statin drug sellers in that country to include a co-enzyme Q10 depletion warning in all statin drug

2004-6594

advertising. That action underscores the need for this agency to act promptly on the Whitaker petitions.

If the agency fails to act within the next thirty days, Dr. Whitaker will seek legal redress to compel the agency to act on the petition. The public health necessity for action cannot be overstated.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. W. Emord', written over a printed name.

Jonathan W. Emord

Michelle C. Gayeski

Counsel to Julian M. Whitaker, M.D.

and the Whitaker Health Freedom Foundation

Attachments (with hard copy)

Date: November 29, 2004

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Before the
Department of Health and Human Services
Food and Drug Administration
Washington, D.C.**

In Re: Petition to)	
Change the Labeling)	
for all Statin Drugs (Mevacor,)	
Lescol, Pravachol, Zocor, Lipitor,)	
and Advicor) to Recommend Use)	Docket No. 02P-0244
of 100 to 200 mg Per Day of)	
Supplemental Co-enzyme Q ₁₀ to)	
Reduce the Risk of Statin-Induced)	
Myopathies (including Cardiomyopathy)	
and Congestive Heart Failure))	

SUPPLEMENT TO CITIZEN PETITION

Julian M. Whitaker, M.D., by counsel, hereby submits this supplement to the citizen petition filed May 24, 2002, under Title 21, Section 201.57 (e) and (f) of the Code of Federal Regulations, to request the Commissioner of Food and Drugs to act immediately to change the labeling for all statin drugs to recommend use of 100 to 200 mg per day of supplemental Co-enzyme Q₁₀ (CoQ₁₀) to reduce the risk of statin-induced myopathies (including cardiomyopathy and congestive heart failure).

I. ACTION REQUESTED

The undersigned requests that the Commissioner of Food and Drugs act immediately to require that the labeling for all HMG Co-A reductase inhibitors (statins) include the following warning statement:

<p style="text-align: center;">Warning:</p> <p>HMG CoA reductase inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q₁₀, required for energy production. A deficiency of coenzyme Q₁₀ 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 Q₁₀.</p>

II. STATEMENT OF GROUNDS

Recent events lend additional support for a citizen petition filed with FDA on May 24, 2002. Petitioner therefore submits this supplement to the original citizen petition, attaching as exhibits relevant new information.

Warnings about decreased CoQ₁₀ (ubiquinone) levels have been added to the labeling and product monographs for statins in Canada. See Exs. A, B, and C (Canadian product monographs for Lipitor®, Zocor®, and Mevacor®) and Exs. D, E (advertisements for Lipitor® and Crestor® appearing in the Canadian version of the June 26, 2003, *New England Journal of Medicine*). The parameters for recommended use of statin drugs have changed, increasing the number of recommended statin users. See Ex. F (July 2004 National Cholesterol Education Program (NCEP) report recommending changes to the 2001 Adult Treatment Panel III (ATP III) guidelines on cholesterol management). The recent withdrawal of rofecoxib (Vioxx®) from the market reveals what happens when safety issues, such as those described in the citizen petition

filed May 24, 2002 are ignored by FDA. See Exs. G, H, I. Each of these points will be discussed in detail infra.

A. Recent Warning Added to Canadian Statin Product Monographs

Under Canadian food and drug regulations, drug manufacturers are required to report all information concerning serious adverse drug reactions that have occurred in Canada. See Ex. J (C.R.C., c. 870, s. C.01.016). Once Health Canada, the Canadian agency that regulates drugs, becomes aware of possible safety issues with a drug, the agency may instruct drug sponsors/manufacturers to place warnings on the labeling of their products. See Ex. K (*How Adverse Reaction Information on Health Products is Used*, Health Canada Fact Sheet). The following warnings regarding decreased levels of CoQ₁₀ now appear on the advertising and product monographs (labeling) of all statin drugs sold in Canada:

Lipitor® (atorvastatin calcium):

Effect on Ubiquinone (CoQ₁₀) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY). Ex. A at 15, D.

Crestor® (rosuvastatin calcium):

Co-enzyme Q₁₀ (ubiquinone)

Ubiquinone levels were not measured in CRESTOR clinical trials. Significant decreases in circulating ubiquinone levels in patients treated with other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY in product monograph). Ex. E.

Zocor® (simivastatin):

Effect on CoQ₁₀ Levels (Ubiquinone)

Significant decreases in circulating CoQ₁₀ levels in patients treated with ZOCOR and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of CoQ₁₀ has not been established (see SELECTED BIBLIOGRAPHY). Ex. B at 4.

Mevacor®:

Effect on CoQ₁₀ Levels (Ubiquinone)

A significant decrease in plasma CoQ₁₀ levels in patients treated with MEVACOR® and other statins has been observed in short-term clinical trials. The clinical significance of a potential long-term statin-induced deficiency of CoQ₁₀ has not yet been established (see SELECTED BIBLIOGRAPHY). Ex. C at 4.

While current prescribing information for the various statin drugs in the United States contains some general information regarding the risk of liver problems and myopathy (defined as muscle aches or muscle weakness), there are no specific warnings (similar to the Canadian warnings) available for physicians and patients in the prescribing information (concerning the association between CoQ₁₀ deficiency and the risk of cardiomyopathy and congestive heart failure).

FDA regulations state that drug 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.” See Ex. L (21 C.F.R. § 201.57(e)). The presence of new warnings about the risk of statin-induced CoQ₁₀ depletion on Canadian labeling shows that the Canadian government has recognized the existence of “reasonable evidence of an association of a serious hazard with a drug.” This should put FDA on notice of possible serious health and safety risks associated with statin-induced CoQ₁₀ depletion and encourage the agency to act on

the pending citizen petition without delay and require the requested warning statement on the labeling of all statin drugs sold in the United States.

B. Changes in Suggested Parameters for Statin Drug Use

The American Heart Association estimates that nearly half of all Americans have total blood cholesterol values that are considered borderline-high risk or high risk for heart disease. See Ex. M (*What Are Healthy Levels of Cholesterol?*, American Heart Association). On July 13, 2004, the National Cholesterol Education Program (NCEP) issued a report recommending changes to the 2001 Adult Treatment Panel III (ATP III) guidelines on cholesterol management. See Ex. F. Based on the results of recent clinical trials, the committee recommended more intensive LDL-lowering therapy (statin drug treatment). Id. Several of the recommended changes offer therapeutic options for LDL-C levels lower than those in ATP III. Id. The committee recommended that millions of people at high and very high risk of heart disease reduce their LDL by 30-40%. Id.

In very high-risk persons, the committee recommended lowering the LDL-C therapeutic option from <100mg/dL to <70 mg/dL. Id. The committee also recommended lowering the LDL-C therapeutic option from <100mg/dL to <70 mg/dL for high-risk persons whose baseline LDL-C is <100. Id. In addition, the committee recommended adding statin drug therapy to high-risk patients with LDL-C levels of 100 mg/dL to 129 mg/ dL. Id. For moderately high-risk persons, the committee recommended lowering the LDL-C therapeutic option from <130mg/dL to <100 mg/dL. Id. Likewise, when the LDL-C level is 100 to 129 mg/dL at baseline or on lifestyle therapy, the committee recommended lowering the LDL-C therapeutic option to <100 mg/dL. Id.

In addition to the recommendations applying to the U.S. population generally, the committee also recommended increased statin use for two special groups of people: diabetics and the elderly. The committee recommended initiating statin therapy for all patients with a combination of diabetes and cardiovascular disease *regardless of LDL-C levels*. Id. The committee suggested that it is reasonable to attempt to achieve an LDL-C level of <70 mg/dL for these persons. Id. The committee also recommended intensive LDL-lowering therapy in older persons with established cardiovascular disease. Id. It is also noteworthy that some cardiologists are now suggesting that everyone over age 55 should take statins until their LDL level drops to 50 mg/dL. See Ex. N (Robert Langreth, *Pills for Everyone*, FORBES.COM); Ex. O (Cheryl Clark, *Benefits of cholesterol-lowering statins well known, but some say potential side effects need closer scrutiny*, SAN DIEGO UNION-TRIBUNE); Ex. P (Barry Chowka, *Statins: The Most Popular Drugs on the Rx Market Get the Push for Even Wider Use (and Bigger Sales)*, NATURALHEALTHLINE).

These changes mean that millions more Americans now fall in the category of those for whom statin drug treatment may be recommended. See Ex. Q (Associated Press, *Experts: Fewer Take Statins Than Should*, NEWSDAY.COM); Ex. R (Gina Kolata, *Health Officials Urge Sharply Lower Cholesterol Levels*, NEW YORK TIMES). According to the Physicians' Desk Reference (PDR), an estimated 0.5% to 2.3% of patients who use statins experience adverse events (including myopathies). See Ex. S (Physicians' Desk Reference, at 1696, 2187). Applying that percentage to the universe of patients now treated with statins (approximately 25,000,000 people worldwide) yields an estimated 125,000 to 575,000 patients who can be expected to experience adverse events, including myopathies. See Ex. T (*Q & A: Heart Drugs Study*, BBC NEWS).

Similar to the request in this petition, on November 15, 2004, FDA announced the addition of a warning statement to the labeling of mifepristone (Mifeprex®). See Ex. U (*FDA To Announce Important Labeling Changes for Mifepristone*, FDA Statement). Part of this new labeling includes a warning about the risk of serious bleeding. According to information in the new Mifeprex® Medication Guide, this recommendation was based on the fact that, “In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.” See Ex. V (Mifeprex® Medication Guide). Based on this number, the risk of serious bleeding occurring with mifepristone is about 1%. This is comparable to the estimated 0.5% to 2.3% of patients who use statins and experience adverse events. See Ex. S at 1696, 2187.

Likewise, on October 15, 2004, FDA announced the addition of a warning statement to the labeling of antidepressant drugs. See Ex. W (*Suicidality in Children and Adolescents Being Treated With Antidepressant Medications*, FDA Public Health Advisory). The boxed warning alerts health care providers to an increased risk of suicidality in children and adolescents being treated with antidepressants. See Ex. X (Labeling Change Request Letter for Antidepressant Medications). According to the “FDA Public Health Advisory” and “Labeling Change Request Letter for Antidepressant Medications,” this labeling change was based on studies showing an increased risk of suicidality of 2% over the risk in patients receiving placebo. See Exs. W, X. Again, this risk is comparable to the estimated 0.5% to 2.3% of patients who use statins and experience adverse events. See Ex. S at 1696, 2187. Based on these two examples showcasing FDA’s recognition of the need for labeling warnings on drugs with comparable rates of adverse effects, FDA should similarly warn the public about the risk of CoQ₁₀ depletion and possible consequences immediately.

In addition to the increased numbers of people who will likely be prescribed statins, with the new intensive therapy recommended, more people will likely be taking statins at much higher doses. See Ex. P. As discussed in the initial petition, the incidence of adverse events increases with increases in the dose amounts of statins administered. See Ex. S at 2187. For those consuming 10 mg to 20 mg doses, the incidence is estimated at 0.2%. Id. For those consuming 40 mg doses, the incidence is estimated at 0.6%. Id. For those consuming 80 mg doses, the incidence is estimated at 2.3%. Id.

Because statin use is only likely to increase based on the new NCEP guidelines, it follows that the number of adverse events related to statin use will also increase. As discussed in detail in the scientific report accompanying the original petition, in patients with preexisting congestive heart failure, the addition of statin therapy causes a decrease in blood CoQ₁₀ levels and a decline in myocardial function. See Ex. A to initial petition at 4-6. That decline can lead to the onset of cardiomyopathy, a disease that weakens the heart muscle and may result in death. Id. at 5. Because the number of adverse events related to statin use is likely to increase, it is imperative that physicians be forewarned about the very real risks associated with CoQ₁₀ depletion and of the need for prophylactic supplementation with CoQ₁₀ to reduce those risks. The FDA should therefore act immediately to protect public health against foreseeable patient risks, including heart damage and death, by requiring use in all statin labeling of the warning the Petitioner has recommended.

C. The Rofecoxib (Vioxx®) Situation

The recent withdrawal of rofecoxib (Vioxx®) from the market provides an example of what can happen when the FDA fails to react to evidence raising safety concerns about approved drugs. Following the withdrawal of Vioxx® from the market on September 30, 2004, evidence

surfaced indicating that FDA knew of possible excess risk of myocardial infarctions and strokes with Vioxx® as early as 2000, with publication of the VIGOR trial. See Ex. G at 1707; Ex. H at 1. Many epidemiologic studies conducted between 1999 and 2004 identified the risk of serious cardiovascular events associated with statin studies, yet FDA did not take the steps required to protect the health of the U.S. population. See Ex. G at 1708.

Some of the most prestigious scientific publications in the world have criticized FDA for not taking appropriate action concerning the safety of Vioxx®. See Ex. H at 1-2 (“This discovery points to . . . lethal weaknesses in the US Food and Drug Administration’s regulatory oversight . . . [T]he FDA acted out of ruthless, short-sighted, and irresponsible self-interest . . . The licensing of Vioxx and its continued use in the face of unambiguous evidence of harm have been public health catastrophes . . .”); Ex. I at 1287-88 (“The Vioxx story is one of . . . repeated episodes of complacency by drug regulators”). See also Ex. G at 1709.

As discussed in detail in the initial petition, studies show that CoQ₁₀ depletion can induce detrimental myopathies, including cardiomyopathy. In order to avoid a public health catastrophe comparable to the one that occurred with Vioxx®, FDA should grant this petition and act without delay to compel inclusion in all labeling for statin drugs the above-referenced warning statement. The failure to do so promptly unnecessarily leaves long-term statin drug users (an estimated 125,000 to 575,000 patients) at risk of statin-induced liver dysfunction and myopathies, including cardiomyopathy and congestive heart failure.

III. Conclusion

The Canadian government has recognized the potential serious health risks involved with statin-induced CoQ₁₀ depletion. That fact and the pending citizen petition filed May 24, 2002, serves to put FDA on notice of possible serious health and safety risks associated with statin-

induced CoQ₁₀ depletion. Because the parameters for recommended use of statin drugs have changed, the number of recommended statin users will likely increase. This likely means an increase in the number of patients experiencing adverse effects as a result of statin use. The recent withdrawal of rofecoxib (Vioxx®) from the market reveals what can happen when the agency ignores evidence of potential safety issues and does not take the action required to prevent risks to public health.

FDA is in a position to reduce the risk of possible myopathies and, in settings of preexisting CoQ₁₀ deficiency, to reduce the risk of markedly worsening myocardial function. To reduce that risk and to avoid a public health catastrophe, the Commissioner of Food and Drugs should act immediately to require the following warning in the labeling for all statin drugs:

Warning:

HMG CoA reductase inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q₁₀, required for energy production. A deficiency of coenzyme Q₁₀ 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 Q₁₀.

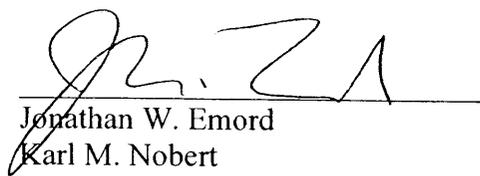
III. Environmental Impact

The requested action will not result in the introduction of any substance into the environment and is thus categorically excluded under the provisions of 21 C.F.R. § 25.30.

IV. Certification

The undersigned certifies, that, to his best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,
DR. JULIAN M. WHITAKER, M.D.

A handwritten signature in black ink, appearing to read 'J. W. Emord', written over a horizontal line.

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Exhibits to Supplement to Citizen Petition

- Exhibit A: Product monograph for Lipitor®
- Exhibit B: Product monograph for Zocor®
- Exhibit C: Product monograph for Mevacor®
- Exhibit D: Advertisement for Lipitor® appearing in Canadian NEW ENGLAND JOURNAL OF MEDICINE, June 26, 2003
- Exhibit E: Advertisement for Crestor® appearing in *NEW ENGLAND JOURNAL OF MEDICINE*, June 26, 2003
- Exhibit F: Scott M. Grundy, et al., *Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines*, CIRCULATION, July 13, 2004, 227-39. (July 2004 National Cholesterol Education Program (NCEP) report recommending changes to the 2001 Adult Treatment Panel III (ATP III) guidelines on cholesterol management)
- Exhibit G: Eric J. Topol, *Failing the Public Health—Rofecoxib, Merck, and the FDA*, NEW ENG. J. MED., Oct. 21, 2004
- Exhibit H: Richard Horton, *Vioxx, the implosion of Merck, and aftershocks at the FDA*, LANCET, Nov. 5, 2004
- Exhibit I: Editorial, *Vioxx: an unequal partnership between safety and efficacy*, LANCET, Oct. 9, 2004,
- Exhibit J: C.R.C., c. 870, s. C.01.016
- Exhibit K: *How Adverse Reaction Information on Health Products is Used*, Health Canada Fact Sheet, available at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/fact_adr_e.pdf.
- Exhibit L: 21 C.F.R. § 201.57(e), (f)
- Exhibit M: *What Are Healthy Levels of Cholesterol?*, American Heart Association, available at <http://www.americanheart.org/presenter.jhtml?identifier=183>
- Exhibit N: Robert Langreth, *Pills for Everyone*, FORBES.COM, Apr. 12, 2004, available at <http://www.keepmedia.com/acct/QuickRegSubmit.do;jsessionid=aStTbEBvND-a>
- Exhibit O: Cheryl Clark, *Benefits of cholesterol-lowering statins well known, but some say potential side effects need closer scrutiny*, SAN DIEGO UNION-TRIBUNE, July 14, 2004, http://www.signonsandiego.com/uniontrib/20040714/news_1c14/statins.html
- Exhibit P: Barry Chowka, *Statins: The Most Popular Drugs on the Rx Market Get the Push for Even Wider Use (and Bigger Sales)*, NATURALHEALTHLINE, July 15, 2004, available at <http://www.naturalhealthvillage.com/newsletter/15jul04/statins.htm>
- Exhibit Q: Associated Press, *Experts: Fewer Take Statins Than Should*, NEWSDAY.COM, Oct. 16, 2004, available at <http://abcnews.go.com/Health/wireStory?id=172308>
- Exhibit R: Gina Kolata, *Health Officials Urge Sharply Lower Cholesterol Levels*, NEW YORK TIMES, July 12, 2004, available at <http://www.nytimes.com/2004/07/12/health/13HEART.html?position=&ei=5070&en=4f046a2ce41871b4&ex=1100667600&adxnnl=1&pagewanted=print&adxnnlx=1100559785-SmqmnCw53pleipqr1EkeA>
- Exhibit S: *Physicians' Desk Reference*, pp. 1696 and 2187 (52nd ed. 1998)
- Exhibit T: *Q & A: Heart Drugs Study*, BBC NEWS, Nov. 13, 2001, available at <http://news.bbc.co.uk/1/hi/health/1654498.stm>.

- Exhibit U: *FDA To Announce Important Labeling Changes for Mifepristone, FDA Statement, Nov. 15, 2004, available at <http://www.fda.gov/bbs/topics/news/2004/NEW01134.html>*
-
- Exhibit V: Mifeprex® Medication Guide, November 12, 2004 revision, *available at <http://www.fda.gov/cder/foi/label/2004/020687s010-medguide.pdf>*.
- Exhibit W: *Suicidality in Children and Adolescents Being Treated With Antidepressant Medications*, FDA Public Health Advisory, Oct. 15, 2004, *available at <http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm>*
- Exhibit X: Labeling Change Request Letter for Antidepressant Medications, Oct. 15, 2004, *available at <http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm>*.

CITIZEN PETITION TO CHANGE THE LABELING FOR
ALL STATIN DRUGS (MEVACOR, LESCOL, PRAVACHOL, ZOCOR,
LIPITOR, AND ADVICOR) RECOMMENDING USE OF
100-200mg PER DAY OF SUPPLEMENTAL CO-ENZYME Q10
TO REDUCE THE RISK OF STATIN-INDUCED MYOPATHIES
(INCLUDING CARDIOMYOPATHY AND CONGESTIVE
HEART FAILURE).

May 24, 2002

Petitioner:

Dr. Julian M. Whitaker, MD.

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02P-0244

CP1

Before the
Department of Health and Human Services
Food and Drug Administration
Washington, D.C.

In Re: Petition to)
Change the Labeling)
for all Statin Drugs (Mevacor,) Docket No. _____
Lescol, Pravachol, Zocor, Lipitor,)
and Advicor) to Recommend Use)
of 100 to 200mg Per Day of)
Supplemental Co-enzyme Q10 to)
Reduce the Risk of Statin-induced)
Myopathies (including Cardiomyopathy)
and Congestive Heart Failure))

CITIZEN PETITION

Julian M. Whitaker, M.D., by counsel, hereby submits this petition under Chapter 21,
Section 201.57 (e) and (f), of the Code of Federal Regulations.

I. ACTION REQUESTED

The undersigned requests that the Commissioner of Food and Drugs act immediately to
require that the labeling for all HMG Co-A reductase inhibitors (statins)¹ include the following
warning statement:

Warning:

HMG CoA reductase inhibitors block the endogenous biosynthesis of **an** essential co-factor,
coenzyme Q₁₀, required for energy production. A deficiency of coenzyme Q₁₀ 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 Q₁₀.

¹The statin drugs are Mevacor (lovastatin), Lescol (fluvastatin), Pravachol (pravastatin), Zocor
(simvastatin), Lipitor (atorvastatin), and Advicor (lovastatin).

02P-0244

CP1

11. STATEMENT OF GROUNDS

A. Interest of the Parties

Dr. Julian M. Whitaker is a physician licensed to practice medicine in California and Washington state. He is the Clinical Director of the Whitaker Wellness Institute in Newport Beach, California. He is the editor of *Health & Healing*, the nation's largest single editor health newsletter with approximately 500,000 subscribers. Dr. Whitaker is the author of numerous books concerning aging and heart-related diseases, including *Reversing Heart Disease* (1985), *What Your Doctor Won't Tell You About Bypass* (1995), and *Is Heart Surgery Necessary: What Your Doctor Won't Tell You* (1997). Dr. Whitaker recommends the use of CoQ10 as a dietary supplement and also licenses the use of his name and likeness in connection with the manufacturing and sale of high quality dietary supplements, including CoQ10.

Dr. Whitaker prescribes statin drugs and is informed that long-term statin use may induce in some patients liver dysfunction and myopathies, including cardiomyopathy and congestive heart failure (CHF), due to the fact that statins block the endogenous biosynthesis of an essential co-factor required for energy production, coenzyme Q10. He therefore requests that the Commissioner of Food and Drugs act without delay to compel inclusion in all labeling for statin drugs, the above-referenced warning statement. The failure to do so promptly unnecessarily leaves long-term statin drug users (an estimated 125,000 to 575,000 patients) at risk of statin-induced liver dysfunction and myopathies, including cardiomyopathy and congestive heart failure.

B. Nature of the Problem

1. Current Safety Concerns with Statin Drugs

HMG-CoA reductase inhibitors (also known as statins) are widely recognized as an effective method for lowering LDL cholesterol. While effective, there have been several adverse events associated with statins in humans. Reported adverse events include liver dysfunction, general muscle myopathy, skeletal muscle myopathy (rhabdomyolysis), and persistent elevations in serum transaminases. See, Physician's Desk Reference (PDR), pp. 809, 1695, 1778, 1863, and 2187 (52nd ed. 1998). The incidence of those adverse events increases with increases in the dose amounts administered. For those consuming 10mg to 20mg doses, the incidence is estimated at 0.2%. PDR at 2187. For those consuming 40mg doses, the incidence is estimated at 0.6%. Id. For those consuming 80mg doses, the incidence is estimated at 2.3%. Id.

Additionally, the PDR states that rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with Zocor (simvastatin) therapy. PDR at 1778. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the normal limit occurred in 0.5% of patients in the Mevacor clinical trials and in 0.1% of patients in the Pravachol clinical trials. PDR at 1696 and 809.

While current prescribing information for the various statin drugs contains some general information regarding the above-mentioned risks, there are no specific warnings available for physicians and patients in the prescribing information.

2. Statin Drugs and CoQ10

Statins have been shown in well-designed clinical trials to deplete an essential co-factor required for energy production, coenzyme q10 (“CoQ10”). As discussed in detail in the attached scientific report, CoQ 10 is a substance found within the mitochondrial enzymes, which aids in the function of (by supplying energy to) cells with particularly high metabolic demands, such as those within the heart muscle. CoQ 10 also has antioxidant functions and is the only known naturally occurring lipid soluble antioxidant for which the body has enzyme systems capable of regenerating the active reduced ubiquinol form. CoQ 10 is thus a necessary and essential element in cellular energy production and in the functioning of the heart muscle due to the heart’s extraordinary energy requirements.

Statin drugs work by blocking the cellular production of cholesterol. That interaction occurs in the mevalonate pathway, where cholesterol is biosynthesized. The mevalonate pathway is also responsible, however, for the biosynthesis of CoQ10. Thus, the method by which statin drugs work to block cholesterol also causes them to block the production of CoQ 10.

3. Dangers of CoQ10 Depletion

As the scientific report of Dr. Langsjoen’s explains (attached as Exhibit A), throughout various statin clinical trials there has been a frequent and significant depletion in CoQ10 levels, particularly when higher doses have been administered (and most notably in the elderly). With that depletion, studies have shown detrimental cardiac effects in humans (with pre-existing cardiac dysfunction) and in animals. CoQ 10 is also known to be deficient in humans suffering from congestive heart failure. In patients with pre-existing congestive heart failure, the addition of statin therapy causes a decrease in blood CoQ10 levels and a decline in myocardial function. That decline can lead to the onset of cardiomyopathy, a disease that weakens the heart muscle

and may result in death. Because statin drugs have become some of the most widely prescribed drugs in America with many millions of patients taking them on a regular basis (and since the National Cholesterol Education Program guidelines call for millions more with low-normal LDL levels to be treated with statins), it is imperative that physicians be forewarned about the very real risks associated with CoQ10 depletion and of the need for prophylactic supplementation with CoQ10 to reduce those risks.

In apparent recognition of the dangers associated with statin-induced CoQ10 depletion, Merck has obtained patents to combine CoQ10 with its statin drugs. See Exhibit B (the Merck patents). Merck describes the risks of CoQ10 depletion as follows: “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.” Exhibit B, Patent No. 4,929,437, at 2. A second Merck patent states: “[CoQ10 supplementation] would be of considerable benefit to counteract the myopathy observed in a small percent 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.” Exhibit B, Patent No. 4,933,165, at 2. Merck’s patents would preclude other companies from combining CoQ10 with statins in a single-dose form. That fact underscores the critical need for FDA to add the requested Warning statement to alert physicians of the need for CoQ10 supplementation to offset statin-induced CoQ10 depletion arising from use of those statins that are not combined with CoQ10 in a single-dose form.

According to the PDR, an estimated 0.5% to 2.3% of patients who use statins experience adverse events (including myopathies). Physicians’ Desk Reference, pp. 1696 and 2187 (52nd

ed. 1998). Applying that percentage to the universe of patients now treated with statins (approximately 25,000,000 people worldwide*) yields an estimated 125,000 to 575,000 patients who can be expected to experience adverse events, including myopathies.

4. Benefits of CoQ10 Supplementation

Fortunately, the decrease of CoQ 10 levels associated with statin drug medication is not irreversible. Replenishing the diminished levels of CoQ 10 can be achieved through oral supplementation. Oral supplementation is necessary, as CoQ 10 is not obtainable from daily dietary sources in the amounts (i.e., 100-200 mgs) needed to bolster statin-induced reductions in CoQ 10 deficiency levels.

In the attached report, Dr. Langsjoen concludes that the ingestion of supplemental CoQ 10 can prevent statin-induced CoQ 10 deficiencies without affecting the cholesterol-lowering efficacy of statins. He also states that supplementation can reverse any CoQ10 depletion that may have occurred as a result of the statins.

CoQ 10 supplementation is an easy, economically-feasible remedy to prevent and/or reverse the dangerous CoQ10 depletion effects of statins. The FDA should therefore act immediately to protect public health against foreseeable patient risks, including heart damage and death, by requiring use in all statin labeling of the Warning recommended here.

5. CoQ10 Safety

According to Dr. Langsjoen's attached report, Coenzyme Q₁₀ is sold in the United States and abroad as an over-the-counter dietary supplement and is widely recognized as completely safe with no reported toxicity in over a thousand published human and animal trials. As he discusses, the most recent animal safety study was published in 1999 by Williams et al. Potential CoQ₁₀ toxicity was assessed in rats administered CoQ₁₀ by oral gavage for 1 year at 100,300,

² Q & A: Heart Drugs Study, BBC News, November 13, 2001.

600, and 1200 mg per kg body weight per day. No adverse changes in mortality, clinical signs, body weight, food consumption, or clinical pathology results were observed.

III. Environmental Impact

The requested action will not result in the introduction of any substance into the environment and is thus categorically excluded under the provisions of 21 C.F.R. 525.30.

IV. Conclusion

In addition to potential risks of liver dysfunction and rhabdomyolysis, all prescribing physicians and pharmacists need to be informed that statin drugs produce a depletion in CoQ10, which increases the risk of myopathies and which in settings of pre-existing CoQ10 deficiency, such as congestive heart failure and aging, may worsen markedly myocardial function.

Accordingly, to reduce that risk, the Commissioner of Food and Drugs should act immediately to require the following warning in the labeling for all statin drugs:

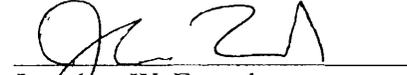
Warning:

HMG CoA reductase inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q₁₀, required for energy production. A deficiency of coenzyme Q₁₀ 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 Q₁₀.

V. Certification

The undersigned certifies, that, to his best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, none of which is unfavorable to the petition.

Respectfully submitted,
DR. JULIAN M. WHITAKER



Jonathan W. Emord
Claudia A. Lewis-Eng
Jonathan R. Goodman
Counsel to Dr. Julian M. Whitaker

Exhibit A

The clinical use of HMG CoA-reductase inhibitors (statins) and the associated depletion of the essential co-factor coenzyme Q₁₀; a review of pertinent human and animal data.

By Peter H. Langsjoen, M.D., F.A.C.C.¹

Introduction

HMG CoA-reductase inhibitors or statins are clearly the most effective class of drugs for lowering LDL cholesterol. Those drugs have been associated with a beneficial impact on cardiovascular morbidity and mortality. As such, statins have become some of the most widely prescribed drugs in the United States with many millions of patients taking them on a regular basis. According to the most recent NCEP (National Cholesterol Education Program) guidelines, the indications for the use of statins have been broadened such that patients with even low normal LDL cholesterol levels are now being treated in hopes of favorably altering the incidence of stroke and myocardial infarction. Statins are frequently used in the elderly and have gained very broad acceptance in the medical community. Statins have been noted to have significant anti-inflammatory and plaque-stabilizing effects which has added to their broader usage.

It is well established that the mevalonate pathway is involved not only in the biosynthesis of cholesterol but also in the biosynthesis of the essential co-factor required for energy production, coenzyme Q₁₀ (CoQ₁₀, ubiquinone). As such, HMG CoA reductase inhibitors block the cellular production of cholesterol and of coenzyme Q₁₀ (Rudney 1981, Goldstein 1990). This drug-nutrient interaction has been reviewed (Bliznakov 1998, Bliznakov 2002).

The peer-reviewed scientific evidence supports the following findings:

1. Statins block the endogenous biosynthesis of both cholesterol and CoQ₁₀ by inhibiting the enzyme HMG CoA reductase, thus decreasing mevalonate, the precursor of both cholesterol and CoQ₁₀.
2. CoQ₁₀ is essential for mitochondrial ATP production and is a potent lipid soluble antioxidant present in cell membranes and carried in the blood by LDL. CoQ₁₀ is biosynthesized in the body and available from dietary sources.
3. Statin-induced decreases in CoQ₁₀ are more than just hypothetical drug-nutrient interactions. Good evidence exists of significant CoQ₁₀ depletion in humans and animals during statin therapy.
4. Scientific evidence confirms the existence of detrimental cardiac consequences from statin-induced CoQ₁₀ deficiencies in man and animals.

¹ Dr. Langsjoen's curriculum vitae is attached.



5. Statin-induced CoQ₁₀ deficiency is dose related and the clinical consequences are notable most in the elderly and in settings of pre-existing congestive heart failure (CHF).
6. Statin-induced CoQ₁₀ deficiency can be completely reversed by supplemental CoQ₁₀.
7. Supplemental CoQ₁₀ is safe and has no adverse effect on statin cholesterol-lowering or on statin anti-inflammatory effects.
8. We are in the midst of a congestive heart failure epidemic in the United States. Approximately 4.8 millions Americans are diagnosed with congestive heart failure. Half of those patients will die within 5 years. Each year, there are an estimated 400,000 new cases of CHF (Congestive Heart Failure Data Fact Sheet, www.nhlbi.nih.gov/health/public/heart/other). Although the causes of this epidemic are unknown, statin-induced CoQ₁₀ deficiency has not been excluded as a possible contributing factor.
9. All large-scale statin trials excluded patients with NYHA class III and IV heart failure such that the long term safety of statins in patients with heart failure has not been established.

Background

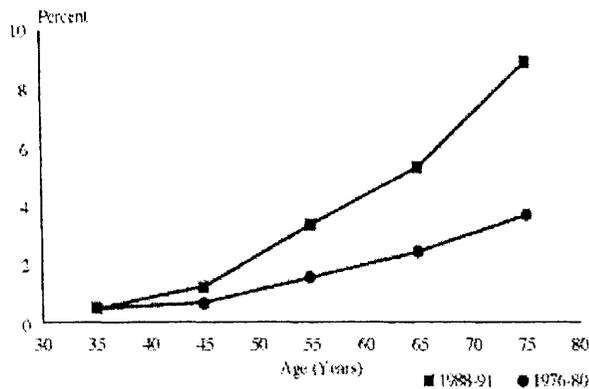
Coenzyme Q₁₀ is the coenzyme for mitochondrial enzyme complexes involved in oxidative phosphorylation in the production of ATP (Mitchell 1976, Mitchell 1990, Lenaz 1991). That bioenergetic effect of CoQ₁₀ is believed to be of fundamental importance in its clinical application, particularly as it relates to cells with exceedingly high metabolic demands such as cardiac myocytes. The second fundamental property of CoQ₁₀ involves its antioxidant (free radical scavenging) functions (Beyer 1990, Villalba 1997). CoQ₁₀ is the only known naturally occurring lipid soluble antioxidant for which the body has enzyme systems capable of regenerating the active reduced ubiquinol form (Ernster 1993). CoQ₁₀ is carried in the blood with low density lipoprotein and serves to diminish the oxidation of LDL cholesterol in settings of oxidative stress (Alleva 1997). CoQ₁₀ is known to be closely linked to Vitamin E and serves to regenerate the reduced (active) alpha-tocopherol form of Vitamin E (Constantinescu 1994) as well as the reduced form of ascorbate (Rodriguez-Aguilera 1995). Other more recently discovered aspects of CoQ₁₀ function include its involvement in extramitochondrial electron transfer, e.g. plasma membrane oxidoreductase activity (Villalba 1997), involvement in cytosolic glycolysis (Lawen 1994), and potential activity in both Golgi apparatus and lysosomes (Gille 2000). CoQ₁₀ also plays a role in improvement in membrane fluidity (Lenaz 1985). The multiple biochemical functions of CoQ₁₀ have recently been reviewed by Crane (Crane 2001).

Coenzyme Q₁₀ is essential for all cellular ATP production and is of particular importance in heart muscle function given that tissue's extreme energy requirements. A deficiency of CoQ₁₀ in the blood and the heart muscle has been documented in congestive heart failure (Kitamura 1984, Folkers 1985). An Australian group of cardiovascular surgeons has recently documented impairment in myocardial function secondary to age-related CoQ₁₀ deficiency in patients undergoing coronary artery bypass surgery (CABG). That impairment was completely

eliminated with incubation of the atrial myocardium with CoQ₁₀ (Rosenfeldt 1999). Later the researchers performed a trial of preoperative supplemental CoQ₁₀ therapy and found improved outcomes in coronary artery bypass surgery (Pepe 2001). The clinical experience with supplemental CoQ₁₀ in cardiovascular disease, including congestive heart failure, ischemic heart disease, hypertensive heart disease and heart surgery has been recently reviewed (Langsjoen 1998, Langsjoen 1999).

In the US we are presently in the midst of a congestive heart failure (CHF) epidemic, with a significant increase in the incidence of congestive heart failure over the past decade (see the figure below as reproduced from the National Center for Health Statistics NIH & NHLB Institute). The annual number of deaths directly from CHF increased from 10,000 in 1968 to 42,000 in 1993. The rate of hospitalizations for heart failure increased more than three times between 1970 and 1994. In the largest health system study of its kind, researchers at the Henry Ford Heart and Vascular Institute in Detroit found that the annual number of heart failure cases more than doubled from 1989-1997. Over that nine-year period, 26,442 cases were identified in the Henry Ford Health System in Detroit. Strikingly, the annual prevalence rose from 9 to 20 cases per 1000 health system patients (Eurekalert.org reference). Those results were compiled in the Resource Utilization Among Congestive Heart Failure (REACH) study (McCullough 2002).

Figure 5
Prevalence of CHF, by Age, 1976-80 and 1988-91



Source: National Health and Nutrition Examination Survey (1976-80 and 1988-91).
National Center for Health Statistics.

Figure 1. Congestive Heart Failure: A New Epidemic.

Reproduced from figure 5 at <http://www.nhlbi.nih.gov/health/public/heart/other/CHF.htm>

Statins were first given pre-market approval in the US in 1987. Since that time, there has been a slow but steady accumulation of scientific evidence that the coenzyme Q₁₀-lowering effect of statin medications has clinical relevance and should be considered by all physicians when prescribing this class of medication.

Human Trials

From 1990 to date there have been 15 published studies in humans evaluating the effects of statins on CoQ₁₀. Nine were controlled trials and eight of those demonstrated significant CoQ₁₀ depletions secondary to statin therapy.

Human observations on the interaction between statins and coenzyme Q₁₀ were first published in 1990 by Folkers et al, who observed that five patients with pre-existing cardiomyopathy exhibited a significant decline in blood coenzyme Q₁₀ level and clinical deterioration following lovastatin (Folkers 1990) treatment. That decrease in coenzyme Q₁₀ blood level and decline in clinical status was reversed through an increase in supplemental coenzyme Q₁₀.

In 1993, Watts et al studied 20 hyperlipidemic patients treated with a low cholesterol diet and simvastatin and compared them to 20 hyperlipidemic patients treated with diet alone and 20 normal controls (Watts 1993). Patients treated with simvastatin had significantly lower plasma coenzyme Q₁₀ levels and a lower coenzyme Q₁₀ to cholesterol ratio than either patients on diet alone or normal controls. The depletion of plasma CoQ₁₀ was significantly inversely associated with the dose of simvastatin. It was concluded that simvastatin may lower plasma coenzyme Q₁₀ concentration and that the reduction may be proportionally greater than the reduction in cholesterol. The authors felt that the adverse effect of simvastatin on the biosynthesis of coenzyme Q₁₀ may be clinically important and requires further study.

In 1993, Ghirlanda et al studied 30 hypercholesterolemic patients and 10 healthy volunteers in a double-blind controlled trial, comparing placebo with either pravastatin or simvastatin for a three-month treatment period (Ghirlanda 1993). Both of those HMG CoA-reductase inhibitors showed significant reduction in total cholesterol and plasma CoQ₁₀ levels, not only in hypercholesterolemic patients but also in the normal healthy volunteers.

In 1994, Bargossi et al performed a randomized controlled trial evaluating 34 hypercholesterolemic patients treated with either 20 mg of simvastatin for six months or 20 mg of simvastatin plus 100 mg of supplemental coenzyme Q₁₀ (Bargossi 1994). The study demonstrated that simvastatin lowered LDL cholesterol and lowered plasma and platelet coenzyme Q₁₀ levels. The depletion of CoQ₁₀ in both plasma and platelets was prevented in the supplemental Coenzyme Q₁₀ group without affecting cholesterol lowering caused by simvastatin.

In 1995, Laaksonen et al. documented a significant decrease in serum Coenzyme Q₁₀ levels in hypercholesterolemic patients treated with four weeks of simvastatin, with no reduction in skeletal muscle ubiquinone (Laaksonen 1995).

In 1996, Laaksonen et al evaluated skeletal muscle biopsy specimens in 19 hypercholesterolemic patients treated with simvastatin at 20 mg per day and found no

depletion of skeletal muscle ubiquinone concentration as compared to control subjects (Laaksonen 1996).

In 1996, De Pinieux et al evaluated 80 hypercholesterolemic patients (40 patients treated with statins, 20 patients treated with fibrates, and 20 untreated controls) (De Pinieux 1996). Further, they evaluated 20 non-hyperlipidemic health controlled patients. Serum ubiquinone levels were significantly lower in statin treated patients and were not depleted in fibrate treated patients or in untreated controls. Lactate to pyruvate ratios were significantly higher in statin treated patients, indicating mitochondrial dysfunction in patients treated with statins, which was not observed in untreated hypercholesterolemic patients or in healthy controls.

In 1997, Palomaki et al. studied 27 hypercholesterolemic men in a double-blind placebo controlled crossover trial with six weeks of lovastatin at 60 mg per day (Palomaki 1997). Lovastatin therapy was associated with a significant decline in serum ubiquinol content as measured per LDL phosphorus, and there was an increased oxidizability of LDL in the lovastatin treated patients.

In 1997, Mortensen et al studied 45 hypercholesterolemic patients in a randomized double-blind trial with either lovastatin or pravastatin for 18 weeks (Mortensen 1997). A dose-related significant decline in total serum coenzyme Q₁₀ was found in the pravastatin group from 1.27 +/- 0.34 to 1.02 +/- 0.31 mmol/L. In the lovastatin group, there was a more pronounced decrease in serum CoQ₁₀ level from 1.18 +/- 0.36 to 0.84 +/- 0.17 mmol/L p<0.001. The authors concluded that although HMG CoA-reductase inhibitors are safe and effective within a limited time horizon, possible adverse consequences from coenzyme Q₁₀ lowering was an important factor in long-term therapy.

In 1998, Palomaki et al evaluated 19 men with hypercholesterolemia and coronary artery disease treated with lovastatin with or without ubiquinone supplementation (Palomaki 1998). The lag time in copper mediated oxidation of LDL increased by 5% (p=0.02). It was observed that the faster depletion of LDL ubiquinol and shortened lag time in conjugated diene formation during lovastatin therapy may partially be restored with ubiquinone supplementation.

In 1999, Miyake et al studied 97 non-insulin-dependent diabetic patients treated with simvastatin and observed a significant decrease in serum CoQ₁₀ concentrations along with the decrease in serum cholesterol (Miyake 1999). Oral CoQ₁₀ supplementation in diabetic patients receiving simvastatin significantly increased serum coenzyme Q₁₀ levels without affecting cholesterol levels. Furthermore, the supplemental coenzyme Q₁₀ significantly decreased cardiothoracic ratios from 51.4 +/- 5.1 to 49.2 +/- 4.7% (p<0.03). The authors concluded that serum coenzyme Q₁₀ levels in diabetic patients are decreased by statin therapy and may be associated with subclinical diabetic cardiomyopathy, reversible by coenzyme Q₁₀ supplementation.

In 1999, De Lorgeril et al. studied in a double-blind fashion 32 patients treated with 20 mg of simvastatin compared to 32 patients treated with 200 mg of fenofibrate (De Lorgeril 1999). Serum coenzyme Q₁₀ levels were significantly reduced after treatment with simvastatin but

not with fenofibrate. No significant change in left ventricular ejection fraction could be determined after 12 weeks of therapy. They observed a loss of myocardial reserve with a flattening of the ejection fraction response to exercise, which could be explained by the statin-induced diastolic dysfunction in those patients. Unfortunately, only systolic measurements of ejection fraction were obtained in this study.

In 2001, Bleske et al. failed to show a depletion in whole blood CoQ₁₀ in 12 young, healthy volunteers with normal cholesterol levels treated with either pravastatin or atorvastatin for four weeks (Bleske 2001).

Also in 2001, Wong et al. documented that the beneficial anti-inflammatory effect of simvastatin on human monocytes was completely reversible with supplemental mevalonate but not with coenzyme Q₁₀, indicating that supplemental coenzyme Q₁₀ would not interfere with this important statin-mediated anti-inflammatory effect (Wong 2001).

The most recent statin/CoQ study was a randomized controlled trial by Jula et al., published in JAMA (Jula 2002). Simvastatin at 20 mg per day caused a reduction in serum CoQ₁₀ of 22% (p<0.001). The clinical consequences of this significant CoQ₁₀ deficiency were not evaluated in this short term trial.

In summary, in human trials evaluating coenzyme Q₁₀ in statin therapy, there appears to be frequent and significant depletion in blood CoQ₁₀ levels, particularly when statins are taken at higher doses and most notably in the elderly. In one study involving patients with preexisting CHF, the depletion in blood coenzyme Q₁₀ levels was associated with a drop in ejection fraction and clinical deterioration. Supplemental coenzyme Q₁₀ has been found to prevent the depletion of CoQ₁₀ in blood and in one study also to prevent the depletion measured in platelet CoQ₁₀. The serum depletion of CoQ₁₀ was associated with an elevation in lactate to pyruvate ratio, suggesting an impairment in mitochondrial bioenergetics, secondary to statin-induced CoQ₁₀ depletion. Furthermore, two trials demonstrated enhanced oxidizability of LDL cholesterol related to the lowering of serum CoQ₁₀ by statins. Supplemental CoQ₁₀ has been shown to increase the CoQ₁₀ content in low density lipoproteins and to decrease significantly LDL cholesterol oxidizability (Allegra 1997). One trial demonstrated no significant CoQ₁₀ depletion in 12 young normolipidemic volunteers treated with statins and one trial found no skeletal muscle depletion of CoQ₁₀ in statin treated hypercholesterolemic patients. In diabetic patients, the CoQ₁₀ depletion with statin therapy appears to be associated with subclinical cardiomyopathy, with significant improvement in cardiothoracic ratios upon CoQ₁₀ supplementation.

From these studies, one can conclude that supplemental coenzyme Q₁₀ prevents the statin induced CoQ₁₀ deficiency state without altering the cholesterol-lowering ability of these drugs and appears to have benefit both in terms of decreasing the oxidizability of low density lipoprotein cholesterol, as well as preventing or reversing observed detrimental clinical changes.

Animal Studies

From 1990 through 2001 there have been 15 published animal studies involving six different animal species (six rat studies, three hamster studies, three dog studies, one rabbit study, one guinea pig study and one study looking at squirrel monkeys, mini pigs and hamsters) evaluating the effect of statins on coenzyme Q blood and/or tissue levels. Nine of these 15 studies looked specifically at the adverse consequences of this statin-induced CoQ depletion: decreased ATP production, increased injury after ischemia/reperfusion, increased mortality in cardiomyopathy, and skeletal muscle injury and dysfunction. Some of the animals use coenzyme Q₉ which is a shorter chain homologue of coenzyme Q₁₀ and in those cases the term coenzyme Q or CoQ is used.

Some of the first animal data was published in 1990 by Willis et al. and documented statistically significant decreases in coenzyme Q (CoQ) concentration in blood, heart and liver in 45 adult male Holtzman rats. This blood and tissue CoQ deficiency could be completely prevented by supplementing the lovastatin treated animals with coenzyme Q₁₀ (Willis 1990).

In 1992, Low et al. found similar decreases in ubiquinone in liver and heart in rats treated with lovastatin (mevinolin), confirming observations by Willis et al (Low 1992).

1993, Fukami et al. studied simvastatin treated rabbits and specifically looked at those animals with elevations in creatinine kinase, lactate dehydrogenase, and skeletal muscle necrosis (Fukami 1993). The simvastatin treated rabbits were noted to have significantly reduced liver and cardiac muscle coenzyme Q content as compared to the control group. Interestingly, skeletal muscle ubiquinone content in this study was not affected.

In 1993, Belichard et al studied lovastatin in cardiomyopathic hamsters and found a 33% decrease in ubiquinone content in heart muscle as compared to control (Belichard 1993). Cholesterol lowering in cardiomyopathic hamsters with fenofibrate did not lower coenzyme Q₁₀ levels. Statins are the only class of lipid-lowering drugs that are known to block the synthesis of mevalonate.

In 1994, Diebold et al documented a depletion in Coenzyme Q₁₀ content in heart muscle in guinea pigs when treated with lovastatin in older age (2 years of age) animals, and further observed no significant depletion in coenzyme Q₁₀ content in heart muscle in the guinea pigs in the younger age group (2 to 4 months of age) (Diebold 1994). The authors evaluated mitochondrial function as measured by the potential to phosphorylate ADP to ATP, and again documented a decrease by up to 45% in cardiac mitochondria in the 2-year-old animals treated with lovastatin, and no significant decrease in phosphorylation in the younger age group animals. This sensitivity for older animals to show clinically relevant heart muscle CoQ₁₀ depletion is of concern in humans as older patients are treated with statin medications and are observed to be more fragile and more susceptible to side effects.

In 1994, Loop et al. documented again that lovastatin decreased coenzyme Q content in rat liver that could be completely prevented with supplemental coenzyme Q₁₀ (Loop 1994).

In 1995, Satoh et al evaluated ischemic reperfusion in dog hearts and documented that simvastatin significantly decreased myocardial coenzyme Q₁₀ levels and worsened ischemia reperfusion injury (Satoh 1995). Water soluble pravastatin was also studied in this dog model and did not appear to cause worsening of mitochondrial respiration in the dog heart muscle, nor did the pravastatin reduce myocardial CoQ₁₀ levels. It is believed that the lipid soluble simvastatin may be more detrimental in this model due to better membrane penetration of that fat soluble drug.

In 1997, Morand et al studied hamsters, squirrel monkeys, and mini pigs, and documented CoQ₁₀ depletion in heart and liver with simvastatin treatment (Morand 1997). They saw no decrease in coenzyme Q₁₀ in heart and liver using the experimental cholesterol lowering drug 23-oxidosqualene:lanosterol cyclase, which blocks the synthesis of cholesterol below the mevalonate level and thus does not impair the biosynthesis of coenzyme Q₁₀.

In 1998, Nakahara et al. evaluated simvastatin (a lipophilic inhibitor of HMG CoA-reductase) or pravastatin (a hydrophilic inhibitor) (Nakahara 1998). In group I, rabbits were treated with simvastatin at 50 mg/kg per day for four weeks. There was a 22% to 36% reduction in ubiquinone content in skeletal muscle and the observation of skeletal muscle necrosis and elevated CK levels. Group II rabbits were treated with pravastatin at 100 mg/kg per day for four weeks, which did not cause skeletal muscle injury and reduced coenzyme Q₁₀ in skeletal muscle by 18% to 52%. In group III, treated with high dose pravastatin at 200 mg/kg per day for three weeks followed by 300 mg/kg per day for another three weeks, there was a greater reduction in ubiquinone skeletal muscle content from 49% to 72% depletion and evidence of skeletal muscle necrosis and CK elevation.

In 1998, Sugiyama observed that pravastatin caused significant decrease in the activity of mitochondrial complex I in diaphragm skeletal muscle in rats age 35-55 weeks (Sugiyama 1998). The authors concluded that careful clinical examination of respiratory muscle function is necessary in patients treated with pravastatin, particularly in the elderly.

In 1999, Ichihara et al studied the effect of statins on ischemia reperfusion in dogs and observed that pretreatment of the dogs with the lipophilic HMG CoA-reductase inhibitors simvastatin, atorvastatin, fluvastatin, and cerivastatin all worsened recovery of myocardial contraction after ischemia reperfusion, but the water soluble pravastatin had no detrimental effect on myocardial contraction in this model (Ichihara 1999).

In 2000, Satoh et al further observed a detrimental effect from atorvastatin, fluvastatin, and cerivastatin in dog ischemia reperfusion, confirming that lipophilic HMG CoA-reductase inhibitors enhance myocardial stunning in association with ATP reduction after ischemia and reperfusion (Satoh 2000).

In 2000, Caliskan et al studied rats treated with simvastatin and found significant reductions in plasma cholesterol and ATP concentrations, indicating an impairment in bioenergetics related to CoQ depletion (Caliskan 2000).

In 2000, Marz et al studied hamsters with inherited cardiomyopathy and concluded that lovastatin but not pravastatin at a dose of 10 mg/kg body weight significantly increased the mortality of cardiomyopathic hamsters, as a result of inhibition of myocardial ubiquinone (Marz 2000).

Finally, the most recent animal study by Pisarenko et al in rats treated with simvastatin at 24 mg/kg for 30 days showed a significant decrease in ATP and creatinine phosphate in myocardium, again indicating that statin-induced CoQ₁₀ depletion has a detrimental impact on energy production in the heart muscle (Pisarenko 2001).

In summary, animal studies to date uniformly document varying degrees of coenzyme Q depletion in blood and in tissue with statin therapy, and that the coenzyme Q deficiency is associated with adverse effects in cardiomyopathic hamster models, in the ischemia reperfusion injury in dog models, as well as in liver and cardiac coenzyme Q content in rabbits with skeletal muscle damage. A decrease in cardiac CoQ content and in ATP production has been documented in 2-year-old (elderly) guinea pigs. Significant CoQ depletion was documented in the heart and liver in hamsters, squirrel monkeys, and mini pigs. It is also noteworthy that the lipid soluble statins appear to show more animal toxicity, particularly in the ischemia reperfusion dog models. One can surmise from these animal studies that statins have the potential to produce clinically meaningful coenzyme Q depletion in several animal species and that the depletion is dose related. In all animal studies where supplemental coenzyme Q was given to the animals prior to the institution of statins, the coenzyme Q blood and tissue depletion was completely prevented.

Safety and Drug Interactions

Coenzyme Q₁₀ is sold in the United States and abroad as an over-the-counter dietary supplement and is widely recognized as completely safe with no reported toxicity in over a thousand published human and animal trials. The most recent animal safety study was published in 1999 by Williams et al. Potential CoQ₁₀ toxicity was assessed in rats administered CoQ₁₀ by oral gavage for 1 year at 100, 300, 600, and 1200 mg per kg body weight per day. No adverse changes in mortality, clinical signs, body weight, food consumption, or clinical pathology results occurred.

To date, there have been at least 34 placebo controlled trials using CoQ₁₀ in cardiovascular disease involving a total of 2152 patients with no toxicity or drug interactions reported in the CoQ₁₀ group as compared to the placebo group. Most of these controlled trials have been reviewed (Langsjoen 1998, Langsjoen 1999). In addition to these controlled trials there have been many open-label long term trials using CoQ₁₀ in doses up to 600 mg per day with up to eight year follow up, again with a complete lack of toxicity. In heart failure alone there have been at least 39 open trials with supplemental CoQ₁₀ published involving 4498 patients again with remarkable safety with the only reported side-effects being rare cases of mild nausea.

Long term safety and tolerability of CoQ₁₀ was documented by Langsjoen in 1990 in a six year study of 126 heart failure patients (Langsjoen 1990). Later, in 1993, Morisco published a double blind controlled trial on 641 heart failure patients treated with either placebo or CoQ₁₀ for one

year (Morisco 1993). The investigators found a significant reduction of hospitalizations for worsening of heart failure in the CoQ₁₀ group and no evidence of side effects. In 1994 Baggio published an open-label multi-center trial on 2664 patients with heart failure, treated with 150 mg CoQ₁₀ per day for three months and reported good tolerability (Baggio 1994). Also in 1994 Langsjoen published long term observations on 424 cardiac patients, treated with 75 to 600 mg of CoQ₁₀ per day for up to eight years with no adverse effects or drug interactions. One out of the 424 patients experienced transient nausea.

There have been two case reports published claiming potential interaction between CoQ₁₀ and coumadin (warfarin), suggesting that CoQ₁₀ has a vitamin K-like effect (Spigset 1994, Landbo 1998). This has not been corroborated by other investigators and was the subject of a prospective trial which was presented at the most recent coenzyme Q₁₀ conference of the International Coenzyme Q₁₀ Association in Frankfurt, Germany, Dec 1-3, 2000 (Engelsen 2000). Physicians wisely and routinely follow prothrombin times very closely in patients on coumadin, particularly after any change in diet, medication or over-the-counter supplements. In this author's 18 year experience with the use of CoQ₁₀ in many thousands of cardiac patients we have yet to see a single case of CoQ₁₀-coumadin interaction at doses up to 600 mg of CoQ₁₀ per day (unpublished observations).

Discussion and Conclusions

The widely prescribed HMG CoA-reductase inhibitors block the endogenous biosynthesis both of cholesterol and of coenzyme Q₁₀, and the decrease in both substances is related to the dose as well as the potency of those drugs. The depletion of the essential co-factor required for energy production, coenzyme Q₁₀, appears to be well tolerated in younger and healthier patients, particularly in the short term, but the data reveal detrimental cardiac effects in humans with pre-existing cardiac dysfunction and in several animal models, particularly in older animals. CoQ₁₀ is known to be deficient in congestive heart failure (CHF), with the degree of deficiency in blood and cardiac tissue correlating with the severity of the CHF (Kitamura 1984, Folkers 1985). Normal whole blood levels of CoQ₁₀ are about 1.0±0.2 :g/ml with deficiency in the range of 0.6±0.2:g/ml. It is also known that CoQ₁₀ levels steadily fall after the age of 40 (Kalen 1989, Soderberg 1990). The best recent data documenting impairment in myocardial function secondary to age-related CoQ₁₀ deficiency in older patients undergoing coronary artery bypass graft surgery is by an Australian group of cardiovascular surgeons who obtained atrial muscle from patients at the time of open heart surgery and evaluated it for a post-ischemic contractile recovery. Older patients had significantly lower myocardial tissue levels of CoQ₁₀. Incubation of the atrial myocardium with CoQ₁₀ completely abolished the difference between the contractile recovery of the senescent atrial tissue (greater than the age of 70) as compared to the atrial tissue from patients under the age of 60 (Rosenfeldt 1999). Later those researchers performed a randomized, double-blind, placebo controlled trial of preoperative supplemental CoQ₁₀ therapy and found improved outcomes in coronary artery bypass surgery. The results of that trial were presented at the 2001 American Heart Association Scientific Sessions in Anaheim (Pepe 2001). Certainly, patients undergoing bypass surgery may be more susceptible to statin-induced lowering of coenzyme Q₁₀ cardiac tissue levels, and elderly patients who are on statin therapy would greatly benefit from supplemental CoQ₁₀.

Thus, all prescribing physicians should be notified that statin drugs produce a depletion in coenzyme Q₁₀, which in settings of pre-existing CoQ₁₀ deficiency, such as in CHF (Folkers 1970, Littarru 1972, Kitamura 1984, Folkers 1985) and ageing (Kalen 1989), has the ability to markedly worsen myocardial function. As the potency of statin drugs increases and as the target LDL cholesterol level decreases, the potential for statin-induced cardiomyopathy must be seriously considered and must be prevented with the concomitant administration of CoQ₁₀ with all statin medications. In addition, since CoQ₁₀ is not obtainable from daily dietary sources sufficient to bolster flagging levels of statin-induced CoQ₁₀ deficiencies, the aforementioned concomitant administration must be in specific supplement form and within 100-200 mg.

A black box warning in the labeling for all statins sold in the United States should read as follows:

Warning:

HMG CoA reductase inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q₁₀, required for energy production. A deficiency of coenzyme Q₁₀ 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 Q₁₀.

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CURRICULUM VITAE

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EDUCATION: Temple High School, Temple, Texas, 1969-1972
The University of Texas at Austin, 1972-1975; Bachelor of Science in
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The University of Texas Health Science Center, San Antonio, Texas,
1976-1980; M.D. degree 1980.
The University of North Dakota, Fargo, North Dakota, Internal
Medicine Residency, 1980-1983.
Scott and White Memorial Hospital, Temple, Texas, Cardiology
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CERTIFICATIONS: Diplomate, American Board of Internal Medicine, 1983.
Diplomate, American Board of Internal Medicine, Cardiovascular Disease,
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MEDICAL LICENSURE: 1980 - present, Texas

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SOCIETIES: Alpha Omega Alpha Honor Society
American College of Cardiology - Fellow
American College of Physicians - Member
Texas Club of Cardiologists - Member (President 1997-1998)
Texas Medical Association - Member
Smith County Medical Society - Member

The International Coenzyme Q₁₀ Association
(<http://www.csi.unian.it/coenzymeQ/index.html>)- Founding Member of
the Executive Committee (1997 to present)

EXPERIENCE:

1983-1985: Involved in the first controlled study of coenzyme Q₁₀ in cardiomyopathy with Per H. Langsjoen, M.D., F.A.C.C. during cardiology fellowship at Scott and White Hospital, Temple, Texas.

1985-1990: Associate Professor of Medicine and staff invasive cardiologist at The University of Texas Health Center at Tyler, Tyler, Texas.

1986-1987: Performed the first exploratory treatment of AIDS patients with Coenzyme Q₁₀ at the University of Texas Health Center in Tyler, Texas.

1990-present: Private practice of non-invasive cardiology, Tyler, Texas, specializing in congestive heart failure and other diseases of the heart muscle.

Presentations at the 6th, 8th and 9th International Symposia on the Biomedical and Clinical Aspects of Coenzyme Q (held in Rome, Italy, 1990, in Stockholm, Sweden, 1993 and in Ancona, Italy, 1996, respectively), at the First Conference of the International Coenzyme Q₁₀ Association (in Boston, USA, 1998) and many other presentations in the US and abroad

Numerous TV and radio appearances and interviews

1997 - Became a Founding Member of the Executive Committee of the International Coenzyme Q₁₀ Association, based in Ancona, Italy and has served on the Executive and Scientific Committee of this Association since then.

Ongoing research into application of coenzyme Q₁₀ to the treatment of the broad range of cardiovascular diseases, including long term follow up study in heart failure and later in primary diastolic dysfunction and hypertensive heart disease.

PUBLICATIONS:

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