DEPARTMENT OF HEALTH & HUMAN SERVICES

JUN 20 2014

Food and Drug Administration
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Building #51
Silver Spring, MD 20993

Chris Fischer
Sidney M. Wolfe, MD
Larry Sasich, Pharm. D., MPH
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Re: Docket No. FDA-2001-P-0283

Dear Mr. Fischer, Dr. Wolfe, and Mr. Sasich:

This letter responds to your citizen petition received on August 27, 2001 (Petition).[1] The Petition requests that the Food and Drug Administration (FDA or Agency) take the following four actions on all marketed 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor drugs, a class of lipid-altering drugs commonly known as *statins*:

- require a black box warning of the risks of rhabdomyolysis at the beginning of the official product labeling (package insert) for all statins sold in the United States (Petition at 2);
- require all labels for statins to include an additional bolded warning of the risks of myopathy and measures doctors and patients can take to reduce these risks (Petition at 2);
- require that an FDA-approved Medication Guide be distributed with all new and refill statin prescriptions warning the public of the risk of muscle pain and weakness and rhabdomyolysis and informing the public to stop using the drugs and contact their physicians if muscle pain, muscle tenderness, muscle weakness, or tiredness develops (Petition at 2); and
- require manufacturers to inform physicians about the risk of rhabdomyolysis associated with statin therapy through a "Dear Doctor" letter sent by registered mail (Petition at 2).

For the reasons discussed below, your Petition is denied except for your request that labeling for all statins include an additional bolded warning of the risks of myopathy, which has effectively been granted.

I. DECISION SUMMARY

The safety and efficacy of statins as a class have been established through multiple, large clinical trials in tens of thousands of patients exposed to these drugs over a period of 3 to 5 years. Statins have been shown to lower cholesterol and reduce the risk of cardiovascular morbidity and mortality. Drug labeling must carefully balance the benefits of drug therapy with the risks of

[1] This Citizen Petition was originally assigned docket number 2001P-0372/CP1. The number changed to FDA-2001-P-0283 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

drug side effects. Although we acknowledge your concern that there are instances of rhabdomyolysis with statin therapy, review of multiple data sources has shown that this is an infrequent event. Moreover, since the Petition was submitted, the Agency has consistently updated labeling for marketed statins to provide detailed information on the risk of muscle toxicity, including rhabdomyolysis.[2] That information includes statin-specific safety concerns and allows health care providers to select the appropriate cholesterol-lowering drug for the patient based on the health care provider's consideration of the degree of efficacy while minimizing risks of muscle toxicity. All statin labeling already contains bolded language on the risk of myopathy. However, an additional risk communication such as your proposed boxed warning, which highlights one rare adverse event without regard to the effectiveness of therapy, may mislead health care providers in their evaluation of the risks and benefits of statins. Such a risk communication therefore may pose an overall public health risk because it may cause health care providers to be disinclined to use the therapy despite strong evidence of its clinical benefit. In summary, we believe that current labeling is adequate to address the risks cited in your Petition. Therefore, we deny your requests, except for your request that the labeling for all statins include an additional bolded warning of the risks of myopathy, which has effectively been granted.

II. BACKGROUND

A. Statins

Statins, or HMG-CoA reductase inhibitors, are lipid-altering drugs that inhibit the enzyme HMG-CoA reductase, which is involved in the biosynthesis of cholesterol. The mean serum cholesterol reduction achieved with these drugs ranges from 15 to 65 percent. The Agency has approved new drug applications (NDAs) for eight statins.[3]

All of the approved statins are prescription drugs indicated for patients with a variety of lipid abnormalities, including familial and nonfamilial forms of hypercholesterolemia and mixed dyslipidemias (elevated cholesterol and triglyceride). Several approved statins are also indicated for the reduction of risk of cardiovascular mortality and morbidity based on findings from multiple large, placebo-controlled clinical trials with average treatment duration of 5 years. Risk reductions for nonfatal myocardial infarction, coronary death, stroke, revascularization procedure, or unstable angina have been observed with these statins in different patient populations across a broad range of baseline cholesterol levels.

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[2] The following Drug Safety Communications announce these labeling changes:
http://www.fda.gov/drugs/drugsafety/ucm293101.htm
http://www.fda.gov/Drugs/DrugSafety/ucm283137.htm
http://www.fda.gov/Drugs/DrugSafety/ucm293877.htm

[3] The eight approved statins, the year when they were initially approved, and NDA holders are as follows: Mevacor (lovastatin), 1987, Merck; Pravachol (pravastatin), 1991, Bristol-Myers Squibb; Zocor (simvastatin), 1991, Merck; Lescol and Lescol XL (fluvastatin), 1993, Novartis; Lipitor (atorvastatin), 1996, Pfizer; Baycol (cerivastatin), 1997, Bayer; Crestor (rosuvastatin), 2003, Astra-Zeneca; Livalo (pitavastatin), 2009, Kowa Research Institute, Inc. Baycol was withdrawn from markets worldwide in August 2001.

In general, statins are well tolerated; however, rare, serious cases of muscle toxicity[4] have been reported. In assessments of muscle effects of statins, the term *myopathy* has been used to designate the condition involving muscle aches and pains accompanied by blood levels of the muscle protein, creatine kinase (CK), that are elevated above 10 times the upper limit of normal. The most severe presentation of statin-associated muscle toxicity is rhabdomyolysis. No single set of diagnostic criteria for rhabdomyolysis has been applied across all analyses of statin muscle effects, whether by FDA or others. As discussed in section III of this response, the incidence of rhabdomyolysis in patients exposed to statin drugs has been estimated as between 0.03 and 0.05 percent.

Despite its very low incidence, muscle toxicity is discussed extensively under the WARNINGS AND PRECAUTIONS section of the approved labeling for all statins because the Agency recognizes that muscle toxicity can be a serious side effect of therapy. A description of the signs and symptoms of muscle injury and instructions to patients who may experience these side effects while taking a statin are also included in all approved labeling. Information on drug–drug interactions that may increase the risk of muscle toxicity and recommendations for dose adjustments to minimize the risk of muscle toxicity are included in the DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections of labeling for the relevant statin, as appropriate.

B. Timing of Petition and Subsequent Events Involving "High-Dose" Simvastatin

1. Baycol

Your Petition was submitted shortly after the statin Baycol (cerivastatin) was voluntarily withdrawn from the market[5] following reports of rhabdomyolysis (sometimes fatal) at higher doses of cerivastatin, especially when used in combination with another lipid-altering drug, gemfibrozil.[6]

Based on the data you referenced in the Petition and our analysis of safety data since the time the Petition was submitted, we find the circumstances associated with cerivastatin to be unique and distinctly different from other statins.

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[4] Muscle toxicity associated with statins has a spectrum of clinical presentations. The most common manifestation is marked by mild, often intermittent, muscle aches and pains. Minor muscle weakness may be an accompaniment, and the entire symptom complex may be readily reversible with discontinuation of the drug or a reduction in dose.

[5] We note that Crestor (rosuvastatin) was not approved at the time you submitted your Petition and was not one of the statins you listed. We addressed issues related to Crestor in the context of your separate Petition on that drug product (Docket Number FDA-2004-P-0009).

[6] Backman JT et al. Gemfibrozil greatly increased plasma concentrations of cerivastatin. *Clin Pharmacol Ther.* 2002;72(6):685-691.

Reporting rates (i.e., spontaneously reported cases to the Agency's Adverse Event Reporting System (AERS)[7] divided by a projected exposure in the population) along with other data sources, may provide an estimated potential risk associated with a drug product. In a study of rhabdomyolysis and statins that examined AERS reports and drug use data, Chang et al.[8] found that the reporting rate for rhabdomyolysis associated with cerivastatin was approximately 100 times that for atorvastatin, a similar statin that was marketed within 1 year of cerivastatin.

As discussed in detail throughout this response, the reporting rate for rhabdomyolysis for all the other approved statins has remained consistently low. In brief, we find that cerivastatin was an outlier in terms of benefit-risk profile and risk of rhabdomyolysis compared to the other marketed statins.

Also, as discussed immediately below, recent experience with the 80-milligram (mg) dose of simvastatin (high-dose simvastatin) constitutes another outlier in terms of the overall safety profile of statins.

2. High-dose Simvastatin

In June 2009, the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) clinical trial was submitted to the Agency. Upon preliminary review, the Agency became aware of increased rates of myopathy, including rhabdomyolysis, associated with high-dose (80 mg) simvastatin, relative to the low dose (20 mg), and issued a Drug Safety Communication on March 19, 2010.[9] Following that communication, the Agency performed a comprehensive review of the muscle safety of statins, including the SEARCH data, clinical trial data from other large statin trials, and adverse event reports from AERS.

The SEARCH trial was a 6.7-year, randomized, double-blind trial comparing the efficacy and safety of 80 mg of simvastatin with that of 20 mg of simvastatin, with or without vitamin B12 and folate, in survivors of myocardial infarction. The primary efficacy end point was the incidence of major adverse cardiovascular events, defined as death from coronary causes or the occurrence of myocardial infarction, stroke, or arterial revascularization.

Myopathy — defined as a serum creatine kinase level more than 10 times the upper limit of normal with unexplained muscle weakness or pain — developed in 52 patients in the 80-mg group (0.9 percent) but in only one patient in the 20-mg group (0.02 percent). Rhabdomyolysis — defined as unexplained muscle pain or weakness with a serum creatine kinase level more than 40 times the upper limit of normal — developed in 22 patients in the 80-mg group (0.4 percent) but in no patients in the 20-mg group. There were no deaths related to rhabdomyolysis.

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[7] On September 10, 2012, the Agency launched the FDA Adverse Event Reporting System (FAERS), successor to AERS. FDA moved data from AERS to FAERS on that date. For ease of reference, we cite to AERS in this response.

[8] Chang J et al. Rhabdomyolysis with HMG-CoA Reductase Inhibitors and Gemfibrozil Combination Therapy. *Pharmacoepidemiology and Drug Safety*. 2004;13:417-426.

[9] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm

The incidence of myopathy and rhabdomyolysis with the high dose of simvastatin were most pronounced early in the course of treatment.[10]

Of the currently marketed statins, simvastatin is *particularly* prone to drug–drug interactions, in part because it is extensively metabolized by the CYP3A4 enzyme system.[11] Data from the SEARCH trial indicate that much of the increase in risk for myopathy noted in the high-dose simvastatin group was due to the concomitant use of medications such as amiodarone, diltiazem, and amlodipine that, like simvastatin, are labeled as CYP3A4 inhibitors. The current labeling for simvastatin products specifies that concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated.

The Agency's review of additional data from other large cardiovascular outcome trials of high-dose statins indicates that the incidence of myopathy, although very low for all statins, was approximately three times higher with the 80-mg dose of simvastatin than with the highest approved doses of rosuvastatin (20 and 40 mg) and atorvastatin (80 mg). An analysis of U.S. rhabdomyolysis reports in AERS also revealed that reporting rates for fatal rhabdomyolysis were higher with 80 mg of simvastatin than with 80 mg of atorvastatin or with 20 or 40 mg of rosuvastatin.

Based on the totality of the data, the Agency in June 2011 recommended that high-dose simvastatin be used only in patients who have been taking this dose "chronically" (i.e, for 12 months or more) and without signs or symptoms of clinically significant muscle toxicity. For these patients, the Agency believes that the cardiovascular benefits of high-dose simvastatin outweigh the low absolute risk of myopathy including rhabdomyolysis.[12]

To help ensure that high-dose simvastatin therapy is not initiated in new patients and that patients receiving any dose of simvastatin do not receive concomitant medications that could increase plasma concentrations of simvastatin to inappropriate levels, the Agency in June 2011 mandated safety labeling changes for Zocor (simvastatin), Vytorin (ezetimibe and simvastatin), and Simcor (simvastatin and extended release niacin). The Agency is monitoring drug utilization data to ensure that the labeling recommendations are being followed.

With regard to your Petition requests, we conclude that the increased risks of myopathy and rhabdomyolysis associated with 80-mg simvastatin are unique to that dosage and drug product. As discussed above, simvastatin is particularly prone to drug–drug interactions, in part because it is extensively metabolized by the CYP3A4 enzyme system. We believe that the increased risk for myopathy found with high-dose simvastatin is partly explained by the concomitant use of medications such as amiodarone, diltiazem, verapamil, gemfibrozil, cyclosporine, danazol, azole

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[10] The SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy — a genomewide study. *N Engl J Med.* 2008;359:789-99.

[11] See http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm.

[12] See http://www.fda.gov/forconsumers/consumerupdates/ucm257884.htm.

antifungals, HIV protease inhibitors, hepatitis C protease inhibitors, and other drugs labeled as strong or moderate CYP3A4 inhibitors.

III. DISCUSSION

In the Petition, you state that you analyzed cases of rhabdomyolysis from AERS and that statin-associated rhabdomyolysis occurred with each of the six statins marketed in the United States during that time. Based on your analysis, you request that FDA require (1) the addition of a black box warning, (2) an additional bolded warning of the risks of myopathy and measures doctors and patients can take to reduce these risks, (3) a Medication Guide, and (4) a Dear Doctor letter. We first discuss clinical studies evaluating the efficacy of statins. We then discuss the risks of statin therapy and how those risks are managed.

A. Clinical Trials Evaluating the Efficacy of Statins

As a class, statins have been shown to lower cholesterol, which can reduce the risk of cardiovascular mortality and morbidity. At the time you submitted the Petition, we had already reviewed five cardiovascular outcomes trials to determine whether cholesterol lowering with statins resulted in any clinical benefit.

These trials demonstrated statistically significant reductions in the risks of nonfatal cardiovascular events in patients whose baseline cholesterol levels were considered only mildly elevated. Two of these trials demonstrated a reduction in the risk of cardiovascular deaths without any offsetting increase in the risks of noncardiovascular deaths (Table 1).

Table 1. Prevention Trials With HMG-CoA Reductase Inhibitors Demonstrating Clinical Benefit*

Clinical Trial (no. of subjects) and Primary Endpoint	Mean Baseline Lipids (mg/dL))	Statin Event Rate	Placebo Event Rate	Relative Risk (95% CI) p-value
Primary Prevention Trials[13]				
WOSCOPS (n = 6,595) NF-MI/fatal CHD	LDL-C 192 TC 272	174/3302 (5.3%)	248/3293 (7.5%)	0.69 (0.57-0.83) < 0.001
AFCAPS/TexCAPS (n = 6,605) NF-MI/fatal CHD/UAP	LDL-C 150 TC 221	116/3304 (3.5%)	183/3301 (5.5%)	0.63 (0.50-0.79) < 0.001
Secondary Prevention Trials				
4S (n=4,444) Total Mortality	LDL-C 189 TC 260	182/2221 (8.2%)	256/2223 (11.5%)	0.70 (0.58-0.85) 0.0003
CARE (n=4,159) NF-MI/fatal CHD	LDL-C 139 TC 209	212/2081 (10.2%)	274/2078 (13.2%)	0.76 (0.64-0.91) 0.003
LIPID (n=9,014) Total CHD Mortality	LDL-C 150 TC 219	287/4512 (6.4%)	373/4502 (8.3%)	0.76 (0.65-0.88) < 0.001

*Key to abbreviations: CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; NF-MI = non-fatal myocardial infarction; UAP = unstable angina pectoris.

Since you submitted the Petition in August 2001, at least six additional cardiovascular outcomes trials have been completed that demonstrated reductions in the risk of cardiovascular events with statin therapy. Several of these trials have been reviewed by the Agency, and some have been the basis for recent updates to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Guidelines.[14] These trials also demonstrated the benefits of aggressive LDL-C lowering in patients at very high risk for recurrent coronary events and the benefits of statin therapy in patients with type 2 diabetes (Table 2). These trials provide further

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[13] Sources:
WOSCOPS: West of Scotland Coronary Prevention Study. Original paper: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group; published in the *New England Journal of Medicine.* 1995 Nov 16;333(20):1301-7.

AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. Original paper: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study; published in the *Journal of the American Medical Association.* 1998 May 27;279(2):1615-22.

[14] 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.

evidence of the clinical benefit of statins in reducing the risk of cardiovascular disease, the primary cause of morbidity and mortality in the United States.

Table 2. Statin Clinical Outcomes Trials Published After August 2001[15]

Clinical Trial and Primary Endpoint Measured	Mean Baseline Lipids (mg/dL))	Statin Event Rate	Placebo/Control Event Rate	Relative Risk (95% CI) p-value
Heart Protection Study (HPS) total mortality	LDL 131 mg/dL TC 226 mg/dL	1328/10,269 (12.9%) simvastatin 40 mg	1507/10,267 (14.7%) placebo	0.87 (0.81-0.94) 0.0003
Anglo-Scandinavian Cardiovascular Outcomes Study (ASCOT) nonfatal MI/CHD and death	LDL 133 mg/dL	100/5134 (1.9%) atorvastatin 10 mg	154/5106 (3.0%) placebo	0.64 (0.50-0.83) 0.0005
Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) fatal CHD, nonfatal MI, and stroke	LDL 147 mg/dL	408/2891 (14.1%) pravastatin 40 mg	473/2913 (16.2%) placebo	0.85 (0.74-0.97) 0.014
Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in MI (PROVE-IT) all-cause mortality, MI, unstable angina, revascularization, and stroke	LDL 106 mg/dL Total-C 180 mg/dL	470/2099 (22.4%) atorvastatin 80 mg	543/2063 (26.3 (%) pravastatin 40 mg	0.84 (0.74-0.95) 0.005
Primary Prevention of Cardiovascular Atorvastatin Diabetes Study (CARDS) acute coronary event, coronary revascularization, and stroke	LDL 117 mg/dL Total-C 206 mg/dL	83/1428 (5.8%) atorvastatin 10 mg	127/1410 (9%) placebo	0.63 (0.48-0.83) 0.001
Treating to New Targets (TNT) CHD death, nonfatal MI, resuscitated cardiac arrest, and stroke	LDL 98 mg/dL Total-C 175 mg/dL	434/5006 (8.7%) atorvastatin 80 mg	548/4995 (10.9%) atorvastatin 10 mg	0.78 (0.69-0.89) < 0.001

[15] Sources:

HPS: Heart Protection Study. Original paper: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial; published in *Lancet.* 2002 Jul 6;360(9326):7-22;

ASCOT-LLA: Anglo-Scandinavian Cardiovascular Outcomes Study-Lipid-Lowering Arm. Original paper: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial.; published in *Lancet.* 2003 Apr 5;361(9364):1149-58;

PROSPER: Prospective Study of Pravastatin in the Elderly at Risk. Original paper: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial; published in *Lancet.* 2002;360:1623-30;

PROVE-IT: Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in MI. Original paper: Intensive versus moderate lipid lowering with statins after acute coronary syndromes; published in the *New England Journal of Medicine.* 2004 Apr 8;350(15):1495-504;

CARDS: Primary Prevention of Cardiovascular Atorvastatin Diabetes Study. Original paper: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial; published in *Lancet.* 2004 UF21-27;364(9435):685-96;

TNT: Treating to New Targets (TNT). Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study; published in *Diabetes Care.* 2006 Jun;29(6):1220-6.

B. Rhabdomyolysis Is a Rare Adverse Event

Based on the totality of data from all available data sources, including AERS, clinical pharmacology studies, published literature, and cardiovascular outcomes trials, we conclude that rhabdomyolysis is a rare adverse event. The sections below discuss these data sources in greater detail.

1. AERS Data

Your Petition requests are based on your review of the AERS database. However, your Petition did not discuss the methodology you applied to reviewing the AERS database. In particular, we note that your analysis did not provide details of case selection or correct for duplicate reporting. Your review also focused solely on the raw counts of cases without placing these numbers in the context of drug usage data during the reporting time period. Finally, your review did not address other data sources, including clinical pharmacology studies, published literature, and cardiovascular outcomes trials, that should be considered in assessing the need for additional risk communications. For these reasons, we believe that a discussion of the nature and significance of adverse event reports is appropriate.

MedWatch is the FDA Safety Information and Adverse Event Reporting System and serves both health care professionals and the medical product-using public.[16] Through MedWatch, we obtain important and timely clinical information about safety issues involving medical products, including prescription and over-the-counter drugs. A component of the safety information available through MedWatch is AERS. AERS collects information about adverse events, medication errors, and product problems that occur after the administration of approved drug and therapeutic biologic products. Certain AERS data are available on FDA's Web site.[17] Health care professionals, patients, and others may report adverse events either directly to FDA or to the holder of the NDA or abbreviated new drug application (ANDA) for the drug product, who then is required to report the adverse event to FDA.[18]

In considering the significance of adverse event reporting rates (reports received divided by a projected exposure, e.g., 100,000 prescriptions), it is important to note that AERS data have limitations. First, there is no certainty that the reported adverse events resulted from use of the product at issue. FDA does not require that a causal relationship between a product and event be demonstrated, and reports do not always contain enough detail to properly evaluate an event. Moreover, the quantity and quality of information in postmarketing adverse event reports is highly variable. This factor further limits our ability to accurately determine whether the drug played a causal role in any particular case.

Second, FDA does not receive reports of all adverse events that occur with a product. The proportion of total incident cases that are reported is variable, and the true number of people

[16] Information about MedWatch is available at http://www.fda.gov/medwatch/index.html.

[17] MedWatch Safety Information is available at http://www.fda.gov/medwatch/safety.htm.

[18] See 21 CFR 314.80.

exposed to a drug cannot be calculated precisely because prescription data may not reflect either total patients treated or duration of therapy.[19] Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Such influences might stimulate reporting in some instances and inhibit it in others. For example, public perception (based, for example, on statements in drug labeling) of the risks associated with use of a particular drug might stimulate the reporting of labeled adverse events, both those caused by the drug and those occurring purely coincidentally with drug use.[20] Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Your Petition states that you analyzed 385 reports (from October 1997 through December 2000) of rhabdomyolysis in persons using the class of HMG-CoA reductase inhibitor drugs not including those in people using the withdrawn drug Baycol (Petition at 1). You state that the importance of the relationship between statins and rhabdomyolysis has been heightened by the withdrawal of cerivastatin following reports of this adverse effect (Petition at 1). You assert that although cerivastatin accounted for slightly more than half of the 772 reported cases of rhabdomyolysis between October 1997 and December 2000, 385 cases of rhabdomyolysis and 52 rhadomyolysis deaths were reported in association with the other statins (Petition at 1). You further assert that most patients with rhabdomyolysis required hospitalization, and an additional 29 deaths from rhabdomyolysis in people using statins other than cerivastatin were reported to the FDA prior to October 1997 for a total of 81 deaths from rhabdomyolysis caused by statins other than cerivastatin (Petition at 1). Based on your analysis, you conclude that "most of the cases of rhabdomyolysis in people using other statins . . . occurred in those not using a fibrate" (Petition at 1).

We agree that most cases of rhabdomyolysis associated with lipid-lowering drugs were reported in patients using statin monotherapy, although, as shown in Tables 3 and 4 below, higher incidence rates of muscle toxicity were reported with statin-fibrate combination therapy.[21] We also acknowledge reports of adverse events received by AERS. Nevertheless, based on the totality of the data available to us as discussed in this response, we conclude that whether taken as monotherapy or in combination with a fibrate, rhabdomyolysis is a rare adverse event.

In general, and as explained above, AERS data are most useful as an initial qualitative signaling tool, alerting the Agency to new events or an event that appears to be more frequent or clinically serious than described in current labeling. Beyond initial signaling, many factors may contribute to any reporting trend changes following, for example, re-labeling and publicity.

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[19] McAdams M et al. Estimating the extent of reporting to FDA: a case study of statin-associated rhabdomyolysis. *Pharmacoepidemiology and Drug Safety*. 2008;17: 229-239.

[20] Scott HD et al. Physician reporting of adverse drug reactions: results of the Rhode Island Adverse Drug Reaction Reporting Project. *JAMA*. 1990;263(13):1785-1788.

[21] As noted in section II.B.1 of this response, a detailed discussion of our method of data extraction and case selection and the reporting rates for statin-associated rhabdomyolysis has been published (Chang J et al. Rhabdomyolysis with HMG-CoA Reductase Inhibitors and Gemfibrozil Combination Therapy. *Pharmacoepidemiology and Drug Safety*. 2004;13:417-426).

Therefore, the reporting of the cases might reflect a stimulated reporting or increased outreach efforts from the application holder. The observed risk of rhabdomyolysis in association with statins following numerous and ongoing efforts to raise awareness of this risk to the prescriber community (as was the case in the aftermath of the Baycol withdrawal) may have contributed to the AERS data you cite in the Petition. These data should be interpreted with caution and in the context of the totality of data from all data sources, including premarketing studies, ongoing controlled clinical trials, and postmarketing safety data.

We have analyzed AERS data and reviewed clinical trial data of statin-fibrate interactions, cardiovascular outcomes trials that evaluated the benefits of statin therapy, and other sources of data from the published literature that provide insight on the risk of statin-associated muscle toxicity in the general population. On these bases, we conclude that rhabdomyolysis is a relatively rare adverse event, when used both as monotherapy and in combination with fibrates, and the risk is adequately communicated in current labeling.

2. Clinical Pharmacology Studies

We have also evaluated clinical pharmacology studies regarding the safety of statins. Prior to the withdrawal of cerivastatin, it was generally believed that the skeletal muscle adverse effects of statins in combination with fibrates resulted from a pharmacodynamic interaction, because both statins and fibrates alone can cause myopathy. It is now known that drug levels of some statins may be increased with concomitant gemfibrozil administration, which may also play a role in the increased risk of muscle toxicity when statins are co-administered with gemfibrozil.

Systemic exposure to cerivastatin was increased 5- to 6-fold in the presence of gemfibrozil, likely contributing to a greater risk of myopathy of cerivastatin compared to other statins co-administered with the fibrate gemfibrozil.[22] Simvastatin and lovastatin drug levels are also increased with concomitant use of gemfibrozil, but to a lesser extent (2- to 3-fold).[23,24] The interaction between gemfibrozil and some statins is thought to be mediated through gemfibrozil's inhibition of glucuronyl transferase, an enzyme responsible for the glucuronidation of certain statins, and not through the CYP isoenzymes.[25] Because of a pharmacokinetic (PK) interaction observed between rosuvastatin and gemfibrozil, FDA required that drug–drug interaction studies with gemfibrozil and fenofibrate be conducted as part of the marketing application for Livalo (pitavastatin).[26]

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[22] Backman JT et al. Gemfibrozil greatly increased plasma concentrations of cerivastatin. *Clin Pharmacol Ther.* 2002;72(6):685-691.

[23] Backman JT et al. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther.* 2000;68:122-129.

[24] Kyrklund C et al. Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther.* 2001;69:340-345.

[25] Prueksaritanont T et al. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos.* 2002;30(11):1280-1287.

[26] A drug–drug interaction study with gemfibrozil and fenofibrate was conducted as part of the marketing application for Livalo (pitavastatin), approved on August 3, 2009 (Kowa Pharmaceuticals America).

The drug–drug interaction studies referenced in notes 23 through 27 provide additional information on the potential mechanism for muscle toxicity with combination statin-fibrate therapy, suggesting that the risk of muscle toxicity associated with combination therapy differs by statin. Consequently, current statin labeling contraindicates the use of gemfibrozil with statins known to have significant drug interactions (simvastatin and lovastatin), while all other statin labeling states that the concomitant use of gemfibrozil should be avoided. Additionally, all statin labeling includes language regarding the increased risk of myopathy when other fibrates are administered concomitantly with statins, and they recommend caution in that setting. Your Petition proposes standard language in all statin labeling that does not take into consideration differences in pharmacodynamic interactions with fibrates across the statin class of drugs. Although the approved labeling for every statin has standard language regarding increased risk of myopathy with statin-fenofibrate combination therapy, the labeling varies across statins with respect to statin-gemfibrozil combination therapy and increased risk of myopathy, which reflects pharmacokinetic data for different statins. As such, and as discussed in section III.C, current labeling appropriately addresses the risks of muscle toxicity you cite in the Petition.

3. Review of Published Literature

Our review of clinical data and the published literature supports our conclusion that statin-associated rhabdomyolysis is a rare event. We reviewed three large-scale observational studies that investigated the risk of rhabdomyolysis associated with statin monotherapy, fibrate monotherapy, and statin and fibrate combination therapy. We also summarize four more recently published studies.

In one study,[27] the authors concluded that "rhabdomyolysis risk was similar and low" for statin monotherapy use (atorvastatin, pravastatin, and simvastatin), although combined statin-fibrate use increased this risk. Investigators established statin- or fibrate-specific cohorts using claims data from 11 managed care health plans across the United States collected from January 1, 1998, through June 30, 2001. Fluvastatin and lovastatin were excluded from analyses due to low usage data. A total of 252,460 patients contributed to 225,640 person-years of statin or fibrate monotherapy and 7,300 person-years of combination statin-fibrate therapy. In all, 24 cases of hospitalized rhabdomyolysis were identified from a review of medical records and selection using a specific case-definition. Sixteen of these cases involved monotherapy with either a statin (n=13) or fibrate (n=3) and eight cases received combined statin-fibrate therapy. The average incidence rate of rhabdomyolysis per 10,000 person-years for monotherapy with atorvastatin, pravastatin, or simvastatin was 0.44 (95% confidence interval (CI): 0.20-0.84). This was markedly lower than the incidence of rhabdomyolysis for cerivastatin, which was 5.34 per 10,000 person-years (95% CI: 1.46-13.68) (Table 3). The incidence rate of rhabdomyolysis per 10,000 person-years for statin monotherapy was also lower than the rate observed for fibrate monotherapy (2.82, 95% CI: 0.58-8.24) and combined statin-fibrate therapy (5.98, 95% CI: 0.72-216.0).

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[27] Graham DJ et al. Incidence of Hospitalized Rhabdomyolysis in Patients Treated with Lipid Lowering Drugs. *JAMA*. December 1, 2004, Vol.1., 292, No,21

Table 3. Rhabdomyolysis per 10,000 Person-Years of Therapy With Lipid-Lowering Drugs Used as Monotherapy or as Combination Therapy With Another Drug, Graham et al., JAMA 2004[27]

Drug	Monotherapy, Incidence Rates (95% CI)	Combination	Combination Therapy Incidence Rates (95% CI)
Atorvastatin	0.54 (0.22-1.12)	Atorvastatin + fenofibrate	22.45 (0.57-125)
Cerivastatin	5.34 (1.46-13.68)	Cerivastatin + gemfibrozil	1035 (389-2117)
Pravastatin	0 (0-1.11)	No cases	0 (0-67.71)
Simvastatin	0.49 (0.06-1.76)	Simvastatin + gemfibrozil	18.73 (0.47-104)
Fenofibrate	0 (0-14.58)	Fenofibrate + atorvastatin	16.86 (0.43-93.60)
Gemfibrozil	3.70 (0.76-10.82)	Gemfibrozil + cerivastatin	789 (166-2138)

A second study[28] followed 473,343 patients treated with lipid-lowering drugs for hospitalized rhabdomyolysis, among other outcomes. Unlike in the study by Graham et al., cases were not validated through medical records, and the definition of rhabdomyolysis was broader, not requiring evidence for elevated creatine kinase concentrations. Consequently, statin-associated incidence rates for hospitalized rhabdomyolysis per 10,000 person-years were higher, ranging from 1.58 (95% CI: 0.2-5.7) for fluvastatin monotherapy to 3.49 (95% CI: 2.1-5.5) for simvastatin monotherapy. Incidence rates for fenofibrate and gemfibrozil monotherapy were comparable with statins other than cerivastatin, where rhabdomyolysis occurred at a rate of 10.59 (95% CI: 3.4-24.7) per 10,000 person-years. Estimates for combination therapy were limited by low case counts.

A third study[29] conducted on behalf of the NDA holder for Trilipix (fenofibric acid)[30] included 584,784 users of statins or fibrates. The investigators applied a case definition that required that cases of severe hospitalized rhabdomyolysis also have a diagnosis of renal insufficiency or renal failure, which resulted in the selection of fewer but more severe cases. In addition, for about 30 percent of suspected cases, medical charts could not be retrieved and these patients were considered non-cases. Fifteen cases occurred during exposure to statin monotherapy (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin) at a rate of 0.33 (95% CI: 0.19-0.53) per 10,000 patient-years of follow-up. Only one case each occurred during

[28] Cziraky MJ et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol.* 2006;97(8A):61C-68C.

[29] Enger C et al. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. *Am J Cardiol.* 2010;106(11):1594-601

[30] Abbott Laboratories, the holder of the approved NDA for Trilipix (fenofibric acid), the first fenofibrate to be approved (December 15, 2008) for co-administration with a statin, was required, under the provisions of the Food and Drug Amendments Act of 2007 (FDAAA), to do a postmarketing epidemiological study to address the incidence rate and risk factors for the development of hospitalized rhabdomyolysis in subjects co-administered a fibrate and a statin, versus statin or fibrate monotherapy. Additionally, the approval included a risk evaluation and mitigation strategy (REMS) consisting of a Medication Guide and a timetable for assessment of the REMS, to inform patients of the serious risk of rhabdomyolysis when statins are co-administered with fibrates.

exposure to fenofibrate, gemfibrozil, and statin and gemfibrozil combination therapy, resulting in imprecise incidence estimates. Four cases of severe hospitalized rhabdomyolysis occurred during combination use of statins and fenofibrate, at an incidence rate of 1.5 (95% CI: 0.05-3.6) per 10,000 patient-years.

Four recently published studies conducted in the United States provided incidence rates of hospitalized confirmed rhabdomyolysis in users of statins and other lipid-lowering drugs (Table 4).[31,32,33,34] The rates ranged from a low of 0.3 (0.1-2.1) per 10,000 person-years for lovastatin[34] to 10.29 per 10,000 person-years for atorvastatin.[33] Considerable variability exists among the results, which, in part, is due to the small number of cases identified.

Table 4. Range of Incidence Rates of Hospitalized Confirmed Rhabdomyolysis in Patients Using Statins and Other Lipid-lowering Drugs, U.S. Studies Published from 2011-2013

Study	Observation	Low Rate/10,000 PY (95% CI)	High Rate/10,000 PY (95% CI)*
Amend et al.[31]	1/1/1998 - 12/31/2007	0.25 (0.16-0.36) statin only	3.86 (1.25-9.00) statin and gemfibrozil
Floyd et al.[32]	1/2006 - 12/2010	0.52 (0.19-1.12) statins besides simvastatin	6.48 (3.23-11.69) simvastatin 80 mg
Reis et al.[33]	4/2000 - 3/2005	6.9 (2.8-14.4) fluvastatin, 7.18 (2.3-17.3) rosuvastatin	10.29 (9.0-11.7) atorvastatin
Cziraky et al.[34]	7/1/2000 - 12/1/2004	0.3 (0.1-2.1) lovastatin	2.0 (0.5-5.2) gemfibrozil; 2.1 (0.3-7.7) niacin ER; 2.1 (0.3-7.8) ezetimibe; 5.5 (0.1-30.8) combination drugs

*Excluding cerivastatin, which is no longer marketed.

Unlike studies reporting rates derived from AERS data, these observational studies used population-based data sources that captured data on outpatient prescription drugs and medical encounters, including hospitalizations and reimbursable medical procedures. A population-based database can provide information on patient demographics, patterns of drug use, concomitant prescription medications, and medical conditions. The database can also be helpful in estimating incidence rates and relative risks, as well as capture adverse events that are rare or undetected in clinical development programs.[35] Our review of the published literature corroborates the results

[31] Amend KL et al. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Ann Pharmacother* . 2011;45:1230-1239.

[32] Floyd JS et al. Use of administrative data to estimate the incidence of statin-related rhabdomyolysis. *JAMA*. 2012;307:1580-1582.

[33] Reis BY et al. A pharmcoepidemiological network model for drug safety surveillance. Statins and rhabdomyolysis. *Drug Saf.* 2012;35:395-406.

[34] Cziraky MJ et al. Risk of hospitalized rhabdomyolysis associated with lipid-lowering drugs in a real-world clinical setting. *J Clin Lipidol.* 2013;7:102-108.

[35] Rodriguez EM et al. The role of databases in drug postmarketing surveillance. *Pharmacoepidemiol Drug Saf.* 2001;10(5):407-410.

of our analysis of AERS that the risk of rhabdomyolysis is rare, but increased when statins are used in combination with fibrates.

4. Cardiovascular Outcomes Trials

We have also reviewed several cardiovascular outcomes trials. In one review of several large statin clinical trials, the incidence of rhabdomyolysis, as defined by investigators in each clinical trial, was estimated to be between 0.03 and 0.05 percent.[36] In this same review, the authors stated that "clinical trial results support a low incidence of severe muscle problems with statin therapy." They noted that among 83,858 patients randomly assigned to either placebo or statin therapy across 30 clinical trials evaluated, there were only seven cases of rhabdomyolysis in the statin treatment group and five cases in the placebo treatment group.

The following table summarizes the number of cases and incidence of rhabdomyolysis reported by study.

Table 5. Incidence of Rhabdomyolysis in Statin Cardiovascular Outcomes Trials

Clinical Trial	Incidence (%) of Rhabdomyolysis in Statin/High Dose Statin Group	Incidence (%) of Rhabdomyolysis in Placebo/Low Dose Statin Group
HPS	5/10,269 (0.048)	3/10,267 (0.029)
ASCOT	2/5134 (0.039)	0/5106 (0)
PROSPER	0/2891 (0)	0/2913 (0)
PROVE-IT	0/2099 (0)	0/2063 (0)
CARDS	0/1428 (0)	0/1410 (0)
TNT	2/4995 (0.04)	3/5006 (0.059)

Based on our review of clinical trials discussed by Thompson et al. and the others listed above, we find that rhabdomyolysis occurs infrequently with statin therapy.

5. FDA Continues to Monitor Statin-Associated Adverse Events

You assert that the National Cholesterol Education Program's (NCEP's) recommendations for changes to the 2001 Adult Treatment Panel III (ATP III) guidelines for cholesterol management will increase statin use, likely leading to an increase in the number of statin-associated rhabdomyolysis cases, and result in hospitalizations and death (Petition at 2). We note that NCEP's recommendations were based on well-designed, controlled, cardiovascular outcomes trials that had already taken into consideration the risks and benefits of expanded statin use in the general population.

Since the time that the Petition was submitted, FDA has conducted extensive reviews of statin safety. As discussed above, our reviews included analyzing rhabdomyolysis cases associated with the use of statins, analyzing drug–drug interactions, and analyzing postmarketing data from AERS reports and clinical trials. FDA continues to monitor statin-associated adverse events and has not encountered new information to alter our conclusion that rhabdomyolysis is a rare

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

adverse event. We find that the reporting rate of rhabdomyolysis for all the currently marketed statins has remained consistently low over a long period of time. As such, labeling for statins must balance the frequency of such serious adverse events with the clinical benefits of therapy. That issue is discussed below.

C. Current Labeling Adequately Addresses the Risks of Muscle Toxicity

In the Petition, you request that FDA:

- Require a boxed warning of the risks of rhabdomyolysis;
- Require all statin labeling to include an additional bolded warning of the risks of myopathy;
- Require that a Medication Guide be distributed with all new and refill statin prescriptions warning of the risk of muscle pain and weakness and rhabdomyolysis and informing the public to stop using the drug and contact their physicians if muscle pain, muscle tenderness, muscle weakness or tiredness develops; and
- Require manufacturers to inform physicians about the risk of rhabdomyolysis associated with statin therapy through a "Dear Doctor" letter (Petition at 2).

In general, currently approved statin labeling contains information on the risks of muscle toxicity that is far more comprehensive than what the Petition proposes. Moreover, as stated throughout this response, although there is some uniformity in statin labeling to communicate class-specific risks, the Agency continues to tailor individual product labeling to specific risks, benefits, or attributes associated with that product. For example, drug–drug interactions vary by statin product. There have also been recent labeling changes that included standardized language that warns about the potential increased risk for myopathy and rhabdomyolysis in patients co-administered a statin and a fibrate medication, as well as variable labeling with respect to statin-gemfibrozil combination therapy. We address your specific requests below.

1. Request for Bolded Warning for Myopathy

In the Petition, you requested that we add enhanced (bolded) warnings to statin labeling regarding the risks of myopathy and provided suggested language (Petition at 4). Your proposed language includes "general measures" to alert patients to promptly report unexplained muscle pain and terminate therapy if myopathy is diagnosed or suspected. In addition, your proposed language includes "measures to reduce the risk of myopathy caused by drug interactions" (Petition at 4).

We have effectively granted your request through revisions to statin labeling since you filed your petition. The labeling for all statins currently contains bolded warnings on the risks of myopathy.

2. Request for Boxed Warning for Rhabdomyolysis

You requested that we require for all statins sold in the United States a black box warning of the risk of rhabdomyolysis and suggested language for that labeling (Petition at 2-4). Your requested language is as follows:

> Rhabdomyolysis has been reported as a serious adverse effect of the use of all HMG-CoA reductase inhibitors. This is an infrequent but potentially life-threatening class effect of these drugs.
>
> The risk of rhabdomyolysis has been reported to be increased with the concurrent use of certain [sic] in drugs, especially fibric acid derivatives such as gemfibrozil. (see DRUG INTERACTIONS). However, most cases of rhadomyolysis have occurred in people treated with HMG-CoA reductase inhibitors without concurrent fibrate therapy.
>
> Onset of rhadomyolysis is often preceded by muscle pain, muscle tenderness, muscle weakness, tiredness and/or increases in serum creatine phosphokinase (CK) levels. Dark urine and fever may also be present in later stages of the disease. All patients using statins should be provided with this information.
>
> *The onset of muscle pain, muscle tenderness, muscle weakness or tiredness calls for immediate withdrawal of HMG-CoA reductase inhibitors and further evaluation by a physician including CK tests.*

You also assert that the labeling of statins is "extremely inconsistent and inadequate" and that although all labeling discusses the risk of myopathy and rhabdomyolysis, no statin labeling includes a black box warning. You state that these warnings and discussions should be consistently applied to all drugs in this class (Petition at 1-2).

FDA may require that "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury . . . be presented in a box" on a drug product's labeling (21 CFR 201.57(c)(1)). A boxed warning is used when, among other situations, there is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug.[37]

As set forth below, FDA concludes that a boxed warning is not necessary in light of the information currently contained in statin labeling. Moreover, the existing labeling describes the risk of muscle toxicity associated with statins more thoroughly and accurately than your proposed boxed warning.

Labeling for prescription drugs must provide accurate information on efficacy and safety based on a thorough assessment of multiple sources of data. The approved labeling for statins is the product of extensive review of nonclinical and clinical efficacy and safety studies, drug–drug interaction studies, postmarketing safety data, and data from published literature. Based on findings from a wide array of data sources, we have determined that statin-associated rhabdomyolysis is a rare adverse event.

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[37] See FDA guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*, available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page.

However, we do recognize that rhabdomyolysis has the potential to be a serious, life-threatening side effect of this class of drugs. Consequently, the approved labeling for every statin contains specific sections on muscle-related adverse events, including rhabdomyolysis. The labeling is not identical for all statins, however, because differences in drug metabolic pathways and drug–drug interactions confer differences in risk of an adverse event and may necessitate specific instructions on dosing.[38]

We further note that all of the items in your proposed boxed warnings are now included in all approved statin labeling and in far greater detail than in your proposed labeling.[39] We refer you to the WARNINGS sections[40] of all approved labeling for statins, which contain a subsection specifically discussing the rare side effects of rhabdomyolyis and myopathy. This subsection is titled *Myopathy/Rhabdomyolysis* (lovastatin, simvastatin, rosuvastatin) or *Skeletal Muscle* (pravastatin, fluvastatin, atorvastatin). Under this subsection of WARNINGS, the labeling for all statins includes information about:

- the risk of rhabdomyolysis/myopathy that may result in renal failure or dysfunction;
- symptoms of this side effect, such as unexplained muscle pain, tenderness, or weakness;
- the need for patients to promptly report to their physician any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by fever or malaise;

[38] For example, the difference between the simvastatin PLR labeling and the rosuvastatin PLR labeling reflects the heightened risk of drug–drug interactions resulting in an increased risk of myopathy/rhabdomyolysis with simvastatin relative to rosuvastatin due to their different routes of metabolism (simvastatin is metabolized via CYP3A4 enzymes and rosuvastatin via CYP2C9 enzymes). It is important to maintain distinctions such as those in the simvastatin and rosuvastatin labeling because prescribers may select one statin over another based on an individual's risk for myopathy (e.g., the selection may determined by whether or not the patient is also taking a CYP3A4 inhibitor).

[39] This information was added to statin labeling after you submitted the Petition in August 2001. For example, in November 2005, the Agency approved changes to the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections of the lovastatin package insert regarding the effect of cyclosporine on lovastatin pharmacokinetics and the potential for increased exposure to lovastatin and lovastatin acid, and thus increased risk of muscle toxicity. The Agency also approved a complete revision of the language in the WARNINGS section regarding myopathy/rhabdomyolysis, including the addition of a table summarizing dose caps for lovastatin when it is co-administered with various other drugs, in order to mitigate the increased risk of myopathy/rhabdomyolysis due to drug interactions. In June 2007, FDA approved revisions of the fluvastatin label to add information about the concomitant use of fluvastatin and colchincine and increased risk of myopathy. The Agency approved updates of the atorvastatin label in September 2007 to provide revisions to the WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections regarding increased risk of myopathy with co-administration with clarithromycin, or the combination of ritonavir plus saquinavir, or the combination of lopinavir plus ritonavir and provided a dose cap of 10 mg when co-administered with the combination of ritonavir plus saquinavir, or the combination of lopinavir plus ritonavir. Finally, in January 2010, labeling for rosuvastatin was updated to provide for changes to the DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, and CLINICAL PHARMACOLOGY sections of the Crestor package insert to add additional information on the protease inhibitors, atazanavir/ritonavir, regarding increased risk for myopathy due to increased rosuvastatin exposure when co-administered with this combination of protease inhibitors.

[40] This section of labeling predominantly focuses on statin monotherapy; however, other risk factors and/or drugs that may increase the risk of muscle toxicity are also discussed under this section. Your proposed labeling does not take into consideration other risk factors such as use of CYP3A4 inhibitor, cyclosporine, or other lipid-altering agents (e.g., niacin).

- when to consider discontinuing therapy, such as if CK levels are elevated or myopathy is diagnosed or suspected; and
- conditions when therapy should be withheld, such as predisposition to the development of renal failure secondary to rhabdomyolysis, sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, or uncontrolled epilepsy, or when certain interacting drugs must be administered.

Current labeling also describes interventions that may mitigate the risk of muscle toxicity. This information is particularly critical for statins that:

(1) are substrates of CYP3A4)an enzyme involved in the metabolism of numerous drugs) and are prone to multiple drug–drug interactions;
(2) have been demonstrated to have increased systemic exposure when administered with certain drugs that are commonly co-prescribed (e.g., gemfibrozil);
(3) have been demonstrated to have increased systemic exposures in special populations (e.g., patients in whom there is renal insufficiency, cyclosporine use, and certain racial/ethnic populations); or
(4) have been reported to be associated with rhabdomyolysis reported in outpatient settings for which no PK data are available (e.g., danazol co-administration).

These conditions of increased risk apply only to some drugs in this class, and as a result, labeling for these statins will include different language.

We note that your proposed risk communication, despite being in a boxed warning, falls short of thoroughly explaining the risk of muscle toxicity associated with statin therapy and does not comprehensively outline the measures that should be taken to reduce this risk to ensure that patients can safely take these drugs that have demonstrated clinical benefit. Your proposal also fails to recognize that certain drugs in this class carry unique risks for muscle toxicity based on differences in drug metabolism.

In summary, we find that the currently available relevant scientific evidence, when considered in accordance with the applicable law,[41] and taking into account risk communication efforts undertaken since your Petition was filed,[42] does not warrant requiring statin prescription drug labeling to include boxed warnings at this time.

As noted throughout this response, the overall rate of rhabdomyolysis associated with approved statin therapy has remained low. We conclude that the warnings in the current labeling for

[41] 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 201.80(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.).

[42] See note 44.

statins provide information in an appropriate manner regarding the risks of rhabdomyolysis and myopathy.

3. *Request for Medication Guides*

You ask that we require that FDA-approved Medication Guides be distributed with all new and refill statin prescriptions, warning the public of the risk of muscle pain and weakness and rhabdomyolysis and informing the public to stop using the drug and contact their physicians if muscle pain, muscle tenderness, muscle weakness, or tiredness develops (Petition at 2,4).

No currently approved statins have Medication Guides.[43] Based on the information you submitted in the Petition, other relevant information we have 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 part 208) 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)). As stated in 21 CFR 208.1(c), FDA will require a Medication Guide if the Agency determines that one or more of the following circumstances exists:

> (1) The drug product is one for which patient labeling could help prevent serious adverse effects.
>
> (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.
>
> (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Based upon the information before FDA, the Agency does not believe that a Medication Guide for statins is appropriate. With respect to the first factor, we do not believe a Medication Guide would have any added benefit in preventing serious adverse events given the numerous communications the Agency has issued on the risks of myopathy and rhabdomyolysis, such as the labeling changes described above as well as the availability of many consumer-focused materials.[44,45]

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[43] A list of current Medication Guides can be found at: http://www.fda.gov/cder/Offices/ODS/labeling.htm.

[44] The most recent Agency communications can be found at http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm294358.htm. Consumer-focused statin information can also be found at http://www.fda.gov/forconsumers/consumerupdates/ucm257884.htm and http://www.fda.gov/downloads/forconsumers/consumerupdates/ucm293705.pdf. Additional sources of patient information include counseling by prescribers and FDA-approved, pharmacy-distributed patient package inserts.

Nor is a Medication Guide warranted under the second factor. As set forth above, rhabdomyolysis and myopathy are rare adverse events. Meanwhile, the safety and effectiveness of statins are well established. We believe that the risks of statins are adequately communicated through current labeling and counseling from prescribing physicians.

The third factor set forth in 21 CFR 208.1(c) does not apply here because the Petition does not claim that a Medication Guide is necessary because patient adherence to directions for use is crucial to the drug's effectiveness.

For these reasons, the Agency declines to require the issuance of a Medication Guide for statins.

D. Dear Doctor Letter

You request that the Agency require companies to inform all physicians through a "Dear Doctor" letter by registered mail about the risk of rhabdomyolysis associated with statins (Petition at 2, 5).

Although such letters are informally known as Dear Doctor letters, FDA designates such communications as Dear Health Care Provider (DHCP) letters because they are frequently disseminated beyond the physician community. The type of DHCP letter that you request, an important Drug Warning DHCP letter, is used to convey important information about a drug that "concerns a significant hazard to health" (21 CFR 200.5). The risk of rhabdomyolysis associated with statin use is not new information, but rather has been recognized since the approval of the first statin (Mevacor) in 1987. Indeed, over the past 12 years, many Dear Doctor (or DHCP) letters addressing the risks of myopathy and rhabdomyolysis with statin therapy have been issued by several statin application holders. The labeling of all approved statins contains language that discusses the risk of muscle toxicity, and the labeling for several statins has been revised over the years to reflect new information on this safety concern. We believe that the information in the approved labeling for statins is sufficient to inform physicians of the risk of rhabdomyolysis and that you have not demonstrated that a DHCP letter is necessary to communicate the risk of rhabdomyolysis.

Moreover, FDA has issued several Drug Safety Communications over the past several years regarding the risk of muscle toxicity associated with use of statins, including high doses of simvastatin.[46] These communications largely involved labeling changes to add new information

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[45] We also note that it would be difficult to develop and implement a Medication Guide that would convey the risks of all statins, given the significant variability among individual members of the statin class in their potential for drug–drug interactions.

[46] These communications have included:

A Drug Safety Newsletter

- Amiodarone – Simvastatin Interaction – Rhabdomyolysis – Summer 2008

Patient Safety News

on such topics as drug–drug interactions, and, in some instances, to reflect evolving scientific knowledge and development, such as removing the recommendation to monitor liver enzymes.

In summary, we believe that the relatively rare adverse events of myopathy and rhabdomyolysis are well known to prescribers, obviating the need for a Dear Doctor letter. We therefore deny your request.

IV. CONCLUSION

For the reasons stated in this response, we deny your requests for boxed warnings, distribution of Medication Guides, and a Dear Health Care Provider letter regarding the risk of rhabdomyolysis with statin therapy. Through labeling changes made since you filed your petition, we have effectively granted your request, to the extent discussed in this response, for additional bolded language in statin product labeling regarding the risk of myopathy.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

- Interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury – February 2013
- Cholesterol-lowering drugs get labeling changes – March 2012 Important safety label changes to cholesterol-lowering statin drugs – February 2012 Simvastatin/Amiodarone – Rhabdomyolysis – November 2008
- CRESTOR – Rhabdomyolysis in Asian-Americans and with 40 mg dose – May 2005
- CRESTOR – Risk factors for myopathy – August 2004

Health Care Professional Letter, Early Communications, etc.

- Simvastatin 80 mg – Rhabdomyolysis – Drug Safety Communication – March 2010
- Simvastatin/Amiodarone – Rhabdomyolysis – HCP Sheet - August 2008
- CRESTOR – Rhabdomyolysis in Asian-Americans and with 40 mg dose – Public Health Advisory – March 2005