

Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions

Use of Cerivastatin and Risk of Rhabdomyolysis

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IN THE 1970S, PRACTOLOL, A β -blocker approved in the United Kingdom, soon became the subject of case reports about sclerosing peritonitis and was withdrawn from the UK market in 1976 before it ever appeared in the United States.¹ The early history of thalidomide is similar. More recently, the proportion of new molecular entities that are first introduced in the United States has increased from 2% to 3% in the early 1980s to 60% in 1998.² For medicines that are effective, prompt approval provides rapid access to the health benefits of new drugs. At the same time, US patients are increasingly the first to receive new medications, some of which are subsequently discovered to have serious adverse effects. As a result, the challenge of early detection is increasingly borne by the US postmarketing systems.

Approved around the same time in Europe and the United States, cerivastatin sodium, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin), was marketed in the United States in early 1998 (TABLE 1). At the initially approved doses of 0.2 and 0.3 mg, the low-density lipoprotein cholesterol

Context In recent years, US patients have increasingly been the first to receive new medications, some of which are subsequently discovered to have suspected adverse drug reactions (SADRs). As a result, the challenge of early detection has largely shifted to the US postmarketing systems.

Objective To review the association between the use of cerivastatin sodium and the risk of rhabdomyolysis in an effort to illustrate the operation and limitations of the current US postmarketing safety-surveillance system.

Data Sources and Selection For the published literature, we used previous reviews and MEDLINE searches from all years through 2003. For the unpublished literature, we used internal company documents that have become part of the public record during a trial in Nueces County, Texas.

Data Synthesis In the published literature, cerivastatin was associated with much larger risks of rhabdomyolysis than other statins. Although only a small percentage of cerivastatin users also took gemfibrozil, approximately half of the case reports of rhabdomyolysis occurred in users of this combination therapy, and a cerivastatin-gemfibrozil interaction was supported by the results of a 3-day pharmacokinetic study. In internal company documents, multiple case reports suggested a drug-drug interaction within approximately 100 days of the launch in 1998; however, the company did not add a contraindication about the concomitant use of cerivastatin and gemfibrozil to the package insert for more than 18 months. Unpublished data available in July 1999 also suggested an increased risk of rhabdomyolysis associated with high doses of cerivastatin monotherapy. In late 1999 and early 2000, company scientists conducted high-quality analyses of the US Food and Drug Administration adverse event reporting system data. These analyses suggested that compared with atorvastatin calcium, cerivastatin monotherapy substantially increased the risk of rhabdomyolysis. To our knowledge, these findings were not disseminated or published. The company continued to conduct safety studies, some of them inadequately designed to assess the risk of rhabdomyolysis, until cerivastatin was removed from the market in August 2001.

Conclusions Despite limitations of the available data, the asymmetry between the information available to the company and the information available to patients and physicians seems striking. A subjective element is present in the effort to infer whether or not the occurrence of untoward outcomes in users of a particular drug was actually the consequence of the use of that drug, and, under the current system, a pharmaceutical company's appraisal of SADRs may be influenced by economic considerations. Such an appraisal would best be made by an independent group. The US Congress should mandate and provide adequate support for independent reviews and analysis of postmarketing data.

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Table 1. Timeline of Some Key Dates in the History of Cerivastatin

Date	Public Information	Internal Company Information
1997 June 26	NDA approved for 0.2 and 0.3 mg of cerivastatin sodium	
1998 February 18	Press release announcing launch of cerivastatin	
May 28		Five of 6 US cerivastatin-associated rhabdomyolysis SADRs occurred in patients also taking gemfibrozil ³
July 21	Label update—rhabdomyolysis added to warnings*	
August 16	Supplemental 0.4 mg NDA submitted	
1999 March		Safety highlights: "overwhelming majority of reports involved concomitant use of gemfibrozil" ⁴
April 1	First published case report of rhabdomyolysis associated with cerivastatin-gemfibrozil combination ⁵	
May	Supplemental NDA, 0.4 mg of cerivastatin approved, label update—additional gemfibrozil warnings†	
July		Clinical trial of 1.6-mg cerivastatin dose revealed "high incidence (about 12%) of severe CK elevation . . . partly connected with symptoms . . ." ⁶
August 2		Committee decides not to publish results of trial of 1.6-mg cerivastatin dose ⁷
September 22	Supplemental 0.8 mg NDA submitted ⁸	
October 19		e-Mail: "frequency of concomitant gemfibrozil use in these cases is about 60%" ⁹
December	Label update—gemfibrozil coprescription contraindication is announced	Plan announced to study pharmacokinetic and pharmacodynamic statin-gemfibrozil interaction ¹⁰ Internal analyses of SADR data suggest that risk of rhabdomyolysis from cerivastatin monotherapy is 10 times higher than monotherapy with other statins ¹⁰
2000 March 10		Company scientists report: "The [SADR] findings indicate that in patients receiving mono-therapy, cerivastatin substantially elevates risk for rhabdomyolysis compared with other statins" ¹¹
July 6		FDA medical review of 0.8-mg cerivastatin supplement identified thin, elderly women at increased risk of CK elevation to greater than 10 times the upper limit of normal ⁸
July 21	Supplemental NDA 0.8-mg cerivastatin approved	
2001 April 4		APZ minutes describe results of pharmacokinetic study of cerivastatin-gemfibrozil interaction ¹²
April 20	Label update—notation that starting dose should be 0.4-mg cerivastatin is added to label	
June 15		Final report of observational study 1 on the risk of myopathy ¹³
August 8	Cerivastatin withdrawn from US market	
August 20	Public citizen petition to the FDA ¹⁴	
2002 February 14	FDA scientists publish data on fatal rhabdomyolysis ¹⁵	
July 2	Hyman publishes cohort data on rhabdomyolysis ¹⁶	
December	Backman et al ¹⁷ publish data on cerivastatin-gemfibrozil pharmacokinetic interaction	
2003 April 2	Thompson et al ¹⁸ publish review of SADR data	

Abbreviations: APZ, Action Committee [on] Adverse Events; CK, creatine kinase; FDA, Food and Drug Administration; NDA, new drug application; SADR, suspected adverse drug reaction.

*Warning section: "Skeletal Muscle: Rare cases of rhabdomyolysis (some with acute renal failure secondary to myoglobinuria) have been reported with cerivastatin and other drugs in this class. . . . The combined use of HMG-CoA [3-hydroxy-3-methylglutaryl coenzyme A] inhibitors and fibrates generally should be avoided." Adverse reactions section: "The following events have been reported since market introduction. While these events were temporally associated with the use of Baycol, a causal relationship to the use of Baycol cannot be readily determined due to the spontaneous nature of reporting of medical events, and the lack of controls: hepatitis, myositis, rhabdomyolysis, some associated with renal failure (most cases involved concomitant gemfibrozil), urticaria, angioedema, visual disturbance, blurred vision. . . . Concomitant therapy with HMG-CoA reductase inhibitors and these agents [immunosuppressive drugs, fibric acid derivatives, erythromycin, azole antifungals or lipid-doses of nicotinic acid] is generally not recommended."

†Skeletal muscle section of warnings indicate that "the combined use of cerivastatin and gemfibrozil should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination." Precautions section, under gemfibrozil, indicates, "The potential for clinically relevant interaction between gemfibrozil and cerivastatin has not been assessed. However, during postmarketing surveillance, patients on cerivastatin who experienced rhabdomyolysis and associated renal failure, were in most cases also taking gemfibrozil." (Quoted from supplementary material [Baycol product label, November 1998, and Baycol product label May 1999, respectively] sent with the letter to Drummond Rennie, MD, on March 12, 2004, from Allen H. Heller, MD, vice-president of regulatory affairs, North America, Bayer Pharmaceuticals Corp.)

Table 2. HMG-CoA Reductase Inhibitors (Statins)*

	Atorvastatin Calcium	Fluvastatin Sodium	Lovastatin	Pravastatin Sodium	Simvastatin	Cerivastatin Sodium
Dose range, mg	10-80	10-80	10-80	10-40	10-80	0.2-0.3
LDL-C reduction, %	26-60	19-35	21-40	22-34	14-47	25-28
Dose needed to decrease LDL-C by 30%, mg	5	60	20	30	10	0.3
Metabolism	CYP3A4	CYP2C9	CYP3A4	Not CYP	CYP3A4	CYP3A4, CYP2C8
Approved indications						
Lipid lowering	Yes	Yes	Yes	Yes	Yes	Yes
Primary prevention	Yes	No	Yes	No	No	No
Secondary prevention	No	No	Yes	Yes	Yes	No

Abbreviations: HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol.
*Data are from Cada et al¹⁹ and Williams and Feely.²⁰

lowering associated with cerivastatin was less pronounced than that of the other available statins. Indeed, the highest initially approved dose of cerivastatin was approximately equivalent in low-density lipoprotein cholesterol lowering only to the lowest dose of atorvastatin calcium (TABLE 2). To achieve comparable levels of cholesterol lowering, the company pursued supplemental applications for the 0.4- and 0.8-mg doses. Soon after marketing, spontaneous reports identified cases of rhabdomyolysis, an uncommon condition in which the breakdown of skeletal muscle cells causes pain, weakness, and, in some cases, renal failure and death. Many but not all of them occurred in cerivastatin users who also took gemfibrozil. After several label changes, studies, and letters to health care professionals, the drug was withdrawn from the market by the manufacturer in August 2001 (Table 1).

This review describes the circumstances that led to the withdrawal of cerivastatin from the market. Included in this report are both findings from published studies—as determined from previous reviews and MEDLINE searches, which included all years through 2003—about the risk of rhabdomyolysis and scientific information from unpublished internal company documents now in the public record. (Trial exhibits used in litigation were requested and received from the Nueces County Clerk in *Hollis N. Haltom v Bayer Corporation, et al*, Trial Court Cause No. 02-60165-2, Nueces County, Texas.) The purpose is not only to review the operation of the postmarketing surveillance system, which for a

period failed to adequately safeguard the health of the public but also to call attention to sources of this failure in the difficult conflict of interest that the current system imposes on the pharmaceutical companies in their efforts to identify and act on adverse effects of the products that they sell.

NATURAL HISTORY OF THE EVALUATION OF PRESCRIPTION DRUGS

The US Food and Drug Administration (FDA) review of applications to market new drugs is designed to maximize the likelihood that approved drugs are safe and effective for their intended use.²¹ The complex approval process usually includes many small, short-term, randomized controlled clinical trials. For statins the efficacy outcome was lipid lowering, and some of the safety outcomes included serum levels of muscle and liver enzymes. By the time each statin was approved, several thousand patient-years of exposure had been accumulated.

“In evaluating drugs for approval,” Friedman and colleagues from the FDA note, “the FDA uses a pragmatic standard: do the demonstrated benefits outweigh the known risks?”²² At the time of regulatory approval for most drugs, a number of issues remain unknown: the occurrence of rare but serious adverse drug events, drug interactions, late events during treatment or after the discontinuation of treatment, effects in pregnancy, or differential effects in subgroups that may be defined by age, sex, or race. In the case of statins, it was not

known at the time of their approval whether the favorable lipid effects would result in improved clinical outcomes. The natural history of prescription drugs, after approval, includes the accumulation of new information on risks and benefits. Regulatory approval for clinical use “does not and cannot guarantee safety.”²² Between 1975 and 1999, 548 new chemical entities were approved by the FDA.²³ Of these 548, 56 (10.2%) subsequently received 1 or more prominent black-box safety warnings (n=45) or were withdrawn from the market (n=16).

In contrast to the highly structured premarketing evaluation, postmarketing surveillance has little structure. According to Gale,²² “the regulatory process creates an evidence-free zone at the time of launch of new drugs.” Pharmaceutical companies often promise postmarketing clinical trials as a condition of approval although, in practice, more than half of these promised studies have not been started.²⁴ The FDA postmarketing regulations require only that pharmaceutical companies collect, review, and report to the FDA all suspected adverse drug reactions (SADRs) thought to be associated with the drug.^{25,26} Timelines for reporting vary according to the seriousness and unexpectedness of the SADR.²⁶ Although both companies and the FDA can analyze the SADR data and recommend actions, such as label changes, additional warnings, or new studies, the FDA regulations largely focus on reporting procedures and thus leave unclear who is required to initiate these actions.

MEDWATCH, the FDA safety information and voluntary adverse event reporting program, encourages physicians to report SADRs “when there is a suspicion that the drug or device may be related to a serious adverse effect.”²⁷ In 2001, for instance, the FDA received 286 755 reports of adverse drug events.²⁸ The SADRs are best suited to identify rare serious adverse drug events that occur early in treatment and that are unrelated to the indication of the drug. Temple²⁹ cites the example of rhabdomyolysis associated with the combination of simvastatin and mibe-fradil dihydrochloride. Although often incomplete and inferior in quality to data from clinical trials or well-controlled epidemiologic studies with adequate power, SADR data are one source, sometimes the only source, of timely information about the adverse events associated with recently marketed drugs.

To market statins for the indication of cardiovascular disease prevention rather than simply for lipid lowering, the pharmaceutical industry was required by the FDA to conduct post-marketing studies with clinical end points.²² These large, long-term trials, often industry funded, eventually provided valuable information about the health benefits of lovastatin, pravastatin sodium, simvastatin, and more recently atorvastatin.³⁰⁻³⁷ In the Heart Protection Study,³⁵ for instance, simvastatin was associated with a 13% reduction in total mortality (95% confidence interval [CI], 6%-19%) and a 27% reduction in all coronary events (95% CI, 21%-33%). On the basis of these trials, the FDA approved lovastatin, pravastatin, simvastatin, and atorvastatin for the primary or secondary prevention of coronary heart disease (Table 2). These long-term trials were the only way to determine whether the favorable changes in the surrogate end points, such as cholesterol lowering, improve clinical outcomes without an excess incidence of adverse events such as rhabdomyolysis.³⁸ In postmarketing trials that included 15 000 patients taking pravastatin for several years, none had

rhabdomyolysis.³² This “reliable safety profile”³² for pravastatin was not available until approximately 10 years after it had first been approved for lipid lowering by the FDA.

In the late 1980s and early 1990s, the pressure from companies and patients alike was not for additional safety evaluations but for shorter approval times.³⁹ In response to the criticism that the FDA approval times were too long, the US Congress introduced user fees in 1992. Pharmaceutical companies that sought drug approvals paid fees that enabled the FDA to hire additional staff, and the FDA was expected to meet new requirements for the timeliness of new drug approvals.⁴⁰ During the approved lifetime of cerivastatin (Table 1), however, the 1992 User Fee Act and its reauthorization in 1997 prohibited the agency from spending users fees “on post-marketing surveillance or other drug-safety programs.”⁴¹ The FDA received no additional funds from the US Congress for postmarketing safety despite the fact that many new drugs were first marketed in the United States. In 2001, for instance, the FDA’s Center for Drug Evaluation and Research approved 66 new drugs, 24 of which were new molecular entities never before marketed in the United States.²¹ This approach—more and faster new approvals without additional funds for safety surveillance—relied increasingly on the pharmaceutical industry to conduct its own postmarketing safety evaluations.

PUBLISHED DATA ON THE INCIDENCE OF RHABDOMYOLYSIS IN STATIN USERS

The purpose of this section is to provide a brief summary of the existing literature without attention to the historical sequence of the published reports.

Large, Long-term Statin Trials

The large, long-term trials of simvastatin, pravastatin, lovastatin, and atorvastatin provide an estimate of the risk of rhabdomyolysis.³⁰⁻³⁷ Among the

33 683 patients randomly assigned to receive 1 of these statins and followed up for a total of 151 000 person-years, 8 experienced rhabdomyolysis (incidence, 5.3 per 100 000 person-years); among the 33 623 patients randomly assigned to receive placebo and followed up for 150 000 person-years, 5 had rhabdomyolysis (incidence, 3.3 per 100 000 person-years). In placebo-controlled trials, these 4 statins were not associated with an appreciably increased risk of rhabdomyolysis (relative risk, 1.59; 95% CI, 0.52-4.86).

Cerivastatin and Rhabdomyolysis

For cerivastatin, on the other hand, the risk of rhabdomyolysis appeared to be relatively high. Between January 1990 and March 2002, 1899 (57%) of the 3339 SADR cases of statin-associated rhabdomyolysis¹⁸ occurred in patients taking cerivastatin. For approximately the same period in the United States,¹⁵ only 9.8 million (2.0%) of the 484 million statin prescriptions were written for cerivastatin (TABLE 3). With 57% of rhabdomyolysis SADRs in approximately 2% of the users, the estimated relative reporting rate (RRR) is almost 65 times higher for cerivastatin than for the all other statins combined.

These descriptive findings were supported by more formal epidemiologic approaches to the SADR data.⁴² In an analysis performed by FDA scientists, who used sales data to estimate the numbers of users of each statin,¹⁵ the reported mortality rates from rhabdomyolysis for cerivastatin users were 16 to 86 times higher than those of the other statins (Table 3). After exclusion of statin users who had also used gemfibrozil, the reported mortality rates were still 10 to 50 times higher for cerivastatin users. These data also suggested a direct relationship between cerivastatin dose and the risk of fatal rhabdomyolysis. Although a number of potential biases make RRRs up to 2 or 3 difficult to interpret,²⁹ the mortality RRRs for cerivastatin were so high that few alternative explanations are credible, and an inference of cause and effect seems warranted.

Population-based cohort data also support the findings that cerivastatin substantially increases the risk of rhabdomyolysis. In one report,¹⁶ 16 6 cases of confirmed rhabdomyolysis occurred in approximately 3000 patients taking 0.4 mg of cerivastatin (monotherapy) for an average of 9 months—an incidence rate of approximately 270 cases per 100 000 person-years. This incidence rate is approximately 50 (95% CI, 17-145) times higher than that of the other statins evaluated in long-term clinical trials.

Concomitant Cerivastatin and Gemfibrozil

The first published case report of cerivastatin-associated rhabdomyolysis describes a woman who had been taking gemfibrozil for 6 months without any apparent adverse effects before she started cerivastatin therapy.⁵ In an analysis of FDA data,¹⁴ statin-associated rhabdomyolysis events were stratified according to the presence or absence of comedication with a fibrate (TABLE 4). Among users of statin monotherapy, cerivastatin was associated with 35.7% of rhabdomyolysis SADR; but among users of the

combination of statins and fibrates, cerivastatin was associated with 80.6% of reported cases (Table 4).

Backman and colleagues¹⁷ evaluated the potential for a pharmacokinetic interaction between cerivastatin and gemfibrozil. In a randomized, double-blind, crossover study, 10 patients took 600 mg of gemfibrozil or placebo twice daily for 3 days and on the third day took a single dose of 0.3 mg of cerivastatin. The area under the plasma time cerivastatin concentration curve was increased in gemfibrozil recipients by an average of 559% (range, 138%-995%). On average, the effect of this interaction would be to increase a 0.3-mg dose of cerivastatin to an effective dose of 1.7 mg, which is more than twice the 0.8-mg daily dose that was eventually the highest dose approved by the FDA.

Summary

The available data indicate that compared with other statins cerivastatin conferred an increased risk of rhabdomyolysis. The elevated risk was most pronounced in concurrent users of cerivastatin and gemfibrozil although it was

also present for users of cerivastatin monotherapy.

UNPUBLISHED Rhabdomyolysis Data Available to the Manufacturer and Made Public in Trial Exhibits Used in Litigation
Concomitant Cerivastatin and Gemfibrozil

Within approximately 100 days of launch, the company had received 7 case reports of patients who had used cerivastatin and who had developed rhabdomyolysis or marked elevation of creatine kinase (CK) levels³ (TABLE 5). Six of the 7 patients were apparently from the United States, and 5 of the 6 US patients had also used gemfibrozil. Other information, such as CK levels, treatment duration, symptoms, and complications, was adequate to evaluate the validity of the diagnosis (Table 5). For lovastatin, a full year of marketing had occurred before 7 cases of rhabdomyolysis were reported with the combination of gemfibrozil.⁴³

The high proportion of rhabdomyolysis cases in patients who had taken both

Table 3. Reported Cases of Fatal Rhabdomyolysis by Statin, Numbers of Prescriptions, Reporting Rate per Million Prescriptions, and Relative Reporting Rate for Cerivastatin vs Each of the Other Statins*

	Atorvastatin Calcium	Fluvastatin Sodium	Lovastatin	Pravastatin Sodium	Simvastatin	Subtotal of All Statins†	Cerivastatin Sodium
Date approved	12/17/96	12/31/93	8/31/87	10/31/91	12/23/91		6/26/97
Prescriptions, No	140 360 000	37 392 000	99 197 000	81 364 000	116 145 000	474 458 000	9 815 000
No. of cases	6	0	19	3	14	42	31
Rate per million prescriptions	0.04	0	0.19	0.04	0.12	0.09	3.16
RRR (95% CI)	74 (30-217)	. . . (≥30)	16 (9-31)	86 (27-438)	26 (14-53)	36 (22-58)	

Abbreviations: CI, confidence interval; RRR, relative reporting rate for cerivastatin compared with each of the other statins or all other statins combined. Ellipses indicate that 0 events for fluvastatin means that 1 dividing by 0 results in an undefined number; thus, 30 represents the lower 95% CI.
*Includes US cases reported to the Food and Drug Administration before June 26, 2001. Data are from Staffa et al.¹⁵
†Subtotal data do not include cerivastatin.

Table 4. Cases of Statin-Associated Rhabdomyolysis by Drug Reported to the Food and Drug Administration Adverse Event Reporting System (October 1997 to December 2000)*

	No. (%) of Cases†						Total
	Atorvastatin Calcium	Fluvastatin Sodium	Lovastatin	Pravastatin Sodium	Simvastatin	Cerivastatin Sodium	
Fibrate coprescription							
With	13 (5.2)	2 (0.8)	2 (0.8)	8 (3.2)	23 (9.3)	200 (80.6)	248 (100)
Without	73 (13.9)	8 (1.5)	30 (5.7)	62 (11.8)	164 (31.3)	187 (35.7)	524 (100)
Total	86 (11.1)	10 (1.3)	32 (4.1)	70 (9.1)	187 (24.2)	387 (50.1)	772 (100)

*Data are from Fisher et al.¹⁴
†Percentages may not sum to 100 due to rounding.

cerivastatin and gemfibrozil strongly suggested a drug-drug interaction. If 1.5% of all cerivastatin users took gemfibrozil,⁴⁴ the probability that 5 of the 6 US cases, by chance alone, also involved gemfibrozil would be approximately 1 in 220 million. Alternatively, if the incidence of rhabdomyolysis were 5.3 per 100 000 person-years, if 1.5% of cerivastatin users also took gemfibrozil, and if all cerivastatin users had accumulated 3 full months of use before May 28, 1998, approximately 25 million US cerivastatin users would have been required to generate 5 cases of rhabdomyolysis in persons who took both cerivastatin and gemfibrozil. The new prescriptions for cerivastatin in the first 4 weeks after launch in the United States numbered approximately 3100.⁴⁵

Although the product label was revised to include mentions of rhabdomyolysis and gemfibrozil (Table 1), the publicly available documentary record shows no evidence that these SADR were regarded as a signal that merited further investigation. In 2000, the "potential for a clinically relevant interaction between fibrates and cerivastatin" was noted in a published review by a company scientist,⁴⁶ but the

article described no plans for pharmacokinetic studies. In a review of 36 trials that examined the efficacy and safety of combination statin-fibrate therapy, all published between 1988 and 2000, none evaluated cerivastatin.⁴⁷

After May 1998, the proportion of patients with rhabdomyolysis who had taken concomitant cerivastatin and gemfibrozil remained high. According to the Safety Assurance Monthly Highlights of March 1999, the "overwhelming majority of reports involved concomitant use of gemfibrozil."⁴ An e-mail from October 19, 1999, indicated that the "frequency of concomitant gemfibrozil use in these cases is about 60%."⁹ In December 1999,⁴⁸ more than 18 months after the initial 6 US case reports, the company's Dear Health Care Professional letter first announced a change to the cerivastatin label, contraindicating the coprescription of gemfibrozil (Table 1).

The meeting minutes of the company's Action Committee [on] Adverse Events (APZ) held on December 14, 1999, recommended, "Pharmacokinetic and pharmacodynamic interactions should be studied in pharmacological experiments comparing various

statins and Gemfibrozil."¹⁰ Approximately 17 months later and almost 3 years after the first 6 US case reports (Table 1), the APZ minutes of April 4, 2001, noted that the findings of the pharmacokinetic study, which were never published, "demonstrated a 2- to 7-fold increase in the AUC [area under the curve] and a prolonged excretion time in a similar range,"¹² results similar to the 3-day pharmacokinetic study by Backman et al.¹⁷

The label change of December 1999 and other company efforts to inform patients and physicians appear not to have had much effect on coprescription with gemfibrozil. During March 1999 to August 1999, the proportion of all confirmed cases of rhabdomyolysis using both cerivastatin and gemfibrozil was 63% (20 of 32); the proportion increased slightly to 70% (91 of 130) during September 1999 to February 2000, the period during which the contraindication was announced; and then the proportion decreased only to 62% (34 of 55) during March 2000 to July 2000.⁴⁹ Other evidence, from a study of cisapride for instance, indicates that label changes are ineffective as a method of changing suboptimal prescribing practices.⁵⁰

Table 5. US Postmarketing Reports to Date (May 28, 1998): Rhabdomyolysis and Similar Reports*

Age, y	Sex	State	Complainant Terms	CPK†	Fibrate Comedication	Duration of Therapy	Notes
74	Woman	Mississippi	Rhabdomyolysis, renal failure	15 590	Gemfibrozil	15 d	Diabetic Hospitalized recovered
65	Woman	Florida	Rhabdomyolysis, muscle cramps, soreness, increased LFT results	71 500	Gemfibrozil	18 d	Diagnosis of hepatitis Hospitalized; improved
Adult	Man	California	Rhabdomyolysis, renal failure, increased LFT results	Not reported	Gemfibrozil	Not reported	Incomplete follow-up
Adult	Woman	Alabama	Rhabdomyolysis, renal failure, generalized myalgia, leg pain	>20 000	Gemfibrozil	3 to 4 wk	Debilitating improved
64	Woman	Pennsylvania	Hepatitis, increased CKP, muscle and back pain or weakness, body aches, headache	27 640	No	28 d	Debilitating Improved
70	Woman	South Dakota	Myopathy, rhabdomyolysis complaints: multiple myalgia, muscular soreness	3180	Gemfibrozil	20 d	Forced diuresis No indication for virus infection Reversible
67	Woman	Non-US	CKP increase	17 220	Gemfibrozil	98 d	

Abbreviations: CKP=creatinine kinase phosphatase; LFT=liver function test.

*Adapted from data are from Plaintiff Exhibit 211.³

†The original document did not provide units of measure.

Table 6. Confirmed Cases of Rhabdomyolysis (United States Only): Concomitant Fibrates and Statins*

Other Treatment	Statin		Relative Reporting Rate
	Atorvastatin Calcium	Cerivastatin Sodium	
Gemfibrozil			
Case No.	1	66	
Rate per 100 000 prescriptions	0.003	2.886	855
Other statin			
Case No.	1	3	
Rate per 100 000 prescriptions	0.003	0.131	39
Other statin or gemfibrozil			
Case No.	16	25	
Rate per 100 000 prescriptions	0.054	1.093	20
Total			
Case No.	18	94	
Rate per 100 000 prescriptions	0.061	4.11	68

*Data are adapted from Plaintiff Exhibit 101, which did not include 95% confidence intervals.⁵¹ Rates are given per 100 000 prescriptions and based on adverse event reporting system data for October 1, 1999, to May 15, 2000.

Cerivastatin Monotherapy

The incidence of rhabdomyolysis was also increased in patients receiving cerivastatin monotherapy. The medical review of the 0.8-mg cerivastatin supplement, submitted to the FDA in September 1999, had identified women who were 62 years or older and who weighed 65 kg or less as a subgroup of cerivastatin, 0.8 mg, users who had an increased incidence of CK levels greater than 10 times the upper limit of normal (ULN).⁸ Based on unpublished clinical trial results available in July 1999 (Table 1), company scientists did not believe that it was “acceptable to study 1.6 mg cerivastatin in a broad population” for 3 reasons: (1) “high incidence (about 12%) of severe CK elevation ($>10 \times$ ULN), partly connected with clinical symptoms”; (2) “high incidence of minor CK elevations (about 50% of cerivastatin treated patients had $CK >3 \times$ ULN)”; and (3) “an exponential increase of side effects from 0.8 to 1.6 mg . . . [which] is supported by animal studies.”⁶ The combination of CK elevations greater than 10 times the ULN with symptoms is one commonly used definition of rhabdomyolysis.¹⁸ Shortly afterward, the minutes of the Cerivastatin Communication Committee Meeting held on August 2, 1999, reported, “The large percentage of patients experiencing CK elevations led to a consensus by

the [company’s] committee not to publish the results of this study.”⁷

In the APZ meeting of December 1999, it was noted that “[t]he incidence of Rhabdomyolysis in . . . [cerivastatin] monotherapy treatment was 2 to 6 cases per 100,000 patient years while the other statins, based on data from the Freedom of Information Act, were in the range of 0.2 to 0.6 cases per 100,000 patient years.”¹⁰ Subsequent internal company analyses⁵¹ (TABLE 6), performed when the largest approved dose was 0.4 mg and including events through May 2000, relied on epidemiologic methods similar to those used by the FDA.¹⁵ The strengths include the use of “confirmed” cases of rhabdomyolysis, the use of atorvastatin as a comparison drug, the use of the same data sources for events and exposure to cerivastatin and atorvastatin, and the restriction of the analysis to the experience in the United States. Compared with atorvastatin plus gemfibrozil (Table 6), the RRR for rhabdomyolysis was 855 for concomitant cerivastatin-gemfibrozil therapy. For patients receiving monotherapy, the RRR was 20 times higher (95% CI, 11-38) for cerivastatin than for atorvastatin. Although company scientists were cautious in interpreting the findings from the SADR analyses, they nonetheless observed: “The findings indicate that in patients receiving monotherapy, cerivastatin substantially elevates risk for rhabdomyo-

sis compared with other statins. In combination with gemfibrozil, cerivastatin patients were also found to be at a remarkable disadvantage compared with patients receiving gemfibrozil and another statin.”¹¹

In response to these data, the company performed an observational study that used existing administrative records to assess the association between myopathy and statin prescriptions.¹³ However, the design of the study constrained its ability to identify a true difference in the incidence of rhabdomyolysis among users of various statins. The use of myopathy rather than rhabdomyolysis as the outcome, the failure to identify fatal cases or validate cases of rhabdomyolysis, the misclassification of statin use, the absence of information about confounders, and the low power of the study meant that this analysis could provide little useful information.¹¹ The study or studies undertaken by the company remain unpublished.

COMMENT

What Are the Limitations and Strengths of This Report?

Trial exhibits used in litigation may provide an incomplete picture of internal company activities. Details about FDA deliberations and activities were not available, and the information from this case study may not be generalizable to other drug withdrawals. Despite limited data, the asymmetry between the information available to the company and the information available to patients and physicians seems striking (Table 1). The publicly available documents appear to reflect a lack of significant and timely efforts to investigate questions, publish findings, and eliminate information asymmetry in the interests of public health and patient safety.

Did the SADR Data Provide Information Sufficient to Take Public Health Action to Reduce the Risk of Rhabdomyolysis?

The reporting rate of rhabdomyolysis for cerivastatin users was strikingly higher than the rate for users of other

statins (Table 6). In the setting of such elevated RRRs, the usual limitations of SADR data were largely overcome, in part because estimates of the number of statin users were available and in part because the experience of cerivastatin was compared with that of atorvastatin, which had been approved by the FDA at about the same time as cerivastatin (Table 3). In contrast to the other statins (Table 2), there was no evidence that treatment with cerivastatin prevented coronary heart disease events. Evaluated against a benefit measured only in terms of the surrogate end point of lipid lowering, even the suspicion of serious SADRs such as rhabdomyolysis would plausibly have been sufficient to take action. With 5 other statins on the market, an earlier suspension of cerivastatin sales would not have deprived physicians and patients of effective, sometimes life-saving lipid-lowering therapies.

Did the Company Have an Obligation to Inform Physicians and Patients of the Risk of Rhabdomyolysis?

The importance of pharmaceutical product safety to the health of the public confers on companies the ethical and moral obligations that are normally associated with medicine and that are higher than the minimum standards of routine economic transactions.⁵² The Tavistock principles, which acknowledge the interdependence in medicine, have been proposed for “everybody in health care.”⁵³ The ethical obligations and responsibilities of the medical profession⁵⁴⁻⁵⁶ devolve to pharmaceutical corporations, which have a duty to disclose risks and inform patients and physicians of safety problems.

In This Instance, Did the Company Take Action in a Timely Manner?

By May 28, 1998, the rhabdomyolysis SADR data suggested the possibility of a strong interaction between cerivastatin and gemfibrozil. Within a matter of weeks, this interaction hypothesis could have been tested in a 3-day pharmacokinetic study. Although minor revi-

sions were incorporated into the label as early as July 1998 (Table 1), the contraindication about the concomitant use of cerivastatin and gemfibrozil was not included in the package insert until December 1999. The company’s cerivastatin-gemfibrozil interaction study was not reported internally until around April 2001. Although company scientists thoroughly analyzed the SADR data on the risks associated with cerivastatin monotherapy (Table 6), this analysis was never published or, according to the available documents, reported to regulatory authorities, physicians, or patients. Apparently, opportunities were missed at several stages to undertake prompt and thoughtful medical and scientific responses to the SADR findings. Like the findings of the company SADR analyses, the results of the 1.6-mg cerivastatin trial^{6,7} were neither disseminated nor published.

The rapid publication of study results is an important method of informing physicians about new findings related to medications. There is a growing consensus that “under-reporting of clinical trials is unethical.”^{57,58} One pharmaceutical company has committed itself to full disclosure of clinical trial results.⁵⁹ Selective publication of favorable articles, called the “pharmaceutical industry bias” by Horton,⁶⁰ misrepresents the evidence for physicians and patients who need complete and accurate information to make informed decisions about therapies.

Why Did the FDA Not Act Sooner?

In 1992 and 1997, the congressional authorizations that introduced and continued the user-fee program also prohibited the FDA from spending these revenues on safety monitoring.⁴¹ At the same time, the FDA was under increased pressure to approve drugs rapidly. According to the report of the Office of the Inspector General,⁴⁰ FDA reviewers of new drug applications were “under constant pressure to meet time goals. . . . Forty percent of FDA survey respondents who had been at the FDA at least 5 years indicated that the review process had worsened during

their tenure in terms of allowing for in-depth science-based reviews.”⁴⁰ In this setting, it is possible that the agency chose to focus only on fatal events.¹⁵

What Is the Conflict of Interest That the Company Experienced?

The development of new drugs is an enormous undertaking that involves thousands of people and hundreds of millions of dollars. Thus, the pharmaceutical industry might have a high threshold for taking action on the basis of SADR data, which are subject to a number of well-known potential biases. Under the current system, pharmaceutical companies are nonetheless responsible for the complete reporting of their SADR data and for making recommendations to the FDA about new studies or label changes. This system works well when there are no serious problems identified after marketing. However, when serious, even rare, SADRs such as rhabdomyolysis are detected, pharmaceutical companies have a complex and almost insurmountable conflict of interest in weighing and interpreting the risks and benefits of various courses of action. A subjective element is present in the effort to infer whether or not the occurrence of untoward outcomes in users of a particular drug was actually the consequence of the use of that drug. For pharmaceutical companies, this appraisal may be influenced by both economic considerations and the emotional investment of those involved in the development process.

Will the Recent Proposed Changes to the SADR Reporting Regulations Solve This Problem?

The proposed revisions to the FDA regulations, published in the *Federal Register* on March 14, 2003,²⁶ attempt to improve the reporting about drug safety and, at the same time, make it easier for pharmaceutical companies to assume their responsibilities for drug safety. For instance, company physicians will be required to review the safety information in the SADR reports.²⁶ In the traditional periodic safety

reports (TPSRs), the FDA will also require an explicit discussion of safety issues: pharmaceutical companies will be required “to include in TPSRs the applicant’s conclusion as to what, if any, safety-related actions should be taken based on the analysis of the safety data in the TPSR (eg, labeling changes, studies initiated). The FDA is proposing this amendment to highlight safety-related actions that may be necessary.”²⁶ Although these regulations help to clarify the regulatory responsibilities of the pharmaceutical companies, revisions to regulations alone cannot guarantee a robust scientific engagement with SADR data or eliminate an inherent conflict of interest.

CONCLUSION

This history of cerivastatin illustrates a flaw in the current US system for SADR reporting and monitoring. When serious adverse effects such as rhabdomyolysis appear after marketing, defects in the safety-surveillance system can, depending in part on the response of the pharmaceutical company, pose a threat to the health of the public.

When SADR data raise strong doubts about the balance between the risks and benefits of a medication, it is possible to act quickly to protect the public health. An example is provided by the rotavirus vaccine. Spontaneous reports of 15 cases of intussusception between September 1, 1998, and July 7, 1999, led to an analysis of data from other populations with more complete reporting, to a recommendation from the Centers for Disease Control and Prevention to postpone the use of the vaccine, and to a decision by the manufacturer after consultation with the FDA to voluntarily cease marketing.^{61,62} Subsequently, the Centers for Disease Control and Prevention conducted a large case-control study that confirmed the association seen in the spontaneous reports.⁶³

To balance the interests of patients and industry, decisions about label changes, new studies, suspension of sales, or withdrawal of drugs might best be made by an outside group of disinterested reviewers. Like Moore and colleagues,⁶⁴ Wood

et al⁴¹ have recommended the creation of an independent drug safety board “to monitor drug safety, investigate reports of drug toxicity, and recommend actions to minimize the risks of drug therapy.” There is precedent. In the setting of large clinical trials, data safety and monitoring boards, not the investigators, apply the criteria for decisions about stopping trials. Investigational review boards perform a similar function in the setting of other human studies. Indeed, the US Congress should mandate and provide adequate support for the FDA or independent advisory groups to conduct their own reviews and make recommendations. Because the SADR data can provide only passive information about rare and serious adverse effects that are unrelated to the indication of the drug, the US Congress also needs to provide the FDA with additional funds to develop and support active systems of surveillance for drug safety.

In the United States, once a drug is approved for marketing, there is no regularly scheduled re-review of the drug. In Europe, drug approvals are re-reviewed every 5 years. This process encourages companies to attend to outstanding issues, such as launching promised phase 4 trials, before the scheduled re-review, and occasionally, companies have withdrawn drugs from the market rather than participate in a re-review. Europe also assesses a post-marketing fee that contributes to post-marketing safety surveillance efforts. Now that most new molecular entities first reach the market in the United States, even these simple European approaches, including the postmarketing fees and the regular re-review for approved drugs, might enhance patient safety in the United States as well.

Author Contributions: Dr Psaty had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Psaty, Furberg, Ray, Weiss.

Acquisition of data: Psaty, Ray.

Analysis and interpretation of data: Psaty, Furberg, Ray.

Drafting of the manuscript: Psaty, Ray, Weiss.

Critical revision of the manuscript for important intellectual content: Psaty, Furberg, Ray.

Statistical analysis: Psaty.

Study supervision: Weiss.

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This article is based solely on published literature and public record documents; none of the confidential information reviewed in the authors’ capacity as experts during the litigation has been used in this article. Like this article, the *litigation* expert reports also included information from the published literature about drug safety and HMG Co-A reductase inhibitors. Much of the review for the plaintiffs’ attorneys was conducted with confidential company documents under court protective orders. The present article was developed after some, but not all, of these documents became publicly available during the trial of the Haltom case in Nueces County, Texas. Information that is not publicly available has been excluded from this article.

The initial review of these now public documents was supported in the authors’ capacity as plaintiff experts. The costs of obtaining trial exhibits from the Nueces County Clerk were paid by the authors, and the time and effort expended on this project by the authors have been in their capacity as professors at their universities. Although as described above plaintiffs’ attorneys commented on the expert reports, this manuscript reflects the views of the authors, and multiple drafts were written and revised without the participation of the attorneys representing plaintiffs in the cases related to cerivastatin. The authors were not compensated by plaintiffs’ attorneys for the time spent in preparation of this article.

As of September 2004, Bayer AG had agreed to settle 2861 cerivastatin lawsuits out of court.

There continues to be litigation related to cerivastatin and rhabdomyolysis or myopathy. The majority of cases that the authors were involved with have been settled by the manufacturer. Specifically, Dr Psaty is not involved in any ongoing cases. On January 14, 2003, Dr Weiss received a letter that confirmed his agreement to serve as an expert for plaintiffs in the Baycol Products Liability Litigation, MDL No. 1431, in the US District Court in Minnesota, and that retention is still active. Several of the cases for which Dr Furberg has served as an expert remain to be settled, and some may go to trial. Dr Ray is still involved in one case. In 2001, Dr Psaty served as a consulting expert in epidemiology on behalf of Bayer Corporation to review reports on another medication that had become the subject of lawsuits.

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