

Cornell University Law School Scholarship@Cornell Law: A Digital Repository

Cornell Law Faculty Publications

Faculty Scholarship

9-2008

Statins and Adverse Cardiovascular Events in Moderate-Risk Females: A Statistical and Legal Analysis with Implications for FDA Preemption Claims


Theodore Eisenberg

Cornell Law School, ted-eisenberg@lawschool.cornell.edu

Martin T. Wells

Cornell University, mtw1@cornell.edu

Follow this and additional works at: <http://scholarship.law.cornell.edu/facpub>

 Part of the [Consumer Protection Law Commons](#), [Food and Drug Law Commons](#), [Health Law Commons](#), and the [Law and Society Commons](#)

Recommended Citation

Eisenberg, Theodore and Wells, Martin T., "Statins and Adverse Cardiovascular Events in Moderate-Risk Females: A Statistical and Legal Analysis with Implications for FDA Preemption Claims" (2008). *Cornell Law Faculty Publications*. Paper 390.
<http://scholarship.law.cornell.edu/facpub/390>

This Article is brought to you for free and open access by the Faculty Scholarship at Scholarship@Cornell Law: A Digital Repository. It has been accepted for inclusion in Cornell Law Faculty Publications by an authorized administrator of Scholarship@Cornell Law: A Digital Repository. For more information, please contact jmp8@cornell.edu.

Statins and Adverse Cardiovascular Events in Moderate-Risk Females: A Statistical and Legal Analysis with Implications for FDA Preemption Claims

Theodore Eisenberg and Martin T. Wells*

This article presents: (1) meta-analyses of studies of cardioprotection of women and men by statins, including Lipitor (atorvastatin), and (2) a legal analysis of advertising promoting Lipitor as preventing heart attacks. The meta-analyses of primary prevention clinical trials show statistically significant benefits for men but not for women, and a statistically significant difference between men and women. The analyses do not support (1) statin use to reduce heart attacks in women based on extrapolation from men, or (2) approving or advertising statins as reducing heart attacks without qualification in a population that includes many women. The legal analysis raises the question of whether Lipitor's advertisements, which omit that Lipitor's clinical trial found slight *increased* risk for women, is consistent with the Food, Drug, and Cosmetics Act and related Food and Drug Administration (FDA) regulations. The analysis suggests that FDA regulation should not preempt state law actions challenging advertising that is not supported by FDA-approved labeling. Our findings suggesting inadequate regulation of the world's best-selling drug also counsel against courts accepting the FDA's claimed preemption of state law causes of action relating to warnings and safety. Courts evaluating preemption claims should

*Address correspondence to Theodore Eisenberg, Henry Allen Mark Professor of Law, Cornell Law School, Myron Taylor Hall, Ithaca, NY 14853; email: ted-eisenberg@lawschool.cornell.edu. Wells is Charles A. Alexander Professor of Statistical Sciences, Cornell University, Professor of Clinical Epidemiology and Health Services Research, Cornell University Weill Medical College, and Elected Member of the Law Faculty, Cornell University.

We thank Kevin Clermont, Dr. Orli Etingin, Dr. Curt Furberg, Valerie Hans, Janey Peterson, Dr. Michael Pignone, Norma Schwab, Stewart Schwab, and referees for comments. Michael Heise served as the editor for this article. We served as consultants for plaintiffs' counsel in litigation relating to Vioxx.

consider actual agency performance as well as theoretical institutional competence. Billions of health-care dollars may be being wasted on statin use by women but the current regulatory regime does not create incentives to prevent such behavior.

I. INTRODUCTION

Lisa W, an active and healthy woman in her 50s, was told she had high cholesterol. Her doctor recommended Lipitor (atorvastatin), a member of the class of statin drugs. Lisa, reluctant to take a prescription medicine when she felt fine, wanted to try to reduce her cholesterol through exercise and diet. She reduced her total cholesterol by 35 points but her doctor continued to recommend Lipitor because her total cholesterol still was above present guidelines. Lisa reports knowing many female acquaintances with similar stories.

Their experiences may be typical of millions of women. A 1996–1997 study found that women without coronary heart disease (CHD) constituted 23.1 percent of statin recipients, that 1.7 percent of women under age 70 without a history of CHD were prescribed statins, and that 9.1 percent of women age 70 or over without a history of CHD were prescribed statins.¹ Data through 2004 show 39.8 percent of statin users were at low risk for cardiovascular disease (CVD).² As of 2004 in British Columbia, 20.9 percent of those aged 65 to 85 years and 7.5 percent of those aged 45 to less than 65 years were using statins, with Lipitor by far the most widely used statin.³ In three Norwegian counties, over 20 percent of women aged 60 to 80 used statins, with Lipitor again the most widely used.⁴ By any reasonable measure,

¹Isabelle Savoie & Arminée Kazanjian, *Utilization of Lipid-Lowering Drugs in Men and Women: A Reflection of the Research Evidence?* 55 *J. Clin. Epidem.* 95, 97–98 (2002).

²Colette B. Raymond et al., *A Population-Based Analysis of Statin Utilization in British Columbia*, 29 *Clin. Therapeutics* 2107, 2115 (2007).

³*Id.* at 2109.

⁴Ingeborg Hartz et al., *Aspects of Statin Prescribing in Norwegian Counties with High, Average and Low Statin Consumption—An Individual-Level Prescription Database Study*, 7 *BMC Clin. Pharmacology* 14 (2007).

females without a history of CHD constitute a major segment of the statins market. Lipitor has been the top-selling drug in the world⁵ and has accounted for over \$12 billion in annual sales.⁶

This article reports meta-analyses that question Lipitor's advertising. Pfizer, Inc., the producer of Lipitor, claims that Lipitor is clinically established to reduce heart attacks without any indication of qualification by gender. Pfizer states:

LIPITOR is clinically proven to reduce the risk of heart attack, stroke, certain kinds of heart surgeries, and chest pain in patients with several common risk factors for heart disease.† [†Risk factors include family history, high blood pressure, age, low HDL ("good" cholesterol), or smoking.]⁷

The words are presumably chosen carefully and one might reasonably conclude that age plus low HDL, for example, would count as "multiple risk factors" for which clinical proof exists that Lipitor reduces heart attack risk. We are unable to find high-quality clinical proof in the medical literature documenting reduced heart attack risk for women. Furthermore, Pfizer's advertising omits label information relevant to women. In discussing the clinical trial of Lipitor, Pfizer's label states:

LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease . . . or nonfatal MI]. . . . Due to the small number of events, results for women were inconclusive.⁸

This express acknowledgment of "inconclusive" results for women contrasts with the cardioprotective claims, not qualified by gender, in Pfizer's advertising. Nor does the label or the advertising disclose that the key clinical trial

⁵Marcia Angell, *The Truth About Drug Companies* 85 (2004).

⁶Stephanie Saul, *Pfizer to End Lipitor Ads by Jarvik*, N.Y. Times, Feb. 26, 2008 (\$12.7 billion in 2007 sales of Lipitor); Peter Loftus, *Pfizer's Lipitor Patent Reissue Rejected*, Wall St. J. Online, Aug. 16, 2007 (\$12.9 billion in 2006 sales of Lipitor); Julie Schmit, *Lipitor Sales on Track to Hit Record Despite Arrival of Generic*, USA Today, July 20, 2006.

⁷See (<http://www.lipitor.com/about-lipitor/benefits.jsp?setShowOn=../about-lipitor/benefits.jsp&setShowHighlightOn=../about-lipitor/benefits.jsp>), accessed Mar. 22, 2008.

⁸Pfizer Label, LAB-0021-15.0, revised Mar. 2007, at 5.

of Lipitor found a modest *increased* risk of heart problems in women.⁹ The nondisclosures continued even after a discussion of relevant statin studies concluded that the existing literature provides no “significant evidence to back up the claim that statin therapy reduces the risk of CHD in women without heart disease”¹⁰ and despite well-documented calls for statin use to be refocused toward those for whom clinical evidence of benefit exists.¹¹

The possibility remains that cardioprotection claims for women might be based on extrapolation from results for men. Recent meta-analyses of statins’ effects for women have yielded conflicting results. Walsh and Pignone’s thorough study finds that cholesterol-lowering drugs did not reduce CHD death or nonfatal myocardial infarction (NFMI).¹² Thavendiranathan et al. appear to report greater cardioprotection for women than men.¹³ Neither study assessed outcomes separately for men and women, thereby leaving unanswered the question of whether cardioprotection claims for women might reasonably be extrapolated from results for men. Our meta-analyses assess random control trials (RCTs) that report statins’ effects for men and women. The outcome of interest is CHD death and NFMI. Consistently with Walsh and Pignone, for women without preexisting heart disease or diabetes, we find no evidence that RCTs support the claim that statins reduce CHD-NFMI. Instead, we find a statistically significant difference between outcomes for men and women. This undermines basing cardioprotection claims for women on extrapolation from men’s results.

⁹Peter S. Sever et al., 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 Randomised Control Trial, 361 *Lancet* 1149, 1155 (2003).

¹⁰John Abramson, *Overdo\$ed America: The Broken Promise of American Medicine* 139 (2005).

¹¹Savoie & Kazanjian, *supra* note 1.

¹²Judith M.E. Walsh & Michael Pignone, Drug Treatment of Hyperlipidemia in Women, 291 *JAMA* 2243 (2004). Similar conclusions are reached in a Russian study. D.V. Preobrazhenskii et al., Hypercholesterolemia in Men and Women of Various Age. Part II. The Problem of Efficacy and Safety of Statins, 47 *Kardiologia* 75 (2007).

¹³Paaladinesh Thavendiranathan et al., Primary Prevention of Cardiovascular Diseases with Statin Therapy: A Meta-Analysis of Randomized Controlled Trials, 166 *Arch. Intern. Med.* 2307, 2310 (2006) (“In our metaregression analysis, reductions in the risk of major coronary events from statin therapy were significantly associated with . . . a smaller proportion of men in the study population ($p = .003$). . . .”). Thavendiranathan et al. do not attempt to reconcile their results with the earlier Walsh and Pignone study.

If we are correct about omissions from Pfizer's advertising, then neither market forces nor Food and Drug Administration (FDA) regulation has effectively regulated the mass marketing of Lipitor. At a minimum, the FDA should use its authority under the Federal Food, Drug, and Cosmetic Act (FDCA) to address massive questionable marketing. In addition, if consumers have not been properly informed about the efficacy of Lipitor or other drugs, reasonable remedies should exist for costs incurred associated with nondisclosure. In our federal system, consumer remedies often are based on state law. State law remedies in areas of federal regulation recently have been an increasing object of federal preemption analysis. In cases relating to medical devices, cigarettes, and insecticides, the Supreme Court has found some common-law actions to be preempted by federal law.¹⁴ The FDA itself has sought to further expand preemption's scope via a preamble to its January 2006 prescription drug labeling rule¹⁵ and through amicus briefs filed in court.¹⁶

Thus, a question relating to remedies for misleading advertising is the relation between state law causes of action and FDA regulation. The Lipitor-statin experience provides an important case study in which to assess legal theories relating to federal preemption. We first suggest that preemption analysis of advertising claims differs from preemption analysis of warnings claims. Existing doctrine supplies no preemption protection from state law false advertising claims challenging advertising that does not disclose material information contained in an FDA-approved drug label. We also suggest that the Lipitor experience has implications for broader preemption issues. Courts evaluating preemption claims should consider actual agency performance as well as theoretical institutional competence.

The health-care policy implications of questionable Lipitor advertising are troubling. A substantial portion of the multibillion dollar statins market

¹⁴Riegel v. Medtronic, Inc., 128 S. Ct. 999 (2008) (preemption of actions relating to preapproved medical devices); Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996) (medical devices); Bates v. Dow Agrosciences LLC, 544 U.S. 431 (2005) (preemption of common-law actions by the Federal Insecticide, Fungicide, and Rodenticide Act); Cipollone v. Liggett Group, Inc., 505 U.S. 504 (1992) (common-law actions preempted by Public Health Cigarette Smoking Act of 1969). See generally Peter Barton Hutt, Richard A. Merrill & Lewis A. Grossman, Food and Drug Law 1488–1501 (3d ed. 2007).

¹⁵FDA, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922–4001 (Jan. 24, 2006), 2006 WL 160271.

¹⁶Hutt et al., *supra* note 14, at 1495 (noting FDA amicus participation).

may include users for whom no clinical study supports statins outperforming a placebo. Billions of health-care dollars may be saved by more prudent approvals, marketing, and policing of statins and other drugs.

Section II of this article describes the selection of studies for the meta-analyses. Section III reports the results, which are discussed in Section IV. Section V shifts to legal analysis and explores possible violations of federal and state law. Section VI addresses the question of federal preemption, including the implications of our scientific analysis for the preemption issue. Section VII concludes.

II. STUDY SELECTION FOR THE META-ANALYSES

This study builds on the work of Walsh and Pignone and Thavendiranathan et al. in assembling studies for a meta-analysis of drugs' effects on cardiovascular risk. Thavendiranathan et al. comprehensively searched the literature for studies of statins' effects on primary prevention of CVD. They conducted electronic literature searches of MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), Cochrane Collaboration (CENTRAL, DARE, and CDSR), and the American College of Physicians Journal Club databases using medical subject headings and keywords related to statins.¹⁷ They limited the studies assessed for statins' effectiveness to English-language studies of human subjects, with a mean followup of at least one year, at least 100 reported cardiovascular disease outcomes, no intervention difference between the treatment and control groups other than the use of a statin, at least 80 percent of participants not known to have CVD, and at least one specified outcome, including CHD death and NFMI. They excluded studies that examined only changes in serum cholesterol concentration or angiographic outcomes, that compared high- to low-dose statins, that prescreened patients with ultrasound for the presence of atherosclerosis, that targeted patients with disease states that are not traditional cardiovascular risk factors, or that did not report the proportion of study participants receiving therapy as primary prevention.¹⁸

To help assure considering all relevant studies that report risks for men and women, we examined a 2007 U.K. *Health Technology Assessment* by Ward

¹⁷Thavendiranathan et al., *supra* note 13, at 2308.

¹⁸*Id.*

et al.¹⁹ They used a MEDLINE search to evaluate the literature relating to statins' prevention of coronary events.²⁰ They report a list of statin studies that allowed separate assessment of men and women²¹ and considered several studies beyond the inclusion criteria of Thavendiranathan et al. We also examined the studies referred to in the *Expert Panel Report of the National Cholesterol Education Program* (NCEP), which concluded that statin therapy "reduced risk for CHD in . . . women, in those with or without heart disease."²² We also examined the primary prevention studies assessed in Walsh and Pignone's review of drug treatment of hyperlipidemia in women.²³

We independently evaluated each study reported by Thavendiranathan et al., by Ward et al.,²⁴ by the NCEP, and by Walsh and Pignone. Thavendiranathan et al. included seven studies in their analysis. Two studies lacked sufficient information to separate results for men and women.²⁵ For the

¹⁹S. Ward et al., A Systematic Review and Economic Evaluation of Statins for the Prevention of Coronary Events, 11 Health Tech. Assessment, No. 14 (2007).

²⁰Id. at 161 (Appendix 1).

²¹Id. at 255 (Appendix 19).

²²Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report, 106 *Circulation* 3143, 3165 (2002). Studies related to CHD risk in women appear id. at 3167 (tbl. II.2-3).

²³Walsh & Pignone, supra note 12.

²⁴Ward et al., supra note 19.

²⁵Thavendiranathan et al. report using only the primary prevention data reported in the Heart Protection Study (HPS). See Thavendiranathan et al., supra note 13, at 2309 (tbl. 1, * footnote to table). This subgroup appears to correspond to those in the HPS who had diabetes but no CVD. See Heart Protection Study Collaborative Group, MRC/BHF Heart Protection Study of Cholesterol-Lowering with Simvastatin in 5963 People with Diabetes: A Randomised Placebo-Controlled Trial, 361 *Lancet* 2005, 2011 (2003) (fig. 4, showing results for patients with diabetes but no CVD). HPS does not report separate results for men and women for this subgroup, id., and Thavendiranathan et al.'s Table 1 report such data to be unavailable. Thavendiranathan et al., supra note 13, at 2309 (tbl. 1). The second study for which separate male-female data were not separately reported is Helen M. Colhoun et al., Primary Prevention of Cardiovascular Disease with Atorvastatin in Type 2 Diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre Randomized Placebo-Controlled Trial, 364 *Lancet* 685, 686 (2004) ("Men and women aged 40–75 years with type 2 diabetes mellitus (defined with 1985 WHO criteria)" and other risk factors were included in the study.).

reasons indicated in Section IV, these studies are also reasonably excluded on the ground that, unlike the other studies, they are limited to diabetic patients. Walsh and Pignone included one additional study (ACAPS) in which all patients had atherosclerosis and in which there were only 19 major cardiovascular events.²⁶ The additional studies considered by Ward et al. and NCEP have characteristics that make them unsuitable for purposes of this study, including patient groups with prior MI,²⁷ prior CHD,²⁸ prior CVD,²⁹ use of nonstatin therapy,³⁰ or different end points.³¹ Although our evaluation also considered all studies included in earlier meta-analyses of statins' effec-

²⁶Curt D. Furberg et al., *Effect of Lovastatin on Early Carotid Atherosclerosis and Cardiovascular Events (ACAPS)*, 90 *Circulation* 1679 (2004). For discussion of ACAPS, see Section III.

²⁷Frank M. Sacks et al., *The Effect of Pravastatin on Coronary Events After Myocardial Infarction in Patients with Average Cholesterol Levels*, 335 *New Eng. J. Med.* 1001 (1996).

²⁸The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, *Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels*, 339 *New Eng. J. Med.* 1349 (1998); B. Pitt et al., *Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): Reduction in Atherosclerosis Progression and Clinical Events*, 26 *J. Am. Coll. Cardiol.* 1133 (1995); W.R. Aengevaeren et al., *Functional Evaluation of Lipid-Lowering Therapy by Pravastatin in the Regression Growth Evaluation Statin Study (REGRESS)*, 96 *Circulation* 429 (1997); Scandinavian Simvastatin Survival Study Group, *Randomised Trial of Cholesterol Lowering in 4444 Patients with Coronary Heart Disease: The Scandinavian Simvastatin Survival Study (4S)*, 344 *Lancet* 1383 (1994).

²⁹Heart Protection Study Collaborative Group, *supra* note 25, at 2006 (women eligible who had history of diabetes mellitus, coronary disease, or occlusive disease of noncoronary arteries); Heart Protection Study Collaborative Group, *MRC/BHF Heart Protection Study of Cholesterol Lowering with Simvastatin in 20536 High-Risk Individuals: A Randomised Placebo-Controlled Trial*, 360 *Lancet* 7, 8 (2002) (same criteria).

³⁰Henry Buchwald et al., *Effect of Partial Ileal Bypass Surgery on Mortality and Morbidity from Coronary Heart Disease in Patients with Hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH)*, 323 *New Eng. J. Med.* 946 (1990).

³¹David Waters et al., *Effects of Cholesterol Lowering on the Progression of Coronary Artherosclerosis in Women: A Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) Study*, 92 *Circulation* 2404 (1995); R. Salonen et al., *The Kuopio Atherosclerosis Prevention Study (KAPS): Effect of Pravastatin Treatment on Lipids, Oxidation Resistance of Lipoproteins, and Atherosclerotic Progression*, 76 *Am. J. Cardiol.* 34 (1995) (men only); R. Salonen et al., *Kuopio Atherosclerosis Prevention Study (KAPS): A Population-Based Primary Preventive Trial of the Effect of LDL Lowering on Atherosclerotic Progression in Carotid and Femoral Arteries*, 92 *Circulation* 1758 (1995).

tiveness,³² we still had no more than five studies for the present analysis. Table 1 summarizes characteristics of those five studies.³³

III. RESULTS

Table 2 reports the relative risk of CHD and NFMI or similar end points for men and women and the source of the data. The table exhibits a consistent pattern. Each study shows a statistically significant effect at $p < 0.05$ for men. Yet no study shows such an effect for women, no study's results for women approach statistical significance, and in two of the four studies with ascertainable female data, the relative risk point estimate exceeds 1.0. A relative risk of less than 1 suggests cardioprotection by a drug; a ratio exceeding 1 suggests that a drug increases risk.

Prior to performing, or as part of, a meta-analysis, it is customary to assess evidence of excess heterogeneity in the underlying effects.³⁴ Heterogeneity arises due to differences across studies in populations, exposures, interventions, outcomes, design, or conduct of studies. Excess heterogeneity in a meta-analysis reduces the confidence of recommendations about the

³²Cholesterol Treatment Trialists' (CTT) Collaborators, Efficacy and Safety of Cholesterol-Lowering Treatment: Prospective Meta-Analysis of Data from 90056 Participants in 14 Randomised Trials of Statins, 366 *Lancet* 1267 (2005); Michael Pignone, Christopher Phillips & Cynthia Mulrow, Use of Lipid Lowering Drugs for Primary Prevention of Coronary Heart Disease: Meta-Analysis of Randomised Trials, 321 *Brit. Med. J.* 1 (2000); John C. LaRosa, Jiang He & Suma Vupputuri, Effect of Statins on Risk of Coronary Disease: A Meta-Analysis of Randomized Controlled Trials, 282 *JAMA* 2340 (1999).

³³Curt D. Furberg et al., Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), 288 *JAMA* 2998 (2002); John R. Downs et al., Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels: Results of AFCAPS/TexCAPS, 279 *JAMA* 1615 (1998); Sever et al., supra note 9 (ASCOT-LLA); James Shepherd et al., Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER): A Randomised Control Trial, 360 *Lancet* 1623 (2002); James Shepherd et al., Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia, 333 *New Eng. J. Med.* 1301 (1995) (WOSCOPS). See also Michael Clearfield et al., Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): Efficacy and Tolerability of Long-Term Treatment with Lovastatin in Women, 10 *J. Women's Health & Gender-Based Med.* 971 (2001) (reporting AFCAPS results for women).

³⁴Julian P.T. Higgins & Simon G.Thompson, Quantifying Heterogeneity in Meta-Analysis, 21 *Stats. in Med.* 1539 (2002).

Table 1: Characteristics of Included Trials

	WOSCOPS, 1995	AFCAPS/TexCAPS, 1998	PROSPER, 2002	ALLHAT-LLT, 2002	ASCOT-LLA, 2003
<i>Study Characteristics</i>					
Design	RCT, double-blind, placebo-controlled	RCT, double-blind, placebo-controlled	RCT, double-blind, placebo-controlled	RCT, nonblinded, control = usual care	RCT, double-blind, placebo-controlled
Target population	Men with hyper-cholesterolemia	Patients with average or below average cholesterol levels	Older patients with at least 1 cardiovascular risk factor	Substudy of patients with hypertension, moderate hyper-cholesterolemia, and at least 1 additional CHD risk factor	Substudy of patients with hypertension, average or lower cholesterol levels, and at least 3 other CV risk factors
Male/female patients	3,302/0	2,805/499	1,396/1,495	2,659/2,511	4,189/979
Male/female controls	3,393/0	2,803/498	1,408/1,505	2,645/2,540	4,174/963
Followup, y	4.9 (mean)	5.2 (mean)	3.2 (mean)	4.8 (mean)	3.3 (median)
Patients treated as primary prevention, %	83.8	100	100	85.8	81.5
<i>Patient Characteristics</i>					
Age, y	55.3	58.0	75.0*	66.4	63.1
Male, %	100	85	42.0*	51	81.1
Diabetes, %	1.0	3.8	12.2*	34.4	24.3
Active smoker, %	44.0	13.0	33.4*	23.3	33.2
SBP, mean, mmHg	135	138	156.6*	145	164.2
Drug, dose, mg/d	Pravastatin, 40	Lowastatin, 20-40	Pravastatin, 40	Pravastatin, 20-40	Atorvastatin, 10

*Data obtained from I. Ford et al., A Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), 3 *Curr. Control Trials Cardiovasc. Med.* 8 (2002), a separate article on baseline characteristics of patients included in the PROSPER trial.

NOTE: RCT = random control trial; WOSCOPS = West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS = AirForce/Texas Coronary Atherosclerosis Prevention Study; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; SBP = systolic blood pressure. Citations to studies are in note 33.

Table 2: Relative Risk of Adverse Coronary Events by Study and Sex

<i>Study (Sex)</i>	<i>End Point Assessed</i>	<i>End Point Relative Risk & 95% CI</i>	<i>Source</i>
ALLHAT (male)	nonfatal MI/fatal CHD (secondary end point)	0.84 (0.71–1.00)	ALLHAT, p. 3005, Fig. 4B
ALLHAT (female)	nonfatal MI/fatal CHD (secondary end point)	1.02 (0.81–1.28)	
AFCAPS (male)	nonfatal or fatal MI/unstable angina/SCD	0.64 (0.51–0.81)	Authors' calculation based on AFCAPS, p. 1621, Fig. 4
AFCAPS (female)	nonfatal or fatal MI/unstable angina/SCD	0.54 (0.22–1.33)	
ASCOT (male)	nonfatal MI/fatal CHD	0.59 (0.45–0.78)	ASCOT, p. 1155, Tbl. 4
ASCOT (female)	nonfatal MI/fatal CHD	1.10 (0.57–2.12)	
PROSPER (male)	nonfatal MI/fatal CHD plus fatal or nonfatal stroke	0.77 (0.65–0.92)	PROSPER, p. 1626, Tbl. 3
PROSPER (female)	nonfatal MI/fatal CHD plus fatal or nonfatal stroke	0.96 (0.79–1.17)	
WOSCOPS (male)	nonfatal MI/fatal CHD	0.70 (0.58–0.84)	Authors' calculation based on WOSCOPS, p. 1303, Tbl. 2

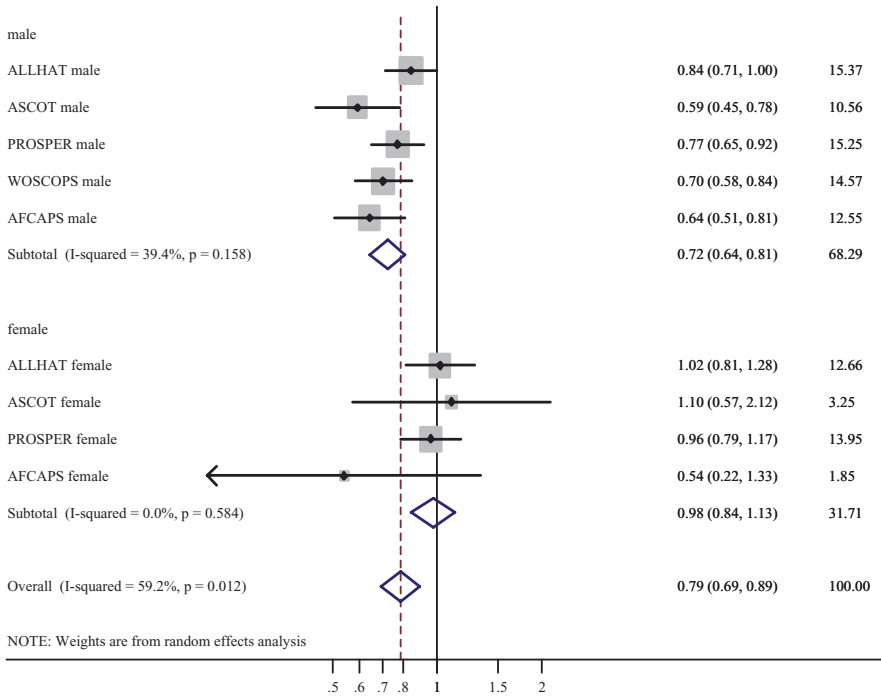
NOTE: CI = confidence interval; SCD = sudden cardiac death; CHD = coronary heart disease. Citations to sources are in note 33.

treatment under study. A forest plot (as in Figure 1) is useful for visually assessing consistency of results across studies. Hypothesis testing can determine whether statistically significant evidence exists against a null hypothesis of no heterogeneity. The I-squared statistic,³⁵ which measures the consistency of findings as the proportion of total variation in point estimates attributable to heterogeneity (rather than sampling error), is used widely to assess the extent of heterogeneity. A simple categorization of values for I-squared assigns adjectives of low, moderate, and high to I-squared values of 25 percent, 50 percent, and 75 percent. The data analysis in Figure 1 uses the DerSimonian-Laird³⁶ approach to random-effects meta-analysis. The

³⁵Julian P.T. Higgins et al., Measuring Inconsistency in Meta-Analyses, 327 *Brit. Med. J.* 557 (2003).

³⁶Rebecca DerSimonian & Raghu Kacker, Random-Effects Model for Meta-Analysis of Clinical Trials: An Update, 28 *Contemp. Clin. Trials* 105 (2007).

Figure 1: Random effects meta-analysis of statin studies.



NOTE: ES = effect size; CI = confidence interval. Citations to studies are in note 33.

performance of the DerSimonian-Laird moment-based estimator has been compared to other competing estimates in terms of both bias and mean squared error, using Monte Carlo simulation, and was found to perform well in the case, such as ours, where a small number of populations are being combined.³⁷

Figure 1 reports the results of the meta-analyses. The male portions of the studies individually and in combination yield a risk ratio of less than 1. The female portions of the studies individually and in combination never yield a risk ratio that excludes 1. Moreover, the combined men portions of the studies and women portions of the studies suggest the need to consider the sexes separately. The two sexes' 95 percent confidence intervals do not

³⁷Kurex Sidik & Jeffrey N. Jonkman, A Comparison of Heterogeneity Variance Estimators in Combining Results of Studies, 26 *Stats. in Med.* 1964 (2007).

overlap and one can reject homogeneity across the male-female groups. The I-squared statistic suggests that about 60 percent of heterogeneity across studies cannot be explained by chance. Within the male and female subgroups, however, I-squared is considerably lower and statistically insignificant. Thus, within-sex differences in the studies are largely explicable by chance but across-sex differences are not.

Importantly, as shown in Figure 1's last column, although the weight contributed to the combined meta-analysis by women is less than that of men it is still substantial. The women meta-analysis carries more weight than any two of the larger men's studies combined. In all the men's studies, the sample was large enough to detect effects at the 95 percent confidence interval level whereas in none of the women's studies was an effect found at that level. Also note that the results for the combined male-female groups are highly statistically significant, but the analysis shows that this is an artifact of combining heterogeneous groups, males, for which evidence supports a statin effect, and females, for which such evidence does not exist.

A. Primary Prevention Ambiguity: PROSPER and ACAPS

As Walsh and Pignone note, the line between primary prevention and secondary prevention is "somewhat artificial."³⁸ Studies may include groups of patients fairly characterized as involving both primary and secondary prevention. The PROSPER study was approximately equally divided between persons with and without prior CHD.³⁹ We therefore repeated the meta-analyses excluding PROSPER and found a relative risk for males of 0.70 (95% CI: 0.60–0.82) and for females of 0.99 (95% CI: 0.81–1.23). As in Figure 1, one can again reject homogeneity of the subgroups ($p = 0.007$).

The ACAPS study, in which all patients had early carotid atherosclerosis,⁴⁰ might also be regarded as not clearly primary or secondary prevention. ACAPS did not report separate results for men and women, but Walsh and Pignone report that there were four female CHD deaths or NFMIs on placebo (of 227 subjects) and one CHD or NFMI on lovastatin (of 218

³⁸Walsh & Pignone, *supra* note 12, at 2244.

³⁹Shepherd et al., *supra* note 33, at 1624 (tbl. 1); Walsh & Pignone, *supra* note 12, at 2245.

⁴⁰Furberg et al., *supra* note 33, at 1680.

subjects).⁴¹ Because of the few ACAPS subjects and events, including ACAPS has no material effect on our results as that study contributes trivially to a meta-analysis (less than 1 percent of the weight).

B. Study Quality: ALLHAT

Walsh and Pignone also note that the ALLHAT results have been challenged on several grounds:

it was unblinded, 32% of the usual care participants started taking lipid-lowering drugs at some point during the study, and a smaller than expected differential in total cholesterol was found between the treatment and usual care groups (9.6%), which is less than half the average for 8 other long-term statin trials with at least 1000 participants.⁴²

To explore results limited to the highest-quality studies, we repeated the analysis excluding ALLHAT and found a relative risk for males of 0.69 (95% CI: 0.62–0.77) and for females of 0.95 (95% CI: 0.79–1.14). One can reject homogeneity of the subgroups ($p = 0.005$).

So excluding either PROSPER or ALLHAT again yields no material evidence of benefit for women and significant evidence of male-female difference. If one excludes both ALLHAT and PROSPER, women contribute less than 6 percent of the weight to the meta-analyses and gender comparisons are not meaningful.

IV. DISCUSSION OF META-ANALYSES

Our review suggests the need for modified labeling, marketing, and information for physicians. Not one of the studies that include women with a mixture of risk factors for heart attacks provides statistically significant support for prescribing Lipitor or other statins to protect against our cardiovascular end points. Pfizer's claims of clinical proof that Lipitor reduces "risk of heart attack . . . in patients with multiple risk factors for heart disease, including family history, high blood pressure, age, low HDL ('good' cholesterol) or smoking" does not appear to be scientifically supported for large segments of the female population.

⁴¹Walsh & Pignone, *supra* note 12, at 2247.

⁴²*Id.* at 2248.

Pfizer's interpretation of results for females is also questionable. In discussing the ASCOT clinical trial, which tested Lipitor, Pfizer's label states: "Due to the small number of events, results for women were inconclusive."⁴³ This "inconclusive" result contrasts with the cardioprotective claims, not qualified by gender, in Pfizer's advertising. Even the claim that results were merely inconclusive is questionable. As a class, the statin drugs have not been shown in *any* of the major RCT primary prevention studies covered here to significantly reduce the clinical end point events for females. The data to date, if anything, are reasonably conclusive that statins have no protective effect against CHD and NFMI for substantial groups of females. In the ASCOT study, women on Lipitor were found to have increased risk of relevant adverse outcomes,⁴⁴ though the result was not statistically significant.

The NCEP's discussion of special considerations for women aged 45 to 75 acknowledges the absence of evidence supporting the use of statins. The NCEP states that the "rationale for therapy is based on extrapolation of benefit from men of similar risk."⁴⁵ It is one thing to extrapolate from men when no data about women are available. But extrapolating when data are not missing—in fact, they show no protective effect for women—is not warranted. Extrapolation from men is questionable because four studies include women and consistently yield statistically insignificant results for them. Extrapolation from the male results requires ignoring the absence of results in the same studies for women.

This study's results are consistent with those of Walsh and Pignone and other statin studies. Walsh and Pignone report conclusions with respect to women not materially different from those here. Our principal added result is that we report results for both men and women. This permits us to provide evidence, shown in Figure 1, of statistically significant differences between men and women. Support for using the statin class of drugs for women should no longer be supported by claims that (1) benefits were shown for men and extrapolation to women is appropriate, or (2) results for women

⁴³Label, *supra* note 8, at 5.

⁴⁴Sever et al., *supra* note 9, at 1155 (tbl. 4).

⁴⁵NCEP, *supra* note 22, at 3351 (tbl. VIII.2-1).

did not statistically significantly differ from those in men.⁴⁶ The results are also consistent with a non-RCT Japanese study of hypercholesterolemic patients in which women substantially outnumbered men. No statistically significant pravastatin effect was found on CHD events, CVD events, or total mortality.⁴⁷ The results are also consistent with CASHMERE, an RCT designed to compare Lipitor “versus placebo in post-menopausal women with moderate hypercholesterolaemia.”⁴⁸ That study, limited to women, had a primary end point of the change in carotid intima-media thickness (IMT). Carotid IMT is a “closer” surrogate than lipid levels “to measures of health benefits such as cardiovascular events.”⁴⁹ CASHMERE found no statistically significant effect of Lipitor compared to placebo.⁵⁰

Our meta-analyses results are also consistent with the heart protection study that was declared as a major success for men and women, although there was no effect on overall mortality in women.⁵¹ Kendrick notes, quoting from a major conference held in 1992 that looked at the data from 523,737 men and 124,814 women from 19 studies and trials: “Many findings for women were discrepant from those for men. Of particular importance in women was considered to be the essentially flat relation of TC [total cholesterol] to total mortality, total CVD [cardiovascular disease], and total cancer

⁴⁶Walsh & Pignone, *supra* note 12, examined the additional secondary end points in AFCAPS/TexCAPS of revascularization, unstable angina, MI, cardiovascular events, and coronary events; none had significant effects.

⁴⁷Junji Koizumi et al., Effect of Pravastatin-Induced LDL-Cholesterol Reduction on Coronary Heart Disease and Cerebrovascular Disease in Japanese: Hokuriku Lipid Coronary Heart Disease Study—Pravastatin Atherosclerosis Trial (Holicos-PAT), 9 *J. Atherosclerosis & Thrombosis* 251, 255 (2002) (tbl. 2). Results are not reported separately for men and women but a Cox proportional hazards model did include gender as an adjustment factor.

⁴⁸Protocol A2581051, 29 Oct. 2007, Final Report, available at (ClinicalTrials.gov), last accessed Mar. 29, 2008. See Tabassome Simon et al., Rationale, Design and Methods of the CASHMERE Study, 18 *Fundamental & Clin. Pharmacol.* 131 (2004).

⁴⁹Bruce M. Psaty & Thomas Lumley, Surrogate End Points and FDA Approval: A Tale of 2 Lipid-Altering Drugs, 299 *JAMA* 1474, 1475 (2008).

⁵⁰Protocol A2581051, *supra* note 48, at 5–6.

⁵¹Arnold J. Jenkins, Might Money Spent on Statins be Better Spent? 327 *Brit. Med. J.* 993 (2003).

(Jacobs et al.).⁵² In our meta-analyses, the findings for women were discrepant from those for men. Grundy points out results, consistent with our meta-analyses, that clinical trials that have included both men and women have shown overall risk reduction from cholesterol-lowering therapy.⁵³ Grundy also conjectures that the post-hoc analyses in any of the individual trials when limited to women failed to show significant risk reduction because of a lack of statistical power. Our meta-analyses show that this is not likely the case.

A. Diabetics: CARDS and HPS

The principal difference between this study and Thavendiranathan et al. is our exclusion of one Lipitor study known as CARDS.⁵⁴ CARDS does not separately report results for men and women so we are unable to include it in our quantitative analysis. Even if the requisite data were available, including CARDS would be questionable. CARDS, unlike the other studies, is limited to diabetic patients. Studies limited to diabetics again test the boundary between primary and secondary prevention because diabetes is so closely associated with CVD. The American Heart Association position is that persons with diabetes “can be considered at a level of risk similar to a patient with established cardiovascular disease”⁵⁵ So if a meta-analysis including CARDS found no male-female difference, it would be appropriate to check the sensitivity of the analysis to excluding CARDS. Studies of diabetics raise other issues as well. Diabetes increases risk of heart disease mortality and does so differentially for men and women.⁵⁶ Without

⁵²Malcom Kendrick, Should Women be Offered Cholesterol Lowering Drugs to Prevent Cardiovascular Disease? No, 334 *Brit. Med. J.* 983 (2007), quoting D. Jacobs et al., Report of the Conference on Low Blood Cholesterol: Mortality Associations, 86 *Circulation* 1046 (1992).

⁵³Scott M. Grundy, Should Women be Offered Cholesterol Lowering Drugs to Prevent Cardiovascular Disease? Yes, 334 *Brit. Med. J.* 982 (2007).

⁵⁴Colhoun et al., *supra* note 25.

⁵⁵Thomas A. Pearson et al., AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update, 106 *Circulation* 388, 389 (2002) (tbl. 1).

⁵⁶National Institute of Health, National Institute of Diabetes & Digestive & Kidney Diseases, *Diabetes in America* 435 (2d ed. 1995).

accounting for these characteristics, meta-regression using the percent of females or males as an explanatory variable could lead to spurious results if CARDS is included.⁵⁷

Moreover, the CARDS results have not been consistently replicated in other Lipitor diabetes-related studies. A separate report on women diabetics from the Lipitor ASCOT study yielded results that were not close to statistically significant.⁵⁸ In another Lipitor diabetes study, no significant benefit was found, even in the combined group of men and women.⁵⁹ In a Lipitor study of diabetics on hemodialysis, no significant benefit was found in the combined group of men and women.⁶⁰ In a study of patients with renal failure, Lipitor was not significantly beneficial with respect to cardiovascular end points or survival; and results for women were less favorable than those for men.⁶¹

Studies using other statins, including non-primary-prevention studies and one branch of the HPS study, report results for diabetic women. Like

⁵⁷This seems to have occurred in Thavendiranathan et al., *supra* note 13, at 2310 (“reductions in the risk of major coronary events from statin therapy were significantly associated with . . . a smaller proportion of men in the study population ($p = .003$)”).

⁵⁸Peter S. Sever et al., Reduction in Cardiovascular Events with Atorvastatin in 2,532 Patients with Type 2 Diabetes, 28 *Diabetes Care* 1151, 1155 (2005) (reporting hazard ratio for women for total cardiovascular events and procedures to be 0.90 (95% CI = 0.53 – 1.51; $p = 0.686$)).

⁵⁹Robert Knopp et al., Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects with Type 2 Diabetes, 29 *Diabetes Care* 1478, 1483 (2006) (“the primary end point . . . did not reach statistical significance”).

⁶⁰Christoph Wanner et al., Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis, 353 *New Eng. J. Med.* 238, 238, 247 (2005) (“Atorvastatin had no statistically significant effect on the composite primary end point of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with diabetes receiving hemodialysis”; authors conclude that treatment of studied group with statins “is not warranted” to reduce the primary composite end point.”). See also Daniel M. Richie & Katie S. McClendon, Role of Statins for the Primary Prevention of Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus, 64 *Am. J. Health-Syst. Pharm.* 1603 (2007) (American Diabetes Association guidelines recommending statin therapy “may be too aggressive”).

⁶¹B.G. Stegmayr et al., Low-Dose Atorvastatin in Severe Chronic Kidney Disease Patients: A Randomized, Controlled Endpoint Study, 39 *Scand. J. Urology & Nephrology* 489 (2005).

CARDS, they show a protective statin effect for CHD events.⁶² The implications of the HPS results are not clear because HPS results for diabetic women are not separately reported for patients with and without prior CHD or CVD.⁶³ Nevertheless, CARDS, HPS, and other studies provide evidence that diabetic patients can benefit from statin treatment. However, the inconsistent Lipitor-specific results and the potential confounding posed by diabetes' heart-related risks⁶⁴ suggest caution in generalizing from statins' beneficial effects for women diabetics to cardioprotection for women patients in a pure primary prevention context or to a specific statin. The absence of evidence of statins' effectiveness in primary prevention nondiabetic women, and the significant difference between men and women, remain a concern in marketing statins to women.

V. POSSIBLE VIOLATIONS OF FEDERAL AND STATE LAW

We consider two kinds of amelioration with respect to Lipitor's marketing. First, we assess under the Federal Food, Drug, and Cosmetic Act (FDCA)⁶⁵ the marketing of Lipitor as cardioprotective, without disclosing relevant scientific information about women. If our scientific conclusions are valid, the FDA should consider taking appropriate actions with respect to Pfizer's

⁶²HPS, *supra* note 25, at 2010 (fig. 3); Cholesterol Treatment Trialists' (CTT) Collaborators, Efficacy of Cholesterol-Lowering Therapy in 18686 People with Diabetes in 14 Randomised Trials of Statins: A Meta-Analysis, 371 *Lancet* 117 (2008); João Costa et al., Efficacy of Lipid Lowering Drug Treatment for Diabetic and Non-Diabetic Patients: Meta-Analysis of Randomised Control Trials, 332 *Brit. Med. J.* 1115 (2006); Sandeep Vijan & Rodney A. Hayward, Pharmacologic Lipid-Lowering Therapy in Type 2 Diabetes Mellitus: Background Paper for the American College of Physicians, 140 *Ann. Intern. Med.* 650 (2004).

⁶³Walsh & Pignone, *supra* note 12, at 2247 (tbl. 2), report a significant reduction for CHD events in women in the HPS study. These data appear to be based on the diabetes female subgroup in HPS. HPS, *supra* note 25 (fig. 3).

⁶⁴Costa et al., *supra* note 62, show that diabetics are at increased risk of major coronary events in statin studies in both primary prevention and secondary prevention contexts.

⁶⁵21 U.S.C. § 301 et seq.; see Section V.A.

advertising and labeling of Lipitor.⁶⁶ Second, if we are correct, the question arises whether women misled by Pfizer's advertising have a legal cause of action against Pfizer. Many women and their physicians undoubtedly were influenced by Pfizer's claims of protection against heart attacks,⁶⁷ claims that we do not believe to be consistent with the RCT evidence, especially ASCOT's Lipitor results. Pfizer's advertising also does not disclose critical portions of the Lipitor FDA-approved label, which acknowledges the absence of evidence with respect to women. Whether women can recover depends both on state law that might provide a cause of action, and on whether federal law preempts state law actions.

A. *Violation of the FDCA*

Misleading or false advertisements violate the FDCA.⁶⁸ The principal federal regulation governing prescription drug advertisements divides advertising characteristics into two classes, those that *are* false, unfair, or misleading and those that *may be* false, unfair, or misleading. We address the two classes of characteristics separately.

1. FDA Guidelines for Advertisements that are False, Unfair, or Misleading

FDA regulations state that advertisements for a prescription drug “*are* false, lacking in fair balance, or otherwise misleading” if they have one or more of 20 enumerated characteristics.⁶⁹ The first characteristic is that the advertising contains “a representation or suggestion, not approved or permitted for use in the labeling, that a drug is . . . useful in a broader range of . . . patients . . . than has been demonstrated by substantial evidence or substantial

⁶⁶The FDCA authorizes a range of actions by the FDA. See 21 U.S.C. § 331 et seq.; Hutt et al., *supra* note 14, at 1196–1370.

⁶⁷Advertising to consumers has been shown to have an effect on physician prescribing patterns. Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Public Health 159* (Alina Baciú, Kathleen Stratton & Sheila P. Burke eds., 2007) (citing five studies).

⁶⁸21 C.F.R. § 202.1(e)(6). Misleading advertising is deemed to cause a drug to be misbranded under the FDCA. *Id.*, § 202.1(k). Introduction or delivery for introduction into interstate commerce of a misbranded drug is prohibited. 21 U.S.C. § 331(a). Violation of § 331 is a crime. *Id.*

⁶⁹21 C.F.R. § 202.1(e)(6)(i)–(xx) (emphasis added).

clinical experience.”⁷⁰ The 18th characteristic is that the advertising “[u]ses headline, subheadline, or pictorial or other graphic matter in a way that is misleading.”⁷¹ The 20th characteristic is that the advertising “[r]epresents or suggests that drug dosages properly recommended for use in the treatment of certain classes of patients . . . are . . . effective for the treatment of other classes of patients . . . when such is not the case.”⁷² Pfizer’s Lipitor advertising may be false, lacking in fair balance, or otherwise misleading under each of these criteria.

With respect to the first criterion, Lipitor’s approved label states that cardioprotective “results for women were inconclusive.”⁷³ Yet much of Pfizer’s available advertising does not mention the inconclusive results. For example, one Lipitor two-page advertisement in the magazine *The New Yorker* states: “LIPITOR can lower the risk of heart attack . . . in patients who have risk factors for heart disease.”⁷⁴ The same advertisement does not indicate that RCT results for most risk factors show no significant reduction in heart attack risk for women, disclose the label’s information about inconclusive results in women, or disclose that the principal underlying RCT stated that no benefit was found for women.

A full-page Lipitor advertisement in the *Wall Street Journal*, a portion of which appears in Figure 2, states in a large graphic and enormous font that “Lipitor reduces the risk of heart attack by 36%.”⁷⁵ The fine print states that this statement is based on a large clinical study. The advertisement, including the fine print, fails to state that what appears to be the same clinical study produced insignificant, inconclusive, and possibly contrary results in women. The ASCOT Lipitor study summarized in Table 2 expressly states, in discussing the primary end point (NFMI plus fatal CHD), “no benefit was apparent

⁷⁰21 C.F.R. § 202.1(e)(6)(i).

⁷¹21 C.F.R. § 201(e)(6)(xviii).

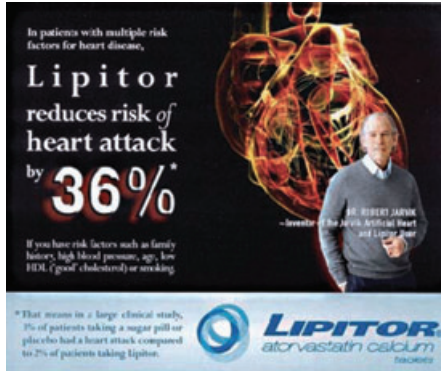
⁷²21 C.F.R. § 201(e)(6)(xix).

⁷³Label, *supra* note 8, at 5.

⁷⁴The New Yorker, Aug. 27, 2007.

⁷⁵Wall St. J., Nov. 26, 2007.

Figure 2: Lipitor advertisement.



among women.”⁷⁶ Indeed, the ASCOT study reports that risk to women of the primary end point *increased* in the relevant RCT trial.⁷⁷ The increase was not statistically significant but is important qualifying information in the context of mass media advertising to consumers of a 36 percent *decrease* without distinguishing between genders.

Similar questions arise with respect to Pfizer’s other advertising. Pfizer’s Lipitor website communicates with consumers and states that, in patients with multiple risk factors for heart disease, Lipitor is used to “reduce the risk of heart attack.”⁷⁸ It does not state that a measure of risk for women actually increased in ASCOT, the key RCT trial, or that the published ASCOT article stated that no benefit for women was found with respect to NFMI or fatal CHD. A key component of Pfizer’s television advertising, removed from the market after assertions were made that it was misleading on grounds not addressed here,⁷⁹ includes a graphic in which Dr. Robert Jarvik states that Lipitor is “FDA-approved to reduce the risk of heart

⁷⁶Sever et al., supra note 9, at 1153. The study does report “no significant interaction between sex and impact of statin on the primary endpoint,” id., but that obviously does not establish a protective effect for women when “no benefit” was found for women with respect to the primary end point. The insignificant interaction could readily be explicable by sample size.

⁷⁷Id. at 1155 (tbl. 4).

⁷⁸See (<http://www.lipitor.com/learn-about-lipitor/home.jsp>), accessed Jan. 11, 2008.

⁷⁹Saul, supra note 6.

attack.”⁸⁰ The oral message is accompanied by a visual image consisting of a large piece of paper that also states that Lipitor is “FDA-approved to reduce the risk of heart attack.” The television commercial does not report the increased risk to women in ASCOT or that Pfizer’s FDA-approved label states that the results for women are inconclusive.

The advertising thus might reasonably be interpreted to suggest, contrary to the label’s report of inconclusive scientific evidence, that Lipitor is useful in a broader range of patients “than has been demonstrated by substantial evidence or substantial clinical experience.” This would violate the FDCA.

With respect to the 18th criterion, some of Lipitor’s television advertising graphically emphasizes the reduction in heart problems found in a study, but neither the graphic, nor the voiceover, nor the text of the television advertisement indicates that no significant reduction in the primary end point was found for women. Similar omissions apply to print advertising for Lipitor, such as the *Wall Street Journal* advertisement in Figure 2. The Lipitor advertising program thus may use “headline, subheadline, or pictorial or other graphic matter in a way that is misleading.”

With respect to the 20th criterion, Lipitor advertising repeatedly fails to report that clinical results were statistically significant for men but not for women and that the ASCOT results tended to go in the opposite direction for women. The advertising therefore may be interpreted to suggest “that drug dosages properly recommended for use in the treatment of certain classes of patients . . . are . . . effective for the treatment of other classes of patients . . . when such is not the case.”

The advertising’s failure to distinguish between men and women is exacerbated by its express reference to pregnant women. The advertising regularly states that pregnant women should not take Lipitor. A woman seeing the advertising might well conclude that appropriate female-specific disclosures had been made. Lipitor’s label’s express reference to inconclusive results in women suggests that the company and the FDA regarded Lipitor’s lack of demonstrated efficacy in women to be important.

The three above-discussed characteristics relate to whether advertisements “*are*” false and misleading under FDA criteria. If the characteristics exist, there appears to be no discretion under FDA regulations not to find the advertisements to be false or misleading.

⁸⁰Lipitor advertisement, WCBS television, aired in New York market on Nov. 4, 2007, and on many other dates.

2. FDA Guidelines for Advertisements that May be False, Unfair, or Misleading

The relevant FDA regulation also states that advertisements “*may be false, lacking in fair balance, or otherwise misleading*” if they have one or more of 13 additional enumerated characteristics.⁸¹ The prohibited characteristics include some that may apply to advertising for Lipitor.

An advertisement may be false and misleading if it:

Contains favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions.⁸²

Lipitor advertising’s non-gender-qualified statements about reduction of heart attack risk are based on a study that Pfizer’s label acknowledges was inconclusive about women. The favorable statements, such as the statement about 36 percent reduction in heart attack risk, are thus based on a study that is inadequate to support the statement in the case of women, who obviously constitute a huge fraction of the target audience.

FDA regulations also state that an advertisement may be false and misleading if it:

Uses reports or statements represented to be statistical analyses, interpretations, or evaluations that are inconsistent with or violate the established principles of statistical theory, methodology, applied practice, and inference, or that are derived from clinical studies the design, data, or conduct of which substantially invalidate the application of statistical analyses, interpretations, or evaluations.⁸³

The Lipitor advertising about heart attack risk contains a statement represented to be “statistical analyses, interpretations, or evaluations,” such as the statement about a 36 percent reduction in heart attack risk, but the failure of the advertising to differentiate between heterogeneous subgroups—men and women—raises the question of whether the advertising is “inconsistent with” and violates “established principles of statistical theory, methodology, applied practice, and inference.” The information contained within the ASCOT study allowed researchers to distinguish between results for men and

⁸¹21 C.F.R. § 201(e)(7) (emphasis added).

⁸²21 C.F.R. § 201(e)(7)(i).

⁸³21 C.F.R. § 201(e)(7)(v).

women. As Figure 1 and Table 2 show, the ASCOT study showed a statistically significant reduction in risk for men and a statistically insignificant increase in risk for women. This pattern or similar patterns exist for every other RCT study analyzed here. Failure to tailor advertising to reflect this material difference could be regarded as not consistent with either everyday prudence or statistical methodology.

B. Violations of State Law: Lipitor Lawsuits and Mismarketing

Although we have not surveyed the full range of Lipitor-related legal actions or available causes of action, allegations in lawsuits are consistent with our meta-analyses and our FDCA analysis. One lawsuit, brought by a former Pfizer marketing employee, provides specific allegations of mismarketing to women based on specific female age and risk features and recommendations by Pfizer software or personnel.⁸⁴

Allegations in another lawsuit also assert the overmarketing of Lipitor. *Prohias v. Pfizer, Inc.* suggests the importance of a 2004 FDA-approved labeling change for Lipitor. Lipitor had, in the 1990s, been approved to reduce cholesterol.⁸⁵ On July 30, 2004, Lipitor was first approved by the FDA “for the prevention of cardiovascular disease in certain patients.”⁸⁶ The additional

⁸⁴Dr. Jesse Polansky is a former Pfizer employee who is said in a lawsuit complaint to have had responsibility for evaluating the integrity of Pfizer marketing programs. Dr. Polansky is described as follows.

From April 2001 until July 2003, Dr. Polansky was employed by Pfizer in New York City as Director of Outcomes Management Strategies. Dr. Polansky also served as the medical director for the Local Marketing Team Review Committee that evaluates and approves the regulatory, legal, and scientific integrity of marketing programs for Pfizer’s major metropolitan markets.

Third Amended Complaint, United States ex rel. Dr. Jesse Polansky v. Pfizer, Inc., No. 04 CV 0704 (ERK) (S.D.N.Y. Dec. 20, 2007), at 4–5, ¶ 9. The allegations in Dr. Polansky’s complaint contain at least two concrete illustrations of mismarketing Lipitor to women based on inadequate scientific support. First, a software program distributed by Pfizer allegedly recommends medication for a hypothetical 43-year-old female with several heart disease risk factors when the guidelines of the NCEP do not recommend medication. *Id.* at 29–30, ¶¶ 90–94. Second, a Pfizer representative recommends statin therapy outside the same guidelines in a case study of a 74-year-old female. *Id.* at 49, ¶ 150.

⁸⁵*Prohias v. Pfizer, Inc.*, 485 F. Supp. 2d 1329, 1331 (S.D. Fla. 2007).

⁸⁶*Id.*; Letter from David Orloff to Pfizer Inc., re NDA 20-702/S-039, July 30, 2004.

labeling approval was for reducing the risk of heart attacks in “adults without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease, such as age 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease.”⁸⁷ That approval was based on the ASCOT study.⁸⁸ In *Prohias*, it was alleged, as our meta-analyses suggest, that no evidence exists that Lipitor’s ability to reduce cholesterol “has any effect on the development of coronary heart disease . . . or mortality rates for women.”⁸⁹

Before the 2004 labeling change allowing claims of cardioprotection, at least some of Pfizer’s advertising expressly disclaimed the existence of evidence that Lipitor prevented heart problems. Advertisements stated, “Lipitor has not been shown to prevent heart disease or heart attacks.”⁹⁰ This disclaimer generated judicial skepticism in *Prohias* about the viability of a class action against Pfizer based on misleading heart-protective advertising before July 2004.⁹¹ The *Prohias* court further found that “Pfizer’s post-July 2004 advertisements were not misleading as a matter of law” because of the FDA label approval with respect to Lipitor’s reduction of heart attack risks.⁹² This legal conclusion is scientifically questionable in the context of an action by women because the studies indicating no significant CHD or NFMI effect for women were available before the 2004 labeling change.

The *Prohias* court’s legal conclusion is also questionable because it ignores the FDA’s own standards regulating advertising. As shown above, Pfizer’s advertising appears to be inconsistent with several express FDA

⁸⁷485 F. Supp. 2d at 1331–32 (quoting Complaint).

⁸⁸Orloff Letter, *supra* note 86.

⁸⁹Complaint, Nilda Prohias and Moses Selesky, on behalf of themselves and all others similarly situated v. Pfizer, Inc., No. 05-22658 (S.D. Fla. Oct. 11, 2005), at 2, ¶ 8.

⁹⁰Lipitor advertising reproduced in Complaint, *supra* note 89, at 34, 42, 44, 47, ¶¶ 84, 99, 104, 106.

⁹¹*Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d 1228, 1235 (S.D. Fla. 2007):

I do, however, have serious doubts about whether the plaintiffs can succeed in presenting evidence of misleading advertisements because most of the advertisements included in the complaint specifically state that Lipitor “has not been shown to prevent heart disease or heart attacks,” *see* Complaint at ¶¶ 89, 101, 106, and those advertisements are not misleading as a matter of law because they substantially comport with the FDA approved label.

⁹²490 F. Supp. 2d at 1235.

advertising regulations. The advertising regulations do not protect the content of all advertising once a label is approved. Advertising content should not materially differ from key information approved in the label. The Lipitor label approved by the FDA does not appear to be consistent with Pfizer's Lipitor advertising program because the advertising does not acknowledge the absence of evidence of benefit for women. In *Prohias*, contrary to the court's conclusion, no apparent conflict exists between state law advertising claims and FDA labeling approval because much of the advertising program appears to have omitted material information included in the label. The court's assertion that "the alleged advertisements derive from, and largely comport with, the approved label"⁹³ seems incorrect with respect to women because the label notes the absence of evidence with respect to women and the advertising does not.

Even if *Prohias* were correct with respect to advertising as of the time of the *Prohias* complaint, Pfizer's subsequent advertising was arguably more aggressively misleading. For example, the prominent "36%" graphic shown in Figure 2 was part of a later Lipitor campaign. Its quantitative statement is affirmatively misleading with respect to women based on the ASCOT results. This and similar advertising were not identified as a source of Pfizer's alleged misbehavior in *Prohias*⁹⁴ and appear not to have been used by Pfizer until later.⁹⁵

VI. PREEMPTION

The *Prohias* Lipitor ruling is understandable in that courts do not wish to substitute their medical "judgment for the FDA's about these medical issues,"⁹⁶ but this deference, however desirable as a matter of legal doctrine, is usually shown in the context of failure to warn about the safety risks of drugs or medical devices when those risks have been addressed by the FDA via its consideration of a drug's label or premarketing approval of a medical

⁹³Id. at 1234.

⁹⁴Complaint, *supra* note 89.

⁹⁵See Saul, *supra* note 6 ("Pfizer has spent more than \$258 million advertising Lipitor since January 2006, most of it on the Jarvik campaign").

⁹⁶*Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 530 (E.D. Pa. 2006).

device.⁹⁷ Whatever one's view of the FDA's preemptive authority with respect to safety warnings and labeling, a matter we discuss below,⁹⁸ it is more difficult to regard FDA scientific activity, or absence of activity, as protective of all possible marketing claims. The possible range of misleading claims is too vast to anticipate. Prominent commentators, including two former FDA Chief Counsels, have noted that the "primary problems posed by advertising for prescription drugs . . . do not appear easily redressable by the authority to issue regulations or, indeed, to invoke the informal enforcement sanctions provided by the FD&C Act."⁹⁹ Traditional civil enforcement methods, such as private party actions, thus should be more reluctantly preempted in the area of questionable advertising.

⁹⁷*Riegel v. Medtronic, Inc.*, 128 S. Ct. 999 (2008) (premarket approved medical devices). In the area of drugs, compare *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85 (2d Cir. 2006), *cert. granted*, *Warner-Lambert Co., LLC v. Kent*, 128 S. Ct. 31 (2007); *In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776 (E.D. La. 2007) (FDA entitled to limited deference); *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230 (E.D.N.Y. 2007); *Barnhill v. Teva Pharms. USA Inc.*, 2007 U.S. Dist. Lexis 44718 (S.D. Ala. Apr. 24, 2007); *Weiss v. Fujisawa Pharm. Co.*, 464 F. Supp. 2d 666 (E.D. Ky. 2006); *Perry v. Novartis Pharm. Corp.*, 456 F. Supp. 2d 678 (E.D. Pa. 2006); *Jackson v. Pfizer, Inc.*, 432 F. Supp. 2d 964 (D. Neb. 2006); *Laisure-Radke v. Par Pharm., Inc.*, 2006 WL 901657 (W.D. Wash. Mar. 29, 2006); *McNellis v. Pfizer, Inc.*, No. 05-1286, 2005 WL 3752269 (D.N.J. Dec. 29, 2005), *stay granted, motion to certify appeal granted*, 2006 WL 2819046 (D.N.J. Sept. 29, 2006); *Ferrari v. American Home Prods. Corp.*, 2007 WL1933129 (Ga. App. July 5, 2007) (vaccine case); *Kelly v. Wyeth*, 2007 WL 1302589 (Mass. Super. Apr. 12, 2007); *Strong v. American Cyanamid Co.*, 2007 WL 2445938 (Mo. App. Aug. 28, 2007), *cause ordered transferred to Mo. S. Ct.* (Dec. 18, 2007); *In re Vioxx Litig.*, Nos. ATLL-3553-05-MT & ATLL-1296-05-MT, slip op. (N.J. Sup. Ct. June 8, 2007); *Deutsch v. Wyeth, Inc.*, 2007 WL 2060072 (N.J. Super. June 22, 2007); *Cona v. Merck & Co.*, Nos. ATLL-3553-05, ATLL-1296-05 (N.J. Super. June 8, 2007); *Coutu v. Tracy*, 2006 WL 1314261 (R.I. Super. May 11, 2006); *Levine v. Wyeth*, 2006 WL 3041078 (Vt. Oct. 27, 2006), *petition for cert. filed* (No. 06-1249), 75 U.S.L.W. 3500 (2007), with *Tucker v. SmithKline Beecham Corp.*, No. 1:04-cv-1748-DFH-WTL, slip op. at *12 (S.D. Ind. Sept. 19, 2007) ("particularly clear showing of conflict" supports preemption); *Bruesewitz v. Wyeth, Inc.*, 2007 WL 2463378 (E.D. Pa. Aug. 24, 2007) (vaccine case); *In re Baycol Prods. Litig.*, 495 F. Supp. 2d 977 (D. Minn. 2007); *Sykes v. Glaxo-SmithKline*, 484 F. Supp. 2d 289, 306-17 (E.D. Pa. 2007); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, MDL 1699, 2006 WL 2374742, at **5-12 (N.D. Cal. Aug. 16, 2006); *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 523-38 (E.D. Pa. 2006); *Conte v. Wyeth, Inc.*, 2006 WL 2692469 (Cal. Super. Sept. 15, 2006); *Prohias v. AstraZeneca Pharms., L.P.*, 958 So. 2d 1054 (Fla. App. 2007); *Abramowitz v. Cephalon, Inc.*, 2006 WL 560639 (N.J. Super. Mar. 3, 2006); *Militrano v. Lederle Labs.*, 810 N.Y.S.2d 506 (N.Y. App. Div. 2006) (vaccine case); *Ledbetter v. Merck & Co.*, 2007 WL 1181991 (Tex. Dist. Apr. 20, 2007); *Brockert v. Wyeth Pharms.*, 2007 WL 2077554 (Tex. Dist. Jan. 31, 2007); *Price v. Cook*, 2007 WL 2154766 (W. Va. Cir. July 9, 2007).

⁹⁸See Section VI.E.

⁹⁹Hutt et al., *supra* note 14, at 541-42.

Thus, despite FDA approval of labeling language that might be interpreted as covering some of the content in an advertisement, that approval does not reasonably support legal protection via preemption. One possible standard is that no implied preemption exists when (1) a company knew or should have known that its marketing is misleading under state or federal law, (2) the advertising omits material scientific information included in the label that pertains to a large segment of the targeted audience, and (3) the allegedly misleading aspect of the advertising has not been expressly addressed by the FDA.

Analysis of Lipitor's advertising has implications for the broader preemption issues relating to safety warnings and a regulatory compliance defense. Our evaluation of the FDA's regulation of the world's best-selling drug suggests that preemption arguments should include consideration of actual agency performance rather than adhere to the legal literature's dominant practice of focusing primarily on theoretical institutional competence.

A. FDA Regulation of Advertising Compared to Labeling and Warnings

Although the FDA specifically approves or is notified of changes to drug labels,¹⁰⁰ no systematic program requires explicit FDA judgment about the content of all consumer advertising. For most prescription drugs, no requirement exists that companies submit promotional materials to the FDA before using them.¹⁰¹ Rather, materials are submitted at the time of the drug's initial marketing.¹⁰² However, mere submission and the FDA's silence as to a

¹⁰⁰The FDA permits two kinds of labeling supplements:

(1) Prior approval supplements, which require FDA approval before a change is made (§§ 314.70(b) and 601.12(f)(1)); and (2) "changes being effected" (CBE) supplements, which may be implemented before FDA approval, but after FDA notification (§§ 314.70(c) and 601.12(f)(2)).

FDA, *supra* note 15, at 3934, 2006 WL 160271. See 21 C.F.R. §§ 314.70, 514.8, 601.12; 72 Fed. Reg. 73589–73602, 2007 WL 4555142.

¹⁰¹Consumer-Directed Promotion of Regulated Medical Products; Public Hearing, 70 Fed. Reg. 54054, 54059 (Sept. 13, 2005); Hutt et al., *supra* note 14, at 558 (noting that FDA did not require premarket review of consumer advertising but encouraged this approach through the use of warning letters); Institute of Medicine, *supra* note 67, at 158–64 (reviewing history of FDA advertising regulation).

¹⁰²21 C.F.R. § 314.81(b)(3)(i); 70 Fed. Reg. at 54059.

particular advertisement does not establish that the FDA determined that the advertisement was not deceptive.¹⁰³

Although advertising can communicate safety information, its primary purpose is to expand a drug's market, not to communicate safety information.¹⁰⁴ The FDA can advise companies on proposed advertising but, absent limited circumstances, it is the drug company's decision whether to seek advance FDA input on the advertising,¹⁰⁵ other than advertising in connection with initial marketing of the drug.¹⁰⁶ According to the FDCA, "except in extraordinary circumstances," the FDA cannot issue a regulation that requires "prior approval by the Secretary of the content of any advertisement."¹⁰⁷ The FDA office responsible for reviewing consumer advertising has been described by the Institute of Medicine of the National Academies as "small" and with "limited resources."¹⁰⁸ In 2004, only 32 percent of broadcast advertising underwent FDA review before airing.¹⁰⁹ FDA warning letters about questionable advertising are frequently sent to drug companies long after the advertising campaign is over.¹¹⁰

¹⁰³In *re* Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig. MDL 1699, 2006 WL 2374742, at *11 (N.D. Cal. Aug. 16, 2006).

¹⁰⁴See, e.g., Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Experimental Evaluation of Variations in Content and Format of the Brief Summary in Direct-to-Consumer Print Advertisements for Prescription Drugs, 72 Fed. Reg. 11889, 11889 (Mar. 14, 2007) ("Although advertising of prescription drugs was once primarily addressed to health professionals, increasingly consumers have become a target audience, as DTC advertising has dramatically increased in the past few years. . . . Frequently, sponsors print in small type, verbatim, the risk-related sections of the approved product labeling (also called the package insert, professional labeling, or prescribing information). This labeling is written for health professionals, using medical terminology."); *Pennsylvania Employees Benefit Trust Fund v. Zeneca Inc.*, 499 F.3d 239, 245 (3d Cir. 2007) (advertising's "primary purpose—unlike labeling—is not to promote safety but rather to promote market expansion").

¹⁰⁵21 C.F.R. § 202.1(j)(4).

¹⁰⁶21 C.F.R. § 314.81(b)(3)(i).

¹⁰⁷21 U.S.C. § 352(n)(3)(A).

¹⁰⁸Institute of Medicine, *supra* note 67, at 163.

¹⁰⁹Julie M. Donohue, Marisa Cevasco & Meredith B. Rosenthal, A Decade of Direct-to-Consumer Advertising of Prescription Drugs, 357 *New Eng. J. Med.* 673, 679 (2007).

¹¹⁰*Id.*

The FDA itself does not regard advertising and safety warning issues as being similarly situated with respect to preemption. The FDA's 2006 statements in its regulatory preamble about preemption of state law actions focus primarily on labeling and warning issues, not on misleading advertising issues.¹¹¹ The FDA preamble that argues for broad preemption specifically relates to labeling. The document's title is "Requirement and Content and Format of *Labeling* . . ." ¹¹² The FDA's preamble expressly indicates that advertising issues are beyond its scope.¹¹³

To the extent the FDA's preamble mentions advertising, allowing recovery on the basis of misleading advertising need not implicate the FDA's concerns. The FDA opposes state laws that "compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated" as well as state laws that "preclude a firm from including in labeling or advertising a statement that is included in prescription drug labeling."¹¹⁴

In the case of Lipitor, accurately describing what we believe to be the evidence about the absence of Lipitor's cardioprotection of women does not "compel a firm to include in . . . advertising a statement that FDA has considered and found scientifically unsubstantiated." The FDA could not have concluded that advertising acknowledging the absence of evidence of protection of women is unsubstantiated because the label it approved states that the evidence with respect to women was inconclusive. It is therefore scientifically unsupportable to argue that the FDA found the absence of evidence of cardioprotection for females to be "scientifically unsubstantiated." The absence of evidence of protection for women exists in relevant RCT studies for reasonably healthy females, including the ASCOT Lipitor study. State

¹¹¹See generally William W. Buzbee, *Asymmetrical Regulation: Risk, Preemption, and the Floor/Ceiling Distinction*, 82 *NYU L. Rev.* 1547 (2007); Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA*, 48 *Boston Coll. L. Rev.* 1089 (2007); Catherine M. Sharkey, *Preemption by Preamble, Federal Agencies and the Federalization of Tort Law*, 56 *DePaul L. Rev.* 227 (2007).

¹¹²FDA, *supra* note 15 (emphasis added).

¹¹³"The agency agrees that advertising and promotional labeling regulations address product promotion issues and that this final rule is not an appropriate context for discussion of these issues." 71 *Fed. Reg.* at 3953.

¹¹⁴71 *Fed. Reg.* at 3935.

laws requiring advertising to disclose the state of research with respect to female cardioprotection would not implicate the FDA's inclusion concern with respect to advertising.

Nor would advertising disclosing the absence of evidence with respect to women implicate the FDA's exclusion concern. A problem with Lipitor consumer advertising appears to be that the huge female consumer audience is not told the labeling information that it clearly would be interested in. Lipitor's label acknowledges the absence of evidence of protection for women, but Lipitor's advertising lacks such acknowledgment. A state legal standard requiring advertising to acknowledge the absence of evidence for women would therefore not preclude advertising from containing a labeling statement. It would require that label-related statements in advertising not be misleading.¹¹⁵ The FDA's preamble's other references to advertising assert preemption only with respect to failure to warn issues, not misleading advertising claims.¹¹⁶

If no persuasive scientific evidence supports the claim that Lipitor reduces fatal CHD or NFMI in women, and such evidence was available to Pfizer before the 2004 labeling change, then one might conclude that Pfizer knew or should have known that its unqualified express heart attack advertising claims could materially mislead consumers.¹¹⁷

¹¹⁵Requiring advertising to include labeling information that is omitted from advertising but necessary to avoid misleading consumers would not appear to fall within the FDA's asserted preemption of "claims that a drug's sponsor breached an obligation to plaintiff by making statements that FDA approved for inclusion in the drug's label." 71 Fed. Reg. at 3936. Statements approved for labels can obviously be misleading if they are de-coupled from important qualifications in the labels but omitted from the advertising.

¹¹⁶FDA believes that at least the following claims would be preempted by its regulation of prescription drug labeling: . . . (2) claims that a drug sponsor *breached an obligation to warn* by failing to include in an advertisement any information the substance of which appears anywhere in the labeling . . . (4) claims that a drug sponsor *breached an obligation to warn* by failing to include a statement in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the sponsor had an obligation to warn (unless FDA has made a finding that the sponsor withheld material information relating to the proposed warning before plaintiff claims the sponsor had the obligation to warn); (5) claims that a drug sponsor *breached an obligation to warn* by failing to include in labeling or in advertising a statement the substance of which FDA has prohibited in labeling or advertising . . .

71 Fed. Reg. at 3935–36 (emphases added).

¹¹⁷Pfizer targets consumers in its advertising, so the learned intermediary doctrine, see, e.g., *Lindsay v. Ortho Pharm. Corp.*, 637 F.2d 87, 91 (2d Cir. 1980) ("manufacturer's duty is to warn

If we have accurately described the relevant science and the contents of the Lipitor label and advertising, it is not reasonable to interpret the FDA's approval of cardioprotective language in the Lipitor label as protecting against actions based on misleading advertising. The FDA cannot reasonably be regarded as having addressed that issue or the untold number of other issues that might arise in a company's translation of FDA label approval into an advertising campaign. No systematic program requires express FDA consideration and approval of all of the content of all advertising.¹¹⁸ Nor is it clear that such a mandated systematic program would be desirable. The FDA's limited resources likely should be primarily focused on scientific review, not marketing claims.

B. Are State Law Actions Based on Misleading Advertising Preempted?

Given the FDA's limited role with respect to advertising, courts generally have not found the FDCA-FDA regulatory scheme to preempt actions based on false or misleading advertising. In a variety of contexts, courts have found

the doctor, not the patient"); *Bukowski v. CooperVision Inc.*, 592 N.Y.S.2d 807 (N.Y. App. Div. 3d Dept. 1993), which focuses on information communicated to professionals, may not be regarded as a complete defense to misleading consumer advertising actions. See *State ex rel. Johnson & Johnson Corp. v. Karl*, 647 S.E.2d 899 (W. Va. 2007); *Perez v. Wyeth Labs., Inc.*, 734 A.2d 1245 (N.J. 1999). But see *Beale v. Biomet, Inc.*, 492 F. Supp. 2d 1360, 1376 (S.D. Fla. 2007) (pre-*Karl* case finding *Perez* was an isolated decision); *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 547 n.30 (E.D. Pa. 2006) (dicta); *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 812 n.19 (N.D. Ohio 2004). Cf. *Vitanza v. Upjohn*, 214 F.3d 73, 78 (2d Cir. 2000) (noting *Perez*). It is difficult to rely on the learned intermediary doctrine in the face of knowledge that advertising to consumers has been shown to have an effect on physician prescribing patterns. Note 67 *supra*. In any event, Pfizer's information for physicians appears to incompletely describe the state of scientific knowledge with respect to cardioprotective effects on women. Qualifications appear to be incompletely offered to the medical community through the Lipitor label, which claims that results for women are inconclusive, text accompanying note 8 *supra*, but even there Pfizer does not acknowledge to physicians the absence of heart attack evidence for females by statins across RCT studies or the increased risk for women found in the ASCOT study. Nor does Pfizer include relevant information from the CASHMERE study, discussed in Section IV, which found no significant arterial thickening benefit for postmenopausal women.

¹¹⁸The Food and Drug Administration Amendments Act of 2007, Pub. L. 110-85, § 901(d)(2), 121 Stat. 939, Sept. 27, 2007, contains a provision under which regulators "may require the submission of any television advertisement for a drug . . . for review . . . not later than 45 days before dissemination of the television advertisement." The provision is codified at 21 U.S.C. § 353b(a).

state consumer protection and related laws not to be preempted.¹¹⁹ Where plaintiffs seek advertising disclosures that parallel those on an FDA-approved label, no conflict exists between the FDA's scientific judgment and state law causes of action. Both the FDA and the courts recognize the absence of conflict and reject preemption. Courts state that requirements consistent with the label create no conflict.¹²⁰ The FDA agrees.

FDA recognizes that FDA's regulation of drug labeling will not preempt all State law actions. The Supreme Court has held that certain state law requirements that parallel FDA requirements may not be preempted. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 . . . (1996) (holding that the presence of a State law damages remedy for violations of FDA requirements does not impose an additional requirement upon medical device manufacturers but "merely provides another reason for manufacturers to comply with federal law").¹²¹

Courts rule against preemption of advertising in part on the ground that the FDA claims no complete preemption in this context.¹²²

These rulings comport with the customary approach to preemption. Unlike the situation with respect to premarketing approval of medical devices,¹²³ legislation cannot be interpreted to have mandated preemption in the FDA-advertising context. Given congressional silence, a presumption

¹¹⁹*Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d 1228, 1233 (S.D. Fla. 2007) (sustaining pre-2004 state law advertising claims against Pfizer against preemption defense); *In re Medtronic, Inc., Implantable Defibrillator Litig.*, 465 F. Supp. 2d 886, 898 (D. Minn. 2006) (rejecting preemption claim with respect to advertising); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.* MDL 1699, 2006 WL 2374742, at *11, 12 (N.D. Cal. Aug. 16, 2006). See also *Mylan Labs., Inc. v. Matkari*, 7 F.3d 1130, 1138 (4th Cir. 1993) (allowing false representation claims with respect to drugs to proceed under the Lanham Act); *Midlothian Labs., L.L.C. v. PamLab, L.L.C.*, 509 F. Supp. 2d 1065, 1085–86 (M.D. Ala. 2007) (no preemption in part because FDCA is primarily concerned with safety and efficacy of drugs while Lanham Act focuses on truth or falsity of advertising claims); *Summit Tech., Inc. v. High-Line Med. Instruments Co.*, 933 F. Supp. 918, 933 (C.D. Cal. 1996) ("false statements are actionable under the Lanham Act, even if their truth may be generally within the purview of the FDA").

¹²⁰*Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d at 1233.

¹²¹Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922–4001, 2006 WL 160271.

¹²²*Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d at 1233; *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.* MDL 1699, 2006 WL 2374742 at *11 ("when the FDA believes that its regulations preempt state law it says so").

¹²³*Riegel v. Medtronic, Inc.*, 128 S. Ct. 999 (2008).

exists favoring the validity of exercises of the states' historical police powers.¹²⁴ No preemption provision appears in the prescription drug provisions of the FDCA.¹²⁵ In fact, a clause preserves state law claims.¹²⁶

C. Claims Attacking Advertising Consistent with Labels May be Preempted

At least one case has found state advertising law to be preempted when state law requirements would conflict with the FDA-approved label. In *Pennsylvania Employees Benefit Trust Fund v. Zeneca Inc.*,¹²⁷ plaintiffs sued pharmaceutical companies (Zeneca) alleging that a marketing campaign for the acid reflux disease drug, Nexium, was deceptive because it misleadingly advertised Nexium as an improvement on another reflux drug, Prilosec (omeprazole). Zeneca obtained FDA approval for the Nexium label. The label reported the results of four studies comparing the healing rate for Nexium compared to Prilosec. After eight weeks of treatment, all four studies showed a higher rate of healing on Nexium than on Prilosec, though most of the differences were not statistically significant.¹²⁸ The approved label thus included data supporting, albeit modestly, the advertising.

This consistency between the advertising and the approved label was the core of Zeneca's preemption defense.¹²⁹ Allowing a state law cause of

¹²⁴E.g., *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947); *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (“[B]ecause the States are independent sovereigns in our federal system, [it] ha[s] long [been] presumed that Congress does not cavalierly pre-empt state-law causes of action.”).

¹²⁵21 U.S.C. §§ 301–397.

¹²⁶The Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962), states:

Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

See Sharkey, *supra* note 111, at 241 n.80.

¹²⁷499 F.3d 239 (3d Cir. 2007).

¹²⁸Nexium Label, NDA 21-153/S-020, June 6, 2005, at 9–10, available at (http://www.fda.gov/MEDwatch/SAFETY/2005/Jun_PI/Nexium_PI.pdf), accessed Jan. 11, 2008.

¹²⁹Defendants' Opening Brief in Support of Their Motion to Dismiss, *Pennsylvania Employee Benefit Trust Fund v. Zeneca, Inc.*, Civ. No. 05-075-SLR, filed July 1, 2005, at 13–16 (“the FDA-approved Nexium labeling conveys the very same message” of Nexium's superiority over Prilosec).

action to deem the *advertising* misleading would have implicated the FDA's conclusion that the *label* was sufficiently accurate to merit approval.

Faced with this situation, the U.S. Court of Appeals for the Third Circuit, over a dissent, applied "implied conflict preemption" to preclude a state law cause of action based on allegedly misleading Nexium advertising. Implied conflict preemption invalidates state laws when, despite no congressional command, state law conflicts with federal law.¹³⁰ The Third Circuit relied in part on the comprehensiveness of FDA regulation of labeling and advertising.¹³¹ The specific conflict identified in the case was that "FDA-approved labeling is the basis for allegedly fraudulent representations made in prescription drug advertising."¹³² Although the Third Circuit opinion is phrased broadly, the facts of the case may support a finding of a state-federal conflict.

The situation appears to differ with respect to Lipitor's advertising. The FDA-approved Lipitor label included information noting the absence of evidence with respect to women. Pfizer's advertising did not disclose differences between male and female results in its own or other statin studies, or that the Lipitor ASCOT study showed increased risk to women, or that the Lipitor CASHMERE study found no significant effect on arterial thickening in reasonably healthy women. Although advertising cannot be expected to include all of the detail in a label, a state might reasonably conclude that it is misleading to fail to disclose in advertising that the claimed cardioprotective effect rests on no RCT scientific support with respect to a substantial part (the female part) of the target audience.

For preemption purposes, the Lipitor situation therefore differs from *Pennsylvania Employees Benefit Trust*. There, the challenged advertising with respect to Nexium was based on key information in the FDA-approved label. To find a false advertising cause of action preempted in the case of Lipitor, one would have to conclude that the label revealing the absence of results for women is somehow inconsistent with a state law cause of action based on advertising that failed to reveal the absence of results for women. There is no federal-state conflict.

¹³⁰*Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992).

¹³¹499 F.3d at 247–52.

¹³²*Id.* at 251.

A broader reading of *Pennsylvania Employees Benefit Trust* is independent of the labeling-advertising facts in the case. That broader view is that the FDA's substantial scheme of drug regulation preempts all state law claims without regard to the content of the FDA-approved label or the content of the advertising. The discussion above suggests that this reading is inconsistent with relevant preemption doctrine. Neither Congress nor the FDA support such a broad view of preemption. Such a reading would unduly fail to discourage misleading advertising. If preemption nullifies all state law causes of action regardless of advertising's content, then drug advertising is not bound by the label except in cases where the FDA chooses to intervene. A manufacturer's advertising could falsely claim that a drug cures many diseases, and millions of people could seek, and some obtain, the drug because of the advertising. The FDA could require the manufacturer to change its advertising or otherwise seek enforcement, but misled consumers would have no basis on which to recover their money at their option.

D. Implications of the Statin Experience for Preemption

The Lipitor advertising experience provides evidence bearing on broader preemption issues. Debate exists about whether the FDA satisfactorily enforces its statutory mandates¹³³ and whether greater institutional agency competence should trump judicial action.¹³⁴ This study supplies information about whether FDA institutional competence is so superior as to warrant precluding state enforcement activity.

¹³³Compare, e.g., Institute of Medicine, *supra* note 6; Curt D. Furberg et al., *The FDA and Drug Safety*, 166 *Arch. Internal Med.* 1938 (2006); U.S. House Committee on Gov. Reform—Minority Staff Special Investigations Division, *Prescription for Harm: The Decline in FDA Enforcement Activity* (June 2006) (prepared for Rep. Henry A. Waxman), available at (<http://oversight.house.gov/documents/20060627101434-98349.pdf>), accessed Jan. 13, 2008, with FDA White Paper, *Protecting the Public Health: FDA Pursues an Aggressive Enforcement Strategy* (June 2003), available at (<http://www.fda.gov/oc/whitepapers/enforce.html>), accessed Jan. 13, 2008.

¹³⁴Compare, e.g., Richard A. Epstein, *Why the FDA Must Preempt Tort Litigation: A Critique of Chevron Deference and a Response to Richard Nagareda*, 1 *J. Tort L.* art. 5 (2006), available at (<http://www.bepress.com/jtl/vol1/iss1/art5>); Peter H. Schuck, *FDA Preemption of State Law in Drug Regulation: Finding the Sweet Spot*, *Roger Williams L. Rev.* (2008) (forthcoming), with Richard A. Nagareda, *FDA Preemption: When Tort Law Meets the Administrative State*, 1 *J. Tort L.* art. 4, 3 (2006), available at (<http://www.bepress.com/jtl/vol1/iss1/art4>); Catherine M. Sharkey, *Federalism in Action: FDA Regulatory Preemption in Pharmaceutical Cases in State Versus Federal Courts*, 15 *J.L. & Pol'y* 1013 (2007).

1. Preemption and the Lipitor Advertising

Statins, including Lipitor, are among the world's most widely used drugs, with cumulative sales of tens of billions of dollars. Yet for years Pfizer appears to have been able to advertise Lipitor's cardioprotective effect without including material scientific information relevant to millions of consumers. The world's top-selling drug's consumer advertising about efficacy likely was inadequately regulated by the FDA. This questionable regulation has occurred notwithstanding concrete evidence, consistently available at least since 2004, that clinical trials do not support claims of cardioprotection for women in a primary prevention context.¹³⁵ If the FDA has not adequately regulated a highly visible drug with an enormous audience, one might be skeptical about regulation of less visible drugs with smaller potential patient populations. This study's findings thus suggest that preempting traditional advertising regulation is questionable not simply because courts have traditional expertise in addressing claims of fraud and misleading sales practices, and in balancing the interests at stake with respect to commercial speech. Preemption is doubtful policy because the underlying assumption—sufficient institutional competence to sufficiently monitor and discipline—may be inaccurate. State law causes of action continue to have an important policy role in generating proper incentives to communicate accurately with consumers.

2. Implications of the Lipitor Experience for Broader Preemption Questions

This Lipitor case study also has implications for preemption debates beyond advertising—debates about warnings and defenses based on compliance with FDA rules. Legal analyses of these matters generally do not account for the reality of FDA performance. As exemplified here and elsewhere, that performance is sometimes seriously incomplete.¹³⁶ In addition to the Lipitor instance of questionably managing one of the world's most visible drugs, specific instances of the drug regulatory system's inadequacy have long been

¹³⁵Walsh & Pignone, *supra* note 12.

¹³⁶Furberg et al., *supra* note 133; Curt D. Furberg, Decisions by Regulatory Agencies: Are They Evidence Based? 8 *Trials* 13 (2007).

recognized.¹³⁷ At times, critics regard the FDA as having been more protective of industry than of the public.¹³⁸

Bottom-line analyses that go beyond anecdotal information are troublesome. The FDA maintains an Adverse Event Reporting System (AERS) that includes drug reaction reports from manufacturers, health-care professionals, and consumers.¹³⁹ Analysis of AERS from 1998 through 2005 shows reported serious adverse drug events increasing by 260 percent from 34,966 to 89,842.¹⁴⁰ Fatal adverse drug events increased by 270 percent from 5,519 to 15,107 and far outpaced the growth in the number of prescriptions.¹⁴¹ Based on these data, analysts concluded that there was a “marked increase in reported deaths and serious injuries associated with drug therapy over the study period.”¹⁴²

In exploring the sources of limited FDA performance, Furberg et al. and others highlight several FDA and AERS features that resonate with the possible mismarketing of Lipitor. In this respect our findings add weight to the views of those concerned about inadequate FDA performance and the undesirability of foreclosing supplementary remedies via state law in nonadvertising contexts. At least three concerns about FDA regulation of safety matters seem supported by analogous findings in this study. These concerns relate to study design, regulation of postmarketing behavior, and limited expertise and resources.

¹³⁷Thomas J. Moore, *Deadly Medicine: Why Tens of Thousands of Heart Patients Died in America's Worst Drug Disaster* (1995).

¹³⁸Devra Davis, *The Secret History of the War on Cancer* 236, 420 (2007) (FDA recommends a limit for exposure to carcinogens in food additives and adhesives but not in bubble bath used on children and tells consumers to seek manufacturer guarantee of level being below FDA-recommended level; FDA approval of aspartame plagued with conflicts of interest); Teresa Moran Schwartz, *Punitive Damages and Regulated Products*, 42 *Am. U. L. Rev.* 1335, 1348–52 (1993); see Institute of Medicine, *supra* note 67, at 73–74 (reviewing concerns about agency capture).

¹³⁹21 C.F.R. § 314.80; (<http://www.fda.gov/cder/aers/default.htm>); (<http://www.fda.gov/medwatch/index.html>) (both accessed Mar. 8, 2008).

¹⁴⁰Thomas J. Moore, M.R. Cohen & C.D. Furberg, *Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998–2005*, 167 *Arch. Internal Med.* 1752 (2007).

¹⁴¹*Id.*

¹⁴²*Id.*

First, study design problems at the preapproval stage are said to permit serious, uncommon adverse events to go undetected.¹⁴³ Study design limitations—in particular, too few women—in ASCOT and other statin studies were tolerated by the FDA, thereby allowing marketing and approval with insufficient information to detect statistically significant male-female differences. This gender-related design failure is all the more troublesome because of a history of having to withdraw from the market drugs that had greater health risks for women and the FDA's knowledge of that pattern.¹⁴⁴

Second, postmarketing underreporting and failure of drug manufacturers to fulfill postmarketing safety commitments contribute to safety problems.¹⁴⁵ Postmarketing behavior contributed to the possible mismarketing of Lipitor. Specifically, assume that Lipitor's approval for cardioprotection was warranted for women despite the ASCOT study's limitations. The increased risk suggested by ASCOT's results for women have nevertheless literally screamed out for studies with enough women to establish Lipitor's possible cardioprotective, or increased risk, effects on CHD, MI, and NFMI for women. Studies not done can signal a questionable regulatory system¹⁴⁶ as strongly as studies with flawed analysis. This problem is exacerbated by the FDA allowing a single study to support drug approval,¹⁴⁷ a practice fraught with danger in any scientific endeavor.¹⁴⁸ The Food and Drug Administration Amendments Act of 2007 (FDAA)¹⁴⁹ enhances FDA authority to require

¹⁴³Furberg et al., *supra* note 133.

¹⁴⁴U.S. General Accounting Office, *Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women* (letter from Janet Heinrich to Senators Harkin, Snowe, and Mikulski and Representative Waxman, Jan. 19, 2001).

¹⁴⁵Furberg et al., *supra* note 133.

¹⁴⁶A study funded by Merck & Co., Inc. assessed lovastatin's performance in women in the AFCAPS cohort. Clearfield et al., *supra* note 33. As Figure 1 shows, AFCAPS had the most favorable efficacy results for women of the studies in this analysis. Pfizer's Lipitor had the least favorable efficacy results for women. Interestingly, to our knowledge, no article has been funded by Pfizer assessing Lipitor's cardioprotective performance in women not at high risk.

¹⁴⁷Hutt et al., *supra* note 14, at 677.

¹⁴⁸Richard Lempert, *Empirical Research for Public Policy: Observations and Cautions*, 5 *J. Empirical Legal Stud.* (2008) (forthcoming).

¹⁴⁹Pub. L. 110-85, 121 Stat. 823 (2007).

postmarket clinical or other studies,¹⁵⁰ but this process requires detailed FDA findings, is limited to safety, does not include studies to assure efficacy,¹⁵¹ and possibly will not be implemented for years to come.¹⁵²

Third, the FDA's limited expertise and resources in drug safety and health are believed to contribute to undue adverse event risk.¹⁵³ The Lipitor experience suggests that the FDA's monitoring of advertising also suffers from expertise or resource limitations. Pfizer is reported to have spent more than \$258 million to advertise Lipitor from January 2006 to February 2008.¹⁵⁴ That amount is roughly 50 percent of an entire year's FDA budget for its Human Drug Program.¹⁵⁵ That budget is completely dwarfed by both the drug industry's consumer advertising, about \$4 billion in 2005, and total promotional spending, about \$30 billion in 2005.¹⁵⁶ However conscientious the FDA is, it is unrealistic to expect it to keep up with an industry that can afford such expenditures. As Robert Rabin has noted in the context of discussing a strong regulatory FDA compliance-based defense, the case for broad reliance on FDA action "is seriously compromised by real-world considerations."¹⁵⁷ The FDAA will increase FDA funding¹⁵⁸ but its resources will continue to be dwarfed by those of drug companies.

Concrete contributions of tort law to knowledge of drug company behavior suggest that the additional information developed by the tort

¹⁵⁰FDAA § 901(a), § 505, 121 Stat. at 922–26 (2007) (to be codified at 21 U.S.C. § 355(o),(p)).

¹⁵¹*Id.*

¹⁵²Margaret Gilhooley, *Addressing Potential Drug Risks: The Limits of Testing, Risk Signals, and the Drug Reform Legislation*, 59 S.C. L. Rev. 347, 351 & n.11 (2008) (noting FDA official's statement that it may take years to implement some of the FDAA provisions).

¹⁵³Furberg et al., *supra* note 133; Institute of Medicine, *supra* note 67, at 193 (FDA "lacks the resources needed to accomplish its large and complex mission today").

¹⁵⁴Saul, *supra* note 6.

¹⁵⁵See <http://www.fda.gov/oc/oms/ofm/budget/2008/TOC.htm> ("Human Drugs" link), accessed Mar. 8, 2008.

¹⁵⁶Donohue et al., *supra* note 109, at 676 (tbl. 1).

¹⁵⁷Robert Rabin, *Reassessing Regulatory Compliance*, 88 Geo. L.J. 2049, 2082 (2000).

¹⁵⁸FDAA § 101 et seq., 121 Stat. at 825 (2007).

system is useful and that strong preemption is therefore doubtful policy.¹⁵⁹ When drug companies withhold or obscure material information about adverse events from the FDA and scientific journals, a disturbingly common practice,¹⁶⁰ the additional resources provided by legal discovery and investments by plaintiffs' lawyers can sometimes help remedy the nondisclosure. For example, private legal actions uncovered the withholding or suppression of critical safety data from the *New England Journal of Medicine* with respect to Vioxx¹⁶¹ and possible senior executive unlawful encouragement of "off label" use of Zyprexa.¹⁶² Other examples of drugs and devices that survived FDA scrutiny but ultimately caused substantial harm abound.¹⁶³ Drug company misbehavior has become such a serious problem that the *Journal of the American Medical Association (JAMA)* requires independent statistical verification of results in articles resulting from sponsored research. "[I]ndustry-sponsored studies in which the data analysis has been conducted only by

¹⁵⁹Cf. Rabin, *supra* note 157, at 2069 ("[I]f we are substantially dependent on the tort system to provide the educational function of revealing massive cover-ups of health information by industries like asbestos, or occasional efforts to conceal risk information from regulatory agencies like the FDA, then it is undeniably the case that tort law is serving a positive function of some consequence.") (footnote omitted).

¹⁶⁰Phil B. Fontanarosa & Catherine D. DeAngelis, JAMA's Policy on Industry Sponsored Studies, 332 *Brit. Med. J.* 176-77 (2006) (numerous "serious scientific and ethical lapses involving industry and industry sponsored studies, such as incomplete reporting of data on celecoxib, suppression of studies of paroxetine, and delayed reporting of design defects in implantable cardioverter defibrillators, have resulted in doctors and the public now having an unprecedented lack of trust and confidence in manufacturers of drugs and devices").

¹⁶¹Gregory D. Curfman, Stephen Morrissey & Jeffrey M. Drazen, Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N Engl J Med* 2000;343:1520-8, 353 *New Eng. J. Med.* 2813 (2005); Gregory D. Curfman, Stephen Morrissey & Jeffrey M. Drazen, Expression of Concern Reaffirmed, 354 *New Eng. J. Med.* 1193 (2006); Bruce M. Psaty & Richard A. Kronmal, Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment: A Case Study Based on Documents from Rofecoxib Litigation, 299 *JAMA* 1813 (2008). Litigation also contributed to establishing the use of unacknowledged authors and later attribution of "authorship to academically affiliated investigators who often did not disclose industry financial support." Joseph S. Ross et al., Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A Case Study of Industry Documents from Rofecoxib Litigation, 299 *JAMA* 1800 (2008).

¹⁶²Alex Berenson, Ely Lilly E-Mail Discussed Unapproved Use of Drug, *N.Y. Times*, Mar. 15, 2008.

¹⁶³Schwartz, *supra* note 138, at 1348-52.

statisticians employed by the company sponsoring the research will not be accepted for publication in *JAMA*.¹⁶⁴

When studies consistently reveal uncertain efficacy for a group as large as women, a system that imposes no duty to further test, but allows continued marketing to millions of women, is insufficient. In the drug arena, as in other areas of tort law, it is too hopeful to expect ready detection of efforts to conceal or spin health information. Even an extremely well-functioning FDA would likely miss concerted efforts to hide or shade results. The actual functioning of the FDA may unintentionally promote concealment and spin. *JAMA*'s editors have noted that "manipulation of studies and misrepresentation of study results could not occur without the cooperation (active and tacit) of . . . the FDA."¹⁶⁵ Tort litigation can play an important role for drugs, as it has in uncovering questionable behavior in the tobacco and asbestos industries.¹⁶⁶

Beyond drug safety, state law causes of action also can contribute to proper incentives with respect to studies of drug efficacy. With all of the attention on drug safety, exemplified in the FDAA and most drug-related lawsuits, the costs of questionable efficacy claims are less visible than they should be. It is shameful that, while accumulating billions of dollars in profits from statins, no drug company has yet published a study adequately powered to test the efficacy of statins with respect to primary prevention of women's cardiovascular outcomes. That the FDA felt powerless to require such studies, or felt that such studies were not needed, establishes that it should not be the sole force shaping this aspect of health-care policy. The economic costs of the questionable efficacy claims for statins may exceed the economic cost of their adverse side effects. The flexibility of the common law and consumer protection laws can contribute to creating appropriate incentives for socially and economically beneficial behavior.

We do not suggest that the FDA should not have the dominant role in regulating drugs. One can acknowledge generally greater agency ability to

¹⁶⁴Phil B. Fontanarosa, Annette Flanagan & Catherine D. DeAngelis, Reporting Conflicts of Interest, Financial Aspects of Research, and Role of Sponsors in Funded Studies, 294 *JAMA* 110, 111 (2005).

¹⁶⁵Catherine D. DeAngelis & Phil B. Fontanarosa, Impugning the Integrity of Medical Science: The Adverse Effects of Industry Influence, 299 *JAMA* 1833 (2008).

¹⁶⁶See, e.g., Paul Brodeur, *Outrageous Misconduct: The Asbestos Industry on Trial* (1985); Peter Pringle, *Cornered: Big Tobacco at the Bar of Justice* (1998).

address matters without foreclosing other checks on drug company behavior. However, a primary role need not be an exclusive role. Theoretical structural arguments based on presumed agency expertise are not persuasive against a history of specific agency failures. Arguments favoring exclusive agency authority should be based on performance, not theoretical conjecture. Given the resources and past behavior of the drug industry, it is likely that more than one check on the industry is needed. Whether the additional check best takes the form of tort actions is difficult to establish, but, for now, the tort system is the leading existing additional regulatory check.

VII. CONCLUSION

Meta-analysis of leading RCT drug trials finds no evidence that statins protect women against NFMI or fatal CHD in a primary prevention context. Unqualified advertising claims of protection against heart attacks therefore may be misleading. Existing legal doctrine supports the viability of state law claims based on questionable advertising.

Our results also counsel against broad preemption of state law warning claims, or broad application of regulatory compliance defenses, against the background of drug company misbehavior, imperfect FDA performance, and limited resources. The progression from the underlying scientific study of Lipitor, ASCOT, expressly reporting no benefit for women, to Pfizer's advertising of the world's best-selling drug while failing to disclose the absence of benefit for women raises grave concern about the FDA's regulation of drugs and drug company candor.

This study also has implications for reining in health-care costs. The growing¹⁶⁷ multibillion dollar statins market significantly contributes to increasing health-care expenses. Our findings indicate that each year reasonably healthy women spend billions of dollars on drugs in the hope of preventing heart attacks but that scientific evidence supporting their hope does not exist.

¹⁶⁷Raymond et al., *supra* note 2.