IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	MDL No. 2:14-mn-02502-RMG
This Document Relates to All Actions	

PLAINTIFFS' MEMORANDUM OF LAW IN RESPONSE TO PFIZER, INC.'S MOTION TO EXCLUDE EXPERT TESTIMONY AND CLAIMS THAT LIPITOR IS NOT EFFECTIVE FOR AND SHOULD NOT BE APPROVED FOR PRIMARY PREVENTION IN WOMEN

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INTRODUCTION

The motion of Defendant Pfizer Inc. ("Pfizer") to exclude, under Fed. R. Evid. 702, expert testimony and claims that Lipitor is not effective for primary prevention in women proceeds from a fundamental mischaracterization of the opinions of the four experts – Barbara Roberts, M.D., Martin Wells, Ph.D., G. Alexander Fleming, M.D., and John Abramson, M.D., M.Sc. – whose testimony it contends are at issue. Contrary to Pfizer's formulation, Plaintiffs do not assert, and their experts do not opine, that Lipitor is *not* effective for primary prevention in women. Rather, these experts opine that there is insufficient evidence to show that Lipitor *is* effective for primary prevention in women. The distinction between these two statements is both enormous and significant, in precisely the same way that the burden of proof at a trial differentiates between what a plaintiff has affirmatively proven, and what a defendant may demonstrate to be simply unproven. As the traditional aphorism reminds, "absence of evidence is not evidence of absence." Here, Plaintiffs' experts opine the former, but Pfizer seeks to preclude them from testifying to the latter.[1]

Construing Pfizer's motion to be addressed to the opinions that Plaintiffs' experts do offer, rather than the opinion they don't, there is no basis to exclude the well-reasoned opinions of these highly qualified experts. Each of their opinions is based on examination of the epidemiological evidence, including randomized clinical trials, meta-analyses, and observational studies. These studies show that the issue of Lipitor's efficacy in women for primary prevention – that is, efficacy in preventing coronary heart disease in women with no prior history of such events – remains an open question. While *lack* of efficacy has not been demonstrated, neither has efficacy in this particular population been demonstrated. Indeed, as Pfizer admits, the Lipitor label itself reports that, in one of Pfizer's clinical trials, the "results for women were inconclusive." *See* Pfizer Br. at

[1] Pfizer also styles it motion to exclude testimony and claims that Lipitor "should not been approved for primary prevention in women." *See* Pfizer Br. at cover and 1. None of Plaintiffs' experts, however, offers the opinion that Lipitor should not approved for primary prevention in women and Pfizer nowhere in the brief addresses such a claim.

11. In light of this statement, the opinions of Plaintiffs' experts should be seen for what they are – incontrovertible assessments of the scientific evidence.

It is easy to understand why Pfizer would contest what the Lipitor label itself reports: as described by Dr. Abramson, despite clear evidence that the benefits of Lipitor in women were unproven, Pfizer orchestrated an elaborate marketing campaign to "market Lipitor to women for the treatment of increased cholesterol." Pfizer Exhibit 1 at 114.[2] Indeed, as Dr. Abramson found, Pfizer's "[s]trategies for increasing Lipitor sales outlined in the 2003 Business Plans were based in large part on the misleading implication that statins had been shown to improve health outcomes for primary prevention [in] women." *Id.*

This issue is significant because of the increased risk of diabetes that has been shown to exist, especially in women. While this risk might be outweighed, for some patients, in the face of certain benefits in the reduction of coronary heart disease, the risk/benefit analysis looks quite different if the benefits are uncertain or unknown. Thus, Pfizer's attempts to persuade doctors and patients of the benefits of Lipitor in women prevented those doctors and patients from appropriately assessing the value of taking the drug. (This problem was, of course, compounded by Pfizer's failure to warn about the risks of diabetes.)

Having manipulated both sides of the risk/benefit equation – overstating the benefits while failing to warn of the dangers – Pfizer now seeks to prevent Plaintiffs from presenting evidence that the benefits of Lipitor were in fact overstated for women without prior coronary heart disease events. Because the uncertainty of efficacy in that population is clear from the studies considered by Plaintiffs' experts, Pfizer's motion to preclude the testimony of these experts under Rule 702 should be denied in its entirety.

[2] For the Court's convenience, Plaintiffs do not resubmit exhibits already provided by Pfizer on this motion. Accordingly, citations in the form of "Pfizer Ex." refer to Pfizer's exhibits from its Motion to Exclude Expert Testimony and Claims that Lipitor is Not Effective for and Should Not be Approved for Primary Prevention in Women (Dkt. 970).

Yoked to Pfizer's Rule 702 motion is another, entirely different motion. Pfizer seeks to preclude introduction of Plaintiffs' evidence about the lack of evidence of efficacy for primary prevention in women on the basis that such evidence is preempted. Separate and apart from whether it is appropriate to include this argument in a motion intended to address the admissibility, under Rule 702, of expert opinions, Pfizer's preemption arguments should be rejected. Pfizer suggests that Plaintiffs wish to argue that Lipitor should not have been approved for use in women, but, as discussed above, that is not Plaintiffs' position. Plaintiffs intend to show that Pfizer's marketing distorted and overstated the benefits of Lipitor beyond what the evidence could support. Pfizer cannot show that any claim or argument Plaintiffs make would create a conflict between state-law duties and federal law, the *sine quo non* of preemption in this context. Pfizer's motion should be denied in its entirety.

BACKGROUND

Lipitor (atorvastatin calcium) is a synthetic lipid-lowering drug that is a member of the cholesterol-lowering class of drugs called statins, or more formally known as 3-hydroxy-3-methylglutaryl-coenzyme A (or HMG-CoA) reductase inhibitors. HMG-CoA reductase is the rate-limiting enzyme that converts 3-hydroxy-3 methylglutaryl-coenzyme A to mevalonate, which is a precursor of sterols, including cholesterol. Thus statins, including Lipitor, effectively diminish the rate of cholesterol synthesis in the human liver. Pfizer Ex. 1 at ¶ 23.

Lipitor was developed by Parke-Davis, a division of Warner-Lambert. Pfizer acquired Warner-Lambert and Lipitor in June 2000. The first statin approved by the FDA was Mevacor (generic name lovastatin), in 1987. Lipitor was approved by the FDA in December 1996 and went on sale in early 1997. Since then, Lipitor has become the biggest-selling prescription drug of all time. Lipitor lost its patent protection in 2011, but has sold more than $130 billion worldwide and over 29 million patients in the U.S. have been prescribed the drug. *Id.* at 24-25.

Lipitor was initially approved for the lowering of cholesterol and triglycerides in people with several conditions causing hyperlipidemia. These indications were for the lowering of lipid levels, but not the prevention of any clinical outcome related to the prevention of cardiovascular

disease. Lipitor's indication was subsequently expanded to include indication to reduce the risk of a variety of cardiovascular disease events, including heart attacks and strokes in particular patient populations. *See* Pfizer Ex. 26.

Plaintiffs do not here contest that Lipitor is effective in lowering cholesterol. Nor do they contest here that Lipitor is effective in reducing cardiovascular disease events in men, or that Lipitor is effective in preventing cardiovascular disease events in women with preexisting cardiovascular disease, a use known as secondary prevention. That is, Plaintiffs do not contend that Lipitor, on the whole, does not work. The issue is whether there is sufficient evidence to determine that Lipitor is effective in reducing cardiovascular disease events specifically in women who do not have preexisting cardiovascular disease, in other words, women taking it for primary prevention.

As discussed above, this question is significant because, like all drugs, Lipitor has side effects. If it did not, doctors could prescribe it without clear evidence of efficacy, in the hope that it might work, knowing there would be no downside in any event. But because Lipitor can cause diabetes specifically in women, it may be important for a woman without preexisting cardiovascular disease to know that Lipitor will actually benefit her, before she runs the risk of its side effects, including the increased risk of diabetes. If evidence of efficacy is lacking, that may be a consideration in the decision whether to run the risk of known side effects. Thus, it is not necessary to know that Lipitor does not work to consider carefully whether it is worth the risks; it may be sufficient to know that the benefit is unproven for a doctor or patient to decide it would not be worth running the risk of diabetes.

After Lipitor was initially approved to lower cholesterol, Pfizer performed clinical trials in an effort to obtain evidence that it was also effective in reducing cardiovascular disease events.[3] The results of these trials were sufficient to persuade the FDA to permit an expansion of the

[3] For a discussion of clinical trials and epidemiological evidence generally, *see* Plaintiffs' Steering Committee Memorandum of Law in Opposition to Pfizer's Motion to Exclude Plaintiffs' Expert Testimony on the Issue of General Causation ("Pltf. Causation Br.") at 9-11.

indication on the Lipitor label to include the prevention of these events. Some trials involved only men, while others involved both men and women. Some trials measured the results of Lipitor in those with preexisting cardiovascular disease and thus provide no information about its efficacy for primary prevention.

One of the trials on which Pfizer placed great reliance in its claim of efficacy for primary prevention was the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), and in particular, the so-called Lipid-Lowering Arm ("LLA") of that trial. *See* Pfizer Ex. 26. As Pfizer reported on the Lipitor label:

> LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the LIPITOR group) or nonfatal MI (108 events in the placebo group vs. 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. *Due to the small number of events, results for women were inconclusive*.

Id. (emphasis added). Plaintiffs contend that ASCOT did not establish that Lipitor is effective for primary prevention in women. The proper interpretation of the ASCOT study is a focus of both this motion and Pfizer's motion to exclude evidence of general causation.

The other significant clinical trial that addressed primary prevention in women was the CASHMERE trial, which included only women. *See* Pfizer Ex. 3 at ¶ 24. At its inception, CASHMERE was regarded as sufficiently important to warrant an article announcing its design. *Id.* Pfizer has not published the results of CASHMERE in a peer-reviewed journal and nowhere mentions it in its motion.[4] As discussed below, CASHMERE showed no significant benefit in those taking Lipitor.

[4] Another trial that Pfizer used to show efficacy was the Collaborative Atorvastatin Diabetes Study (CARDS) study. Because CARDS was specifically a study of the effect of Lipitor in those with preexisting diabetes, however, it is not helpful here, where Plaintiffs are women without preexisting diabetes who contend they developed new onset diabetes as a result of taking Lipitor.

PLAINTIFFS' EXPERTS

Martin Wells, Ph.D.

Dr. Wells opines that "[t]here is no statistically significant evidence to support the claim that statins provide primary cardioprotection for women." Pfizer Ex. 3 at ¶ 4. In reaching this opinion, Dr. Wells analyzed leading randomized control clinical trials evaluating statins and reviewed meta-analyses of others. Pfizer Ex. 3 at ¶ 4.[5] In particular, Dr. Wells analyzed the ASCOT trial to determine whether the results in women could be assumed to be the same as in men, as Pfizer has claimed.

Pfizer does not challenge Dr. Wells' qualifications to provide this statistical analysis as Dr. Wells is the Charles A. Alexander Professor of Statistical Sciences at Cornell University, a Professor of Biostatistics and Epidemiology at Cornell Weill Medical School, as well as a Professor of Social Statistics and the Director of Research in the School of Industrial and Labor Relations at Cornell University. Dr. Wells is also a Fellow of the American Statistical Association, the Royal Statistical Society, Institute of Mathematical Statistics and an elected member of the International Statistics Institute. Pfizer Ex. 3 at ¶ 2.

Pfizer's only criticism of Dr. Wells' qualifications is that he is not a physician and has no clinical expertise. *See* Pfizer Br. at 18. However, Dr. Wells is providing a statistical opinion, not a medical opinion; accordingly, Pfizer's criticism has no bearing on his opinions.

Barbara Roberts, M.D.

Dr. Roberts opines that there is no convincing evidence that Lipitor is effective for primary prevention of heart disease in women. Pfizer Ex. 2 at 4. Dr. Roberts also states that Lipitor increases the risk of developing diabetes in women, *see* Pfizer Ex. 2 at 26; that opinion is the subject of Pfizer's motion to exclude evidence that Lipitor can cause diabetes.

Dr. Roberts reached her opinion that there is no convincing evidence that Lipitor is effective for primary prevention of heart disease in women by analyzing and critiquing various relevant studies, including the ASCOT, JUPITER, CARDS, and ASPEN studies. Pfizer Ex. 2 at

[5] For a discussion of meta-analyses generally, *see* Pltf. Causation Br. at 11-14

4-8. Since 1977, Dr. Roberts has been in cardiology practice in Providence, Rhode Island and on the clinical faculty at the Alpert Medical School of Brown University. She currently holds the rank of Associate Clinical Professor of Medicine and is the Director of the Women's Cardiac Center at the Miriam Hospital. Dr. Roberts is certified by the American Board of Internal Medicine and the American Board of Cardiovascular Diseases. Pfizer Ex. 2 at 1-2.

John Abramson, M.D.

Dr. Abramson will testify that physicians and patients were not adequately, timely and sufficiently informed about the significant risks of clinically meaningful hyperglycemia and new-onset diabetes associated with Lipitor therapy. Pfizer Ex. 1 at ¶ 22. Dr. Abramson will also testify that physicians and patients were not adequately informed that the chief piece of scientific evidence supporting the recommendation to initiate Lipitor therapy for the primary prevention of cardiovascular disease in women — the ASCOT trial — did not demonstrate a benefit in women. Pfizer Ex. 1 at ¶ 22. Ultimately, it is Dr. Abramson's opinion that this information would have been of critical importance to physicians and patients trying to make evidence-based decisions about what role, if any, Lipitor should have played in the primary prevention of heart disease in women given the significantly increased risk of clinically meaningful hyperglycemia and new-onset diabetes associated with it. Pfizer Ex. 1 at ¶ 22.

Dr. Abramson is a medical doctor licensed to practice medicine in the State of Massachusetts since 1982. Pfizer Ex. 1 at ¶¶ 1-2. He currently teaches at Harvard Medical School and has been a Lecturer in the Department of Health Care Policy since 2008. While Dr. Abramson does rely upon the statistical analysis from Dr. Wells, he also evaluates the data at issue. For instance, Dr. Abramson notes that "although the CTT patient-level meta-analyses of 2005, 2010, 2012, and 2015 provide information about efficacy, they fail to provide information about the efficacy of cholesterol-lowering therapy in primary prevention of fatal and nonfatal CAD in women." Pfizer Ex. 1 at ¶ 248.

G. Alexander Fleming, M.D.

Dr. Fleming has been board certified in Internal Medicine since 1981, and board certified in the subspecialty of Endocrinology and Metabolism since 1984. Dr. Fleming had a 12-year tenure with the FDA, retiring as the Supervisory Medical Officer in the Division of Metabolism and Endocrine Drug Products in 1998. Pfizer Ex. 4 at 1.

Dr. Fleming's opinions relate to the labeling of Lipitor, including the FDA's process and methods for health risk assessments, health hazard evaluations, safety reporting requirements, and labeling review, approval, and updating. Pfizer Ex. 4 at 4. Dr. Fleming builds upon the expertise of Dr. Wells in regards to the evidence of the effectiveness of Lipitor in primary prevention with women, to reach his opinion that the labeling for Lipitor is insufficient. Pfizer Ex. 4 at 35, 39. Significantly, Dr. Fleming offers no general opinion about the lack of evidence for efficacy in women for primary prevention. Rather, Dr. Fleming opines only that Pfizer's ASCOT trial did not demonstrate efficacy in women and that the description of the ASCOT trial on the Lipitor label is misleading on that point.

LEGAL STANDARDS

Pfizer relies upon the United States Supreme Court's decision in *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993) and the subsequent case law in its attempt to exclude the Plaintiffs' experts' testimony.[6] However, as detailed below, it is well established that the Fourth Circuit evaluates the methodology not the conclusions of an expert in conducting its *Daubert* analysis and under the broad discretion of the Court, rejection of expert testimony is the exception rather than the rule.

"All *Daubert* demands is that the trial judge make a 'preliminary assessment' of whether the proffered testimony is both reliable and helpful." *Maryland Cas. Co. v. Therm-O-Disc, Inc.*, 137 F.3d 780, 783 (4th Cir. 1998). In evaluating whether the testimony is helpful, "[t]estimony

[6] On the first page of its Motion, Pfizer moves to exclude the expert testimony, pursuant to Federal Rules of Evidence 104(a), 702, 703, and 401, 402, and 403, but it offers no arguments under Rules 104, 401, 402, 403, or 703. Because Pfizer has failed to support those portions of its motion, the Court should disregard them.

from an expert is presumed to be helpful unless it concerns matters within the everyday knowledge and experience of a lay juror." *Kopf v. Skyrm*, 993 F.2d 374, 377 (4th Cir. 1993) (internal citations omitted).

In evaluating the reliability of expert testimony, "the court should consider a variety of factors, including whether the method used is generally accepted in the scientific community; the rate of error, if known; the existence and maintenance of standards; and whether the expert's work has been subjected to peer review." *Summers v. Cnty. of Charleston*, 2012 WL 3867108, at *2 (D.S.C. June 13, 2012) (quoting *United States v. Moreland*, 437 F.3d 424, 431 (4th Cir. 2006), *overruled on other grounds by Gall v. United States*, 552 U.S. 38, 128 S.Ct. 586, 169 L.Ed.2d 445 (2007)).

The *Daubert* test is flexible, however; "[r]ather than providing a definitive or exhaustive list, *Daubert* merely illustrates the types of factors that will bear on the inquiry." *United States v. Crisp*, 324 F.3d 261, 266 (4th Cir.2003). As the Court of Appeals for the Fourth Circuit has noted: "In making its initial determination of whether proffered testimony is sufficiently reliable, the court has broad latitude to consider whatever factors bearing on validity that the court finds to be useful; the particular factors will depend upon the unique circumstances of the expert testimony involved." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 261 (4th Cir.1999). "There is no requirement in *Daubert*, or any other controlling authority, that the proffering party must 'prove' anything to the court before the testimony in question can be admitted." *Maryland Cas. Co.* at 783.

Thus, in addition to prescribing fluid and general standards for the admission of scientific testimony, "*Daubert* also described the trial court's role as that of a 'gatekeeper' who should exercise broad discretion in admitting scientific testimony that could later be tested by '[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof....'" *Id*. (quoting *Daubert* at 596, 113 S.Ct. at 2798) Plaintiffs do not "have to prove their case twice—they do not have to demonstrate to the judge by a preponderance of the evidence that

the assessments of their experts are *correct*, they only have to demonstrate by a preponderance of evidence that their opinions are reliable." *Id*. (internal citations omitted) (emphasis in original).

"A review of the case law after *Daubert* shows that the rejection of expert testimony is the exception rather than the rule." *Palmetto Pharm. LLC v. AstraZeneca Pharm. LP*, 2014 WL 1334215, at *4 (D.S.C. Apr. 2, 2014) (*citing* Fed.R.Evid. 702, Advisory Committee's Note to 2000 Amendments). In the Fourth Circuit, it is well settled that "[i]n applying *Daubert*, a court evaluates the methodology or reasoning that the proffered scientific or technical expert uses to reach his conclusion; the court does not evaluate the conclusion itself." *TFWS, Inc. v. Schaefer*, 325 F.3d 234, 240 (4th Cir. 2003) (citing *Freeman v. Case Corp*., 118 F.3d 1011, 1016 n. 6 (4th Cir.1997)).

ARGUMENT

I. THIS COURT SHOULD NOT EXCLUDE THE OPINIONS OF PLAINTIFFS' EXPERTS THAT THE EFFICACY OF LIPITOR FOR PRIMARY PREVENTION IN WOMEN IS UNPROVEN

Pfizer makes five arguments in support of its claim that Plaintiffs' experts' opinions regarding Lipitor's efficacy in women for primary prevention should be excluded under Rule 702. First, Pfizer claims that Plaintiffs' experts' opinions are not generally accepted; second, Pfizer argues that Plaintiffs' experts have no biologically plausible explanation for their opinions; third, Pfizer argues that Plaintiffs' experts rely on flawed, results-driven re-analyses of the data; fourth, Pfizer claims that these experts fail to address the totality of the evidence; and fifth, Pfizer contends that Plaintiff's experts' opinions are misleading and a threat to public health. None of these arguments has merit.

A. The Techniques Used by Plaintiffs' Experts to Assess the Evidence Are Widely Accepted in the Scientific Community

Pfizer makes two fundamental mistakes in arguing that the opinions of Plaintiffs' experts are not generally accepted. First, as already noted, Pfizer misstates the substance of the opinions it is attacking. Second, and equally significant, Pfizer gets the *Daubert* factor of "general acceptance" completely wrong: *it is an expert's methodology, not his conclusions, that the Court is instructed to assess.*

This is clear from the *Daubert* opinion itself. First, as already noted, in *Daubert*, the Supreme Court insisted that "*[t]he focus, of course, must be solely on principles and methodology, not on the conclusions that they generate*." *Daubert*, 509 U.S. at 594-95 (emphasis added) (internal citations omitted). In addition, for each of the factors the Court enumerates, it repeats this instruction. Thus, the Court states that "a key question to be answered in determining *whether a theory or technique* is scientific knowledge that will assist the trier of fact will be whether it can be (and has been) tested." *Id.* at 593 (emphasis added). Next, the Court notes that "[a]nother pertinent consideration is whether *the theory or technique* has been subjected to peer review and publication." *Id.* (emphasis added). Third, the Court finds that "in the case of a *particular scientific technique*, the court ordinarily should consider the known or potential rate of error." *Id.* at 594 (emphasis added). Finally, the Court discussed the factor of general acceptance:

> Finally, "general acceptance" can yet have a bearing on the inquiry. A reliability assessment does not require, although it does permit, explicit identification of a relevant scientific community and an express determination of a particular degree of acceptance within that community. . . . Widespread acceptance can be an important factor in ruling particular evidence admissible, and *a known technique* which has been able to attract only minimal support within the community. . . may properly be viewed with skepticism.

Daubert, 509 U.S. at 594 (emphasis added) (citations omitted).

Indeed, the limitation of "general acceptance" to the technique or the methodology becomes even clearer when the history of the *Daubert* ruling, as recited within the opinion itself, makes clear. In *Daubert*, the Supreme Court rejected the prior *Frye* test, so-named after the case that first announced it, *Frye v. United States*, 54 App.D.C. 46, 47, 293 F. 1013 (1923), pursuant to which "general acceptance" in the scientific community was the sole basis on which expert testimony was admitted. But the *Frye* rule itself was about techniques and methodologies, not conclusions. The issue in *Frye* concerned "the admissibility of evidence derived from a systolic blood pressure deception test, a crude precursor to the polygraph machine." *Daubert*, 509 U.S. at 586. The question was whether the technique was sufficiently accepted for its results to be offered in court. The Court of Appeals in *Frye* held:

> Just when a scientific principle or discovery crosses the line between the experimental and demonstrable stages is difficult to define. Somewhere in this twilight zone the evidential force of the principle must be recognized, and while courts will go a long way in admitting expert testimony deduced from *a well-recognized scientific principle or discovery*, the thing from which the deduction is made must be sufficiently established to have gained general acceptance in the particular field in which it belongs.

54 App.D.C. at 47, 293 F. at 1014 (emphasis added). Thus, the "general acceptance" test in its original formulation was about techniques, not conclusions.

In *Daubert*, the Supreme Court rejected the "general acceptance" test as not conforming with Fed. R. Evid. 702, but kept the focus firmly on techniques and methodologies, not on conclusions. 509 U.S. at 594-95. In granting that "general acceptance" could "yet have a bearing on the inquiry," 509 U.S. at 594; moreover, it is crystal clear that the Court was again referring to techniques and methodologies that had been generally accepted, not specific conclusions (noting that the failure of known technique to gain acceptance could be viewed as significant).

Here, the techniques and methodology used by Plaintiffs' experts to determine that efficacy in women had not been proven are generally accepted in the scientific community. Specifically, Dr. Roberts, Dr. Abramson, and Dr. Wells, who opine that efficacy has not been proven in women, analyzed randomized clinical trials, meta-analyses, and observational studies, the firm and well-established bases for epidemiological analyses. *See* Pfizer Ex. 1 at ¶¶ 172-279; Pfizer Ex. 2 at 4-8; Pfizer Ex. 3 at ¶ 4. In response to their analysis, Pfizer can say no more than that, using standard methodologies and techniques, Drs. Abramson, Roberts, and Wells have arrived at a conclusion that is not universally accepted; it may even be a minority view. But nothing in *Daubert* restricts expert testimony to universally-accepted conclusions or even majority views. Separate and apart from the fact that "general acceptance" is but one non-mandatory factor (and, arguably, the least important of the factors identified by the Supreme Court, given the Court's grudging admission that it might yet have a bearing on the inquiry, *see* 509 U.S. at 594), nothing about the "general acceptance" test calls for exclusion of expert opinions grounded in such mainstream, well-accepted methodologies, regardless of what Pfizer may think of the conclusion these experts have reached.

B. Plaintiffs' Experts Consider the Totality of the Evidence

Pfizer claims that Plaintiffs' experts have not considered the totality of the evidence in reaching their opinions that the case for Lipitor's efficacy in women has not been proven. First, an expert's failure to address studies that indicate the opposite of the opinion offered goes to the weight of the testimony, not its admissibility. *Kruszka v. Novartis Pharm. Corp.*, 19 F. Supp. 3d 875, 888 (D. Minn. 2014), *as amended* (May 19, 2014). The *In re Zoloft (Sertraline Hydrochloride) Products Liab. Litig.*, 26 F. Supp. 3d 449, 461 (E.D. Pa. 2014) case cited by Pfizer, was an extreme circumstance, where the Court was especially concerned that the expert failed to discuss her *own* peer-reviewed, published studies.

Of greater significance, however, Pfizer is simply wrong. Reading Pfizer's motion, one might well believe that the efficacy opinions of Dr. Abramson, Dr. Roberts, and Dr. Wells are based entirely on Dr. Wells's analysis of the ASCOT-LLA trial. They are not. A review of Dr. Abramson's report shows extensive, detailed discussion of the very studies Pfizer claims have been ignored. *See* Pfizer Ex. 1 at ¶¶ 222-279. Dr. Abramson gives in-depth consideration to most of the very studies highlighted in Pfizer's motion – the JUPITER study, *see* Pfizer Ex. 1 at ¶¶ 104-105, 266-273; the CARDS study, *see id.* at ¶ 272, the Mora paper, *see id.* at ¶¶ 269, 470; the Cochrane Collaborative analysis, *see id.* at ¶¶ 250-261; the CTT collaborative, *see id.* at ¶¶ 243-261 – as well as to the various guidelines Pfizer cites, *see id.* at ¶¶ 222-241.

Dr. Wells, too, considers in detail the evidence Pfizer claims was ignored. *See* Pfizer Ex. 3 at ¶¶ 24-37. This includes specific, in-depth discussion of the JUPITER trial, the Mora and Kostis papers cited by Pfizer, as well as the CTT collaborative results. *See id.* Dr. Wells also discussed the CASHMERE study that Pfizer pointedly ignores. *See id.* at 18, 31.

Similarly, Dr. Roberts discusses the JUPITER study, the AFCAPS/TexCAPS trial, and the ASPEN study, in addition to her discussion of the ASCOT study. *See* Pfizer Ex. 2 at 4-8. A review of her list of materials considered shows that she considered the other studies cited by Pfizer, including the Kostis paper, the Mora paper, the Taylor paper and the CTT paper, *compare* Pfizer Br. at 12-13 *with* Roberts Report Exhibit B, Pfizer Ex. 2. Thus, none of these opinions was formed

on the basis of a single study, nor with disregard for the total body of evidence. Rather, Plaintiffs' experts have considered a vast body of evidence in reaching their conclusion that efficacy in women has not been demonstrated.

Indeed, Pfizer *acknowledges* the experts' discussion of these studies, but disagrees with their analysis of them. *See* Pfizer Br. at 25-26. Differing views about the strengths of various studies are not, however, a basis to exclude expert testimony. *Knight v. Kirby Inland Marine Inc*., 482 F.3d 347, 354 (5th Cir. 2007) (because, in epidemiology "hardly any study is ever conclusive," experts are not required to support their opinions with studies that "unequivocally support their conclusions"); *United States v. Bonds*, 12 F.3d 540, 561 (6th Cir. 1993) ("[a]bsolute certainty of result or unanimity of scientific opinion is not required for admissibility."); *In re Vioxx Products Liab. Litig*., 401 F. Supp. 2d 565, 599 (E.D. La. 2005) (where both sides relied on same scientific material, but interpreted it differently and came to different conclusions, expert testimony from both sides was admissible); *Beck v. Koppers, Inc*., No. 03-cv-60, 2006 WL 270260, *5 (N.D. Miss. Feb. 2, 2006) (failure of expert to specify weight accorded to various studies did not render ultimate judgment about the overall weight of the scientific evidence inadmissible).

C. Plaintiffs Do Not Rely on Flawed, Results-Driven Re-Analyses of the Data

Pfizer claims that Plaintiffs rely on a flawed, results-drive re-analysis of data to support their opinion. Under this category, they make two entirely distinct arguments, neither of which is correct.

1. Dr. Wells Properly Applied the Aalen Model to Differentiate the Results for Women in the ASCOT Study

First, Pfizer claims that Dr. Wells's statistical analysis is methodologically flawed because he used the so-called "Aalen model" for his statistical analysis of heterogeneity in the so-called ASCOT trial. They claim this was error because the ASCOT protocol specified use of the Cox proportional hazards method and that is what the study's authors used, and because Dr. Wells has not personally published analyses using the Aalen model. To see why Pfizer is wrong, it is important to understand the ASCOT trial, and heterogeneity, and the Cox method.

Pfizer's Anglo-Scandinavian Cardiac Outcomes Trial ("ASCOT") trial was a multicenter, randomized factorial study design with two antihypertensive regimens and 10 mg atorvastatin compared with placebo. The lipid-lowering arm (LLA or ASCOT-LLA), which compared atorvastatin and placebo, was double-blind. The primary efficacy endpoint for the lipid- lowering portion of the study was a composite endpoint of non-fatal MI (symptomatic and silent MI) and fatal coronary heart disease. Secondary objectives included comparing the effect of 10 mg atorvastatin versus placebo on multiple alternative endpoints including all-cause mortality and total cardiovascular mortality. Pfizer Ex. 3 at ¶ 6. As a result of pre-established criteria for participation of the study, 81% of the patients in ASCOT's lipid-lowering arm were male; 19% were female. *See* Plaintiffs' Exhibit A. The study results were to be analyzed using the Cox proportional hazards model of statistical analysis, a method for exploring the effects of several variables on the occurrence or non-occurrence of a particular event.

The ASCOT-LLA study included both men and women. "Heterogeneity" refers to the possibility of different results among the study population, depending on the gender of the subject. Pfizer recognized the problem of heterogeneity and specified that statistical analyses, using the Cox model, would be performed to see if there were meaningful differences between the results among men and the results among women. That is, Pfizer recognized the need to test for heterogeneity.

In October 2002, ASCOT-LLA was stopped and unblinded. As planned, Pfizer analyzed the results for women separately from the results for men, and, while the study showed a benefit in men, as Pfizer admits, the results of ASCOT-LLA for women were "inconclusive." That is, *ASCOT-LLA failed to demonstrate efficacy in women*. Pfizer claimed, however, that "it is probable that given a longer duration of study, the primary endpoint would have allowed a meaningful interpretation for females," *see* Pfizer Ex. 3 at ¶ 12. Indeed, Pfizer claims that "the test for heterogeneity is non-significant for all subgroups in ASCOT." *Id.* at 5. In English, "Pfizer is representing that the results for the subgroups should not be interpreted differently from the results for the entire study population," *id.*, meaning that Pfizer contends that the results for men are in

fact valid for women as well because there is no meaningful difference between the subgroups. It is this statement that Dr. Wells assesses.

The question Dr. Wells set out to analyze was thus whether a longer period of time would have shown different results for women in the ASCOT-LLA. Although the study protocol for the ASCOT-LLA study specified use of the Cox proportional hazard method for analyzing the results, as Dr. Wells points out, the Cox test is not suited to testing Pfizer's hypothesis that a longer time period would have allowed a "meaningful interpretation for females" because "Cox proportional hazards models assume that the hazard ratio is constant over time." Pfizer Ex. 3 at ¶ 7. That is, the Cox test *assumes* that if hazard ratio of a fatal heart attack in women taking placebo compared with women taking atorvastatin is 2:1 at one particular time, it would be 2:1 at all later times as well, because it assumes that the proportions – the ratio of the hazards – are constant over time.

Thus, the Cox test, which Pfizer insists Dr. Wells ought to have used, was by definition incapable of testing Pfizer's claim that a different hazard ratio would have emerged over a longer time period. It was also incapable of properly differentiating the results in women compared to the results in men *if the fundamental Cox assumption of constant proportional hazards over time was incorrect.* Moreover, and significantly, at the time Pfizer specified the Cox proportional hazards model to be used in analyzing the data from the ASCOT-LLA, it did not know that the results for women would be inconclusive or that it would claim that a longer time period would have shown a different result. Nor did it know whether the assumption of constant ratios over time would prove to be correct or incorrect. For these reasons, Pfizer's claim that it was improper for Dr. Wells to use anything other than the Cox proportional hazards method should be rejected. Indeed, if it is improper for Plaintiffs to use a statistical model other than the one specified in the ASCOT-LLA protocol, it is all the more improper for Pfizer to make a claim about the results of ASCOT-LLA in women that can only be tested by a model not specified in the protocol.

Because the Cox model is constrained to assume that the hazard ratio remains constant over time, it is important, Dr. Wells, explains, "to evaluate its validity." Pfizer Ex. 3 at ¶ 7. And, "[i]f the assumption fails, additional analysis must be conducted to evaluate heterogeneity," *id*.,

which is to say that a different tool is needed to separate out in the results in women vs. the results in men if the relationship between those results varies over time. Moreover, when Dr. Wells tested the fundamental Cox assumption, using a well-recognized technique for doing so, one that has been the subject of peer-reviewed publication, *see* Pfizer Ex. 3 at ¶¶ 7-10 & p. 5 n.1, the assumption turned out not to be valid with respect to heterogeneity of results in men and in women. It is ludicrous for Pfizer to insist that Dr. Wells was constrained to use a pre-specified methodology to analyze the difference in results between men and women when the fundamental assumption on which the methodology is based has been demonstrated to be false.

Once the Cox assumption turned out to be invalid *for this particular computation*, Dr. Wells turned to a different statistical tool that does not make the same assumption and thus is better suited to this particular task. The Aalen model, which Dr. Wells used, is named for its creator, Odd Aalen, who received his PhD at the University of California – Berkeley. Pfizer Ex. 14 at 323: 20-23. He is a leader in the survival analysis in the Scandinavian community and one of the leading researchers in the survival modeling. Pfizer Ex. 14 at 323: 23-25, 324: 1-2. The Aalen model is a standard, reliable model that has been published and is well used. Pfizer Ex. 14 at 324: 3-15. Pfizer does not challenge the use of the Aalen model in the field of statistics.

In the Aalen model, "regression coefficients are allowed to vary over time." Pfizer Ex. 14 at 324: 15-17. As Dr. Wells explains, "[s]ince temporal effects are not assumed to be proportional for each covariate, Aalen's model is capable of providing detailed information concerning the temporal influence of each covariate." Pfizer Ex. 3 at ¶ 8. The Aalen model thus allowed Dr. Wells to separate the results in women from the results in men without making the false assumption that the relationship between those results would be the same at all points in time. Using this test, Dr. Wells found that "the treatment effect of the primary endpoint is non-significant for women, and this nonsignificant effect is heterogeneous from the significant male treatment effect." *Id.* at 7. He also found that "the plot of the cumulative coefficient for the primary endpoint treatment effect for females in Figure 2 flattens out quickly and does not change as the duration of the study

increases." *Id.* at 7-8. He thus concludes that Pfizer was wrong when it said that a longer study would have shown the same benefit in women as in men.

In examining Dr. Wells' methodology, it is important to consider the field of statistics. "Statistics, broadly defined, is the science and art of gaining information from data. Statistical inference—whether done with confidence intervals or significance probabilities, by objective methods or subjective—depends on the validity of the statistical models for the data. If the data are collected on the basis of a probability sample or a randomized experiment, there will be statistical models that fit the situation very well, and inferences based on these models will be quite secure." *Falise v. Am. Tobacco Co.*, 258 F. Supp. 2d 63, 67 (E.D.N.Y. 2000) (*citing* Lincoln E. Moses, *The Reasoning of Statistical Inference, in Perspectives on Contemporary Statistics* 107, 117–118 (David C. Hoaglin & David S. Moore eds., 1992) ("[A] given data set can be viewed from more than one perspective, can be represented by a model in more than one way. Quite commonly, no unique model stands out as 'true' or correct; justifying so strong a conclusion might require a depth of knowledge that is simply lacking. So it is not unusual for a given data set to be analyzed in several apparently reasonable ways.") (additional internal citations omitted).

Here, as noted, the Aalen method is a generally-accepted technique that has been tested and has been the subject of peer-reviewed publication. Pfizer does not contend otherwise. Its only arguments that use of the method is improper are that the Cox method was pre-specified for the ASCOT trials, that Dr. Wells has not personally published an analysis using the Aalen method, and that Dr. Wells's use of the Aalen method was "litigation-driven." None of these criticisms are valid. As noted above, it certainly not consistent with the scientific method to continue using a technique that has shown to be based on an invalid assumption, merely because the technique was pre-specified before the invalidity was known. Nor does it matter when Dr. Wells has personally published results with the Aalen method. He is a highly-qualified statistician, with numerous statistical publications to his name. Pfizer does not contend, nor could it, that Dr. Wells does not know how to use the Aalen method or that he used it incorrectly. It is sufficient, under *Daubert* that the technique itself has been the subject of peer-reviewed publication. *See Daubert*, 509 U.S.

at 593 ("[a]nother pertinent consideration is whether *the theory or technique* has been subjected to peer review and publication.") *Id.* (emphasis added)

Although Pfizer claims that Dr. Wells' analysis "is solely litigation-driven, post hoc analysis designed to manipulate the data in a manner that ostensibly supports his preordained opinion," Pfizer Br. at 29, Pfizer provides no factual support for this baseless acquisition and Pfizer ignores entirely Dr. Wells's reasoned explanation, in his report, for use of the method. Indeed, Pfizer nowhere challenges Dr. Wells's essential finding that the underlying assumption of the Cox method proved to be false in the case of the heterogeneity analysis of the ASCOT-LLA trial. That unchallenged finding stands as a rebuke to Pfizer's attempt to portray Dr. Wells's work as anything other than a scientific inquiry.[7]

2. Dr. Abramson and Dr. Roberts Are Not Precluded by Their Prior Statements and Opinions from Offering Opinions Here

Pfizer claims that Drs. Abramson and Roberts have become "advocates" who are unable to provide objective expert testimony. Although each of these doctors has written a book touching on the issues in this case, Plaintiffs strongly dispute that either of them is biased. Nonetheless, "an expert witness's bias goes to the weight, not the admissibility of the testimony, and should be

[7] Both Dr. Abramson and Dr. Fleming rely on Dr. Wells's analysis of the ASCOT trial and it is perfectly proper for them to do so. "While experts may not simply 'parrot' ideas of other experts, they 'are permitted to rely on materials used by other experts in developing their own opinions.'" *Leese v. Lockheed Martin Corp.*, 6 F. Supp. 3d 546, 553 (D.N.J. 2014) (*quoting I.B.E.W. Local Union 380 Pension Fund v. Buck Consultants*, No. 03–4932, 2008 WL 2265269, at *3 (E.D.Pa. June 3, 2008)). "Experts 'may use a mix of objective data and subjective analysis from another expert to ... create an admissible report,'" and the testifying expert's knowledge regarding the underlying facts 'go[es] to the weight accorded to [that expert's] report and testimony, rather than its admissibility.'" *Id.* In addition, an "expert's testimony may be formulated by the use of the facts, data and conclusions of other experts." *Ohio Envtl. Dev. Ltd. P'ship v. Envirotest Sys. Corp.*, 478 F. Supp. 2d 963, 976 (N.D. Ohio 2007) (*quoting Asad v. Cont'l Airlines, Inc.*, 314 F.Supp.2d 726, 740 (N.D.Ohio 2004)). Drs. Abramson and Fleming built upon the analysis from Dr. Wells to form their own opinions in their respective field of expertise. They are not merely reciting Dr. Wells' opinions and trying to pass off his opinions as their own. Accordingly, their testimony is admissible.

brought out on cross-examination." *Glass v. Anne Arundel Cnty*., 38 F. Supp. 3d 705, 715 (D. Md. 2014) (internal citations omitted).

Moreover, as discussed more fully in Plaintiffs' opposition to Pfizer's separate motion to exclude Dr. Abramson's testimony, *see* Plaintiffs' Steering Committee Memorandum of Law in Opposition to Pfizer's Motion to Exclude Testimony of John Abramson, M.D., and Opinion Testimony Regarding Clinical Trial Data in Lipitor New Drug Application ("Pltf. Abramson Br.") at 16-18, what Pfizer calls "bias" in this context is nothing more than evidence that these experts' opinions were *not* formed for the purpose of litigation, but rather are the results of their own scientific work. Dr. Roberts's book, *The Truth About Statins* was written in 2012, before she was hired in this case and reflects views she formed as a practicing physician and scientist. Roberts Rep. at 2. Dr. Abramson's book, *Overdosed America*, was similarly written long before he was hired to give expert testimony here (or for anybody); most of his articles assessing the evidence for the use of statins long predate his retention as an expert here. *See* Abramson Report at 6, 7. What these publications evidence is disinterested scientific research, not bias. Indeed, Pfizer cannot have it both ways – it cannot both claim that Drs. Abramson and Roberts have formed opinions that Lipitor has not been shown to work in women solely because Plaintiffs are paying them to say that and also claim that these doctors have a long history of holding precisely that opinion. Indeed, to see how silly Pfizer's argument, consider that by its reasoning the medical researchers who discovered that cigarette smoking causes cancer would have been uniquely disqualified from providing that opinion in court because, according to Pfizer, their very knowledge and expertise, formed outside of litigation, would constitute disqualifying "bias." Here, what Dr. Abramson's and Dr. Roberts's prior work shows is that Plaintiffs have retained as experts scientists who, working on their own, had already reached the conclusions Plaintiffs seek to offer here. To the extent Pfizer wishes to challenge that conclusion, it may do so on cross-examination.

D. It Is Nonsensical to Require a "Biologically Plausible Explanation" for a Lack of Evidence of Efficacy

For its next argument, Pfizer creates a burden for Plaintiffs' experts to offer a "testable biological explanation" for why Lipitor would reduce the risk of CVD in men, but not in women with the same level of risk. Pfizer Br. at 27. Pfizer cite authorities that seem to impose such a requirement, but Pfizer's citations are misleading. First, "biological plausibility" is one of the factors suggested by Dr. Austin Bradford Hill to be used by epidemiologists in assessing whether an association demonstrated through epidemiological evidence is in fact causal. (As discussed in Plaintiffs' separate opposition to Pfizer's motion to exclude evidence of general causation, it is weak factor that Dr. Hills specifically cautioned was not required. *See* Pltf. Causation Br. Point IA4.) Here, of course, Plaintiffs' experts make no determination of causality; they simply opine that the epidemiological evidence shows a lack of statistically significant association in the relevant population. How a "biologically plausible" explanation could enter into the analysis of a lack of an association is left entirely unstated by Pfizer. Surely, Plaintiffs' experts are not called upon to explain why the studies failed to find the association Pfizer believes should exist. Indeed, in the context of its motion to Plaintiffs' expert opinions of general causation, Pfizer insists that it is the proponent of a causal theory who must offer a biologically plausible explanation, *see* Docket Entry #972 at 26. Apparently, Pfizer believes that science requires everyone except drug manufacturers to make this showing.

Pfizer compounds the confusion by citation to authorities that call for parties *lacking* epidemiological evidence to explain the mechanism of action in order to establish causation. *See Soldo v. Sandoz Pharm. Corp*., 244 F. Supp. 2d 434 (W.D. Pa. 2003) ("[i]n the absence of an understanding of the biological and pathological mechanisms by which disease develops, epidemiological evidence is the most valid type of scientific evidence of toxic causation"). But Plaintiffs *do not seek here to prove causation* and do not lack epidemiological evidence. These cases do not require Plaintiffs to explain why Pfizer has been unable to demonstrate that Lipitor is effective for primary prevention in women.

E. Plaintiffs' Evidence Cannot Be Censored on the Grounds that It Would Be Better for the Public Not to Know the Facts

Pfizer argues that, because an Australian Broadcasting Corporation's series on statins was associated with a reduction in statin use there, Plaintiffs should be prevented from telling jurors that the case for primary prevention in women has not been made. This stretches the *Daubert* inquiry and Rule 702 well beyond the bounds of what is permissible. Simply put, nothing in Rule 702, or any case law of which Plaintiffs are aware, permits this Court to exclude reliable scientific evidence on the grounds that the public might misunderstand it or that it would be better, from a public health perspective, for the public not to know. Indeed, nothing could be more antithetical to the principles of *Daubert* and its respect for the scientific method than Pfizer's attempt to quash legitimate scientific dissent with the claim that scientific understanding of statins is closed and that robust debate is dangerous because it might be misunderstood. Even if such an argument could be countenanced anywhere – and it ought not be – it makes no sense in the context of the adversary system, where Plaintiffs' evidence is *least* likely to be misunderstood for the simple reason that Pfizer's counsel and experts have an opportunity to respond to it and to persuade the jurors, if they can, of the rightness of their position.[8]

II. PLAINTIFFS' CLAIMS AND EXPERT TESTIMONY ARE NOT PREEMPTED BY FEDERAL LAW

Pfizer argues that the contention that efficacy in women for primary prevention is unproven is preempted by the Federal Food, Drug, and Cosmetic Act ("FDCA") because the FDA approved Lipitor without regard to gender. This is argument is both silly and wrong. Wrong, because the

[8] Pfizer claims, in a footnote, that an article by Dr. Abramson (Abramson *et al*., *Should people at low risk of cardiovascular disease take a statin?*, 347 BMJ f6123 (2013) about statins had an effect similar to that of the Australian Broadcasting Corporation series and that the article contained errors. The minor error in Dr. Abramson's article has no bearing upon his methodology in this litigation and no connection with Australian Broadcasting Corporation's series. Therefore, it has no relevance to Pfizer's motion to exclude Dr. Abramson. Moreover, Pfizer neglects to say that an external panel appointed by the editor of the BMJ was unanimous in its decision that the BMJ article did "not meet any of the criteria for retraction." (Pfizer Ex. 1, ¶ 257). In fact, the panel commented about the importance of ending the lack of transparency in the data from cholesterol-lowering clinical trials. (Pfizer Ex. 1, ¶ 257).

Supreme Court's decision in *Wyeth v. Levine*, 555 U.S. 555 (2009), which Pfizer barely acknowledges, precludes the argument, and silly because Plaintiffs' contention about Lipitor's efficacy can be no more preempted than the contention that Pfizer's FDA-approved label misstated the risk of diabetes, a claim Pfizer well knows is *not* preempted. Yet Pfizer can provide no legitimate basis why FDA approval in one context is preemptive when it is clearly not in the other. In particular, Pfizer cannot show that Plaintiffs' arguments about Lipitor's efficacy for primary prevention in women subject Pfizer to conflicting obligations under state and federal law so as to invoke impossibility preemption.

A. Pfizer Cannot Overcome the Presumption Against Preemption or Meet Its Heavy Burden to Establish Impossibility Preemption

The Supremacy Clause of the United States Constitution provides that the law and treaties of the United States "shall be the supreme law of the Land . . . Laws of any State to the Contrary notwithstanding." U.S. Const., Art. VI, cl. 2. Consequently, state laws that conflict with federal law are "without effect." *Mut. Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466, 2472-73 (2013) (citing *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981)). The preemption doctrine derives from the Supremacy Clause. *Id.* at 2473. Impossibility preemption exists where it is "impossible for a private party to comply with both state and federal requirements. *Id.*

In *Levine*, the Supreme Court reiterated two fundamental principles of preemption jurisprudence:

> First, "the purpose of Congress is the ultimate touchstone in every preemption case. . . .Second, in all preemption cases, and particularly in those in which Congress has legislated in a field which the States have traditionally occupied, we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.

555 U.S. at 565 (citations omitted). Applying these principles, the *Levine* Court rejected the argument that state law claims should be held preempted on the ground that they obstruct the purposes and objectives of federal drug labeling regulation. 555 U.S. at 573.

The Court found that Congress did not intend to preempt traditional state-law remedies, noting that "[a]s it enlarged the FDA's powers to protect the public health and assure the safety,

effectiveness, and reliability of drugs, Congress took care to preserve state law." 555 U.S. at 567 (citation omitted). The Court found, moreover, that Congress' failure to enact an express preemption provision for drugs, or to provide for a federal remedy for consumers harmed by unsafe or ineffective drugs "coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id*. at 574-75. The Court further explained:

> The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access information about their drugs, especially in the postmarketing phase as new risks emerge. State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times. Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.

555 U.S. at 578-79.

The *Levine* Court also rejected the argument that failure-to-warn claims are preempted by the doctrine of impossibility. The Court note that "[i]mpossibility preemption is a demanding defense." *Levine,* 555 U.S. at 572. In rejecting impossibility preemption in *Levine,* the Court acknowledged that "[t]he FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label." 555 U.S. at 568. It also recognized that "[g]enerally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application." *Id*. But, it found:

> There is . . . an FDA regulation that permits a manufacturer to make certain changes to its label before receiving the agency's approval. Among other things, this "changes being effected" (CBE) regulation provides that if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval.

555 U.S. at 569. Because it was not impossible to comply with both state and federal law, the Court held, state law claims were not preempted. *Id.* at 573.

Unsurprisingly, since *Levine*, courts have consistently rejected impossibility preemption defenses asserted by branded prescription drug manufacturers. *See Lefaivre v. KV Pharm. Co.*, 636 F.3d 935, 938-41 (8th Cir. 2011) (reversing district court preemption finding); *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 391-96 (7th Cir. 2010) (same); *Wimbush v. Wyeth*, 619 F.3d 632, 645-46 (6th Cir. 2010); *see also Desiano v. Warner-Lambert & Co.*, 467 F.3d 85, 98 (2d Cir. 2006).

In order to establish that claims based on the lack of evidence of efficacy in women for primary prevention are preempted, Pfizer must distinguish this case from *Levine* and show that Plaintiffs' argument would subject it to conflicting obligations under state and federal law. It cannot do this.

B. Plaintiffs' Contentions About the Lack of Evidence for Efficacy in Women Do Not Subject Pfizer to Conflicting Obligations and Are Not Preempted

The FDCA mandates that all drug manufacturers gain approval from the FDA prior to marketing any new drug in interstate commerce by submitting a new-drug application (NDA). 21 U.S.C. § 355(a), (b)(1)-(2). The NDA must include "the labeling proposed to be used for such drug." *Id.*; § 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i). The labeling must include a discussion of why the drug's "benefits exceed the risks under the conditions stated in the labeling." 21 C.F.R. § 314.50(d)(viii). The FDA may only approve the drug if the NDA provides "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d)(5). The FDA must determine, "based on a fair evaluation of all material facts," that the proposed label is not "false or misleading in any particular." *Id.* § 355(d)(7); 21 C.F.R. § 314.125(b)(6).

Branded drug manufacturers bear primary responsibility for the adequacy of the labeling on their drugs "at all times." *Levine*, 555 U.S. at 570-71. In other words, branded drug manufacturers have an on-going responsibility to ensure the accuracy of the labeling on their drugs.

Generally, a manufacturer may only change an FDA-approved label by submitting a supplemental application. *Id.* at 568. However, under the Changes Being Effected (CBE) regulation, if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction," it may make the label change upon filing of the supplementation application and need not wait for FDA approval. 21 C.F.R. § 314.70(c)(6)(iii).

One circumstance that can initiate the CBE process is when "newly acquired information" regarding a drug exists including, amongst other things, a contraindication, warning, precaution, or adverse reaction. *Levine*, 555 U.S. at 569 (citations omitted). The newly acquired information is not limited to new data; rather it may also include "new analysis of previously submitted data." *Id.* This rule accounts for the "fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." *Id.* For example, "if the sponsor submits adverse event information to FDA, and then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA, the sponsor meets the requirement for 'newly acquired information.'" *Id.*

Under the CBE regulation, manufacturers can "unilaterally" "add or strengthen" a "contraindications, warning, precaution, or adverse reaction," and in doing so, they "need not wait for FDA approval." *Levine*, 555 U.S. at 568, 573. And "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* at 570-71; *see also PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2574 (2011) ("A brand-name manufacturer seeking new drug approval is responsible for the accuracy and adequacy of its label."). Thus, manufacturers have a responsibility to ensure the primary and the on-going accuracy of the labeling on their drugs.

Pfizer contends that it could not invoke the CBE regulations and make a unilateral change to the label because there is no new information here. *See* Pfizer Br. at 34. Pfizer is wrong, for three reasons. First, Pfizer claims that new analyses of previously-submitted data are insufficient to justify a CBE change. *Id.* As noted above, however, the Supreme Court in *Levine* held precisely

the opposite, that new analyses of previously-submitted data meet the requirement for "newly acquired information." 555 U.S. at 569.

Second, Pfizer has collected a wealth of new data about Lipitor's efficacy in women in the years since the drug was first approved. The results of ASCOT were new data when the study was first concluded; so were the results of CASHMERE, which Pfizer has refused to publish. The problem is not that Pfizer has not had new data suggesting a failure of proof of efficacy in women; the problem is that, over the years, Pfizer has consistently refused to recognize the inadequacy of the evidence to support its claim of efficacy in this group.

Third, new information about the increased risk of diabetes associated with statins generally, and Lipitor in particular, has continued to accumulate, even though that increased risk was known from the beginning. This accumulating information about diabetes and Lipitor has cast the lack of evidence of efficacy in a new light, giving new significance to it. As discussed above, the absence of proof of a benefit calls for additional evaluation of known risks. *See* Gale Report (Exhibit B) at 12-13, 19-20. For example, as Dr. Roberts points out, a study using data from the Women's Health Initiative published in 2012, found that "[t]he increase in diabetes incidence in women on statins seen in the WHI was not confined to women who were obese, a known risk factor for developing diabetes. In fact, women of normal or below normal weight for height (body mass index or BMI) had the highest relative risk of developing diabetes if they were on a statin." Pfizer Ex. 2 at 9-10. To the extent that these non-obese women were also at lower risks of cardiovascular disease, the results of the WHI study created a new context for the inadequacies of the evidence of efficacy in women taking Lipitor for primary prevention. In short, had Pfizer wished to change its label to make the lack of evidence of efficacy in this group clearer, it could have. Additionally, without impacting its duties under federal law in the slightest, it could simply have stopped marketing Lipitor specifically to women without prior history of cardiovascular disease. Either way, without conflicting duties, there can be no preemption here.

Pfizer relies on two cases for its contrary argument, *In re Celexa & Lexapro Mktg & Sales Practices Litig.*, 779 F.3d 34 (1st Cir. 2015), and *Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d 1228

(S.D. Fla. 2007), but these cases do not support Pfizer's argument for preemption here.[9] The decision in *Prohias* is particularly unhelpful because it pre-dates the Supreme Court's decision in *Levine*. Its holding, based not on impossibility preemption, but rather on potential interference with the FDA regulatory scheme, *see* 490 F. Supp. 2d at 1234, was overruled in *Levine*, where the Supreme Court found that "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness," 555 U.S. at 574-75. After *Levine*, only "impossibility" preemption, a claim of conflicting state and federal duties, will suffice to invoke preemption under the FDCA. 555 U.S. at 573-581. *Prohias* is no longer good law.

Although the *Celexa* decision, by contrast, is quite recent, it is entirely distinguishable. In *Celexa*, plaintiffs argued that the FDA ought never to have approved the drug Lexapro. They claimed that the manufacturer should have disclosed information showing a lack of efficacy, *but all of the information on which they relied for that claim had been submitted to the FDA with the New Drug Application*. 779 F. 3d at 36-43. Indeed, the *Celexa* court searched the record for anything relating to the efficacy of the drug that had not in fact been considered by the FDA in approving the drug, and found nothing but an opinion piece arguing that the FDA ought not to have approved the drug. *Id.* at 42. As broadly as the Supreme Court construed the CBE process and the phrase "newly acquired information" in *Levine*, the allegations in *Celexa* could not be fit into that category because the gravamen of plaintiffs' complaint there was that the FDA should never have approved the drug in the first place and because plaintiffs were unable to offer a single piece of new information since the time of the drug's approval that supported their position.

Here, by contrast, Plaintiffs do not allege that Lipitor should never have been approved, or should never have been approved for use by women.[10] To the contrary, Plaintiffs are asserting

[9] Pfizer also cites *PLIVA* and *Bartlett*, but neglects to note that these cases involved generic drugs, which are subject to an entirely different regulatory scheme and to which the CBE regulations permitting unilateral label changes are not usually available.

[10] As noted earlier, *see supra* n.1, Pfizer purports to move to exclude opinions that Lipitor should not be approved in women, an opinion Plaintiffs' experts have not offered, but even Pfizer does

that Pfizer failed in its on-going duty to ensure the accuracy of its Lipitor label after it became apparent that there was insufficient evidence to show that Lipitor is effective for primary prevention in women and after a wealth of new studies confirmed the increased risk of diabetes associated with statins generally and Lipitor specifically in women. This information clearly falls within the scope of "newly acquired information" as defined by the Supreme Court in *Levine* (and impliedly by the court in *Celexa,* which searched for any information that had not been included in the NDA), so that Pfizer could have used the CBE procedure to make clear that efficacy had not been shown in precisely the population at increased risk for diabetes. Plaintiffs' claims are not preempted.

Finally, Pfizer's contention that Plaintiffs' claims are preempted because airing the lack of evidence for efficacy described here could create a "public health crisis by advancing misinformation about statins," Pfizer Br. at 31, is preposterous. Plaintiffs have already addressed this argument in the context of Pfizer's arguments under Rule 702, *see supra* Point IE. Plaintiffs note here only that the FDA has the power to reject, after the fact, changes made through the CBE process. *See Levine*, 555 U.S. at 571. Such actual rejection preempts subsequent claims that the specific, rejected changes ought nonetheless have been made. *Levine*, 555 U.S. at 571. Thus, the FDA has the power to ensure that label changes are accurate and contain no misinformation, and thus to avert any looming public health crises. Nor, of course, would a label change more clearly revealing the lack of evidence of efficacy contain misinformation in the first place; it would contain only the truth that Pfizer has worked so hard to conceal.

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not contend that Plaintiffs are offering the opinion that it *ought never to have been* approved for primary prevention in the first place.

CONCLUSION

For the reasons stated herein, Pfizer's motion to exclude Plaintiffs' efficacy evidence should be denied in its entirety.

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Respectfully Submitted,

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