Nos. 02-55372, 02-55498

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

FLORA MOTUS,

Plaintiff-Appellant and Cross-Appellee,

v.

PFIZER, INC.,

Defendant-Appellee and Cross-Appellant.

Appeal from the United States District Court
for the Central District of California

BRIEF OF AMICUS CURIAE PUBLIC CITIZEN IN SUPPORT OF CROSS-APPELLEE FLORA MOTUS

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INTEREST OF AMICUS CURIAE

Public Citizen is a national non-profit consumer advocacy organization founded in 1971.[1] On behalf of its 125,000 members, including more than 25,000 members in California, Public Citizen engages in research, education, lobbying, and litigation on a broad range of consumer issues. Public Citizen believes that state tort law is rightly a matter of state, not federal, concern and that, absent an express congressional determination to the contrary, California, like its sister states, should remain free to compensate tort plaintiffs as it deems appropriate. Public Citizen lawyers have represented plaintiffs on appeal, and Public Citizen has participated as amicus curiae in numerous cases involving a question of preemption of state-law tort claims, including cases involving medical devices, *see*, *e.g.*, *Medtronic v. Lohr*, 518 U.S. 470 (1996), pesticides, *see*, *e.g.*, *Taylor AG Indus. v. Pure-Gro*, 54 F.3d 555 (9th Cir. 1995), and hazardous substances, *see*, *e.g.*, *Jenkins v. James Day & Co*., 634 N.E.2d 998 (Ohio 1994). Public Citizen is concerned about a trend in the lower courts toward immunizing defendants from tort liability by holding that federal statutes preempt the claims of tort plaintiffs. These holdings have often been rejected by the United States Supreme Court. *See*, *e.g.*, *Sprietsma v. Mercury Marine*, 537 U.S. __, 123 S. Ct. 518 (2002); *Medtronic,* 518 U.S. 470; *Freightliner Corp. v . Myrick*, 514 U.S. 280 (1995);

[1] All parties have consented to the filing of this amicus curiae brief.

Cipollone v. Liggett Group, 505 U.S. 504 (1992). Nonetheless, drug manufacturers have recently begun to make preemption arguments in product liability cases. This Court's decision in this case will likely be the first circuit court decision to address a drug manufacturer's preemption argument since the many Supreme Court preemption cases of the past ten years. Accordingly, this appeal is critically important to consumers around the country. For the reasons set forth below, Public Citizen urges this Court, if it reaches the preemption issue, to affirm the district court's decision.

STATEMENT OF THE ISSUE

Whether the general requirements of the Food, Drug, and Cosmetic Act ("FDCA") and federal regulations concerning the labeling of drugs preempt common-law failure-to-warn claims, where the federal requirements do not prohibit drug manufacturers from adding safety warnings to labels of products that the Food and Drug Administration ("FDA") has approved for marketing.

STATEMENT OF THE CASE

Victor Motus was prescribed the antidepressant Zoloft by his doctor. He took it for approximately one week, during which time he became agitated and confused and began to have thoughts of suicide. Appellant's Br. 13 (citing record evidence). His behavior was symptomatic of akathisia, which is characterized by agitation, restlessness, confusion, and suicidal thoughts. *Id.* at 15. Pfizer agrees that Zoloft can

cause akathisia. *Id.* at 15 (citing testimony and publications). At the end of the week, Mr. Motus shot and killed himself. *Id.* at 14.

Flora Motus, Victor Motus's widow, sued Pfizer, alleging claims including failure to warn and strict liability. Pfizer moved for partial summary judgment on the theory that plaintiff Motus's failure-to-warn claims are barred by conflict preemption. Pfizer explained that "the ruling sought by this motion is a narrow one, addressing only cases in which, as here, there is a clear conflict between the plaintiff's claimed need for a particular warning and the agency's consideration and rejection of exactly that type of warning." Memo in Support of Motion for Partial SJ at 3.

The district court denied the motion for partial summary judgment. The court began by observing that other courts had found FDA requirements to be minimum standards, that FDA approval of a new drug application did not shield the manufacturer from liability, and that Pfizer had not cited a single case to the contrary. Morever, although the FDA had previously rejected citizen petitions asking the agency to require that the labeling of similar antidepressants warn of a suicide risk, the court noted that the FDA had also never prohibited Pfizer from giving such a warning. In addition, because Ms. Motus had not specified the precise warning that was lacking, the court found that Pfizer's challenge was overbroad. That is, the court could not find that every possible warning would conflict with the FDA's action and

objectives. The court also relied on 21 C.F.R. § 314.70(c)(2)(i), which permits manufacturers to strengthen warning labels without prior FDA approval. *See* 127 F. Supp. 2d 1085 (C.D. Cal. 2000).

Months later, Pfizer moved for summary judgment, arguing lack of causation. The court granted that motion and dismissed the case in its entirety.

SUMMARY OF ARGUMENT

1. A prevailing party cannot appeal unless it is in some way aggrieved by the judgment below and seeks to alter that judgment. Here, the district court dismissed the case in its entirety, and Pfizer's appeal does not seek to alter that result. Accordingly, its appeal should be dismissed for lack of jurisdiction.

Moreover, both Pfizer and the FDA as amicus curiae argue that Ms. Motus's claims based on the failure to warn about the risk of suicide are preempted, but not that her other claims are preempted. Therefore, this Court's decision on the question of whether the inadequate warning claim is preempted with regard to suicide risk will not resolve this case. Preemption, therefore, does not offer grounds to affirm the judgment of dismissal below. For this reason as well, the Court should decline Pfizer's invitation to address the interlocutory preemption issue.

2. If the Court reverses the lower court's causation ruling (the subject of Ms. Motus's appeal) and reaches out to decide the interlocutory preemption issue, it

should affirm the district court's finding of no conflict preemption. Implied conflict preemption occurs in either of two situations: "where state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress,'" *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995) (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)), or "where it is impossible for a private party to comply with both state and federal requirements.'" *Id.* at 16 n.4 (quoting *English v. General Electric Co.*, 496 U.S. 72, 79 (1990)). Neither of these circumstances is presented by Ms. Motus's failure-to-warn claims.

Pfizer's and the FDA's arguments are based on the agency's decision not to require a suicide warning, yet the Supreme Court's recent decision in *Sprietsma v. Mercury Marine*, 123 S. Ct. 518 (2002), makes plain that a decision *not* to impose a requirement has no preemptive effect. Moreover, if Ms. Motus prevails in her lawsuit, the only requirement imposed on Pfizer will be that it pay damages to her. Neither Pfizer nor the FDA suggests that it would be impossible for Pfizer both to pay damages and to comply with all applicable FDA requirements. In addition, the goal of the drug provisions of the Food, Drug, and Cosmetic Act is to protect the public from unsafe and ineffective drugs. Ms. Motus's claim that Pfizer should have warned about an association between Zoloft and suicide does nothing to interfere with that goal. She is complaining, among other things, that Victor Motus did not receive

information about an association between Pfizer's product and suicide—an association that is conclusive enough that the connection has been brought to the FDA's attention by a variety of parties on several instances and has been incorporated into required warning language on Zoloft labeling in Britain. The FDA's statement that "*all* imaginable warnings that could reasonably have been read as describing or alluding to such a [causal] relation" would render the product misbranded (US Br. 14 (emphasis in original)) is disingenuous. As the district court held, there is no basis for such a finding at this stage of the litigation.

Finally, even if the Court finds preemption of the inadequate warning claim as to suicide, it should not extend that finding to warnings related to akathisia. As set forth in Motus's opening brief (at 15), Pfizer does not deny that Zoloft can cause akathisia. And notably lacking from Pfizer's and the FDA's briefs is any discussion of the FDA's review of warnings related to akathisia or of any FDA decisions regarding such warnings. Accordingly, Pfizer's theory does not support a finding of preemption of the failure-to-warn claim as to akathisia, even if this Court accepts the theory as to suicide.

ARGUMENT

I. THE PREEMPTION ISSUE IS NOT PROPERLY BEFORE THIS COURT.

If the Court affirms the lower court's decision as to causation, it will have no cause to consider the preemption question. However, even if it reverses as to causation, consideration of the preemption issue is not proper at this time. First, Pfizer's cross-appeal from the interlocutory order of the district court denying the motion for partial summary judgment on preemption grounds is not proper because Pfizer wholly prevailed below and is not seeking any modification of the district court's final judgment. *Deposit Guaranty Nat'l Bank v. Roper*, 445 U.S. 326, 334 (1980); *United States v. Lewis County*, 175 F.3d 671, 679 (9th Cir. 1999); *see* Plaintiff's Motion to Dismiss Cross-Appeal, dated Oct. 17, 2002. The cross-appeal should be dismissed and the reply brief stricken.

Second, neither Pfizer nor the FDA as amicus curiae suggests that claims that are not based on the failure to warn about the risk of suicide are preempted: They do not argue that Ms. Motus's strict liability claim, her negligent design claim, or her claim of failure to warn about the risk of akathisia is preempted. Therefore, a decision on the question whether the inadequate warning claim is preempted would be interlocutory. In short, preemption simply does not offer grounds to affirm the judgment of dismissal below.

For both of these reasons, the preemption issue is not properly before this Court, and the Court should decline Pfizer's invitation to address it.

II. THE SUPREME COURT'S PREEMPTION JURISPRUDENCE DICTATES A FINDING OF NO PREEMPTION HERE.

A. The Presumption Against Preemption

The federal preemption doctrine has its origin in the Supremacy Clause, Article VI, clause 2 of the Constitution of the United States, which states:

> This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, and any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

The Supremacy Clause provides the constitutional authority for the proposition that conflicts between federal and state law are resolved in favor of federal law. *See McCulloch v. Maryland*, 4 Wheat. 316, 427, 4 L. Ed. 579 (1819); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992). Preemption is said to be "express" if a federal statute explicitly addresses the domain of state law that is or is not preempted, and "implied" if the structure and purpose of federal law, but not its actual words, preempt state law. *See id*.

The Supremacy Clause is restricted by other principles implicit and explicit in the constitutional plan. In particular, the Tenth Amendment provides:

> The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people.

In light of this constitutional imperative of federalism, "[c]onsideration under the Supremacy Clause starts with the basic assumption that Congress did not intend to displace state law." *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981). A party seeking preemption of state law thus bears a heavy burden, for "[p]reemption of state law by federal . . . regulation is not favored 'in the absence of persuasive reasons—either that the nature of the regulated subject matter permits no other conclusion, or that Congress has unmistakably so ordained.'" *Chicago & North Western Transp. Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311, 317 (1981) (quoting *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142 (1963)). The strong presumption *against* preemption may be overcome only by "clear and manifest" congressional intent to the contrary. *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 715 (1985); *see also Hawaiian Airlines, Inc. v. Norris*, 512 U.S. 246, 252 (1994); *Wisconsin Public Intervenor v. Mortier*, 501 U.S. 597, 605, 611 (1991).

Moreover, the presumption against preemption is even stronger where "Congress [has] legislated . . . in a field which the States have traditionally occupied, [involving] the historic police powers of the States." *Rice v. Santa Fe Elevator Corp.*,

331 U.S. 218, 230 (1947). In other words, the presumption is "that state and local regulation of health and safety matters can constitutionally coexist with federal regulation" because "the regulation of health and safety matters is primarily, and historically, a matter of local concern." *Hillsborough County*, 471 U.S. at 716, 719. This presumption applies where a defendant is seeking preemption of state tort remedies because, in that situation, preemption would displace the historic power of the states to protect the health and safety of their citizens. *See, e.g., Medtronic v. Lohr*, 518 U.S. 518 U.S. 470, 484-86 (1996).

The FDA's amicus brief in this case suggests that the presumption against preemption does not apply here because the federal government has regulated adulterated and misbranded drugs since 1906. US Br. 20 n.9. However, the Supreme Court has applied the presumption in cases involving medical devices (federally regulated since 1938, 21 U.S.C. §§ 351, 352), the blood supply (federally regulated since 1944, 42 U.S.C. § 262), and other products that have been federally regulated for many, many years. *See Medtronic*, 518 U.S. 475, 484 (medical devices); *Hillsborough County*, 471 U.S. at 719 (blood supply).

Furthermore, where the allegedly preemptive federal regulatory scheme does not itself provide a damages remedy, preemption would leave injured individuals without any state *or* federal remedy. In that situation, the Supreme Court has ascribed

preemptive intent to Congress only in the most compelling circumstances. *See English v. General Electric Co.*, 496 U.S. 72, 87-90 (1990); *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984); *see also Sprietsma*, 123 S. Ct. at 527 ("perfectly rational for Congress not to pre-empt common-law claims" when preempting state positive law because common-law claims "perform an important remedial role in compensating accident victims"). This principle is important here because, although Pfizer is not expressly arguing that all of Ms. Motus's claims are preempted, its reasoning is susceptible to broad application and, if accepted by the Court, would open the door to sweeping preemption of personal-injury claims brought by patients seeking redress for injuries caused by prescription drugs.

B. Preemption And The Federal-State Balance

The foregoing anti-preemption precepts are not mere precedential idiosyncrasies. Rather, they are deeply embedded in the "federal-state balance" that is fundamental to the constitutional plan. *Hillsborough County*, 471 U.S. 707; *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977); *see also* Corboy & Smith, *Federal Preemption of Product Liability Law: Federalism and the Theory of Implied Preemption*, 15 Am. J. Trial Advoc. 435, 444-57 (1992) (presumption against preemption in context of Tenth Amendment and federalist principles). Thus, the Supreme Court's Supremacy Clause jurisprudence reflects "an acknowledgment that

the States retain substantial sovereign powers under our constitutional scheme, powers with which Congress does not readily interfere." *Gregory v. Ashcroft*, 501 U.S. 452, 461 (1991); *see also Jones*, 430 U.S. at 525 (presumption against preemption "provides assurance that the 'federal-state balance' will not be disturbed unintentionally by Congress or unnecessarily by the courts") (quoting *United States v. Bass*, 404 U.S. 336, 349 (1971)).

Here, when Congress was considering legislation that ultimately was enacted as the Food, Drug, and Cosmetic Act of 1938, it made its intentions clear. Congress specifically rejected a proposal to include a private right of action for damages caused by faulty or unsafe products regulated under the Act on the ground that such a right of action already existed under state common law. *See*, *e.g.*, Hearings Before Subcomm. Of Comm. On Commerce on S. 1944, 73d Cong., 2d Sess. 400, 403 (1933); Adler & Mann, *Preemption and Medical Devices: The Courts Run Amok*, 59 Mo. L. Rev. 895, 924 & n. 130 (1995) ("Congress rejected a provision in a draft of the original FD&C providing a federal cause of action for damages because 'a common law right of action [already] exists'") (quoting legislative history). Thus, it is not surprising that, since enactment of the FDCA 65 years ago, no reported decision has held that the Act preempts common-law damages actions with respect to drugs.

Neither defendant Pfizer nor amicus curiae United States has cited a single case to the contrary.

Pfizer's and the FDA's position runs contrary to Congress's purpose in enacting the FDCA to protect public health. The view that Congress declined to provide a private right of action based on its knowledge that state common law provided one, but at the same time approved a regulatory scheme that impliedly preempted those state remedies, is illogical. *Cf. Medtronic*, 518 U.S. at 487 (rejecting similar argument with respect to scope of express preemption). Accordingly, to the extent that the answer is ambiguous to the question whether Ms. Motus's inadequate-warning claim is preempted as to suicide, that ambiguity must be resolved in Ms. Motus's favor.

III. THE INADEQUATE WARNING CLAIM IS NOT IMPLIEDLY PREEMPTED WITH RESPECT TO SUICIDE WARNINGS OR TO WARNINGS REGARDING AKATHISIA.

1. In *Sprietsma v. Mercury Marine*, the Supreme Court considered whether the Coast Guard's decision not to require propeller guards on motor boats impliedly preempted a state-law damages action that alleged, among other things, that the manufacturer's motor boat was unreasonably dangerous because the motor was not protected by a propeller guard. Rejecting the manufacturer's preemption argument, the Court explained that "[i]t is quite wrong" to view a decision declining to impose a requirement as the "functional equivalent" of a prohibition against state regulation

of the subject matter. Rather, a decision not to take regulatory action leaves the applicable law "exactly the same" as it was before the agency's consideration of the matter. 123 S. Ct. at 527; *accord Freightliner Corp.*, 514 U.S. at 289 (where agency had no standard either requiring or prohibiting antilock brakes, state common law as applied to antilock brakes not preempted); *Puerto Rico Dept. of Consumer Affairs v. Isla Petroleum Corp*., 485 U.S. 495, 501, 503 (1988) (absent explicit statement of intent, federal inaction has no preemptive effect).

Here, the FDA's decision not to require a suicide (or akathisia) warning closely mirrors the situation presented in *Sprietsma*. In both cases, the defendant-manufacturer premised its conflict preemption argument on agency action *not* taken, as opposed to the agency's imposition of a requirement or prohibition. With regard to Zoloft, the FDA has neither required a suicide warning nor prohibited Pfizer from adding one. Just as in *Sprietsma*, where the agency had considered whether to impose a requirement and decided not to do so, here the FDA—in each instance recited in Pfizer's brief and in the FDA's amicus brief—considered whether to impose a suicide warning as a requirement of marketing a particular antidepressant (usually Prozac) and decided to deny third-party requests that the manufacturer be *required* to add such a warning. *See* US Br. 9 (citing SER 1194-95). However, the FDA never determined that Pfizer, or even Prozac's manufacturer, could *not* include one. As the United

States recently explained to the Supreme Court, "the mere fact that the agency has made a considered decision to forgo federal regulation does not, in and of itself, give rise to an inference that all state law on the subject—including state tort law—is meant to be preempted." US Br. 18, in *Sprietsma*, S. Ct. No. 01-706 (filed March 2002) (available at www.usdoj.gov/osg/ briefs/2001/3mer/ 1ami/2001-0706.mer.ami.html).

In this regard, the Court should not credit the statement in the FDA amicus brief that *any* suicide-related warning for Zoloft would be false or misleading. To be sure, federal agency action having the force of law may preempt conflicting state requirements, just as a federal statute may preempt. *Sprietsma*, 123 S. Ct. at 527; *Fidelity Federal Savings & Loan Ass'n v. De La Cuesta*, 458 U.S. 141, 153 (1982). But as the United States has agreed in other cases, a statement in an amicus brief falls far short of the sort of final agency action necessary to evaluate the potential for conflict between state-law claims and federal action. *See* US Br. in *Sprietsma*, *supra*, at 23 ("as a general matter, state law is not preempted by a mere expression of an opinion or statement of policy by a federal agency, untethered to any agency action that has legal effect in its own right."); *see also United States v. Mead Corp*., 533 U.S. 218, 228 (2001) (degree of deference due to government depends on, among other things, consistency, formality, and thoroughness).

Indeed, not only is the amicus brief's threat of an enforcement action insufficient to create a conflict, no conflict would exist even if Pfizer added a suicide or akathisia warning and the FDA then took enforcement action because the determination that a drug is misbranded is not in fact the FDA's to make. Rather, if the FDA wants to pursue enforcement action for alleged misbranding, the agency must initiate an action against the manufacturer in a federal district court. The manufacturer is even entitled to a jury trial. 21 U.S.C. § 332 (injunctions), § 333 (criminal penalties), § 334 (seizure). Thus, because the filing of an enforcement action does not guarantee that the FDA will prevail, no conflict would exist until the FDA had won the action. As the Supreme Court has explained: "The existence of a hypothetical or potential conflict is insufficient to warrant the preemption of the state [law]." *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982).

Both Pfizer and the FDA rely on *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000). That case, however, supports Ms. Motus's position. In *Geier*, the Court found that the plaintiff's state-law claims seeking to hold Honda liable for not installing an air bag in her car would conflict with the agency's implementation of a regulation requiring passive restraints in passenger cars. The finding of a conflict was based on the agency's "own contemporaneous explanation" of the objectives of the regulation, which included giving auto manufacturers flexibility in their choice of

passive restraint systems. *Id.* at 877-80; *see also* US Br. in *Sprietsma*, *supra*, at 19 ("*Geier* does not suggest that common-law suits will be preempted whenever the federal agency has focused its attention upon the particular aspect of motor vehicle performance that forms the basis of the plaintiff's claim."). In contrast here, neither Pfizer nor the FDA grounds its argument in any prior FDA statement about implementation of the FDCA or the functioning of the labeling and misbranding regulations.

Because the FDA's decision not to require a suicide warning for Zoloft "does not convey an 'authoritative' message of a federal policy against" such a warning, *Sprietsma,* 123 S. Ct. at 528, a jury verdict finding Pfizer liable for failure to warn would not conflict with any federal requirement. Accordingly, Ms. Motus's failure-to-warn claim with regard to the risk of suicide is not preempted.

3. The FDA argues that it would be "misleading" to warn of a possible risk without proof of a causal relationship between Zoloft and that risk. That argument is contrary to both the agency's regulations and its practice.

The FDA's carefully worded amicus brief makes clear that the agency's consideration was limited to whether it should require a warning to address a *causal* relationship between the antidepressants and suicide—not to whether there existed an *association* between the two. The difference is neither semantic nor lost on the FDA.

As FDA regulations state: "The labeling shall be revised to include a warning as soon as there is reasonable evidence of an *association* of a serious hazard with a drug; a *causal* relationship need not have been proved." 21 C.F.R. § 314.126(b) (emphasis added).

An association may be evidenced by either statistical evidence or by reports of specific incidents, and it does not necessarily indicate a causal relationship. In many cases, controlled clinical studies establish causation or provide reasonable assurance of it. However, controlled studies are not always available, nor are they always necessary. Sometimes the causal connection may be clear enough without a study. For example, the causal connection between smoking and lung cancer, although now widely accepted, even by tobacco companies, is a conclusion based on observational evidence, not on controlled clinical studies. Other times, a study may be impractical. For example, clinical studies usually have somewhere between several dozen and several hundred subjects. Yet in some cases, the incidence of a given injury or condition may be small enough that thousands of study subjects would be needed to show a statistically significant connection. Suicide risk falls into this category. The incidence of suicide in the population is so small—1.7 in 10,000, according to the Centers for Disease Control, *see* CDC, National Center for Health Statistics, Fastats A to Z, Suicide, www.cdc.gov/nchs/fastats/suicide.htm—that even if a drug increased

that risk ten-fold, thousands of study subjects would be necessary to demonstrate a statistically significant increase that would substantiate a causal connection.

For present purposes, the difference between association and causation is crucial because the FDA's brief is very clear that the warning to which it objects is a warning about Zoloft having a causal relation to suicide. The agency's brief does not address association. Yet the agency very often approves or requires labels to warn about associations where no causal connection has been established. For example, the original labeling for the drug Lotronex stated, in part, "Acute ischemic colitis was infrequently reported in patients receiving LOTRONEX in 3-month clinical trials. . . . A causal association between treatment with LOTRONEX and acute colitis has not been established, nor have risk factors been identified." *Physicians' Desk Reference* at 1438 (55th ed. 2001). Pfizer too warns about adverse reactions associated with its products, without proof of causation. *See* Pfizer & Pharmacia, Labeling for Bextra at 2, www.bextra.com/CONSUMER/PAGES/pi.pdf (stating under "adverse reactions": "The following reactions have been identified during postmarketing use of BEXTRA. . . . Because these reactions were reported voluntarily from a population of uncertain size, *it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure*.") (emphasis added). Accordingly, the FDA's determination that the studies it reviewed did not justify requiring a warning to

describe a *causal* relationship between Zoloft and suicide does not conflict with a determination that Pfizer failed to warn about an *association* between Zoloft and suicide.

The FDA's assertion that any warning that satisfied Ms. Motus would be inherently misleading because it would wrongly "call[] attention to an asserted causal relation between Zoloft and suicide," US Br. 20, is thus neither correct nor consistent with FDA practice. Indeed, it flatly contradicts 21 C.F.R. § 314.126(b), which requires warnings based on reasonable evidence of an association, even absent proof of a causal relationship. Here, Pfizer could have provided a warning modeled after the warning for Lotronex: "Suicide has been infrequently reported in patients receiving Zoloft during the first few weeks of drug therapy. A causal connection between Zoloft and suicide has not been established." According to Pfizer's and the FDA's briefs, everything in that warning would be true, and thus the FDA would have no basis for taking enforcement action based on alleged misbranding. Similarly, a warning stating that "Zoloft is associated with a risk of akathisia, a condition that can be characterized by extreme agitation, confusion, violent thoughts, and, in extreme cases, thoughts of suicide," would reflect Pfizer's deposition testimony in this litigation and the conclusions set forth in two published articles by Pfizer's prior Medical Director of the Zoloft Product Strategy Team. *See* Appellant's Br. 15.

Again, because the statement is true, the FDA could not properly have taken enforcement action if Pfizer had provided such a warning.[2]

4. The history of FDA consideration of the relationship between Zoloft and similar products, on the one hand, and suicide, on the other, reveals no agency action with the force of law sufficient to preempt Ms. Motus's failure-to-warn claim as it relates to risk of suicide. That history does, however, reveal an important fact about Ms. Motus's claim as it relates to risk of akathisia: The FDA's consideration focused on the relationship between antidepressants such as Zoloft and suicide, not between those drugs and akathisia. Yet Ms. Motus's failure-to-warn claim plainly encompasses the relationship between Zoloft and akathisia, as it expressly alleges that aka-

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[2] The British counterpart of the FDA recommends that antidepressants such as Zoloft be accompanied by a warning that states: "occasionally, thoughts of suicide or self harm may occur or increase in the first few weeks of treatment with [Zoloft], until the antidepressant effect becomes apparent. Tell your doctor immediately if you have any distressing thoughts or experiences." US Br. 20-21. The FDA's only objection to this warning is that "it is ambiguous as to causality," and "suggesting a casual [sic] relation to suicide" is false or misleading. *Id.* at 21. As the above examples show, however, both a suicide warning and an akathisia warning that incorporates a reference to suicide can be drafted without suggesting causation; indeed, they can be drafted to disavow causation expressly. Such warnings, even in the FDA's view, would not be false or misleading and, therefore, would not provide a basis for an enforcement action.

In addition, of course, an akathisia warning could be drafted that did not refer to suicide at all. Such a warning could have made a big difference to Victor Motus because, with such a warning, he might have spoken to his doctor before killing himself.

thisia is an adverse side effect of Zoloft and then alleges a failure to warn of "dangers, contra-indications, and side effects" generally. *See* SER 8 (complaint ¶ 28(d), (f), (j)); *see also id.* at 9 (¶ 29). Akathisia can be characterized by suicidal thoughts and can lead to suicide, but suicide is not a necessary consequence of akathisia. Warning about akathisia is thus not the same as warning about suicide. Accordingly, even under Pfizer's theory of preemption, the failure-to-warn claim is not even arguably preempted insofar as it relates to warnings regarding the risk of akathisia.

5. Because no court has held a drug-related product liability claim to be impliedly preempted by the FDCA or the FDA's implementation of that statute, Pfizer's brief relies on cases finding preemption of claims involving injuries caused by medical devices. Pfizer Br. 48-50. Those cases are inapposite because each of them addresses an *express* preemption provision of the FDCA, 21 U.S.C. § 360k(a), which preempts certain state medical device requirements "different from or in addition to" federal medical device requirements. That provision does not apply to drugs, and there is no comparable provision for drugs. Therefore, those cases have no bearing on the implied conflict preemption issue presented here.

Moreover, even to the extent that the analogy to express preemption cases is appropriate, Pfizer's brief tells only half the story, as it neglects to mention that the courts are in conflict over the question whether FDA approval of a device expressly

preempts inadequate warning and strict liability claims such as Ms. Motus's. *See*, *e.g.*, *Goodlin v. Medtronic*, 167 F.3d 1367 (11th Cir. 1999) (no preemption); *Weiland v. Telectronics Pacing Sys.*, 721 N.E.2d 1149 (Ill. 1999) (same); *Oja v. Howmedica*, 111 F.3d 782 (10th Cir. 1997) (same).

Like the defendants in the medical device cases, Pfizer errs by trying to "convert the FDA's finding and the accompanying permission to market its [product] into the federal government's implied validation of the safety of its device . . . and, then, to use that validation as a shield against liability in tort." *Goodlin*, 167 F.3d at 1376-77. As demonstrated by the FDA's summary of the new drug application approval process and its review of the Zoloft marketing application, US Br. 5-9, the FDA's approval imposed no substantive prerequisite that a court can compare to a purportedly conflicting state requirement. *Id.* at 1367.

6. Pfizer's reliance on cases rejecting "fraud-on-the-FDA" claims in medical device product liability cases is equally misplaced. Pfizer Br. 51-53. Those cases reject claims premised on the theory that the FDA would have acted differently had the manufacturer provided the agency with additional information; that is, they reject claims that are based on the theory that the manufacturer gained marketing approval dishonestly. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 343 (2001). Fraud-on-the-agency claims are preempted because they require a court or jury to

predict what the FDA would have done had it been presented with different information and to review the approval application submitted to the FDA to decide whether the application should have been approved. *Id.* at 349-50. Those concerns simply are not present here. The inadequate-warning claim does not challenge the FDA's decision to allow marketing of Zoloft or its decision that Zoloft could be labeled for certain indications. Instead, it challenges *Pfizer*'s decision not to include —either initially or later—a warning about the association between Zoloft and suicide (among other things, including akathisia). *See* 21 C.F.R. § 314.70(c)(2)(i) (manufacturer may add warning without prior agency approval). Therefore, a finding in favor of the plaintiff would not require the court or jury to interfere with the FDA's decisionmaking process. *See Eve v. Sandoz Pharm. Corp.*, 2002 WL 181972 (S.D. Ind. Jan. 28, 2002) (*Buckman* does not support preemption of inadequate-warning and other tort claims in suit against drug manufacturer); *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018 (N.D. Ill. 2001) (same).

Not only does this case not challenge the FDA's approval decision, it does not challenge any final FDA determination. Indeed, the history recited by Pfizer and the FDA shows that the agency has repeatedly looked at the connection between certain SSRI antidepressants and suicide risk, which evidences the lack of final agency action. Of course, the denials of the citizen petitions asking that the warnings be required

were final decisions as to those petitions; however, those denials did not forbid Pfizer from adding a warning voluntarily. The FDA has never taken any action to prohibit Pfizer from doing so.

The labeling of other drugs provides myriad examples of instances in which neither the manufacturer nor the FDA initially determined that a certain warning should appear on a drug label, and one or both later changed its mind based on reports of adverse events in patients. For instance, in 1997, the FDA approved the Parke-Davis drug Rezulin for use in treating certain types of diabetes. The label noted under the heading "precautions" that some incidents of "liver function test abnormalities" had occurred during the clinical studies. However, Parke-Davis did not ask to include a warning about an association between Rezulin and liver problems, and the label did not do so. *Physicians' Desk Reference* at 2120 (52d ed. 1998). By the next year, reports of liver failure in Rezulin patients prompted the FDA to require a boxed warning about the association between Rezulin and liver failure. *Physicians' Desk Reference* at 2310 (53d ed. 1999). The warning was strengthened several times, always based on adverse event reports and not on clinical studies, before the drug was pulled from the market. Thus, the agency's initial decision to allow Rezulin to be marketed without a warning about the association with liver failure was not a final decision to foreclose further consideration of a warning. Similarly, just last month,

two manufacturers announced that they were adding warnings to the labels of prescription drugs, both already on the market, based on adverse event reports. *See* FDA, MedWatch, 2003 Safety Information Summaries, www.fda.gov/medwatch/SAFETY/2003/safety03.htm#drugs.

The above examples are just three of many. "Many serious ADRs [adverse drug reactions] are discovered only after a drug has been on the market for years. Only half of newly discovered serious ADRs are detected and documented in the *Physicians' Desk Reference* within 7 years after drug approval." Lasser, et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J. A.M.A. 2215, 2218 (May 1, 2002). Moreover, an association between a drug and an adverse reaction is often identified or identifiable from premarketing trials, but no warning is given until after the FDA receives adverse event reports from patients. *Id.* Given the absence of final agency action here, Pfizer's attempt to analogize this case to *Buckman* must fail.

Notably, whereas a fraud-on-the-FDA claim necessarily draws the regulatory process into the litigation—a factor weighing in favor of preemption, *see Buckman*, 531 U.S. at 351 n.6; *id.* at 354 (Stevens, J. concurring) (noting FDA's central concerns regarding fraud-on the-agency claims are that they second-guess FDA decisionmaking and overburden agency personnel)—Ms. Motus's inadequate-warning claims do not

do that. Rather, Pfizer, through its preemption theory, was the party that drew the regulatory process into this case. Pfizer argues that the inadequate warning claim is preempted insofar as it concerns suicide risk because the FDA has specifically looked at the relationship between this class of drugs and suicide and decided not to require a label warning. That argument, whether or not correct, requires consideration of the FDA's review of the product and the subsequent citizen petitions and a determination of whether the FDA decided that a warning was not required or whether it decided that a warning was prohibited, and a prediction about whether the FDA would take enforcement action if Pfizer added such a warning.

Although the answers to these questions are unclear from the history recited in the briefs, the FDA, via this litigation, has offered further "evidence." *But cf. Martin v. OSHRC*, 499 U.S. 144, 156 (1990) ("[A]gency 'litigating positions' are not entitled to deference when they are merely appellate counsel's 'post-hoc rationalizations' for agency action, advanced for the first time in the reviewing court.") (citation omitted). The proceedings in this case thus show that Pfizer's preemption theory poses the same problem posed by the plaintiffs' claims in the fraud-on-the-FDA cases. Whereas in the fraud-on-the-FDA cases the plaintiffs' theory of liability requires the courts to review the FDA's decisionmaking and improperly draws the agency into the litigation, Pfizer's theory does the same thing here: It requires the parties to argue over what

information the FDA considered, the meaning attached to the decision to allow one label, as opposed to another, and what the FDA's reaction would be if the manufacturer added language to the label—all of which are avoided under plaintiff's (and our) view of preemption.

* * * * *

It is worth remembering that Ms. Motus does not seek to require Pfizer to change Zoloft's label or seek any other form of injunctive relief; her lawsuit seeks only damages. SER 12 (complaint). Pfizer and the FDA address the preemption issue as though Ms. Motus were seeking to force Pfizer to add a warning or to penalize Pfizer for complying with FDA regulations. She is not. Yet even if her lawsuit did seek to require Pfizer to add a warning, no conflict would be presented. Pfizer could have both provided a warning and complied with FDA regulations. If it had, Victor Motus's death, and thus this lawsuit, might never have occurred.

CONCLUSION

For the foregoing reasons, if this Court reaches the preemption issue, the district court's decision denying Defendant's motion for summary judgment on preemption grounds should be affirmed.

Dated: April 16, 2003

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CERTIFICATE OF COMPLIANCE
PURSUANT TO CIRCUIT RULE 32-1

Case Nos. 02-55372, 02-55498

I certify that the foregoing brief is proportionately spaced, has a type-face of 14 points or more, and contains 6,537 words.

Dated: April 16, 2003

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Allison M. Zieve

CERTIFICATE OF SERVICE

I hereby certify that on this 16th day of April, 2003, I served the foregoing BRIEF OF AMICUS CURIAE PUBLIC CITIZEN IN SUPPORT OF CROSS-APPELLEE FLORA MOTUS on the parties listed below, by causing two true and correct copies thereof to be served by mail on counsel at the following addresses:

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