Nos. 02-55372, 02-55498

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

FLORA MOTUS, individually, as Successor of the Estate of Victor Motus, Deceased, and as Guardian Ad Litem for Lauren Motus, a Minor,

Plaintiff-Appellant and Cross-Appellee,

v.

PFIZER, INC. (Roerig Division),

Defendant-Appellee and Cross-Appellant.

AMICUS BRIEF FOR THE UNITED STATES IN SUPPORT OF THE DEFENDANT-APPELLEE AND CROSS-APPELLANT, AND IN FAVOR OF REVERSAL OF THE DISTRICT COURT'S ORDER DENYING PARTIAL SUMMARY JUDGMENT TO DEFENDANT-APPELLEE AND CROSS-APPELLANT

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES:

CONSTITUTION:

STATUES:

The Food, Drug and Cosmetic Act:

REGULATIONS:

RULES:

MISCELLANEOUS:

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STATEMENT OF INTEREST OF THE UNITED STATES

This case involves a significant preemption issue concerning the extent, if any, to which the manufacturer of a drug may be held liable in tort for a failure to warn of an alleged danger, notwithstanding the Food and Drug Administration's (FDA's) repeated and contemporaneous determination that there is no scientific basis for such warning. The FDA, the federal agency charged with regulating the manufacture, sale, and labeling of

prescription drug products,[1] has a clear interest to ensure that state tort law does not undermine the agency's authority to protect the public health through enforcement of the FDCA's prohibition against false or misleading labeling of drug products. To require a warning of a supposed danger that FDA concludes has no actual scientific basis, no matter the warning's language, would be to require a statement that would be false or misleading, and thus contrary to federal law. In such a case, federal law must prevail. The United States files this amicus curiae brief pursuant to Fed. R. App. P. 29(a) and 28 U.S.C. 517 to make clear the basis for federal preemption and the error in the district court's opinion.

STATEMENT OF THE ISSUE PRESENTED FOR REVIEW

Plaintiff-Appellant and Cross-Appellee Flora Motus's husband, who had been suffering from depression, committed suicide within a week of his beginning to take the anti-depressant prescription drug, Zoloft, prescribed by his doctor. As of that time, FDA had examined the matter and had repeatedly found that there was no causal relation between taking the class of drug products known as SSRIs, which includes Zoloft, and an

[1] The FDA is a component of the United States Department of Health and Human Services. The Federal Food, Drug and Cosmetic Act (FDCA, 21 U.S.C. 301 et seq.) vests regulatory and enforcement authority in the Secretary of Health and Human Services, who has delegated his authority to the Commissioner of the FDA. 21 C.F.R. 5.10.

increased risk of suicide. Zoloft's manufacturer, Pfizer, while providing the warnings specified by FDA under federal law, had not provided any warning of such a possible relationship. Motus seeks tort damages against Pfizer based on that omission.

The question presented is:

Whether the FDCA (21 U.S.C. 331(a), (b), (k); 352(a)), and applicable regulations (21 C.F.R. 201.56(b)) preempt plaintiff's tort claims in that, at the time Zoloft was prescribed, any warning that suggested a causal relation between Zoloft and suicide would have been false or misleading, and thus would have misbranded the drug in violation of federal law.

STATEMENT OF THE CASE

1. This is a suit against a drug manufacturer, Pfizer, brought by Flora Motus, the widow of a former patient, Victor Motus. SER 1189. Victor Motus suffered from depression. Id. In November 1998, he committed suicide after having taken, as prescribed, Pfizer's anti-depressant drug, Zoloft, for approximately one week. Id.

Flora Motus filed a lawsuit alleging that (1) Pfizer "'negligently * * * fail[ed] to adequately warn the medical community, the general public and plaintiff's [husband] * * * of the dangers, contraindications and side effects * * * of Zoloft,'" (2) "'Zoloft was not properly labeled * * * and was not accompanied by proper warnings for safe, informed use * * * [and

(3)] the labeling ... did not warn physicians in general and [Victor Motus] in particular of the dangers inherent in its use, particularly that the drug can cause the user to become violent and suicidal.'" Id. at 1189-90. Significantly, for purposes of this case, Pfizer had provided verbatim the suicide-related warning specified by FDA for its product. SER 1190, 1192.

The district court rejected Pfizer's argument that federal regulation of prescription drugs preempted Ms. Motus's claims as related to failure to warn. Id. at 1190. But the court ultimately granted summary judgment to Pfizer on the ground that her claims were barred by lack of causation. ER 536. Motus filed an appeal from that judgment, and Pfizer filed a cross appeal on the denial of partial summary judgment as to preemption.

2. Congress charged FDA with ensuring that drugs sold in the United States are safe and effective (21 U.S.C. 355(d) and 393(b)(2)(B)) and not misbranded. 21 U.S.C. 331(a), (b), and (k). To obtain the agency's approval of a drug, a manufacturer must submit a New Drug Application (NDA). 21 U.S.C. 355(b). The applicant must provide "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. 355(b)(1)(A). The applicant must also include "adequate tests * * * to show whether or not such drug is safe for use under the conditions

prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. 355(d). An applicant seeking approval of a new drug must submit proposed labeling in the NDA. 21 U.S.C. 355(b)(1)(F). In addition, the applicant must furnish "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." 21 U.S.C. 355(d)(5). Where FDA concludes that a prescription drug is both safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling, the agency approves the NDA. 21 U.S.C. 355.

Under federal law, the evaluation of a drug's safety and effectiveness is thus inextricably intertwined with its labeling. FDA's decision as to appropriate labeling is based on the evidence submitted by the applicant, as well as on the agency's review of other relevant information. Commonly, a drug manufacturer and FDA will discuss in detail the proposed drug labeling, including the various warnings to be placed on the product. Based on the known scientific evidence, appropriate warnings are drafted to express the known risks, while avoiding the statement of unsubstantiated risks that may unnecessarily deter use of the drug. When the agency ultimately approves the NDA, it also approves the final version of the product labeling.

FDA may not approve an NDA that includes labeling that is false or misleading in any particular. 21 U.S.C. 355(c), 355(d)(7).

The FDCA prohibits the misbranding of drugs in interstate commerce. 21 U.S.C. 331(a), (b), (k). Violators may be subject to regulatory and enforcement actions, including injunction (21 U.S.C. 332), seizure (21 U.S.C. 331(b), 344(a)), and criminal prosecution (21 U.S.C. 333(a)). A drug is misbranded when, among other things, its labeling is false or misleading in any particular or does not provide adequate warnings against any use dangerous to health. 21 U.S.C. 352(a), (f), (j). FDA's regulations establish specific requirements for prescription drug product labeling, 21 C.F.R. Part 201 (Subparts A, B, G). These requirements are designed to mandate warnings that reflect the known risks based on reliable scientific evidence. 21 C.F.R. 201.56, 201.57.

Drug manufacturers generally may not deviate from FDA-approved product labeling without submitting an NDA supplement that provides a full explanation for the basis of the change. 21 C.F.R. 314.70. FDA permits two kinds of labeling supplements: (1) "pre-approval supplements," which require FDA approval prior to a change; and (2) "changes being effected supplements," which the manufacturer may implement before FDA approval. 21 C.F.R. 314.70(b), (c). A manufacturer may use a "changes being

effected" supplement to make labeling changes to add or strengthen a warning, but must still give to FDA "a full explanation of the [scientific] basis for the change." 21 C.F.R. 314.70(c). FDA then conducts an analysis to determine whether the proposed labeling change is appropriate. If the agency disapproves the proposed changes, the firm may not utilize the unapproved labeling.[2] 21 U.S.C. 352, 355(a).

3. In 1988, Pfizer filed its NDA for Zoloft, one of a class of "'selective serotonin reuptake inhibitors'" (SSRIs). SER 1191. The submissions included information about "suicidality" in patients given Zoloft, placebos, and other drugs. Id. at 1192. As it often does in considering NDAs, in 1990, FDA had convened a committee of experts, the Psycho-pharmacological Drugs Advisory Committee (PDAC), to review the Zoloft NDA. SER 1192. During the meeting, one of the agency's experts, "Dr. James Knudson, addressed suicide attempts in Zoloft, placebo and active-control treated patients during the clinical studies of [the drug]." Id. Dr. Knudson stated that the data "'show[ed] that disproportionate numbers of suicides do

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[2] FDA also has the authority to prohibit the marketing of misbranded products in interstate commerce (21 U.S.C. 331(a), (b), and (k)) and to alert patients and their physicians if it determines that a prescribed drug creates an "imminent danger to health or gross deception of the consumer" (21 U.S.C. 375(b)). Additionally, private persons and organizations may request FDA to take either such measure or to require alterations to the labeling, pursuant to a "citizen petition" provision. 21 C.F.R. 10.30.

not occur among the three treatment groups.'" Id. Subsequently, the PDAC unanimously concluded that Zoloft "'is safe when used in the treatment of depression.'" Id.

In 1991, FDA issued its "approvable" letter for the Zoloft NDA. Id. The precaution section of the proposed labeling, which FDA instructed Pfizer to use "verbatim," included the following statement:

> Suicide--The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Zoloft (sertraline) should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. SER 1192.

On December 30, 1991, FDA granted approval to market Zoloft for treatment of depression. Id. at 1193. The agency's "'Summary Basis of Approval,'" which addressed the occurrence of suicide in the database of tested Zoloft users, stated that trials showed "'results favoring [the drug] over placebo and supported the comparability of [Zoloft] and active control groups.'" Id. Later, FDA also approved Zoloft as safe and

effective for treatment of four other psychiatric disorders (three approvals before the death of Victor Motus, and one thereafter). Id. at 1193-94. In connection with one of the approvals that occurred before the suicide of Mr. Motus, a report prepared by Pfizer at FDA's request addressed "the relation between the use of Zoloft by adults and children for obsessive compulsive disorder and suicide related behavior." Id. at 1193 n.4. The report concluded that the "rate of suicidal behavior for adolescents treated with sertraline for obsessive-compulsive disorder was within the range described in normal population samples of adolescents." Id. at 1193-94 n.4.

Before and during FDA's consideration of the Zoloft NDA (as late as June 1997), the agency three times considered and rejected claims that other SSRIs, such as Prozac, cause suicide. SER 1194-95. PDAC, FDA's expert committee, voted unanimously that there was no "'credible evidence [(1)] to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors,'" and (2) no evidence "'to indicate that a particular drug or drug class poses a greater risk for the emergence and/or intensification of suicidal thoughts and acts and/or violent behaviors.'" Id. Addressing the PDAC on the subject of one SSRI, Prozac, Dr. Paul Leber, then Director of FDA's Division of Neuropharacological Drug Products, had expressed his "'concern'"

that an unnecessary warning "'beyond being false and misleading, might well have a net adverse effect'" on the drug's beneficial use. (SER 1207).

4. In denying partial summary judgment to Pfizer, the district court held that the company "failed to establish that a plaintiff is barred from asserting state law tort claims based on failure to warn of a suicide risk."[3] SER 1190. The court noted that "Pfizer makes no express or field preemption argument," but the company argues that "'plaintiff's attempt to use state tort law to require warnings that Zoloft causes suicide' conflicts with (1) FDA's various determinations regarding Zoloft's and SSRI's warnings and (2) the federal statutory and regulatory objective of ensuring that labeling effectively communicates the scientific information physicians need to make informed judgments." Id. at 1198.

The court observed that "most courts have found that FDA regulations as to design and warning standards are minimum standards which do not preempt state law defective design and failure to warn claims." SER 1198-99. The court stated that "even if standards deemed 'minimum' could conflict with state law tort suits, the warning labeling standards here do not because

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[3] In a subsequent opinion, however, the district court granted summary judgment in favor of Pfizer on the ground that any failure to warn did not cause the suicide. ER 535.

* * * Pfizer has not established that federal regulations or FDA meant to prohibit Pfizer from strengthening its warnings." Id. at 1199 n.7. The court then acknowledged that "some of the federal statutory and regulatory law Pfizer cites does appear to apply to Zoloft's warning label," ("prescription drug labeling may not be 'false or misleading in any particular'" (21 U.S.C. 355(d); 21 C.F.R. 201.56(b)); "labeling must be based on 'the essential scientific information needed for the safe and effective use of the drug'" (21 C.F.R. 201.56(a)). SER 1203. Nevertheless, the court found that "that law does not establish conflict preemption because Pfizer has not established that plaintiff's theory of liability would require warnings that would violate federal law."

In these circumstances, the court "f[ound] Pfizer's attack overbroad" in that while "certain suicide warnings could violate federal law because they were false or misleading or were not based on 'the essential scientific information needed' for safe use, the Court does not think that any and every suicide-related warning that might be required under state law is necessarily false or misleading, or not based on 'the essential scientific information needed' for safe use." Id. at 1203. The court acknowledged that "[o]n the occasions cited by Pfizer that FDA considered links between suicide and SSRIs, FDA did find [("consistent with the regulatory provision governing warning

labels, 21 C.F.R. 201.57(e), which indicates only those warnings that must be included in drug labeling, but does not prohibit any warnings")] that the evidence did not support requiring manufacturers to include additional suicide-related warnings." SER 1204. The court stressed, however, that "FDA never stated that it would be impermissible to include additional warnings." Id.

The court also rejected Pfizer's argument that the plaintiff's state law failure to warn claims obstruct congressional purposes. Id. at 1205. The court emphasized that since "plaintiff's * * * claims do not necessarily call for false and misleading labeling or labeling not based on scientific information," such claims "do not necessarily conflict with the regulations' straightforward purpose of ensuring that doctors receive accurate, scientifically based information." Id. The Court also was "not persuaded that FDA has found or has relied on a finding that strengthened suicide warnings would overdeter SSRI use," and "f[ound] an absence of persuasive evidence establishing a threat of overdeterrence from strengthening suicide warning labeling for SSRIs." SER 1207.

SUMMARY OF ARGUMENT

1. The Supremacy Clause bars a state from demanding that the manufacturer of a drug choose either to avoid tort liability or comply with the FDCA. Yet, under Motus's theory of liability,

any omitted warning would have had to state a causal relation between Zoloft and suicide - the very relation that FDA determined was scientifically unsupported. In short, any warning by Pfizer that suggested causation would have been false or misleading, and thus a misbranding that could have subjected the company to federal regulatory and enforcement action.

As the district court observed, FDA regulations do permit a drug's manufacturer to "'add[] or strengthen[] a contraindication, warning, precaution, or adverse reaction'" "'before FDA approval.'" SER 1201. Ultimately, however, FDA, not each state court system applying its own standards, must approve the warning. And given the agency's repeated negative determinations on the subject, had Pfizer given a warning as to a causal relation between Zoloft and suicide, FDA would have disapproved that warning. Indeed, based on its current scientific knowledge, FDA would still do so today.

Significantly, the district court acknowledges the "occasions" (as recently as June 1997, less than 1 ½ years prior to Mr. Motus' suicide) on which "FDA considered links between suicide and SSRIs," such as Zoloft, and the agency concluded "that the evidence did not support requiring manufacturers to include additional suicide-related warnings." SER 1204. In fact, the court accepts the possibility that certain additional warnings would have been inconsistent with FDA's finding, and

thus "false or misleading." Id. at 1203. The court's response is unpersuasive.

First, the court notes that the "FDA never stated that it would be impermissible to include additional warnings." Id. at 1204. But the implication that there must be such a statement (forbidding a warning that neither FDA nor Pfizer considered to be scientifically justified) to support a finding of preemption under the FDCA's self-executing provisions is unsupported and erroneous. Second, focusing on what it terms the "overbr[eadth]" (id. at 1203) of Pfizer's preemption argument, the court emphasizes that it is evaluating only the firm's attack on Motus's general allegation of failure to warn, so that one or more unspecified warnings might be valid. But Motus's case, as related to failure to warn, entirely depended on Pfizer's failure to provide a warning that in some way called attention to a causal relation between Zoloft and suicide. And in 1998, when Zoloft was prescribed for Victor Motus, all imaginable warnings that could reasonably have been read as describing or alluding to such a relation would have been false or misleading for lack of scientific support, and therefore in conflict with federal law.

2. The Supremacy Clause also bars an application of state law that would obstruct the purposes and objectives of federal law. Here, for many of the same reasons just discussed, imposition of liability on the basis of a failure to warn would

thwart the FDCA's objective of ensuring a drug's optimal use by requiring that manufacturers disseminate only truthful information as to its effects. Thus, the dissemination of a false warning that a patient taking Zoloft would incur the most dire risk - that the drug could cause suicide - would unjustifiably curtail its otherwise beneficial use.

ARGUMENT

THE FDCA AND APPLICABLE REGULATIONS PREEMPT MOTUS'S TORT CLAIMS IN THAT, AT THE TIME ZOLOFT WAS PRESCRIBED, ANY WARNING THAT SUGGESTED A CAUSAL RELATION BETWEEN ZOLOFT AND SUICIDE WOULD HAVE BEEN FALSE OR MISLEADING, AND THUS WOULD HAVE MISBRANDED THE PRODUCT

A. A State May Not Hold A Drug's Manufacturer Liable For Having Omitted A Warning That Would Have Misbranded The Drug In Violation Of Federal Law

Under the Supremacy Clause (U.S. Const. art. VI, cl.2), a state may not cause a drug's manufacturer to choose either to avoid tort liability or comply with federal law. Geier v. American Honda Motor Co., 529 U.S. 861, 873 (2000) (Supremacy Clause forbids "'conflicts' that make it 'impossible' for private parties to comply with both state and federal law"); Florida Lime & Avocado Growers, Inc. v. Paul, 373 U.S. 132, 142-43 (1963 ("federal exclusion of state law is inescapable and requires no inquiry into congressional design where compliance with both federal and state regulations is a physical impossibility"); Fireman's Fund Ins. Co. v. City of Lodi, __ F.3d __, No. 99-

15614, 2002 WL 1792612 *9 (9th Cir. Aug. 6, 2002). Thus, despite the district court's ultimate ruling, the court properly recognized that state law may not require the manufacturer of a drug to warn of a specific danger that FDA, based on scientific analysis, concludes does not exist.[4] Such a warning label, one not based on reliable scientific evidence of known risks (21 C.F.R. 201.56, 201.57.), would be "false or misleading" (21 U.S.C. 352(a), 352(f)), and thus would misbrand the drug. 21 U.S.C. 331(a), (b).[5] It is a violation of the FDCA to market a misbranded product. 21 U.S.C. 331(a), (b), and (k).

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[4] See Hurley v. Lederle Labs., 863 F.2d 1173, 1179 (5th Cir. 1988) ("assuming that the FDA has processed all the relevant and available information in arriving at the prescribed warning, its decision as to the proper wording must preempt by implication that of a state"); Robert B. Leflar & Robert S. Adler, The Preemption Pentad: Federal Preemption Of Products Liability Claims After Medtronic, 64 Tenn. L. Rev. 691, 717 (1997) (supporting preemption "if FDA is aware of the full evidence concerning the alleged risk * * * and has determined * * * that because of the data's speculative nature, that the alleged risk may not be included in the drug's labeling").

[5] See Henley v. Food And Drug Admin., 77 F.3d 616, 621 (2d Cir. 1996) ("FDA possesses the requisite know-how * * * to determine the most accurate and up-to-date information regarding a particular drug, and how those data affect human usage"); Public Citizen Health Research Group v. Commissioner, Food & Drug Admin., 740 F.2d 21, 28 (D.C. Cir. 1984) (Congress has entrusted to FDA, "in the first instance," "subtle scientific judgments" as to whether a drug "'may be dangerous.'").

B. Any Warning Of A Causal Relation Between Zoloft And Suicide Would Have "Misbrand[ed]" The Drug

The district court erred when, based on FDA regulations permitting a drug's manufacturer to "'add[] or strengthen[] a contraindication, warning, precaution, or adverse reaction'" "'before FDA approval'" (emphasis supplied) (citing 21 C.F.R. 314.70(c)(2)(i)), the court concluded that "[t]here appears to be no inherent conflict between state law requiring a stronger warning for Zoloft and the FDA's approval of Zoloft's present warning." SER 1201. The regulations invoked by the court do not dispense with review by FDA. Ultimately, FDA, not each state applying its own standards, must approve the warning. Certainly, given the agency's repeated negative determinations on the subject, had Pfizer given a warning as to a causal relation between Zoloft and suicide, FDA would have disapproved that warning. As discussed below, the warning would have misbranded the product because the warning would not have been supported by science. At least in such circumstances, preemption is required.[6] See Restatement (Third) Of Torts §6 cmt. c (1998)

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[6] Thus, it is unnecessary to address here the argument that the scheme for FDA's initial specification of warnings and for the manufacturer's subsequent modification of or addition to such warnings is sufficiently comprehensive as to foreclose the states from requiring warnings other than those specified by FDA. See United States v. Locke, 529 U.S. 89 (2000) (addressing claim of field preemption).

(recognizing that federal law may preempt state law as to adequate warnings).

Significantly, the district court acknowledges that "[o]n the occasions cited by Pfizer that FDA considered links between suicide and SSRIs, FDA did find that the evidence did not support requiring manufacturers to include additional suicide-related warnings." SER 1204. The court further acknowledges that (1) there is the possibility that certain additional warnings would have been inconsistent with FDA's finding, and thus subject to the requirements that prescription drug labeling may not be "false or misleading in any particular" (21 U.S.C. 355(d); 21 C.F.R. 201.56(b)), and (2) labeling must be based on "the essential scientific information needed for the safe and effective use of the drug" (21 C.F.R. 201.56(a)).[7] SER 1203. The court then responds, however, that "FDA never stated that it would be impermissible to include additional warnings." SER 1204.

Yet FDA does not have to state in advance that a particular warning would misbrand the product in order to make the placement of such a warning a violation of federal law. The manufacturer's

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[7] Given this specific conflict, it is irrelevant that, as stated by the district court, "most courts have found that FDA regulations as to design and warning standards are minimum standards which do not preempt state law defective design and failure to warn claims" (citing Hill v. Searle Labs., 884 F.2d 1064, 1068 (8th Cir. 1989)). SER 1198-99.

inclusion of a false or misleading warning misbrands the product per se. And the court offers no basis for its erroneous implication that such a prior statement by FDA (that would bar a warning that neither the agency nor Pfizer considered to be scientifically justified) is necessary to support a finding of preemption by the self-executing statutory prohibition of misbranding. See Geier v. American Honda Motor Co., Inc., 529 U.S. 861, 884 (2000) ("the Court has never before required a specific, formal agency statement identifying conflict in order to conclude that such a conflict in fact exists").

The court also emphasizes that it was evaluating only Pfizer's attack on "plaintiff's general allegation of failure to warn" (SER 1203), and that "plaintiff evidently has not yet identified the precise warning that she thinks Pfizer should have provided."[8] SER 1203 n.10. Thus, the court concludes that "Pfizer has not established that plaintiff's theory of liability would require warnings that would violate federal law." In essence, the court focused on what it termed the "overbr[eadth]" (id. at 1203) of Pfizer's preemption argument.[9]

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[8] Arguably, the district court should have required the plaintiff to be more specific. But it is clear from the complaint that the warning had to deal in some fashion with Zoloft's alleged causal role in suicide.

[9] In Caraker v. Sandoz Pharms. Corp., 172 F. Supp. 2d 1018, 1031-43 (S.D. Ill. 2001), involving a postpartum lactation control drug, the court applied a similar analysis in finding (continued...)

The court is correct that not every conceivable additional warning that Pfizer might have given as to Zoloft would have been false or misleading, given the FDA's scientific determinations as specifically directed to causation of suicide. For example, it might have come to Pfizer's attention that there was an unforeseen problem with an allergic reaction to Zoloft. The critical point is that, even though Mrs. Motus did not state the specific warning that Pfizer allegedly had a duty under state law to provide, her case, as it related to failure to warn, entirely depended on Pfizer's failure to provide a warning that in some way called attention to an asserted causal relation between Zoloft and suicide.

The example of a supposedly permissible SSRI warning actually invoked by the court fits that description. The warning, recommended by the British counterpart to the FDA (the Medicines Control Agency) - that "'occasionally, thoughts of suicide or self harm may occur or increase in the first few weeks

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[9](...continued)
that there was no preemption in a failure to warn case. As in the present case, the court emphasized the "'minimum' standards approach used by "many courts." 172 F. Supp. 2d at 1033. Unlike the court here, however, Caraker relied on the presumption that absent express preemption, Congress does not intend to displace state law, particularly in the areas such as health and safety that the states have traditionally occupied. But see United States v. Locke, 529 U.S. 89, 108 (2000) ("'assumption'" of non-preemption is not triggered when the State regulates in an area where there has been a history of significant federal presence"). Federal food and drug regulation legislation was enacted in 1906, and thus has been in place over nearly 100 years.

of treatment with sertraline, until the antidepressant effect becomes apparent. Tell your doctor immediately if you have any distressing thoughts or experiences'" (SER 1203) - is ambiguous as to causality.[10] Since the British warning could reasonably have been construed as suggesting a casual relation to suicide, federal law would have barred Pfizer from giving it.

Thus, in 1998, when Zoloft was prescribed for Victor Motus, any warning, no matter how worded, that could reasonably have been read as describing or alluding to such a relation would have been false or misleading, and therefore in conflict with federal law because there was no (and still is not) scientific support for such a warning. This is not just because FDA had rejected any link between Zoloft and suicide when, in 1991, the agency approved the drug as a treatment for depression.[11] Subsequently, in response to petitions making similar allegations as to the

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[10] The Medicines Control Agency had also concluded that no causal relation had been "'scientifically established.'" See Plaintiff's Opposition To Defendant's Motion For Partial Summary Judgment Re: Inadequate Warning Claims (Preemption/Standard Of Care) 23.

[11] On four subsequent occasions, three before (October, 1996 and July and October, 1997) and one (December 1999) after Mr. Motus's death, FDA approved Zoloft for treatment of other psychiatric disorders and did not require the inclusion of a causation warning in the labeling. SER 1193.

related drug, Prozac, FDA found no link between antidepressants and suicide.[12]

Additionally, in June 1997, the PDAC voted unanimously that there was no "credible evidence (1) to support a conclusion the antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors," or (2) "to indicate that a particular drug or drug class poses a greater risk for the emergence and/or intensification of suicidal thoughts and acts and/or violent behaviors." SER 1195. FDA informs us that in 2002 the agency completed an internal review of SSRIs.[13] This review of the data disclosed that there is no difference in the risk of suicide between those on SSRI's and those on placebo. Thus, the agency concluded once again that, at present, no credible scientific evidence exists to show that SSRI drug products, including Zoloft, cause suicide.

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[12] Thus, the circumstances here are unlike those in Wooderson v. Ortho Pharm. Corp., 235 Kan. 387, 409, 681 P.2d 1038, 1057 (FDA's "letter [(relied on by drug manufacturer)] cannot be construed as a clear determination * * * that contraceptive-induced HUS [(hemolytic uremic syndrome)] does not merit warnings, and thus this argument has no merit") (emphasis supplied), cert. denied, 469 U.S. 965 (1984).

[13] See Andrew D. Mosholder, Medical Officer, FDA Division of Neuropharmacological Drug Products, Mortality and Suicide Rates in Randomized Controlled Trials of Psychiatric Drugs: Update 2002, 42nd Annual National Institute of Mental Health's New Clinical Drug Evaluation Unit Meeting (June 10-13, 2002).

C. Any Warning Of A Causal Relation Between Zoloft And Suicide Would Have Obstructed The FDCA's Purposes And Objectives

Given the just discussed conflict, the effectuation of California tort law in this case would also impermissibly "prevent 'the accomplishment and execution of the full purposes and objectives of Congress'" (Jones v. Rath Packing Co., 430 U.S. 519, 543 (1977)). See Geier, 529 U.S. at 873 ("Court has not * * * driven a legal wedge - only a terminological one - between 'conflicts' that prevent or frustrate the accomplishment of a federal objective and 'conflicts' that make it 'impossible' for private parties to comply with both state and federal law"). And such federal-state conflict of duties is not the only ground on which to conclude that there would be a frustration of congressional intent.

FDA's regulation of prescription drugs is designed to ensure each drug's optimal use through requiring scientifically substantiated warnings. Under-utilization of a drug based on dissemination of scientifically unsubstantiated warnings, so as to deprive patients of beneficial, possibly lifesaving treatment, could well frustrate the purposes of federal regulation as much as over-utilization resulting from a failure to disclose a drug's scientifically demonstrable adverse effects. Further, allowing unsubstantiated warnings may also diminish the impact of valid warnings by creating an unnecessary distraction and making even

valid warnings less credible. See Lars Noah, Medicine's Epistemology: Mapping The Haphazard Diffusion Of Knowledge In The Biomedical Community, 44 Ariz. L. Rev. 373, 454-55 (2002); Thomas Scarlett, The Relationship Among Adverse Drug Reaction Reporting, Drug Labeling, Product Liability, and Federal Preemption, 46 Food Drug. Cosm. L. J. 31, 36 (1991) ("overstated warnings could tip judgment of the medical profession in an undesirable direction").

Here, contrary to the opinion of the district court (SER 1206-07), the concern with over-deterrence was of necessity a factor in FDA's decision-making process. The PDAC considered the statement of the then Director of FDA's Division of Neuropharacological Drug Products, Dr. Paul Leber (id. at 1207), and the testimony of representatives of several mental health groups that opposed warnings that would have suggested a causal relation of SSRIs to suicide.[14] In sum, it is inescapable that any warning so dire as to suggest that there was a causal relation between Zoloft and suicide would have chilled the drug's otherwise beneficial use.

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[14] For example, the Executive Director of the National Depressive and Manic-Depressive Association stated that a change in labeling to suggest a causal relation between antidepressant medications and suicide, "especially when there is no scientific evidence to support such action, would generally harm the patient community and make it more difficult to be treated with these life-saving medicines." SER 701-03. See also SER 90-91, 47-53, 99-107.

CONCLUSION

For the foregoing reasons, the district court's Preemption Order should be reversed.

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CERTIFICATE OF SERVICE

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