No. 06-3107

IN THE UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

JOSEPH C. COLACICCO, Individually and as Executor of the Estate of Lois Ann Colacicco, Deceased,
Plaintiff-Appellant,

v.

APOTEX, INC.; APOTEX CORP., as Subsidiary of Apotex, Inc.; SMITHKLINE BEECHAM, d/b/a/ GlaxoSmithKline,
Defendants-Appellees.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

BRIEF OF THE UNITED STATES AS AMICUS CURIAE IN SUPPORT OF DEFENDANTS-APPELLEES

DANIEL MERON
General Counsel
Department of Health and Human Services

SHELDON T. BRADSHAW
Chief Counsel
ERIC M. BLUMBERG
Deputy Chief Counsel
JENNIFER E. CARUSO
Associate Chief Counsel
Food and Drug Division
Department of Health and Human Services
Office of General Counsel

PETER D. KEISLER
Assistant Attorney General

C. FREDERICK BECKNER III
Deputy Assistant Attorney General

PATRICK L. MEEHAN
United States Attorney

DOUGLAS N. LETTER
(202) 514-3602
SHARON SWINGLE
(202) 353-2689
Attorneys, Appellate Staff
Department of Justice
Civil Division
950 Pennsylvania Ave., N.W.
Washington, DC 20530-0001

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INTERESTS OF THE UNITED STATES

Pursuant to 28 U.S.C. § 517 and Federal Rule of Appellate Procedure 29(a), the United States files this brief as amicus curiae in support of affirmance.

The plaintiff in this litigation seeks to impose tort liability on drug manufacturers for failure to warn of an alleged danger, notwithstanding the Food and Drug Administration's repeated determination during the relevant period that the existing scientific knowledge did not support such a warning. Although the Food and Drug Administration (FDA) has the deepest sympathy for the plaintiff because of the death of his wife, it is vital to ensure that state tort law does not

undermine the agency's statutory authority and its ability to protect the public health by prohibiting the false or misleading labeling of drug products. To base a tort judgment on drug manufacturers' failure to warn in October 2003 of an association between adult use of paroxetine hydrochloride and suicide or suicidality, despite FDA's judgment at that time that there was not reasonable scientific evidence of such an association, would be to demand a warning statement that would have been false or misleading, and thus contrary to federal law. In such a case, as the district court properly recognized, federal law must prevail.[1]

STATEMENT

A. Statutory and Regulatory Framework.

1. FDA is the expert federal agency charged by Congress in the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (FDCA), with regulating the manufacture, sale, and labeling of prescription drug products.[2] In particular,

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[1] In appearing as amicus curiae in this litigation, the Government has limited its analysis to the application of federal preemption to the failure-to-warn claim arising out of defendants' failure in October 2003 to warn on the drug labeling for their products of an asserted association between paroxetine hydrochloride and adult suicide or suicidality. Contrary to the plaintiff's assertion (at Br. 3-4), the Government has not taken a position on the plaintiff's other claims.

[2] FDA is a component of the United States Department of Health and Human Services (HHS). The Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et*

(continued...)

FDA has been charged with ensuring that drugs sold in the United States are safe and effective, *id.* § 355(d) and § 393(b)(2)(B), and that they are not misbranded, *id.* §§ 331(a), (b), and (k), 352, and 321(n).

In order to obtain FDA approval to market a new innovator drug, a manufacturer must submit a New Drug Application. *See* 21 U.S.C. § 355(b). The manufacturer must provide full reports of investigations conducted to determine the safety and effectiveness of the drug. *Id.* § 355(b)(1)(A). The manufacturer must also provide "specimens of the labeling proposed to be used for such drug." *Id.* § 355(b)(1)(F). FDA will deny the application if the manufacturer does not provide, *inter alia*, adequate tests to show that the "drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." *Id.* § 355(d)(1).

Once an innovator drug has been approved for sale, a drug manufacturer may seek approval under the FDCA to market a generic form of that drug. The approval process for a generic drug is abbreviated, and does not require the manufacturer to show independent clinical evidence of efficacy or safety. Instead,

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[2](...continued)
seq. (FDCA), vests regulatory and enforcement authority in the Secretary of Health and Human Services. The Secretary has delegated this authority to the Commissioner of FDA. FDA Staff Manual Guides, Vol. II, § 1410.10 (available at http://www.fda.gov/smg/1410_10.html).

the manufacturer must show that the generic drug generally has the same active ingredients as the innovator drug and is bioequivalent to that drug. *See* 21 U.S.C. § 355(j)(2)(A)(ii), (iv). The manufacturer must also show that the "labeling proposed for the [generic] drug is the same as the labeling approved for" the innovator drug. *Id.* § 355(j)(2)(A)(v). The only labeling changes permitted to be made are changes to reflect a different manufacturer or that the generic drug has "a different active ingredient" or a different "route of administration, dosage form, or strength." *Id.* § 355(j)(2)(A), (j)(2)(C); *see also* 21 C.F.R. §§ 314.94(a)(8), 314.127(a)(7).

Following FDA approval to market a drug, manufacturers are subject to continuing obligations under the FDCA. *See* 21 U.S.C. § 355(k); 21 C.F.R. §§ 314.80, 314.98. A manufacturer must keep a record of any "adverse event associated with the use of a drug in humans, whether or not considered drug related," and must periodically report these adverse events to FDA. 21 C.F.R. §§ 314.80(a), (c), 314.98(a). For adverse events that are "serious and unexpected," the manufacturer is required to report the event to FDA within 15 days, and to conduct an investigation and provide follow-up information to the agency. *Id.* §§ 314.80(c)(1), 314.98(a).

2. The preemption issue raised in this appeal implicates the labeling provisions of the FDCA, as implemented by FDA. Under the FDCA, a drug is

unlawfully misbranded when its labeling is false or misleading in any particular, or does not provide adequate directions for use or adequate warnings against any use dangerous to health. *See* 21 U.S.C. § 331(a), (b), and (k); *id.* § 352(a), (f), (j); *id.* § 321(n). A prescription drug label satisfies federal requirements if it gives physicians and pharmacists sufficient information, including indications for use and "any relevant hazards, contraindications, side-effects, and precautions," to allow those medical professionals to "use the drug safely and for the purposes for which it is intended * * *." 21 C.F.R. § 201.100(c)(1). Under federal law, therefore, the evaluation of a drug's safety and effectiveness is inextricably linked with the drug labeling. *See also* 50 Fed. Reg. 7452, 7470 (1985) ("Drug labeling serves as the standard under which FDA determines whether a product is safe and effective.").

FDA regulations set forth specific requirements for prescription drug labeling. *See* 21 C.F.R. Part 201, Subparts A, B, and G. Prescription drug labels must contain "a summary of the essential scientific information needed for the safe and effective use of the drug," which includes indications for use as well as a description of "clinically significant adverse reactions" and "other potential safety hazards" associated with use of the drug. 21 C.F.R. § 201.57(c)(6)(i). The labeling regulations are designed to require warnings of all known risks that are based on reliable scientific evidence. *See id.* (requiring as a condition of warning

that there be "reasonable evidence of a causal association" between use of a drug and "a clinically significant hazard").

As noted, applications for both innovator drugs and generic drugs must include copies of the proposed labeling for FDA's review and approval. For innovator drugs, FDA considers evidence submitted by the applicant, as well as other relevant scientific information, to determine whether the label is accurate, truthful, not misleading, and adequate. FDA and drug manufacturers 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 that identify established risks while avoiding inadequately substantiated risks, the mention of which could improperly deter use of the drug and result in harm to patients who unnecessarily forego medication. When FDA approves a new drug application for an innovator drug, it also approves the precise final version of the drug labeling. *See* 21 C.F.R. § 314.50(e)(2)(ii), (*l*)(1)(i); *id.* § 314.105(b).

For generic drugs, FDA confirms as a condition of approval that, with exceptions not applicable here, the labeling is the same as the labeling approved for the innovator drug of which the drug is a generic form. 21 U.S.C. § 355(j)(4)(G). As noted, generic drug manufacturers are required to use labeling

that is, for relevant purposes, identical to the approved labeling for the innovator drug.

A manufacturer may not deviate from FDA-approved product labeling except in limited circumstances set forth in FDA regulations. If the manufacturer of an innovator drug wishes to add or strengthen a warning statement on the approved labeling, the manufacturer may provide FDA with a supplemental submission, providing a full explanation of the basis for the proposed change. *See* 21 C.F.R. § 314.70(c)(1), (3), (6)(iii)(A).[3] If the FDA has not rejected the supplement within 30 days after its submission, the manufacturer may distribute the drug with the new labeling — although FDA can reject the change even after this date, and can order the manufacturer to cease distributing the drug with the new labeling. *See* 21 C.F.R. § 314.70(c)(7).

For a generic drug manufacturer, there is no statutory or regulatory provision permitting a labeling change to be made without prior FDA approval. To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. *See* 21 C.F.R. § 314.150(b)(10); *see also* 57 Fed. Reg. 17,950, 17,953, 17,961 (1992). If a generic drug manufacturer believes

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[3] Indeed, if the drug manufacturer has "reasonable evidence of an association of a serious hazard with a drug," the manufacturer has an obligation to seek FDA approval for a labeling change, in order to add a warning of the new potential hazard. *See* 21 C.F.R. § 201.80(e).

that new safety information should be added to the label for its drug, it is directed to contact FDA with "adequate supporting information." 57 Fed. Reg. at 17,961. The agency will consider this information and determine whether the labeling for both the generic drug and the innovator drug should be revised. *Id.*[4]

B. Regulatory History of Paroxetine Hydrochloride.

This litigation involves the drug paroxetine hydrochloride, which is the active ingredient of the brand-name drug Paxil. FDA approved GlaxoSmithKline's new drug application for Paxil in 1992, and approved Apotex Corp.'s application to market a generic form of the drug in 2003. Paroxetine hydrochloride is in the class of drugs known as "selective serotonin reuptake

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[4] The plaintiff asserts that 21 C.F.R. § 314.70(c) empowers a generic drug manufacturer to add a new warning to the label for its drug without prior FDA approval. That regulatory provision, however — like the other provisions of Title 21, Part 314, Subpart B of the Code of Federal Regulations — applies to applications involving drug products for which a full application has been submitted, *i.e.*, innovator drug products. Drug manufacturers that submit abbreviated applications to market generic drugs are subject to the requirements set forth in Title 21, Part 314, Subpart C. Although Subpart C contains a provision requiring applicants to "comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application," 21 C.F.R. § 317.97, that provision does not modify the requirement that the drug label for a generic drug must be the same as the label for the approved innovator drug (with limited exceptions not relevant here). Any ambiguity in the regulatory text has been clarified by FDA, which explained at the time of promulgation that the regulations do not authorize generic drug manufacturers to add new warnings to the approved labeling for the innovator drug. *See* 57 Fed. Reg. at 17,961, 17,953, 17,955.

inhibitors" (SSRIs), which are used to treat depression and other psychological disorders.

In order to evaluate the safety and efficacy of paroxetine hydrochloride and other SSRIs, and to ensure that warning statements in the labeling are accurate and not misleading, FDA must distinguish between events that result from use of the drug and those resulting from the underlying disease. Drawing that distinction is most difficult where, as in the case of depression treated with an SSRI, the adverse events in question — suicide and suicidality — are also a known consequence of the disease.

Since 1992, the FDA-approved label for Paxil (and, subsequently, generic forms of paroxetine hydrochloride approved for marketing) has reflected the risk of suicide in patients using the drug. The original approved label warned that "[t]he possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs." The label recommended "[c]lose supervision of high-risk patients," and also indicated that prescriptions "should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose." FDA Approval Letter NDA 20-031/S029, Attachment 1, at 5, Addendum ("Add.") 1-3.[5]

[5] This history of FDA's regulatory actions involving SSRIs is derived from (continued...)

Prior to October 2003, however, FDA had repeatedly determined, based on its scientific analysis of then-available information, that there was not adequate evidence of an association between adult use of paroxetine hydrochloride or other SSRIs and suicide or suicidality.

In July 1991, the FDA denied a citizen petition seeking FDA withdrawal of approval for Prozac, based on FDA's conclusion that "[t]he data and information available at this time do not indicate that Prozac causes suicidality or violent behavior." July 26, 1991, letter from FDA to S. Block, at 1, Add. 4.

In September 1991, FDA's Psychopharmacological Drugs Advisory Committee met and, after hearing testimony and reviewing relevant scientific studies, voted against any change to the labeling for Prozac to warn of a risk of suicide or suicidality, based on the conclusion that there was not credible evidence that antidepressant drugs or any particular class of antidepressant drugs "cause the emergence and/or intensification of suicidality and/or other violent behaviors." Psychopharmacological Drugs Advisory Committee, Sept. 20, 1991, Transcript at 302, 331-332, Add. 5, 6-8. The head of FDA's Psychopharmacology Unit

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[5](...continued)
public documents, which are available at FDA's web site (www.fda.gov). FDA attached a number of the documents in their entirety as an addendum to the district court amicus brief. For the convenience of this Court, FDA is also attaching selected documents and excerpts from documents as an addendum to this brief.

explained to the Advisory Committee at that meeting that FDA had decided that "suicidal ideation" and "violent behaviors" should be added to the section of adverse reactions on the drug labeling entitled "Post-Introduction Reports," but should not be listed in the "Precautions" section of the labeling because of the agency's "lack of confidence in a causal link between the taking of the drug and those behaviors." Transcript, at 136-137, Add. 9-11.

In 1992 and 1997, FDA denied citizen petitions requesting that FDA revise the approved labeling for Prozac to include a warning of suicide or suicidal thought. *See* June 3, 1992, letter from FDA to I. Hellander, Add. 12; June 25, 1997, letter from FDA to R. Meysenburg, Add. 29. In its 1992 response, FDA explained that the "currently available, relevant evidence" was "not sufficient to reasonably conclude that the use of Prozac is possibly associated with suicidal ideation and behavior." Add. 12. FDA reached the same conclusion in 1997, noting that, although the agency had received numerous drug experience reports concerning Prozac and suicidal ideation and suicidality, the agency had determined after careful consideration "that no labeling revisions were warranted" as of that date, and that then-current labeling for Prozac "appropriately reflect[ed] the level of concern about Prozac and suicidality." Add. 30.

In 2002, FDA conducted a review of SSRIs, in order to evaluate the state of scientific knowledge regarding a connection between the use of SSRIs and

suicide. *See* Andrew D. Mosholder, *Mortality and Suicide Rates in Randomized Controlled Trials of Psychiatric Drugs: Update 2002*, Add. 31. Based on that review, the agency concluded that the scientific evidence did not show an association between the use of anti-depressants, including SSRIs, and suicide. *See* Mosholder presentation, at 35, Add. 32 (summarizing finding that "[t]here were no significant differences in suicide rates between active treatments and placebo").

In May 2003, FDA received a report from GlaxoSmithKline suggesting that *pediatric* patients who used Paxil were at an increased risk for suicide and suicidality. Based on this report and FDA's subsequent internal analysis, FDA subsequently issued a public health advisory in October 2003 for *pediatric* users of Paxil, explaining that preliminary data suggested an excess of reports for suicidality in pediatric patients with major depressive disorder. *See* www.fda.gov/cder/drug/advisory/mdd.htm. However, FDA declined to take any similar action with respect to adult users of the drug, and in June 2003 explicitly reaffirmed the agency's conclusion that "[t]here is no evidence that Paxil is associated with an increased risk of suicidal thinking in adults." *See* FDA Talk Paper, www.fda.gov/bbs/topics/ANSWERS/2003/ ans01230.html.

On July 30, 2003, FDA approved Apotex's application to market its generic form of paroxetine hydrochloride, concluding that "the drug is safe and effective for use as recommended in the submitted labeling." *See* July 30, 2003, Letter from

Gary Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA, to Apotex Corp., ANDA 75-356 (available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist).

In February 2004, FDA convened an advisory committee meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee, and, following that meeting, issued a public health advisory in March 2004 directing manufacturers of ten SSRIs, including Paxil, to include stronger warnings on drug labels about the need to monitor adult patients for signs of worsening depression or suicidality. *See* FDA Talk Paper, www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html; FDA Public Health Advisory, www.fda.gov/cder/drug/AntidepressanstPHA.htm. Even as of that date, FDA emphasized that it had "not concluded that these drugs cause worsening depression or suicidality" in adult patients. FDA Public Health Advisory; *see also* FDA, Questions and Answers on Antidepressant Use in Children, Adolescents, and Adults, www.fda.gov/cder/drug/antidepressants/Q&A_antidepressants.htm.

In 2005, FDA launched a comprehensive scientific review of existing studies to determine whether there is an increased risk of suicide or suicidal behavior in adults treated with antidepressant drugs. *See* FDA Public Health

Advisory, http://www.fda.gov/cder/drug/advisory/SSRI200507.htm; FDA Talk Paper, July 1, 2005, www.fda.gov/bbs/topics/ANSWERS/2005/ANS01362.html. As part of that review, GlaxoSmithKline conducted a meta-analysis[6] of studies on Paxil that disclosed a higher incidence of suicidal behavior in young adults treated with paroxetine compared with placebo. *See* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=448. GlaxoSmithKline filed a supplemental submission with FDA in April 2006 and, after the 30-day waiting period expired and FDA did not reject the proposed labeling change, modified the label for Paxil to include a warning that "[y]oung adults, especially those with [major depressive disorder], may be at an increased risk of suicidal behavior when treated with" PAXIL. *See* Paxil label, available via link from http://www.gsk.com/products/prescription_medicines/us/paxil.htm.

C. Factual and Procedural History of Litigation.

Between October 6 and October 18, 2003, Lois Ann Colacicco was treated with paroxetine hydrochloride manufactured by Apotex. On October 28, 2003, at the age of 55, she committed suicide.

Ms. Colacicco's husband sued Apotex, the manufacturer of the paroxetine hydrochloride taken by Ms. Colacicco, and GlaxoSmithKline, the manufacturer of

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[6] A meta-analysis is a comprehensive evaluation of the data contained in a number of studies.

brand-name Paxil. The plaintiff alleges in relevant part that the defendants failed warn of an increased risk of suicide or suicidality in adult users of their drugs. Mr. Colacicco also brought a variety of other state-law claims against the defendants.

The district court dismissed the plaintiff's failure-to-warn claim on federal preemption grounds. The court held that state tort liability would conflict with FDA's determination as of October 2003 that "associating use of paroxetine hydrochloride with suicidality would have constituted misbranding" because there was inadequate scientific evidence to support such a warning. Slip op., at 17. The court also noted that imposition of liability on Apotex, Inc., for failure to provide a different warning on the label for its generic drug would conflict with federal prohibitions on making such a change without prior FDA approval. Slip op., at 18. In reaching these conclusions, the court gave weight to FDA's views as set forth in its amicus brief on the potential conflict between state tort liability and the accomplishment of federal regulatory objectives, as well as FDA's interpretation of its own regulations. Slip op., at 18-20.

ARGUMENT

FEDERAL LAW PREEMPTS A STATE TORT CLAIM ARISING OUT OF DRUG MANUFACTURERS' ALLEGED FAILURE TO PROVIDE A WARNING THAT FDA DETERMINED WAS NOT SCIENTIFICALLY SUPPORTED

A. FDA's scientific judgment in October 2003, when paroxetine hydrochloride was prescribed to, and taken by, Ms. Colacicco, was that there was no reasonable evidence available at that time of an association between adult use of the drug and suicide or suicidality. To include on a drug's label a warning about a drug's effects, when FDA has specifically determined that such a warning is not based on reliable scientific evidence, would be "false or misleading," 21 U.S.C. §§ 352(a), (f), and would constitute unlawful misbranding. 21 U.S.C. § 331(a), (b), and (k).

In considering the agency's views on drug labeling, it is critical to understand that, where warnings are concerned, more is not always better. In setting standards for drug labeling, FDA seeks to encourage the optimal level of use in light of reasonable safety concerns, by requiring scientific evidence that establishes an association between a drug and a particular hazard before warning of that association on a drug's labeling. *See* 21 C.F.R. § 201.80(e). Under-use of a drug based on dissemination of unsubstantiated warnings may deprive patients of efficacious and possibly lifesaving treatment. Further, allowing unsubstantiated

warnings would likely reduce the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible. In order to make appropriate judgments about drug use, prescribers need a "careful and truthful representation of benefits and risks," which does not "discourage appropriate use of a beneficial drug" through the inclusion of unsubstantiated risks. 71 Fed. Reg. 3922, 3935 (2006).

In this case, the label for paroxetine hydrochloride has since 1992 recognized the risk of suicide or suicidality in patients treated with the drug, alerting physicians to be aware of the "possibility of a suicide attempt" and to undertake "[c]lose supervision of high-risk patients." The plaintiff asserts that the label for Paxil and its generic forms should have warned of an *increased* risk for suicide or suicidality in adults. But during the twelve-year period leading up to October 2003, FDA specifically considered and repeatedly rejected the addition of such a warning to the labeling for the drug. *See* pp. 8-13, *supra.* In responses to citizen petitions, in reviewing scientific studies and presenting its findings to advisory committees, and in its public statements, FDA concluded that the available scientific evidence did not support an association between adult SSRI use and suicide or suicidality.[7]

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[7] The plaintiff challenges the district court's reliance on public documents (continued...)

The plaintiff argues that the defendants could have warned of an increased risk of suicide or suicidality in adult users of paroxetine hydrochloride under federal regulations permitting a drug manufacturer to submit a supplemental application to add or strengthen a warning on a label, and to implement that change if the FDA does not object. *See* Br. 15 (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)). The regulation does not apply to the manufacturer of a generic drug. *See* pp. 7-8, *infra*. In addition, the regulation requires that even the manufacturer of an innovator drug must provide "a full explanation of the [scientific] basis for the change" sought to the labeling, 21 C.F.R. § 314.70(c)(3), (6)(iii), and does not alter the requirement that any warning must be based on "reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 314.80(e). As of October 2003, any warning of an association between adult use of paroxetine hydrochloride and suicide or suicidality would have been misleading, because it would have been contrary to FDA's determination that

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[7](...continued)
reflecting these decisions by FDA. *See* Br. 24-25 & n.9. A district court may take judicial notice of public records for the purpose of establishing the fact of an agency decision, rather than the truth of the underlying facts. *See, e.g., Lum v. Bank of Am.*, 361 F.3d 217, 221 n.3 (3d Cir.), *cert. denied*, 543 U.S. 918 (2004); *Pension Benefit Guar. Corp. v. White Consol. Indus., Inc.*, 998 F.2d 1192, 1197 (3d Cir.1993), *cert. denied*, 510 U.S. 1042 (1994). The plaintiff cannot reasonably claim that FDA did not take the actions reflected in public documents and referenced by the district court.

there was not adequate scientific evidence to establish such an association. Had the defendants added to their label the warning that the plaintiff seeks, they would have acted in violation of federal law. *See* 21 U.S.C. § 352(a), (f).

As the Supreme Court recognized in *Bates v. Dow Agrosciences LLC*, 544 U.S. 431 (2005), the imposition of a common-law duty through a state tort suit can be preempted under the Supremacy Clause if the duty at issue is inconsistent with the requirements of federal law.[8] Here, Mr. Colacicco seeks to impose liability under state tort law for defendants' alleged failure to provide a warning that had been specifically rejected by FDA as of October 2003, and accordingly would have constituted unlawful misbranding had it been included on the labeling for the defendants' drugs.[9] In such circumstances, the Supremacy Clause bars the

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[8] Amici curiae Jacquelyn Giles and Annabel Dobbs suggest (at Br. 3-4) that federal requirements do not preempt inconsistent state law unless they are carried out by FDA through means of a formal enforcement action. That puzzling suggestion — which would have sweeping consequences — is without precedential support. *Cf. Geier*, 529 U.S. at 882 (rejecting similar argument that state tort duty is not preempted because it does not impose mandatory requirement on liable party, who can pay judgment rather than modify its conduct).

[9] Amici curiae Giles and Dobbs argue that FDA would not have rejected a proposed warning about an increased risk of adult suicide or suicidality, relying on congressional testimony by an FDA official about a drug manufacturer's change to the labeling for Effexor in August 2003 to add a warning relating to pediatric use of the drug. *See* Giles Br. 5-6. The fact that FDA had evidence suggesting an association between *pediatric* treatment with SSRIs and suicide or suicidality, *see* p. 12, *supra*, does not mean that reasonable scientific evidence suggested an

(continued...)

imposition of liability under state law. *See, e.g., Geier v. American Honda Motor Co.*, 529 U.S. 861, 881-882 (2000); *Hurley v. Lederle Labs.*, 863 F.2d 1173, 1179 (5th Cir. 1988).

B. The plaintiff argues that federal preemption cannot apply because FDA did not affirmatively prohibit the defendants from adding a warning about suicide or suicidality to the labeling for their drugs. *See* App. Br. 23-24 & n.8. As the Supreme Court held in *Geier*, however, it is not necessary to have a "specific, formal agency statement identifying conflict" for federal preemption to apply. 529 U.S. at 884. Rather, state law is preempted if it would "stand[] as an obstacle to the accomplishment and execution" of the objectives of federal law. *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).

In the context of drug labeling, Congress has authorized FDA to apply its scientific expertise to determine, in the first instance, what warnings are appropriate and necessary for a particular drug. *See Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996); *Public Citizen Health Research Group v. Commissioner*, 740 F.2d 21, 28 (D.C. Cir. 1984). Given FDA's repeated and specific determinations

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[9](...continued)
association between *adult* use of SSRIs and suicide or suicidality. FDA's own actions leading up to and in October 2003, when the agency issued a public health advisory for pediatric users of Paxil but declined to warn adult users of the drug, foreclose the argument that FDA would have permitted the warning that the plaintiff seeks.

during the relevant time that it would be inappropriate to warn on the label for paroxetine hydrochloride of an association between adult use of the drug and suicide or suicidality, it would frustrate the regulatory scheme established by Congress to hold as a matter of state law that the defendants are liable for failing to provide that very warning on the label for their drugs.

The fact that FDA's judgment was not made in response to an application filed by the defendants does not preclude the application of federal preemption to the plaintiff's failure-to-warn claim in this litigation. A holding that FDA's labeling decision only has preemptive force if made in the course of rejecting a manufacturer's supplemental application for a labeling change would undermine FDA's regulatory authority, and would encourage manufacturers to file supplemental applications for unsubstantiated labeling changes, in order to shield themselves from tort liability.

In arguing that federal preemption does not apply, the plaintiff relies heavily on *Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002), but the regulatory scheme in that case explicitly provided that compliance with "minimum safety standards" imposed by the Coast Guard would "*not* relieve a person from liability at common law or under State law." *Id.* at 58-59 (emphasis added). Furthermore, and in accordance with its delegated authority under the statute, the Coast Guard had determined that federal preemption of state safety standards was limited to matters

covered by federal regulations. *See id.* at 60. After the Coast Guard declined to adopt a regulation requiring propeller guards on all motorboats, the Court properly held that this action did not bar a state tort liability for failure to install a guard on a particular motorboat — relying heavily on the Coast Guard's view that the state claim would not conflict with federal regulatory objectives. *Id.* at 65-66.

Here, in sharp contrast, the imposition of liability under state law for defendants' alleged failure to warn *would* interfere with FDA's accomplishment of regulatory objectives. The Supreme Court explicitly recognized in *Sprietsma* that, where an agency's decision not to impose a requirement in a particular setting reflects its judgment that the requirement would be inappropriate or unsound, the agency's decision must be given preemptive effect. 537 U.S. at 66-67. Here, FDA's repeated rejections of the proposed warning prior to October 2003 were based on its determinations that there was not adequate scientific evidence of an association between adult SSRI use and suicide or suicidality. Permitting a judge or jury to second-guess this judgment would interfere with FDA's authority over drug labeling, and is barred by the Supremacy Clause. *See, e.g., Sprietsma*, 537 U.S. at 67-68; *Geier*, 529 U.S. at 884-885; *Jones v. Rath Packing Co.*, 430 U.S. 519, 543 (1977).[10]

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[10] In explaining that federal preemption bars the plaintiff's failure-to-warn (continued...)

C. The plaintiff's failure-to-warn claims against Apotex, the manufacturer of the generic form of paroxetine hydrochloride with which Ms. Colacicco was treated, are barred by federal preemption for an additional reason: under federal law, a generic drug manufacturer is prohibited from changing the label for its drug product without prior FDA approval.

By statute and regulation, generic drug labels are required to replicate the warnings contained in the approved labeling for the innovator, or name-brand,

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[10](...continued)
claim, FDA wishes to make clear that state tort liability is not preempted as a matter of law in every case in which liability is premised on a manufacturer's alleged common-law duty to provide a warning not yet required by FDA. Federal regulations explicitly recognize that manufacturers can, and in some limited instances must, modify their labels to add new warnings of hazards associated with the drug, without awaiting prior FDA approval. *See* 21 C.F.R. § 314.70(c)(7); 21 C.F.R. § 201.56. Where, in light of new scientific evidence or other changed circumstances, a drug label no longer ensures safe and effective use, FDA allows drug manufacturers to work quickly and collaboratively with the agency to make necessary labeling changes. Of course, even in these instances, FDA retains ultimate responsibility to determine whether the proposed change is appropriate, and may reject a labeling change and order the drug manufacturer to cease distributing the product with the new label. *See* 21 C.F.R. § 314.70(c)(5).

In order to determine whether the imposition of state tort liability on a drug manufacturer for failure to warn would conflict with FDA's regulatory authority or interfere with the accomplishment of federal objectives, therefore, a court must analyze the agency's public actions with regard to a particular drug as well as the common-law duty sought to be imposed. If the agency had made a determination at the relevant time that a particular warning was unsubstantiated or would otherwise render a drug misbranded, then federal preemption bars liability for the failure to provide that warning.

drug. *See* 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(2)(C); 21 C.F.R. § 314.150(b)(10). Accordingly, a generic drug manufacturer may not modify the labeling for its drug product to add a new warning or caution. If a generic drug manufacturer "believes that new safety information" should be included on the product's labeling, the manufacturer must "provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and [innovator] drugs should be revised." 57 Fed. Reg. at 17,961. Without prior FDA approval, however, no such change can be made.

The plaintiff's claim against Apotex is premised on the theory that Apotex had an obligation to modify its label under 21 C.F.R. § 314.70(c) to add a new warning for suicide or suicidality. As we have explained, however (at pp. 7-8, *supra*), that provision does not permit generic manufacturers to modify their drug labeling without FDA approval. *See* 57 Fed. Reg. 17,950, 17,961. Generic drug manufacturers are required both by statute and by regulation to use drug labeling that is the same in relevant respects "as the labeling approved for the listed drug." 21 U.S.C. § 355(j)(2)(a)(v); *see also* 21 C.F.R. § 314.150(b)(10) (providing for FDA withdrawal of approval for generic drug application if the drug label is not identical to the label for the innovator drug).

In arguing that 21 C.F.R. § 314.70(c) permits generic drug manufacturers to make labeling changes without prior FDA approval, the plaintiff cites a recent

agency guidance document, *see* Br. 44, but that document explicitly provides that it is not "intended to expand the circumstances in which an applicant may effect labeling changes" under that provision, particularly "*those pertaining to generic drugs*." http://www.fda.gov/cder/guidance/7113dft.htm (emphasis added). The agency's construction of its governing statute and its own regulations not to permit labeling changes by generic drug manufacturers without prior FDA approval, which was set out with a full and cogent explanation at the time of FDA's adoption of procedures for abbreviated new drug applications for generic drugs, was properly given deference by the district court.

D. In addition to challenging the substance of the district court's holding that state tort liability for failure-to-warn would conflict with federal law, the plaintiff also challenges the general legal standards applied by the court. Specifically, the plaintiff argues that the court should not have based preemption on a federal regulation; and that the court gave undue deference to FDA's view of the preemptive effect of labeling decisions relating to Paxil. *See* Br. 33-35, 41-47. As we next demonstrate, those contentions lack merit.

The plaintiffs' argument that FDA's labeling decisions cannot have preemptive effect because only Congress can displace state law, *see* App. Br. 11-12, is flatly inconsistent with *Fidelity Federal Savings & Loan Ass'n v. de la Cuesta*, 458 U.S. 141 (1982). There, the Supreme Court held that it was

"misdirected" for a court to focus narrowly "on Congress' intent to supersede state law." *Id.* at 154. The relevant question, the Court held, was whether the federal agency intended for its actions to preempt state law and, if so, whether those actions were within the scope of the agency's delegated authority from Congress. *Id.* Here, Congress has empowered the FDA to determine whether a particular warning is appropriate for the labeling of a prescription drug, and any state law that stands as an obstacle to this regulatory objective is accordingly preempted. *See, e.g., Geier*, 529 U.S. 881-882.

Furthermore, it was wholly appropriate for the district court to give weight to FDA's views on the applicability of implied conflict preemption in this case. Both the Supreme Court and this Court have recognized that a reviewing court should give weight to a federal agency's views in determining whether imposition of liability under state law would interfere with the accomplishment of federal regulatory objectives. *See, e.g., Geier*, 529 U.S. at 883 (relying on agency amicus brief); *Horn v. Thoratec Corp.*, 376 F.3d 163, 171, 177-179 (3d Cir. 2004) (relying on FDA amicus brief). After all, Congress has delegated to the agency the authority to implement the statutory scheme, and the agency is "likely to have a thorough understanding of its own regulation and its objections and is uniquely qualified to comprehend the likely impact of state requirements." *Geier*, 529 U.S. at 883 (quotation marks omitted).

Here, the agency has repeatedly explained that federal preemption bars the imposition of state tort liability for the failure to provide a warning for a drug product that conflicts with or is contrary to FDA-approved labeling. *See* 71 Fed. Reg. 3922, 3934 (rejecting suggestion that drug manufacturer has state-law duty to label products "with specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated"). FDA has expressed similar views in amicus briefs dating back to at least 2000.[11] Furthermore, FDA rules adopted in 1979 reflect the agency's views that the ultimate decision whether to require a warning on a drug label rests with FDA, and that federal law prohibits inclusion of statements on a label that FDA has determined not to be supported by substantial evidence. *See*, *e.g.,* 44 Fed. Reg. 37,434, 37,435, 37,441, 37,447 (1979). A

[11] *See, e.g., Kallas v. Pfizer, Inc.*, No. 2:04cv0998, Amicus Brief for United States (D. Utah. filed Sept. 15, 2005) (explaining that drug manufacturer may not be held liable for failure to warn of association between pediatric use of Zoloft or other SSRIs and suicide, where FDA had determined at relevant time that there was not reasonable evidence of such an association); *Motus v. Pfizer, Inc.*, No. 02-55498, Amicus Brief for United States (9th Cir. filed Sept. 3, 2002) (explaining that drug manufacturer may not be held liable for failure to warn of alleged danger where FDA had made contemporaneous determination that there is no scientific basis for such warning); *Bernhardt v. Pfizer, Inc.*, No. 00 Civ. 4042 (LMM), Statement of Interest of United States (S.D.N.Y. filed Nov. 13, 2000) (explaining that federal law preempts state claims seeking to require additional warnings on drug labels, and emphasizing that approval of drug labels is within primary jurisdiction of FDA).

fortiori, where state law seeks to impose a conflicting or contrary requirement, it must be preempted.

The plaintiff attempts to manufacture an inconsistency in the agency's views by pointing to a statement in a proposed rulemaking in 2000 that new guidelines for drug labels would not "have federalism implications or [] preempt State law." Br. 42 (quoting 65 Fed. Reg. 81,082, 81,103 (2000)). The plaintiff fails to understand, however, that the basis for federal preemption is not the guidelines themselves or the preamble to that proposed rulemaking, but rather FDA's repeated determinations prior to October 2003 that there was insufficient scientific evidence of an association between adult use of SSRI and suicide or suicidality to permit a warning on the labeling for those drugs — in tandem with statutory and regulatory requirements prohibiting the misbranding of drug products and barring generic drug manufacturers from modifying their labels without prior FDA approval.

The plaintiff also argues that FDA expressed a contrary view on preemption in a preamble to a 1998 agency rule, in which FDA explained that a regulation providing for agency approval of patient labeling of products was "not intended to preclude the states from imposing additional labeling requirements." 63 Fed. Reg. 66,378, 66,384 (1998). Nothing in that preamble — which explicitly recognized that state law cannot "alter" FDA-required labeling, *id*. — suggests that, where

FDA has rejected a specific warning as lacking an adequate scientific basis, that warning may nonetheless be required by operation of state law. In any event, even if FDA's position did mark a change in position, it would still be entitled to deferential consideration by this Court. *See, e.g., Horn*, 376 F.3d at 171; *Buckman v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347-379, 354 n.2 (2001); *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 714-715 (1985).

CONCLUSION

For the foregoing reasons, the Court should affirm the district court's dismissal on federal preemption grounds of the plaintiff's failure-to-warn claims.

Respectfully submitted,

DANIEL MERON
General Counsel
Department of Health and Human Services

SHELDON T. BRADSHAW
Chief Counsel
ERIC M. BLUMBERG
Deputy Chief Counsel
JENNIFER E. CARUSO
Associate Chief Counsel
Food and Drug Division

Department of Health and Human Services
Office of General Counsel

PETER D. KEISLER
Assistant Attorney General

C. FREDERICK BECKNER III
Deputy Assistant Attorney General

PATRICK L. MEEHAN
United States Attorney

DOUGLAS N. LETTER
(202) 514-3602
/s/ Sharon Swingle
SHARON SWINGLE
(202) 353-2689
Attorneys, Appellate Staff
Department of Justice
Civil Division
950 Pennsylvania Ave., N.W.
Washington, DC 20530-0001

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CERTIFICATE OF COMPLIANCE WITH
FEDERAL RULE OF APPELLATE PROCEDURE 32(a)

I hereby certify that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 6,723 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii). This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the typestyle requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared with Word Perfect 12 in a proportional typeface with 14 characters per inch in Times New Roman.

/s/ Sharon Swingle
Sharon Swingle
Counsel for the United States

CERTIFICATE OF SERVICE AND ELECTRONIC FILING

I hereby certify that on December 4, 2006, I served the Court and the following counsel of record with an electronic copy of the Brief for Amicus Curiae the United States of America in PDF format. The electronic copy of the brief was scanned with Trend Micro OfficeScan and found to be virus-free. The text of the electronical copy of the brief is identical to the text of the hard copy of the brief. I also caused ten hard copies of the Brief for Amicus Curiae the United States of America to be served on the Court and two hard copies to be served on the following counsel by overnight delivery, postage prepaid:

Harris Pogust
Derek Braslow
Cuneo, Pogust & Mason, LLP
161 Washington Street, Suite 1520
Conshohocken, PA 19428

Charles A. Fitzpatrick, III
Arthur B. Keppel
Mylotte, David & Fitzpatrick
Whetstone Run Office Complex
450 Parkway, Suite 300
Broomall, PA 19008

Chilton D. Varner
Andrew T. Bayman
Erica M. Long
S. Samuel Griffin
King & Spaulding
1180 Peachtree Street
Atlanta, GA 30309

Joseph K. Hetrick
David J. Stanoch
Joshua G. Schiller
Dechert, LLP
2929 Arch Street, 18th Street
Philadelphia, PA 19104-2808

/s/ Sharon Swingle
Sharon Swingle
Counsel for the United States

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