No. 08-437

IN THE

Supreme Court of the United States

JOSEPH C. COLACICCO, INDIVIDUALLY AND AS EXECUTOR OF THE ESTATE OF LOIS COLACICCO,
Petitioner,

v.

APOTEX, INC., APOTEX CORPORATION, AND GLAXOSMITHKLINE,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF FOR RESPONDENTS APOTEX, INC., APOTEX CORPORATION, AND GLAXOSMITHKLINE IN OPPOSITION

CHARLES A. FITZPATRICK, III
RAWLE & HENDERSON
1339 Chestnut Street
One South Penn Square
Philadelphia, PA 19107
(215) 575-4200

Counsel for Respondents Apotex, Inc. and Apotex Corporation

CHILTON DAVIS VARNER
Counsel of Record
KING & SPALDING LLP
1180 Peachtree Street, NE
Atlanta, GA 30309
(404) 572-4600

Counsel for Respondent GlaxoSmithKline

December 3, 2008

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20002

QUESTION PRESENTED

Is the Pennsylvania legal standard governing product liability for failure to warn claims preempted by federal law where that state standard would require a particular warning in the labeling of a prescription drug, despite the rejection by the U.S. Food & Drug Administration of that warning as without scientific basis?

PARTIES TO THE PROCEEDING

The United States Court of Appeals for the Third Circuit consolidated two appeals from two federal district courts. The first, *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006), involved claims brought by Petitioner Colacicco against Respondents Apotex, Inc., Apotex Corporation, and GlaxoSmith-Kline relating to the prescription drug Paxil and the suicide of Lois Colacicco. The second, *McNellis v. Pfizer, Inc.*, No. Civ. 05-1286, 2005 WL 3752269 (D.N.J. Dec. 29, 2005), involved claims brought by Petitioner Beth McNellis against Respondent Pfizer Inc. relating to the prescription drug Zoloft and the suicide of Theodore DeAngelis. The Third Circuit issued one opinion ruling on both appeals. This Opposition is filed on behalf of Apotex, Inc., Apotex Corporation, and GlaxoSmithKline in response to Petitioner Colacicco's Petition.

RULE 29.6 CORPORATE DISCLOSURE STATEMENT

Respondent **Apotex Corporation** makes the following disclosure:

B. Sherman (Canadian) through Sherman Holdings Inc. (Canadian) (66.6%) and B. Sherman, Trustee (Canadian) through The Bernard Sherman 2000 Trust (Canadian) - beneficiaries Lauren, Jonathan, Alexandra & Kaelen Sherman (Canadian) (33.2%) - are parent corporations of Shermco Inc. (Canadian), which is parent of Sherfam, Inc. (Canadian), which is parent of Apotex Holdings Inc. (Canadian), which is parent of Aposherm, Inc. (Canadian), which is parent of Apotex Corporation (US). None of the foregoing is publicly held.

There are no publicly held companies that hold 10% or more of the party's stock.

Respondent **Apotex, Inc.** makes the following disclosure:

B. Sherman (Canadian) through Sherman Holdings Inc. (Canadian) (66.6%) and B. Sherman, Trustee (Canadian) through The Bernard Sherman 2000 Trust (Canadian) - beneficiaries Lauren, Jonathan, Alexandra & Kaelen Sherman (Canadian) (33.2%) - are parent corporations of Shermco Inc. (Canadian), which is parent of Sherfam, Inc. (Canadian), which is parent of Apotex Holdings Inc. (Canadian), which is parent of Apotex Pharmaceutical Holdings Inc. (Canadian) (94%, 6% held by Apotex Employees (Canadian)) which is parent of Apotex Inc. (Canadian). None of the foregoing is publicly held.

There are no publicly held companies that hold 10% or more of the party's stock.

Respondent **SmithKline Beecham Corporation d/b/a Glaxo-SmithKline** makes the following disclosure:

SmithKline Beecham Corporation, which does business under the name of GlaxoSmithKline, is owned, through several layers of wholly-owned subsidiaries, by GlaxoSmithKline plc, a publicly held English limited company. To the knowledge of SmithKline Beecham Corporation and GlaxoSmithKline plc, none of the shareholders of GlaxoSmithKline plc owns beneficially ten percent or more of its outstanding shares.

The following are parents, trusts, subsidiaries, and/or affiliates of said party and have issued shares or debt securities to the public or own more than ten

percent of the stock of SmithKline Beecham Corporation d/b/a GlaxoSmithKline:

- GlaxoSmithKline Consumer Healthcare Limited (India);
- GlaxoSmithKline Pharmaceuticals Limited (India);
- GlaxoSmithKline Consumer Nigeria plc (Nigeria);
- GlaxoSmithKline Pakistan Limited (Pakistan);
- GlaxoSmithKline plc;
- GlaxoSmithKline S.A.E. (Egypt);
- Amoun Pharmaceutical Industries Co. S.A.E. (Egypt);
- Burroughs Wellcome (India) Limited;
- GlaxoSmithKline Bangladesh Limited;
- Glaxo Wellcome Ceylon Limited (Sri Lanka);
- GlaxoSmithKline plc (U.K.);
- GlaxoSmithKline Capital plc (U.K.);
- GlaxoSmithKline Finance plc (U.K.);
- GlaxoSmithKline Capital K.K. (Japan);
- Glaxo K.K. (Japan);
- GlaxoSmithKline Holdings (Americas) Inc. (U.S.);
- GlaxoSmithKline Capital, Inc. (U.S.).

TABLE OF CONTENTS

TABLE OF AUTHORITIES

TABLE OF AUTHORITIES—Continued

TABLE OF AUTHORITIES—Continued

IN THE

Supreme Court of the United States

No. 08-437

JOSEPH C. COLACICCO, INDIVIDUALLY AND AS EXECUTOR OF THE ESTATE OF LOIS COLACICCO,
Petitioner,

v.

APOTEX, INC., APOTEX CORPORATION, AND GLAXOSMITHKLINE,
*Respondent*s.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF FOR RESPONDENTS APOTEX, INC., APOTEX CORPORATION, AND GLAXOSMITHKLINE IN OPPOSITION

STATEMENT OF THE CASE

Petitioners' narrative of the record is sufficiently incomplete and inaccurate in some respects that Respondents GlaxoSmithKline ("GSK"), Apotex, Inc. and Apotex Corporation (collectively, "Apotex") provide the Court with the following statement of the case.

Proceedings Below

A. Colacicco alleged that his spouse, Lois Colacicco, was diagnosed with breast cancer in March 2003, when she was 55 years of age. C.A. App. A90. She underwent surgery and four months of chemotherapy. *Id.* In early October 2003, at a chemotherapy appointment, she complained to her physician that she was depressed. *Id.* A91. Her physician prescribed the drug Paxil® (paroxetine hydrochloride) to treat her depression. *Id*. Ms. Colacicco committed suicide on October 28, 2003. *Id*.

B. Paxil is marketed by GSK, and a generic version of Paxil is marketed by Apotex. It is undisputed that Ms. Colacicco's prescription for Paxil was dispensed with Apotex's generic version. Federal law requires the labeling of the generic version to be identical to the branded or "listed" drug, and prohibits the generic manufacturer from unilaterally changing the labeling. 21 U.S.C. § 355(j)(2)(A). Colacicco's Petition does not mention the Third Circuit's assessment of labeling for generic manufacturers such as Apotex. *See* Pet. App. 19-20 (acknowledging FDA's position).

C. Colacicco alleged that his spouse's suicide was proximately caused by the failure of GSK to warn her physician that "Paxil causes an increased risk of . . . suicidality in some adults" and "that Paxil can cause suicide." C.A. App. A94; Colacicco's Third Circuit Reply Br. 7-8. The parties stipulated that Colacicco's failure to warn claim was based on the law of Pennsylvania. C.A. App. A7, A323. Colacicco attached to his complaint the labeling or "prescribing information" for Paxil that was in effect at the time Ms. Colacicco's physician prescribed Paxil to treat her depression. That information consequently is part of

the pleadings. FED. R. CIV. P. 10(c). In pertinent part, the prescribing information included the following "Precaution":

> ***Suicide:*** The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for PAXIL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose….

C.A. App. A436. In addition, the labeling identified "suicide attempt or suicidal ideation" as one of the symptoms of major depressive disorder, a condition for which Paxil was indicated. *Id.* A432. Colacicco alleged that this warning was "inadequate" under Pennsylvania law. *Id.* A90, A99, A101.

D. The physician who prescribed Paxil to Ms. Colacicco was not named as a defendant, and Respondents are unaware of any claim made against the prescribing physician.

E. Absent from the complaint and record is any allegation that Colacicco ever invoked the undoubted primary jurisdiction of the U.S. Food & Drug Administration ("FDA") over prescription medication safety and effectiveness, *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 627 (1973) ("The heart of the new procedures designed by Congress [*i.e.*, in the 1962 Drug Amendments] is *the grant of primary jurisdiction* to FDA, the expert agency it created.") (emphasis added), by, *e.g.*, submitting a citizen petition to FDA under authority of 21 C.F.R. § 10.30. There is no allegation that Colacicco ever communi-

cated with FDA regarding the allegedly inadequate warnings in the FDA-approved prescribing information for Paxil.

F. GSK and Apotex moved to dismiss the complaint for failure to state a claim under FED. R. CIV. P. 12(b)(6), on the ground that the alleged failure to warn was preempted under the Supremacy Clause, U.S. CONST. art. VI, cl. 2, by the Federal Food, Drug, and Cosmetic Act of 1938 ("FDCA"), Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301 to 399a), and FDA's regulations adopted pursuant to the FDCA. The District Court granted that motion and dismissed the complaint. Colacicco appealed. The Third Circuit consolidated Colacicco's appeal with another prescription medication preemption case, *McNellis v. Pfizer, Inc.*, No. Civ. 05-1286, 2005 WL 3752269 (D.N.J. Dec. 29, 2005). The Third Circuit affirmed the District Court's dismissal of Colacicco's complaint. Colacicco, along with the plaintiff in *McNellis*, then sought certiorari in this Court.

Paxil

A. Paxil is one of a class of prescription antidepressant drugs known as "Selective Serotonin Reuptake Inhibitors," or "SSRIs." The first SSRI approved in the United States was Prozac® (fluoxetine), which FDA approved in late 1987. In November 1989, a predecessor of GSK submitted a New Drug Application ("NDA") to FDA seeking approval to market Paxil for use in treating depression. As required by 21 U.S.C. § 355(b)(1), the NDA for Paxil included "proposed labeling" for the medication, plus "reports of all investigations," including clinical investigations conducted to determine whether Paxil was safe and effective for use as directed in the proposed labeling. In December 1992, FDA approved the

NDA for Paxil for the treatment of depression. FDA's approval of Paxil was "conditioned" upon GSK's use of the labeling "exactly as directed." 21 C.F.R. § 314.105(b).

B. After FDA approved Paxil in 1992, FDA continued to have extensive regulatory authority over Paxil. GSK was required to report adverse events associated with Paxil to FDA promptly, *see* 21 C.F.R. §§ 314.80-.81, and to submit to FDA a detailed annual report on post-marketing clinical experiences with, and clinical investigations of, Paxil, *see* 21 C.F.R. § 312.33. In addition, over the years GSK submitted twelve supplemental NDAs (known as "sNDAs") for new adult indications for Paxil, each of which was considered and approved by FDA. As the Third Circuit below noted, FDA "repeatedly approved the Paxil labeling in effect at the time of Lois Colacicco's prescription of Paxil . . . and her death . . . approving it for a new indication, the treatment of generalized anxiety disorder [with the same information about suicide that Colacicco is challenging here], just a year before those events." Pet. App. 42. The Court of Appeals also recognized that "FDA approved Paxil for new indications on the condition that the final drug labeling *be identical to the labeling approved by FDA*." *Id.* 43 n.16 (emphasis added). Colacicco, in his Petition, nowhere disputes either of these statements by the Third Circuit. In short, FDA considered the growing body of data and – both before and after Ms. Colacicco's death – approved the warnings about suicide that Colacicco challenges here.

FDA-Approved Drug Labeling

A. "Labeling" is a defined term in the FDCA. It refers to any "written, printed, or graphic matter"

that "accompan[ies]" a drug. 21 U.S.C. § 321(m). FDA requires the labeling for prescription medications to follow a standard, detailed format to make the information easier for physicians to access and use. *See* 21 C.F.R. §§ 201.56-.57.

B. In 1962, Congress enacted legislation that transformed FDA's authority to regulate prescription medications. *See* Drug Amendments Act of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in scattered sections of 21 U.S.C.). The Amendments directly tied the prescribing information to FDA's determination of whether that medication is safe and effective. The sponsor of an NDA (such as GSK here for Paxil) was required by the Amendments to demonstrate, by "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested *in the proposed labeling thereof*." Pub. L. No. 87-781, §102(c) (codified at 21 U.S.C. § 355(d)(5)) (emphasis added). The term "substantial evidence" was defined to mean, "evidence consisting of adequate *and well-controlled* investigations, including clinical investigations." *Id.* (codified at 21 U.S.C. § 355(d)) (emphasis added). This statutory text remains essentially unchanged in the FDCA today. *See* 21 U.S.C. § 355(d). The 1962 Amendments are the foundation of FDA's plenary authority over prescription medication labeling and regulation.

FDA's Rejection of any "Increased Risk" in Adults Before October 2003

A. Prior to Ms. Colacicco's suicide, FDA repeatedly considered and *rejected* the warning of increased risk of suicide that Colacicco alleges in his complaint was required by the law of Pennsylvania. Colacicco's statement that "FDA had made *no authoritative*

federal determination with respect to this risk," Pet. 1 (emphasis added), is hopelessly at odds with the public administrative record which the Third Circuit properly considered. Pet. App. 40 n.13. Indeed, during oral argument before the Third Circuit below, a member of the panel asked Colacicco's counsel whether, prior to Colacicco's suicide, FDA's position was "we don't want you to change the label that we've approved." Counsel replied, "yes, that was FDA's position." Hr'g Tr. 12-13, *Colacicco v. Apotex, Inc.*, Nos. 06-3107/5148 (3d Cir. Dec. 10, 2007).

B. The Third Circuit concluded as follows:

> [FDA] has *repeatedly rejected* the scientific basis for the warnings that Colacicco and McNellis argue should have been included in the labeling. The FDA has actively monitored the possible association between SSRIs and suicide for nearly twenty years, and has concluded that *the suicide warnings desired by plaintiffs are without scientific basis and would therefore be false and misleading.*

Pet. App. 40 (emphasis added; note omitted).

C. While some of FDA's early decisions on suicidality warnings were made in the context of Prozac, these decisions have direct relevance to Paxil, which is in the same SSRI class as Prozac. In terms of labeling about suicide, FDA has treated SSRIs as a class. *See infra*, pp. 10-12.

D. In 1991, FDA convened an "Advisory Committee" to consider whether Prozac was possibly associated with an increased risk of suicidality. Following that Advisory Committee meeting, FDA concluded that the data "have *not led us to conclude that there is a differential rate of risk* for Prozac related to suicidal

thoughts, acts, or other violent behavior." C.A. App. A745 (emphasis added). Colacicco, in his Petition, quotes a statement by an FDA official who declined to dismiss the "possibility" of a causal relation between antidepressants and "injurious behaviors," Pet. 7, but he fails to tell this Court that the same FDA official, on the same occasion, also said that, "if antidepressants do cause any kind of [injurious] behaviors, *the incidence is too low to detect them.*" C.A. App. A746 (emphasis added).

E. In 1991 and 1992, FDA denied two separate citizen petitions requesting FDA to require the labeling of Prozac to contain exactly the "increased risk" warning that Colacicco claims was *required* by Pennsylvania law. In denying these petitions, FDA stated that "[t]he data and information available at this time do not indicate that [the drug] causes suicidality or violent behavior," *id.* A597, and that "[t]here is no reasonable evidence of an association between the use of [the drug] and suicidality," *id.* A977. Colacicco, in his Petition, fails to mention FDA's denial of these citizen petitions.

F. In 1997, FDA rejected another citizen petition requesting FDA to require the Prozac labeling to contain the "increased risk" and causation warnings that Colacicco claims were required by Pennsylvania law. FDA denied that petition and stated that "FDA carefully considered the issue of whether Prozac was associated with suicidal ideation and suicidality and concluded that no labeling revisions were warranted." *Id.* A981-82.

G. On June 19, 2003 – just four months before Ms. Colacicco took her life – FDA issued a public statement that "[t]here is *no evidence* that Paxil is associated with an increased risk of suicidal thinking

in adults."[1] Pet. App. 43 (emphasis added). The Third Circuit relied upon this public statement that FDA made shortly before Ms. Colacicco's death, but Colacicco, in his Petition to this Court, does not mention it. This explicit public statement by FDA that there is "*no evidence*" of an increased risk of suicidal thinking in adults treated with Paxil, issued four months before Ms. Colacicco's death, and following years of expert review by the agency with primary jurisdiction over drug safety, *Hynson*, 412 U.S. at 627, constituted an "authoritative" federal determination squarely rejecting the very warning that Colacicco contends was required by Pennsylvania law.

H. Colacicco's statement in his Petition that "[u]ntil 2004, FDA neither required *nor prohibited* a warning of this association to patients of any age," Pet. 7 (emphasis added), is contradicted by FDA's June 2003 statement.

I. On October 27, 2003 – *one day before* Ms. Colacicco took her life – FDA issued a Public Health Advisory in which it announced it would convene an Advisory Committee to consider the possible risk of suicidality in pediatric patients treated with antidepressants (including Paxil) for major depressive disorder.[2] Pet. App. 43. FDA noted reports in the press and the medical literature of suicide attempts and completed suicide in pediatric patients receiving

---

[1] FDA Statement Regarding the Anti-Depressant Paxil for Pediatric Population, *available at* http://www.fda.gov/bbs/topics/answers/2003/ans01230.html (emphasis added) (last visited Dec. 1, 2008).

[2] *See* FDA Public Health Advisory, *available at* http://www.fda.gov/cder/drug/advisory/mdd.htm (last visited Dec. 1, 2008).

antidepressants, but cautioned that these "reports are very difficult to interpret, in the absence of a control group, as these events also occur in untreated patients with depression." *Id.* Finally, FDA reemphasized the "Precaution" concerning suicide that was contained in the labeling for all antidepressants. (This is the same suicide "Precaution" that is contained in the Paxil labeling that Colacicco attached to his complaint.)

As the Third Circuit below correctly noted, "[t]his advisory was limited to pediatric patients; *a warning for adult patients was not issued.*" Pet. App. 43 (emphasis added). FDA's Public Health Advisory, issued the day before Ms. Colacicco's suicide, makes this case quite similar to the hypothetical posed by the Court during oral argument in *Wyeth v. Levine*, No. 06-1249, where Respondent's counsel was asked about the proper legal outcome if the injury occurred the day after FDA "prescribed the label that now appears on the drug." Hr'g Tr. 33-34 (Nov. 3, 2008). Respondent's counsel replied, "That [would] be preempted." *Id.* at 34. This case is the Court's hypothetical, and Colacicco's claims *are* preempted.

FDA's Actions After Ms. Colacicco's Suicide

A. In the years following Ms. Colacicco's suicide, FDA continued to review the issue of whether SSRIs are associated with an increased risk of suicide or suicidality. The Third Circuit correctly considered regulatory events subsequent to Ms. Colacicco's death as showing FDA's "close scrutiny of the effect of SSRI drugs on suicidality of adults." Pet. App. 48.

B. For instance, in March 2004, while FDA was reviewing data relating to a possible risk of suicidality in pediatric patients, FDA issued a Public Health

Advisory requiring SSRI manufacturers to implement warnings reminding physicians "about the need to monitor adult patients for signs of worsening depression or suicidality." C.A. App. A580-81; Pet. App. 48-49. Petitioner suggests that, at this time, "FDA issued [the Advisory] warning of the risk of increased suicidality in adult patients." Pet. 10. On the contrary, at this time, FDA stressed that "it is not yet clear whether antidepressants contribute to the emergence of suicidal thinking and behavior."[3]

C. The current FDA-approved labeling for *all* SSRIs, including Paxil, states:

> Short-term studies *did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24*; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide.

Pet. App. 51 n.20 (emphasis added). The labeling also states that "a causal link . . . has not been established" between adverse events reported in patients using antidepressants and "the worsening of depression and/or the emergence of suicidal impulses."[4] The current FDA-approved warning is at direct odds with the warning that Colacicco claims was required in October 2003 by Pennsylvania law. Currently, the

---

[3] FDA Talk Paper (Mar. 22, 2004), *available at* www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html (last visited Dec. 1, 2008).

[4] PAXIL PRESCRIBING INFORMATION, at 12, http://www.fda.gov/cder/foi/label/2008/020031s060,020936s037,020710s024lbl.pdf.

approved FDA labeling plainly states that there is *no* increase in the risk of suicidality for patients of Ms. Colacicco's age (55).[5]

The Labeling Changes By GSK and Wyeth

A. Colacicco makes much of the proposed labeling changes made by GSK in 2006, with respect to Paxil, and by Wyeth in August 2003, for its antidepressant drug Effexor® (venlafaxine HCl). Pet. 2, 11-13. Colacicco claims that these proposals show that GSK, in October 2003, could have unilaterally included the warning he contends was required by Pennsylvania law. The administrative history, however, is to the contrary: FDA *rejected* both proposals.

B. In 2006, GSK submitted a proposed labeling change to FDA and sent a "Dear Doctor" letter to physicians in which GSK reported on a meta-analysis[6] of its clinical trials relating to Paxil. GSK reported that, in adults treated with Paxil for major depressive disorder, there was a significant increase

---

[5] Petitioner is wrong to suggest that FDA required a boxed warning in the labeling for antidepressants that stated "a causal role for antidepressants in inducing suicidality has been established in pediatric patients." Pet. 9. FDA instructed all manufacturers not to use this language. Instead, FDA determined that the warning should state: "Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents. . . ." *See* CLASS SUICIDALITY LABELING LANGUAGE FOR ANTIDEPRESSANTS, http://www.fda.gov/cder/foi/label/2005/20031s045,20936s020lbl.pdf.

[6] The term "meta-analysis" is a term-of-art in the disciplines of epidemiology and biostatistics. It refers to the statistical synthesis of data from separate but comparable clinical studies, usually with the goal of increasing the power of the combined studies. *See* A DICTIONARY OF EPIDEMIOLOGY 114 (John M. Last ed., 4th ed. 2001).

in suicidal behavior (but not completed suicide) compared to those patients given placebo. C.A. App. A1069. GSK noted that there were, however, only 11 reported events of suicidal behavior across the trials it analyzed, and eight of those events were in adults 30 years of age or younger. GSK alerted physicians that, with such a small number of events, the data must be "interpreted with caution." *Id.* One year later, FDA instructed all antidepressant manufacturers, including GSK, to use the current suicide warning (quoted *supra* p. 11). Pet. App. 49-51. FDA's warning, based on its own meta-analysis of the aggregate data of the clinical trials from *all* manufacturers, rejected the findings in GSK's 2006 submission to FDA and its "Dear Doctor" letter. FDA's decision on what the current mandated warnings should say flatly contradicts the warning Colacicco claims should have been given. This administrative record does not advance Colacicco's arguments.

C. Similarly, FDA expressly rejected the labeling change for Effexor that Wyeth proposed to FDA in August 2003. The proposed language concerned adverse events of hostility and suicidality in pediatric patients. FDA rejected the warning, stating that "we do not agree with the labeling changes proposed in your August 8, 2003 submission" and cautioned that if Wyeth failed to remove the language from Effexor's labeling, then "FDA may proceed to withdraw [the drug's] supplemental applications."[7] FDA's rejection of Wyeth's proposed labeling is inconsistent with Colacicco's theory of the case.

---

[7] *See* Letter from FDA to Wyeth (Mar. 19, 2004), at pp. 10, 14, http://www.fda.gov/cder/foi/nda/2004/020151_S028_EFFEXOR_TABLETS.pdf.

The Amicus Brief for the United States in the Third Circuit

In the Third Circuit below, the United States, on behalf of FDA, filed an *amicus* brief in which it explained that, by the time of Ms. Colacicco's death, it had both considered and then rejected the warning Colacicco contended was required by Pennsylvania law. *See* Br. for the United States as *Amicus Curiae* Supporting Defendants-Appellees, 2006 WL 5691532, *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008). There, the United States told the Third Circuit:

> 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.

Id. at *16 (emphasis added). In his Petition to this Court, Colacicco simply does not mention the views of the United States in its *amicus* brief submitted to the Third Circuit below.

REASONS FOR DENYING THE WRIT

I. The Third Circuit Properly Concluded That FDA's Repeated Rejection of the Warnings Colacicco Alleges Should Have Been Given Preempts Colacicco's Claims

In 2003, the year that Ms. Colacicco took her life, 27,239 American adults (over the age of 24) committed suicide, which is an average of 75 deaths by suicide each day of the year.[8] According to the

[8] Centers for Disease Control and Prevention ("CDC"), *available at* http://webappa.cdc.gov/sasweb/ncipc/mortrate10_sy.

National Violent Death Reporting System ("NVDRS") managed by the Centers for Disease Control and Prevention ("CDC"), in 2003 "[r]oughly half of [suicide] victims were described by family or friends as being depressed before the time of death."[9] (Ms. Colacicco, as alleged in the complaint, complained of depression to her physician at a chemotherapy appointment in early October 2003. C.A. App. A91.) Even aside from the personal tragedy of each of these deaths, the number of adult suicides in the United States is a serious public health issue. Depression is a significant factor in many adult suicides.

FDA, in approving Paxil for the treatment of depression, found that there is "substantial evidence" in the form of "adequate and well-controlled . . . clinical investigations" within the meaning of the 1962 Amendments that Paxil is effective for use under the conditions stated in its labeling. Depression, in some people, leads to suicidal thinking, suicide attempts, and, unfortunately, completed suicides. Indeed, "a suicide attempt or suicidal ideation" is a signature *symptom* of depression for which Paxil is explicitly indicated in its FDA-approved labeling. C.A. App. A432. As stated in the current Paxil labeling, "[s]uicide is a known risk of depression and certain other psychiatric disorders, and these disorders

---

html (WISQARS database of injury statistics, including suicide) (last visited Dec. 1, 2008).

[9] CDC, Homicides and Suicides -- Nat'l Violent Death Reporting System, United States, 2003-2004, *available at* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5526a1.htm#fig1 (last visited Dec. 1, 2008). In 2003, the year CDC launched NVDRS, seven States, with 12.5% of the U.S. population, reported to NVDRS. There is no reason, however, to conclude that these States were unrepresentative of the Nation as a whole.

themselves are the strongest predictors of suicide."[10] As an effective treatment for adult depression, Paxil provides important treatment for a life-threatening illness.

FDA has spent two decades carefully considering the difficult scientific and medical issues presented by the risk of suicide that is inherent in depression. As the Third Circuit correctly stated: "The FDA has *actively monitored* the possible association between SSRIs and suicide for nearly twenty years, and has concluded that the suicide warnings desired by plaintiffs are *without scientific basis* and would therefore be false and misleading." Pet. App. 40 (emphasis added; note omitted). FDA's consideration of this scientific and medical question reflects FDA's core mission of protecting the public health. There is no principled justification for simply casting FDA aside and allowing a lay jury, instructed under State law, and acting as a "shadow" FDA, to make its own *ad hoc* determination of whether FDA correctly assessed the risks and benefits of this life-saving medication.

The conflict between FDA's authority over prescription medication labeling and competing State-law failure-to-warn claims is especially stark here, because FDA *explicitly, specifically, and publicly* reaffirmed the adequacy – under federal law – of the suicide Precaution in the labeling of all antidepressant medications, including all SSRIs, such as Paxil, *the day before* Ms. Colacicco took her life. Four months earlier, in June 2003, FDA issued a public statement that contained the statement: "There is *no*

---

[10] PAXIL PRESCRIBING INFORMATION, at 11, http://www.fda.gov/cder/foi/label/2008/020031s060,020936s037,020710s024lbl.pdf.

evidence that Paxil is associated with an increased risk of suicidal thinking in adults." Pet. App. 43 (emphasis added). Colacicco, in his Petition, simply ignores these dispositive public statements by FDA made shortly before Ms. Colacicco's suicide.

The entire timeline of FDA's consideration of the suicidality issue, especially its specific public statements shortly before Ms. Colacicco was prescribed her antidepressant, presents a stark, indeed inescapable, case of "impossibility" conflict warranting preemption. This is *not* a case where it might be possible to design labeling of a prescription medication that would both satisfy FDA and be consistent with the warning that a lay jury might decide was required by State law.[11] Here FDA – which has primary jurisdiction under the 1962 Amendments – stated publicly that there was "no evidence" to support the warning Colacicco alleges should have been given here.[12] As of the time of Ms. Colacicco's suicide, there was no conceivable labeling that would satisfy both FDA and what Colacicco alleged is required by the law of Pennsylvania. As such, there is nothing remarkable about the Third Circuit's decision that the FDCA and FDA's regulations preempt Colacicco's state law claims.

---

[11] *See* Hr'g Tr. 3-4, *Wyeth v. Levine,* No. 06-1249 (Nov. 3, 2008) (discussion on possible labeling that would be consistent with both State law and FDA regulations).

[12] Colacicco alleged in his complaint that GSK failed to warn that "Paxil causes an increased risk of . . .suicidality." C.A. App. A94. Given FDA's public statements in June and October 2003, it would be plainly impossible to reconcile the warning Colacicco alleges should have been given with FDA's position that there was no evidence supporting such a warning.

Under the facts here, there is a flat "impossibility" conflict between the warning that Colacicco alleges was required by Pennsylvania law on the one hand, and on the other, FDA's scientific conclusions that there was no evidence to support such a warning. The decision of a fact-finder, such as a lay jury, that a warning in FDA-approved labeling is inadequate for purposes of State law due to the absence of a warning the Agency found scientifically unsubstantiated would impose on the manufacturer an obligation to distribute the medication – at least in that State – with labeling *different* from the labeling approved and required by FDA. Distribution of the prescription medication with that different and unapproved labeling would violate the misbranding provisions of the FDCA, subjecting the company and responsible individuals to civil and criminal liability. *See, e.g.*, 21 U.S.C. §§ 331(a), (b), & (k) (misbranding); § 332 (injunctions); § 333 (criminal penalties); *see also United States v. Park*, 421 U.S. 658, 672-73 (1975) (affirming conviction of corporate executive for violations of the FDCA on ground that "[t]he Act does not … make criminal liability turn on 'awareness of some wrongdoing' or 'conscious fraud.'").[13] Both cannot have legal effect simultaneously, and under the Supremacy Clause, it is Pennsylvania law that must give way. Indeed, the Third Circuit, in finding Colacicco's failure-to-warn claims preempted, emphasized the limited scope of its holding: "Our holding is

[13] As Respondent Pfizer points out, it is FDA's repeated determinations that reasonable evidence of an association did not exist to warrant a different warning juxtaposed against Petitioners' state law claims that such a warning must be given which gives rise to the conflict and forms the basis of preemption in this case.

limited to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires." Pet. App. 46.

That limited holding is undoubtedly correct and should remain undisturbed. No other circuit court has held otherwise.

II. State-Law Failure-to-Warn Claims That Challenge FDA-Approved Labeling Should Be Preempted by the FDCA

FDA has statutory authority under the FDCA to ensure that prescription medications are safe and effective for use under the conditions stated in their approved labeling. 21 U.S.C. §§ 355(a), (d) (prohibiting distribution of any new drug without FDA approval of an application showing the drug to be safe and effective). Congress has stated in the FDCA that FDA's mission is to "promote the public health by promptly and efficiently reviewing clinical research . . . [and] ensuring that . . . drugs are safe and effective." *Id.* § 393(b); *see Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348-49 (2001) (noting FDA's "difficult (and often competing) objectives," and the "somewhat delicate balance of statutory objectives" committed to FDA's responsibility).

A State-law products liability standard for failure-to-warn claims that purports to authorize a finder of fact, including a lay jury, to second-guess the warnings in FDA-approved labeling for a prescription medication should be preempted because it stands as an obstacle to FDA's regulation of prescription medication labeling and, therefore, conflicts with the FDCA. *See Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).

The conflict arises because, when FDA approves a medication, its approval takes place in the context of extensive scientific and medical review and – importantly – is expressly conditioned on the use of the labeling "*exactly*" as approved by FDA. 21 C.F.R. § 314.105(b) (emphasis added). As demonstrated by the regulatory history relating to Paxil, FDA weighed the risks and benefits of the medication, and made a deliberate decision, on numerous occasions, as to what warnings about the risk of suicide were and were not appropriate for the medication's labeling. FDA explained to the Third Circuit that ensuring that only substantiated warnings appear in a medication's labeling is vital to "FDA's accomplishment of regulatory objectives" because "[u]nder-use of a drug based on dissemination of unsubstantiated warnings may deprive patients of efficacious and possibly lifesaving treatment." Pet. App. 54. FDA said that "allowing unsubstantiated warnings would likely reduce the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible." *Id.*

This concern is particularly manifest here. There is no dispute that depression and other psychiatric disorders lead to suicide and suicidality. Nor is there any dispute that FDA approved SSRIs, such as Paxil, for treating these disorders in part because of the life-threatening risks these disorders carry. Allowing a lay jury to contravene FDA's determinations regarding the careful and scientific balancing of risk and benefit would undoubtedly undermine FDA's position as the expert agency responsible for assuring the safety and efficacy of prescription medications. Stated differently, Colacicco should not be able to disregard how FDA makes scientific determinations concerning the very subject matter that the Agency is

authorized by Congress to regulate and, instead, argue for a decision that he believes is appropriate in this particular case.

This approach also undermines the importance of a uniform federal system. As the Third Circuit recognized, "[a]bsent a determination that the FDA-approved labeling and the FDA's refusal to require the warnings suggested by [Colacicco] preempt state tort actions, the manufacturers may be subjected to considerable liability based on varying standards, with no benchmark that they should follow." Pet. App. 36.

With respect, a jury instructed under State law cannot replicate FDA's expert balancing of the public health considerations and scientific evidence. In *Riegel v. Medtronic, Inc.*, 128 S.Ct. 999, 1008 (2008), this Court reasoned that State tort law applied by juries might be even "less deserving of preservation" than a state regulation applied by a regulatory agency. Such an agency "could at least be expected to apply cost-benefit analysis similar to that applied by the experts at the FDA. . . . A jury, on the other hand, sees only the cost of a more dangerous design, and is not concerned with benefits; the patients who reaped those benefits are not represented in court." *Id.* Although *Riegel* involved a medical device approved by FDA, the Court's observation about the asymmetry of the jury process is equally applicable in the prescription medication context.

FDA, as this Court has held, has primary jurisdiction over prescription drugs. *Hynson*, 412 U.S. at 627. FDA has provided a practical and effective mechanism for invoking FDA's consideration of any issue, which is the citizen petition. 21 C.F.R. § 10.30; *see Buckman*, 531 U.S. at 349 ("[C]itizens may report

wrongdoing and petition [FDA] to take action."). By its own regulation, FDA is required to take action on a citizen petition within six months of the filing of the petition. Indeed, FDA's receipt of a citizen petition played a role in FDA's decision to convene an Advisory Committee to consider evidence and expert opinion relating to whether Prozac was associated with a possible risk of suicidality. *See supra* pp. 7-8.

Thus, a citizen petition to FDA is not some empty, bureaucratic *cul de sac*; to the contrary, it is a meaningful way of getting FDA's attention. Colacicco *never* sought to invoke FDA's primary jurisdiction to consider his claim that the labeling for Paxil should have included a different Precaution about the risk of suicide. Because Colacicco rushed past FDA on his way to the courthouse and never sought FDA's views using the mechanism plainly available to him, this Court should not permit him to now say that FDA would have done this, might have done that, or failed to understand something else. He should have asked FDA first. As the Third Circuit correctly held, in reference to Colacicco's conclusory contention that GSK misled FDA: "Such a claim, if supported by sufficient evidence, should be brought before the FDA. As far as we know from the record, Colacicco has not done so." Pet. App. 48.

Had FDA denied Colacicco's citizen petition, Colacicco would have had a right of judicial review under the Administrative Procedure Act. As this Court observed in *Hynson*, the availability of judicial review means that "FDA does not have unbridled discretion to do what it pleases." *Hynson*, 412 U.S. at 627. But such judicial review takes place within the well-defined structure of federal administrative law, based on an administrative record setting forth the reasons

for FDA's actions, rather than in the context of a lay jury instructed under State law and asked to speculate about what the Agency might have done in a counterfactual context.

This Court should be wary of adopting a preemption rule that invites the lower courts to delve into FDA's decision-making processes. This case is perhaps unusual in that FDA repeatedly, emphatically, and publicly rejected the very warning that Colacicco claims was required by Pennsylvania law.[14] Should this Court adopt a rule that invites inquiry into FDA's decision-making processes, FDA will become the center of discovery. Indeed, Colacicco, in his brief in the Third Circuit, argued that the District Court should be reversed because he had been denied discovery against FDA. Colacicco's Third Circuit Br. at 25; *see also* C.A. App. A1057 (requesting discovery against FDA in District Court). The lower courts would become "shadow" FDAs. This Court should seriously consider the adverse consequences of any preemption rule that requires close examination of FDA's internal exercise of its primary jurisdiction over prescription drug labeling.

---

[14] FDA's extensive regulatory review of Paxil and other SSRIs for the past twenty years belies Petitioner's reliance on various statements referenced in his Petition (which are not in the record below) that GSK allegedly misrepresented or withheld information from FDA. Pet. 12-13, 34-36. Indeed, FDA's conclusions in 2007 – that there is no increased risk of suicidality in adults over age 24 – took into account the data which Petitioner claims GSK withheld from FDA prior to Paxil's approval. *Id.* 35.

III. A Clear Conflict Preemption Rule Would Not Leave Plaintiffs Empty-Handed or Manufacturers Free to Disregard Safety Concerns

Preemption of State-law claims challenging the FDA-approved labeling of prescription medications does *not* leave patients who believe they have been injured by a prescription drug without recourse. First, a prescription medication, under federal law, is available only by a prescription from a State-licensed physician or other appropriately licensed healthcare provider. The treating physician or other provider is governed by State law and is appropriately accountable under State law if the standard of care is breached. (In contrast, the distribution of approved drugs by a manufacturer is governed by federal law, specifically the FDCA.) Indeed, Respondent Levine, in *Wyeth v. Levine*, No. 06-1249, sued her treating physician and recovered a settlement. Here, as far as the record reveals, Colacicco did not make a claim against the physician who prescribed Paxil for Ms. Colacicco, and Respondents are unaware of any such claim. That, of course, is Colacicco's free choice, but it is incorrect to state that, if his claim against Respondents is preempted, he is without recourse.[15]

---

[15] Whether to make a claim against the treating physician in a case where a prescription drug was prescribed is an important tactical question for plaintiffs. In many States, if the physician was aware of the "risk" of prescribing the medication, then, under the learned intermediary doctrine, the manufacturer of the medication may not be liable. Thus, the testimony of the treating physician is, to say the least, critical to the plaintiff's case against the manufacturer. The manufacturer normally may not interview the treating physician because of patient confidentiality concerns, while in contrast plaintiff's counsel has full access to the treating physician. The manufacturer is

Second, a rule of preemption based on FDA's approval of the labeling for a prescription medication and rejection of different labeling is limited. It would not generally bar claims based on adulteration of the drug, or on the distribution of a drug with *unapproved* labeling. In these instances, a plaintiff generally might frame a claim under State law that would not be preempted.

Third, a plaintiff who filed a citizen petition with FDA and obtained a favorable ruling, either from FDA or from a federal court reviewing FDA's decision, might in appropriate circumstances then have redress under State law against the drug manufacturer. *See Buckman*, 531 U.S. at 354 (Stevens, J., concurring with Thomas, J.) ("This would be a different case if, prior to the instant litigation, FDA had determined that petitioner had committed fraud . . . . Under those circumstances, [the] state-law fraud claim would not depend on speculation as to the FDA's behavior in a counterfactual situation but would be grounded in the agency's explicit actions."). Of course, in this case, Colacicco could have – but did not – pursue this avenue of relief.

Finally, preemption does not leave pharmaceutical manufacturers free to do as they please once their medication is approved by FDA. FDA claims the authority to recover restitution and "disgorgement" from drug companies who have violated the FDCA. Indeed, in 2002, FDA recovered $500 million in "disgorgement" from one drug company. Jeffrey Gibbs & John Fleder, *Can FDA Seek Restitution or Disgorgement?*, 58 FOOD & DRUG L.J. 129 (2003); *see*

---

usually limited to a formal deposition of the physician with plaintiff's counsel present.

also United States v. Lane Labs-USA, Inc., 427 F.3d 219 (3d Cir. 2005) (affirming order requiring payment of restitution to consumers under the FDCA). Thus, FDA claims authority to recover substantial restitution or "disgorgement" for consumers who are prescribed medications that violate the FDCA.

Patients who are prescribed medications that they claim caused them injury have a wide array of potential routes for monetary recovery. It is simply incorrect to assume that a bright-line rule of preemption based on FDA's approval of labeling for a prescription medication and rejection of different labeling bars any recovery for injury allegedly caused by a prescription medication.

IV. Congress in the 1962 Drug Amendments Explicitly Recognized the FDA's New Authority Over Prescription Medications Would Preempt Conflicting State Laws

Congress, in the 1962 Amendments, recognized that State law that conflicted with the federal structure that Congress put in place in those amendments would be preempted under the ordinary rules of conflict preemption:

> Nothing in the amendments made by this Act to the [FDCA] shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments *unless there is a direct and positive conflict between such amendments and such provision of State law.*

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (emphasis added). The 1962 Amendments fundamentally changed FDA's authority over medications in ways that survive unchanged in the FDCA today. *Compare,*

e.g., § 102(c) (amending 21 U.S.C. § 355(d) to require FDA to disapprove proposed drug labeling if, "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular") *with* 21 U.S.C. § 355(d)(7) (current version unchanged from 1962 Amendments). This Court in *Hynson* noted that "[t]he Senate Report [on the 1962 Amendments] makes clear that an abrupt departure was being taken from old norms for marketing drugs." *Hynson*, 412 U.S. at 619. FDA's current authority over medications is firmly rooted in the 1962 Amendments.

The significance of section 202 is that Congress explicitly recognized that it was possible that there would be State laws that conflicted with the new structure of federal drug regulation, and that those laws would be preempted under the ordinary workings of this Court's conflict preemption jurisprudence. As with the statutory provisions and common law claims at issue in *Geier v. American Honda Motor Co.*, 529 U.S. 861, 870-71 (2000), section 202 "reflect[s] a neutral policy, not a specially favorable or unfavorable policy, toward the application of ordinary conflict pre-emption principles." That section shows plainly that Congress understood and accepted the possibility that its "abrupt departure" from "old norms" of drug regulation might well preempt conflicting state laws. The phrase "direct and positive conflict" that appears in section 202 has been used by this Court to refer to conflict preemption principles generally. *See, e.g.*, *United Constr. Workers v. Laburnum Constr. Corp.*, 347 U.S. 656, 663 n.5 (1954). That is the sense which it should be given in section 202, no more and no less.

As this Court in *Geier* explained: "Why, in any event, would Congress not have wanted ordinary pre-emption principles to apply where an actual conflict with a federal objective is at stake? Some such principle is needed. In its absence, *State law could impose legal duties that would conflict directly with federal regulatory mandates* . . . ." *Geier*, 529 U.S. at 871.[16] Section 202 shows that Congress did want ordinary conflict preemption to apply in the prescription medication context.

V. The Lower Courts Do Not Share "Concurrent" Jurisdiction With FDA Over Its CBE Regulation

Stripped to its essentials, Colacicco's argument against preemption is based on his theory that a court, applying State law, has authority to decide whether GSK *could have* under federal law, and *should have* under State law, unilaterally added a warning to the Paxil labeling to the effect that "Paxil causes an increased risk of . . . suicidality in some adults" and "that Paxil can cause suicide." C.A. App. A94; Colacicco's Third Circuit Reply Br. 7-8. The flaw in Colacicco's "could have, should have" argument, which is based on 21 C.F.R. § 314.70(c) (the CBE regulation), is that FDA has primary jurisdiction over the question of whether GSK could have or

[16] During the oral argument in *Wyeth v. Levine,* the Court questioned the distinction between the express preemption provisions for certain medical devices vis-à-vis the absence of an express preemption provision relating generally to drugs. Hr'g Tr. 9-10, No. 06-1249 (Nov. 3, 2008). The answer to this question is that section 202 is in effect an express preemption provision that simply recognizes the applicability of ordinary conflict preemption principles in the drug context.

should have added such a warning at a particular time.

Indeed, this Court in *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 648-49 (1973), faced a similar theory that the lower courts had "concurrent" authority with FDA to determine whether a drug was a "new drug" as that term is defined by the 1962 Amendments. *See also* 21 U.S.C. § 321(p) (defining "new drug"). This Court rejected that theory, holding that because FDA's jurisdiction is *primary*, not concurrent, "[t]he determination whether a drug is [a "new drug" or not] necessarily implicates complex chemical and pharmacological considerations. Threshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency, while the court stays its hand." *Bentex*, 412 U.S. at 654.

Bentex is persuasive authority for the proposition that Colacicco's "could have, should have" claim can be decided in the first instance only by FDA in the exercise of its primary jurisdiction. FDA by regulation has provided for administrative proceedings "whenever any court, on its own initiative, holds in abeyance or refers any matter to the agency for an administrative determination." 21 C.F.R. § 10.25(c). Colacicco never requested either the District Court or the Third Circuit to refer his "could have, should have" claim to the FDA for an administrative determination. GSK, as the sponsor of the approved NDA for Paxil, was permitted to change the labeling of Paxil – with FDA's approval – by filing with FDA a "supplement" to the NDA, and FDA retains the authority to approve or disapprove any such supplement. Colacicco argues that, under the applicable

regulation, 21 C.F.R. § 314.70(c),[17] "drug manufacturers have the power to add a warning without *prior* FDA approval." Pet. 18 (emphasis added). A supplement permitted by this section of the regulations is often called a "changes being effected" supplement, or, simply, a "CBE." A CBE supplement is required to include "a *full explanation* for the change." 21 C.F.R. § 314.70(c) (emphasis added).

FDA has made clear that CBE supplements fall squarely within its regulatory jurisdiction. In 2006, when FDA modified the regulations governing the content and format of labeling for prescription medications, FDA explained that a manufacturer submitting a CBE for labeling did so at its own peril:

> While a sponsor [*i.e.,* of an NDA, usually the manufacturer] is permitted to add risk information to the [labeling] without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval of the supplement, and *the labeling remains subject*

[17] The Third Circuit noted that this regulation was amended by FDA after October 2003, but that, "for practical purposes," the regulation was simply "relocated." Pet. App. 16 n.4. After the Third Circuit's decision, FDA amended this regulation to clarify FDA's "longstanding view concerning when a change to the labeling of an approved drug . . . may be made in advance of the agency's review and approval of such change." *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 49603-01, 49603 (Aug. 22, 2008). FDA explained that adding a warning to the labeling before FDA approval is appropriate "only if there *is reasonable evidence of a causal association* with the approved drug." *Id.* at 49608 (emphasis added). FDA also pointed out that adding an unsubstantiated warning "can expose a manufacturer to liability" under the FDCA. *Id.* at 49605.

> *to enforcement action* if the added information makes the labeling false or misleading….
>
> . . . .
>
> In fact, the determination whether labeling revisions are necessary is, in the end, *squarely and solely FDA's under the act* [*i.e.*, the FDCA]…. [I]n practice, manufacturers *typically consult with FDA* before [changing labeling via a CBE supplement] so to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might *subject the manufacturer to enforcement action*).

Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) (emphasis added).

This statement makes clear that FDA reserves to itself the jurisdiction to approve or deny a CBE supplement, and, if it disapproves a CBE supplement that added an unsubstantiated warning to the labeling, the manufacturer may be subject to enforcement action. (Enforcement action would be authorized because distribution of a medication with an added warning that FDA has disapproved would be a "prohibited act" within the meaning of 21 U.S.C. § 331.)

FDA considers whether to approve a CBE supplement that adds a warning to labeling in the context of the standards for labeling in the FDCA, *e.g.*, 21 U.S.C. § 355(d), and FDA's extensive regulations governing the content and format of prescription medication labeling. For example, FDA's decisions here to reject the warnings Colacicco claims were required by Pennsylvania law took place against the

backdrop of 21 C.F.R. § 201.57(e),[18] which requires "reasonable evidence of an association" between the medication and a serious adverse reaction or safety hazard before FDA will approve an additional warning. As the Third Circuit concluded, FDA considered extensive clinical data in repeatedly finding that there was no evidence of such an association between antidepressants, including Paxil, and suicide or suicidality. Pet. App. 40. This is exactly the type of medical and scientific question that should be decided in the first instance by FDA, not by the lower courts applying State law.

Colacicco's "could have, should have" theory means that lower courts, applying State law, and without reference to FDA, have the authority to decide at least the following questions:

- Whether and when a drug manufacturer could have submitted a CBE supplement, together with the required "full explanation," that would have added a warning putatively required by State law;
- Whether the added warning putatively required by State law met the FDCA standard for drug labeling, *e.g.*, 21 U.S.C. § 355(d); 21 C.F.R. 201.57(e); and
- Whether FDA, after considering that CBE supplement, *would have approved it*.

Under Colacicco's theory, the lower court would be authorized to decide, without reference to FDA, that a CBE supplement adding the putative warning, with

---

[18] FDA's 2006 final rule modified the language of 21 C.F.R. 201.57(e). *See* 21 C.F.R. § 201.57(c)(6). The standard for "older drugs," including Paxil, is now located at 21 C.F.R. § 201.80(e).

a "full explanation," could have been submitted, that the added warning would have been consistent with the FDCA, and that *FDA would have approved it*. (Obviously, if the lower court found that FDA would have *disapproved* the CBE supplement, then the "impossibility" conflict for preemption would be even more manifest.) Thus, for Colacicco, the lower courts would become "shadow" FDAs.

This would be flatly inconsistent with two of this Court's landmark decisions (handed down on the same day in 1973) interpreting the 1962 Amendments: *Bentex* and *Weinberger v. Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609 (1973). The thrust of both *Bentex* and *Hynson* was that "[t]he heart of the new procedures designed by Congress is the *grant of primary jurisdiction to FDA*, the expert agency it created." *Hynson*, 412 U.S. at 627. In *Bentex*, as noted above, this Court rejected the theory that courts shared "concurrent" jurisdiction with FDA over classifying drugs as "new drugs." In *Hynson*, the Court echoed that holding, stating that FDA "cannot administer the Act intelligently and rationally unless it has authority" to make determinations about the safety and efficacy of drugs. *Hynson*, 412 U.S. at 624. This Court – while recognizing the role of judicial review – again rejected the notion that FDA shared its primary authority with the lower courts.

Colacicco's "could have, should have" argument that the lower courts have concurrent jurisdiction over FDA's CBE regulation will open – or reopen – the question of the scientific data that is actually considered by FDA in balancing the public health and scientific evidence. "Reopen" may be the better term, because this Court in *Buckman* held that "[s]tate law fraud-on-the-FDA claims *inevitably conflict* with the

FDA's responsibility to police fraud consistently with [FDA's] judgment and objectives."[19] *Buckman*, 531 U.S. at 350. If a plaintiff claims that a drug manufacturer defrauded FDA by, for example, withholding clinical data that were required to be submitted to FDA, *see* 21 U.S.C. § 355(b)(1)(A) (requiring "full reports of investigations"), and that, had the data been submitted, FDA would have found "reasonable evidence" of an association, *see* 21 C.F.R. § 201.57(e), then FDA under *Buckman* should decide those claims in the first instance.

Any decision by this Court giving concurrent jurisdiction to the lower courts would be in tension with the holding in *Buckman* because it would invite the lower courts to begin sifting through the voluminous administrative records of FDA's approval of NDAs and supplements to NDAs, looking for snippets of information about what data FDA considered and the scientific and medical judgments FDA made.

Even worse, disregarding FDA's primary jurisdiction would inevitably lead to litigation over whether particular data or documents should have been provided to FDA in regulatory submissions under the FDCA. There will then be a new cottage industry of legal specialists and, inevitably, expert witnesses, to

---

[19] In *Buckman*, this Court relied on the provision of the FDCA that explicitly limits enforcement of the Act to the United States. *Buckman*, 531 U.S. at 352 (citing 21 U.S.C. § 337(a) ("[A]ll such proceedings for the enforcement, or to restrain violations, of this chapter [*i.e.*, the FDCA] shall be by and in the name of the United States.")). This Court has invited the Acting Solicitor General to express the views of the United States on a pending certiorari petition, *Albertson's Inc. v. Kanter*, No. 07-1327, that presents a question involving the preemptive effect of Section 337(a), albeit in the context of FDA's regulation of food.

speculate on what should have, could have, or might have been submitted to, and considered by, FDA. That would both undermine this Court's holdings in *Bentex, Hynson,* and *Buckman* and lead to an unprincipled conflict preemption jurisprudence.

Thus, this Court should reject Colacicco's claim that the lower courts, applying State law, share jurisdiction with FDA over the CBE supplement regulations and hold that, if Colacicco's claim requires findings under that regulation, those findings, in the first instance, must come from FDA exercising its undoubted primary jurisdiction over drug safety and effectiveness.

VI. This Case Is Not Certworthy

There is perhaps no other situation in the entire history of FDA's regulation of prescription drugs where FDA has devoted the amount of time, resources, and attention to a particular risk-benefit calculus as it has with the question of the comorbidity of suicide and depression and the appropriate warnings to be given to physicians about this comorbidity. FDA's allocation of its resources to this question has been entirely appropriate from a public health perspective, given the tragic burden of suicide deaths each year in the United States. But that continuing assertion makes this an easy case – FDA made clear public statements of its position that Colacicco simply cannot circumvent. He deals with FDA's June and October 2003 statements only by ignoring them. Just as this Court does not sit to correct error, it also does not sit to decide straightforward cases. Certiorari is not appropriate here.

CONCLUSION

The Petition should be denied; the Petition should not be held pending a decision in *Levine*; and this case should not be remanded back to the Third Circuit.

Respectfully submitted,

CHARLES A. FITZPATRICK, III
RAWLE & HENDERSON
1339 Chestnut Street
One South Penn Square
Philadelphia, PA 19107
(215) 575-4200

Counsel for Respondents Apotex, Inc. and Apotex Corporation

CHILTON DAVIS VARNER
Counsel of Record
KING & SPALDING LLP
1180 Peachtree Street, NE
Atlanta, GA 30309
(404) 572-4600

Counsel for Respondent GlaxoSmithKline

December 3, 2008