PRECEDENTIAL

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 06-3107

JOSEPH C. COLACICCO,
INDIVIDUALLY AND AS EXECUTOR OF THE ESTATE
OF LOIS ANN COLACICCO, DECEASED,
Appellant

v.

APOTEX INC.; APOTEX CORP., AS SUBSIDIARY OF
APOTEX, INC.; SMITHKLINE BEECHAM,
d/b/a GLAXOSMITHKLINE

No. 06-5148

BETH ANN MCNELLIS,
ON BEHALF OF THE ESTATE OF
THEODORE DEANGELIS,
DECEASED AND IN HER OWN RIGHT

v.

PFIZER INC.; JOHN DOES 1-5; ABC DOE CORP.;
DEF DOE CORP.; GHI DOE CORP.

PFIZER INC.,
Appellant

No. 06-3107
On Appeal from the United States District Court
for the Eastern District of Pennsylvania
(D.C. No. 05-cv-05500)

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District Judge: Honorable Michael M. Baylson

No. 06-5148
On Appeal from the United States District Court
for the District of New Jersey
(D.C. No. 05-cv-01286)
District Judge: Honorable Jerome B. Simandle

Argued December 10, 2007

Before: SLOVITER, AMBRO, Circuit Judges, and RESTANI*, Judge

(Filed April 8, 2008)

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OPINION OF THE COURT

SLOVITER, Circuit Judge.

The issue before us is one of preemption, an area of the law that need delicately balance federal interests and those of the states. It harks back to the very beginning of our republic, and has continued to occupy us ever since. Preemption is not a doctrine that lends itself to a black-letter rule. One size does not fit all. The decision must be based on the circumstances presented in the particular situation.

The plaintiffs in these consolidated cases are the husband and daughter, respectively, of two adults who committed suicide

after taking medication from the class of antidepressants known as selective serotonin reuptake inhibitors ("SSRIs"). The common question presented by the cases is whether the plaintiffs may maintain their state-law tort actions against the manufacturers of two such drugs on the theory that the drugs' labeling failed to warn of their association with an increased risk of suicidality. The central issue is whether actions taken by the Food and Drug Administration ("FDA") pursuant to its authority under the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301-397, and the corresponding regulatory scheme preempt the plaintiffs' state-law failure-to-warn claims.

I.

SmithKline Beecham, d/b/a GlaxoSmithKline ("GSK"), manufactures Paxil, an SSRI that is used to treat depression. On October 6, 2003, Lois Colacicco's physician prescribed Paxil for her depression. After her prescription was filled with a generic version of Paxil, Lois Colacicco began taking that medication. Less than a month later, on October 28, 2003, at the age of fifty-five, she committed suicide in her New York home.

At the time of Lois Colacicco's death, the labeling for Paxil included the following language in its "Precautions" section:

> 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 . . . .

Colacicco App. at 436. Apotex, Inc. and Apotex Corp. (together, "Apotex") manufacture and distribute the generic version of paroxetine hydrochloride (the active ingredient in Paxil) ingested by Lois Colacicco. The labeling for Apotex's generic paroxetine was identical to GSK's labeling for Paxil.

After Lois Colacicco's death, her husband, Joseph C. Colacicco, filed suit against Apotex and GSK in the United States District Court for the Eastern District of Pennsylvania, alleging that those companies violated state common-law tort rules and New York state consumer protection laws by selling their products with labels that failed to warn consumers of the increased risk of emergent suicidality and worsening depression in adults taking paroxetine. On May 26, 2006, Apotex and GSK moved to have Colacicco's complaint dismissed on the ground that it was preempted by federal law and, alternatively, that GSK did not owe a duty of care to the consumers of generic paroxetine, such as Lois Colacicco. The District Court dismissed the complaint on the basis of preemption. Colacicco v. Apotex, Inc., 432 F. Supp. 2d 514, 537-39 (E.D. Pa. 2006).

Pfizer is the manufacturer of Zoloft, another SSRI that is used to treat depression. On January 22, 2003, sixty-four-year-old Theodore DeAngelis was prescribed Zoloft for anxiety and depression. DeAngelis ingested that drug in the days leading up to his death by suicide on January 30, 2003. At the time of his death, the suicide precaution on Zoloft's labeling read as follows:

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

McNellis App. 499-500.

Following DeAngelis' death, Beth Ann McNellis, his daughter and the executrix of his estate, filed suit in New Jersey state court, alleging that Pfizer violated various New Jersey products liability and consumer fraud statutes by selling Zoloft without warning consumers that it increased the risk of suicidality in those ingesting the drug. Pfizer removed the action to the United States District Court for the District of New Jersey

and moved for summary judgment on the ground that McNellis' claim was preempted by federal law. The Court denied that motion on December 29, 2005. McNellis ex rel. DeAngelis v. Pfizer, Inc. ("McNellis I"), No. Civ. 05-1286 (JBS), 2005 WL 3752269, at *13 (D.N.J. Dec. 29, 2005). On September 29, 2006, following the dismissal of Colacicco's complaint in the Pennsylvania District Court, the New Jersey District Court denied Pfizer's motion to vacate its denial of the summary judgment motion, but certified its order for interlocutory appeal. The District Court framed the question for appeal as follows:

> Whether . . . the United States Food and Drug Administration's requirements for the form and content of the labeling for the prescription antidepressant Zoloft preempted New Jersey's failure-to-warn law, under the doctrine of conflict preemption, where the FDA's regulations at 21 C.F.R. 201.57(e) [(2003)] and 314.70(c)(6)(iii) [(2007)] permit a manufacturer to unilaterally enhance its warning when the manufacturer has reasonable evidence of an association of a serious hazard with a drug.

McNellis ex rel. DeAngelis v. Pfizer, Inc. ("McNellis II"), No. Civ. 05-1286 (JBS), 2006 WL 2819046, at *13 n.9 (D.N.J. Sept. 29, 2006). We must decide which of the two fine opinions authored by two of the ablest district judges in this circuit most closely expresses our view of the difficult issue presented.

II.

The FDA is charged with "promot[ing] the public health by promptly and efficiently reviewing [drug manufacturers'] clinical research and taking appropriate action on the marketing of regulated products in a timely manner" and "protect[ing] the public health by ensuring that . . . drugs are safe and effective." 21 U.S.C. § 393(b)(1), (b)(2)(B). In this capacity, the FDA regulates the introduction of all new drugs. Id. § 355(a). Persons intending to market a drug must first file a new drug application ("NDA") with the FDA. Id. § 355(b). An NDA must include, inter alia, full reports of investigations into the

drug's safety and effectiveness, the components and production methods used to manufacture the drug, and "specimens of the labeling proposed to be used for such drug." Id. § 355(b)(1); see also 21 C.F.R. § 314.50(c)(2)(i) (requiring manufacturers to include "statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57 of this chapter"), (e)(2)(ii).

Although "labeling" may be commonly understood as the label affixed to a prescription bottle, in this context it also encompasses the written material sent to the physician and included with the drug provided to the patient.[1] The FDA regulations require prescription drug labeling to include "a summary of the most clinically significant information . . . critical to safe use of the drug," including, inter alia, potential safety hazards associated with use of the drug. 21 C.F.R. § 201.57a(10), (c)(6)(i). Applicants must also include a "summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling." Id. § 314.50(d)(5)(viii).

The FDA must deny an NDA if it finds that:

> (1) the investigations [discussed above] do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;
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> (2) the results of such tests show that such drug is unsafe

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[1] "Labeling" is defined by statute as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C § 321(m). Thus, labeling "embraces advertising or descriptive matter that goes with the package in which the articles are transported," Kordel v. United States, 335 U.S. 345, 350 (1948), in addition to any label that may be placed directly on a pill bottle.

> for use under such conditions or do not show that such drug is safe for use under such conditions;
> . . . . or
>
> (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.

21 U.S.C. § 355(d). The FDA shall otherwise approve the NDA. Id. The "FDA will approve an application and issue the applicant an approval letter . . . on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling." 21 C.F.R. § 314.105(b). However, "[s]uch approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing." Id.

The FDA's post-approval oversight of drug labeling is governed primarily by regulation.[2] At the times relevant to this litigation, 21 C.F.R. § 201.56 described the general requirements for the content and format of drug labeling, while 21 C.F.R. § 201.57 set forth the specific requirements for such labeling.[3]

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[2] Because many of the relevant regulations were revised or relocated after the dates relevant to this litigation (both DeAngelis and Lois Colacicco were prescribed SSRIs and committed suicide between January and October of 2003), we set forth the regulations in effect during that time period in the text and, where applicable, provide parallel citations to the current language and location of those regulations in footnotes. Unless otherwise noted, the substance of the regulations cited in this opinion have remained consistent between January of 2003 and the present.

[3] As part of the FDA's amendments to its labeling regulations in 2006, additional labeling requirements for recently approved drugs were added to § 201.56 and that section was retitled. See 21 C.F.R. § 201.56 (2007); see also 71 Fed. Reg. 3922, 3986 (Jan. 24, 2006). Meanwhile, the specific requirements relating to drugs introduced prior to the amendments were amended and redesignated as § 201.80. See 71 Fed. Reg. at 3988, 3996. Of

Section 201.57(e) required manufacturers to "describe serious adverse reactions and potential safety hazards" under the heading "Warnings." 21 C.F.R. § 201.57(e) (2003). Moreover, "[t]he labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." Id. The same section states that "[s]pecial problems, particularly those that may lead to death or serious injury, may be required by the [FDA] to be placed in a prominently displayed box. . . . If a boxed warning is required, its location will be specified by the [FDA]." Id.

FDA regulations also govern the procedures for revising drug labeling. At all times relevant to this litigation, an applicant was required to notify the FDA of any changes to an approved drug, including its labeling, by one of three methods, depending on the magnitude of the intended change. See § 314.70(a)-(d) (2003). Section 314.70(b) covered "supplements requiring FDA approval before the change is made." Id. § 314.70(b). "Any change in labeling, except one described in [subsections] (c)(2) or (d) of this section" required FDA pre-approval. Id. § 314.70(b)(3)(i). Subsection (d) was limited to minor changes that may be submitted with the drug manufacturer's annual report, and is not implicated by this litigation. See id. § 314.70(d). Subsection (c), however, described "changes that may be made before FDA approval." Id. § 314.70(c). In particular, "[a]n applicant shall submit a supplement at the time the applicant makes" a change to its labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction." Id. § 314.70(c)(2)(i). The supplemental submissions by which § 314.70(c) changes are accomplished are sometimes referred to as "changes being

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primary importance to this litigation, the text formerly appearing at § 201.57(e) now appears at § 201.80(e). The relevant language remains unchanged. Compare 21 C.F.R. § 201.57(e) (2003), with 21 C.F.R. § 201.80(e) (2007). See also 71 Fed. Reg. at 3996.

effected" or "CBE" supplements.[4]

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[4] The FDA also amended § 314.70 in 2006. The regulation now refers to changes under subsections (b), (c), and (d) as "major," "moderate," and "minor" changes, respectively. 21 C.F.R. § 314.70(b), (c), (d) (2007). For the purposes of this litigation, subsections (b) and (d) are not materially different. Subsection (c), however, is now titled "Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes)." Id. § 314.70(c). Nonetheless, that subsection also states that the FDA "may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change." Id. § 314.70(c)(6). The listed categories include changes in labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction." Id. § 314.70(c)(6)(iii)(A). Thus, for all practical purposes, subsection (c)(2)(i) has simply been relocated to subsection (c)(6)(iii)(A), but the FDA may determine that products incorporating such labeling changes may not be distributed until the agency has received the CBE supplement or thirty days thereafter. Finally, the FDA now provides express notice that if it "disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change." Id. § 314.70(c)(7).

After oral argument, the FDA submitted a proposed rule that would further limit the type of changes that may be effected pursuant to § 314.70(c)(6)(iii). See 73 Fed. Reg. 2848 (Jan. 16, 2008). Specifically, that regulation would be limited to: "Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following: (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under 201.57(c) of this chapter . . . ." 73

Drug manufacturers have continuing obligations to report adverse drug experiences, id. § 314.80(c), and any "significant new information . . . that might affect the safety, effectiveness, or labeling of the drug product," id. § 314.81(b)(2)(i). Failure to abide by these obligations may result in withdrawal of an approved drug. Id. §§ 314.80(j), 314.81(d).

Although regulations describe the particulars of the FDA's oversight of drug labeling, the FDCA describes the primary penalties for a drug manufacturer's failure to comply with those regulations. The FDA must withdraw approval of a drug if it finds "on the basis of new information before [it,] . . . that there is a lack of 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 labeling thereof." 21 U.S.C. § 355(e). The FDA may withdraw approval of a drug if, "on the basis of new information before [it,] . . . the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the [FDA] specifying the matter complained of." Id.

The distribution of "misbranded" drugs is also prohibited by the FDCA. Id. § 331(a), (b). A drug is misbranded if its "labeling is false or misleading in any particular," id. § 352(a), if its labeling lacks "adequate warnings against use . . . where its use may be dangerous to health," id. § 352(f), or if "it is dangerous to health when used in the . . . manner . . . prescribed, recommended, or suggested in the labeling thereof," id. § 352(j). The FDA has the authority to enforce the prohibition on misbranding by initiating injunction proceedings, see id. § 332, criminal prosecutions, see id. § 333(a), and the seizure of misbranded drugs, see id. § 334.

Once a drug has been approved, it is included in the FDA's published list of approved drugs. See 21 U.S.C. §

Fed. Reg. at 2853.

355(j)(7). Such a drug is then referred to as a "listed drug." Id. § 355(j)(2)(A)(i). A listed drug is sometimes also referred to as an "innovator" or "pioneer" drug. See, e.g., Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1494, 1497-98 (D.C. Cir. 1996). Although the manufacturers of listed drugs, such as GSK and Pfizer in this case, are governed by all of the requirements associated with NDAs, the manufacturers of generic drugs, such as Apotex, are not required to submit an NDA. Rather, such manufacturers must abide by certain statutes and regulations that are based on the equivalence of generic drugs to the listed drugs.

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) relaxed the approval procedures for generic drug manufacturers, allowing them to submit an abbreviated NDA ("ANDA"). Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355(j), 35 U.S.C. §§ 156, 271, 281). An ANDA must contain information showing the generic drug's bioequivalency to the listed drug and that "the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . ." 21 U.S.C. § 355(j)(2)(A)(iv) & (v).[5] FDA regulations also provide that the agency may seek withdrawal of a generic drug, pursuant to notice and the opportunity for a hearing, if "the labeling for the [generic drug] is no longer consistent with that for the listed drug referred to in the [ANDA]." 21 C.F.R. § 314.150(b)(10).

III.

The District Courts had jurisdiction over the plaintiffs' claims under 28 U.S.C. § 1332. We have jurisdiction over Colacicco's appeal pursuant to 28 U.S.C. § 1291 following the entry of the order of the Pennsylvania District Court dismissing Colacicco's complaint; we have jurisdiction over Pfizer's appeal from the New Jersey District Court's interlocutory order denying

[5] The FDA states that generic drug manufacturers may not add new warnings to the approved labeling for the listed drug. 57 Fed. Reg. 17,950, 17,953, 17,955, 17,961 (April 28, 1992).

Pfizer's motion for summary judgment in McNellis' case because the District Court certified that order pursuant to 28 U.S.C. § 1292(b).

The issue underlying the District Courts' orders presents a question of law. We apply plenary review over their preemption determinations. See Pennsylvania Employees Benefit Trust Fund v. Zeneca Inc., 499 F.3d 239, 242 (3d Cir. 2007) (motion to dismiss); Horn v. Thoratec Corp., 376 F.3d 163, 166 (3d Cir. 2004) (motion for summary judgment).

IV.

The doctrine of preemption is rooted in the Supremacy Clause, U.S. Const. art. VI, cl. 2, which provides that the "Constitution, and the Laws of the United States which shall be made in Pursuance thereof . . . shall be the supreme Law of the Land." Early in our constitutional history, the Supreme Court interpreted this language to invalidate state laws that "interfere with, or are contrary to," federal law, the genesis of the preemption doctrine. Gibbons v. Ogden, 22 U.S. (9 Wheat.) 1, 211 (1824). The Supreme Court has identified three major situations where there is preemption. They were described in Hillsborough County v. Automated Med. Labs., Inc. as: (1) "express" preemption, applicable when Congress expressly states its intent to preempt state law; (2) "field" preemption, applicable when "Congress' intent to pre-empt all state law in a particular area may be inferred [because] the scheme of federal regulation is sufficiently comprehensive" or "'the federal interest is so dominant that the federal system will be assumed to preclude enforcement of state laws on the same subject;'" and (3) "conflict" preemption, applicable when "state law is nullified to the extent that it actually conflicts with federal law," even though Congress has not displaced all state law in a given area.[6]

[6] Both field and conflict preemption are sometimes referred to as forms of implied preemption. See, e.g., Geier v. Am. Honda Motor Co., 529 U.S. 861, 884 (2000); Freightliner Corp. v. Myrick, 514 U.S. 280, 287 (1995). However, the Supreme Court has also

471 U.S. 707, 713 (1985) (quoting Rice v. Santa Fe Elevator Corp., 331 U.S. 218, 230 (1947)).

An express preemption situation is exemplified by the Supreme Court's recent decision in Riegel v. Medtronic, Inc., --- U.S. ----, 128 S. Ct. 999 (2008), where it considered the effect of the express preemption provision of the Medical Device Amendments of 1976 ("MDA") to the FDCA.[7] It held that in light of that provision, plaintiffs' claims that an arterial catheter was designed, labeled, and manufactured in a way that violated New York common law were preempted. Id. at 1003, 1005, 1011. See also Horn, 376 F.3d at 166.

In the Colacicco case, the Pennsylvania District Court noted that GSK and Apotex conceded that express and field preemption are not implicated, and proceeded exclusively under a conflict preemption analysis. 432 F. Supp. 2d at 523. After reviewing the applicable principles and relevant precedent, and according considerable deference to the FDA's position, the Court held that Colacicco's claims are preempted. Id. at 537-38. In so holding, the Court rejected Colacicco's argument that the

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asserted that these three categories are not "rigidly distinct;" for example, "field pre-emption may be understood as a species of conflict preemption: A state law that falls within a pre-empted field conflicts with Congress' intent (either express or plainly implied) to exclude state regulation." English v. Gen. Elec. Co., 496 U.S. 72, 79-80 n.5 (1990).

[7] The statutory language provides that:

> no State or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement (1) which is different from, or in addition to, any requirement applicable under [the MDA] to the device, and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under [the Act].

21 U.S.C. § 360(k)(a).

FDA's position should not be accorded deference because it was inconsistent with the FDA's prior statements. The Court concluded that "after 2000, the FDA has been very consistent." Id. at 531-32.

A directly contrary conclusion was reached by the New Jersey District Court in the McNellis case. In the first of two opinions on the issue, the Court denied defendant Pfizer's motion for summary judgment, holding that it was unwilling to find that Congress intended to obviate the state laws upon which McNellis' complaint was based. McNellis I, 2005 WL 3752269, at *10. The Court held that discovery was needed on whether Pfizer had reasonable evidence of an association between Zoloft and suicidality. Id. at *11. In its opinion the following year, the Court declined to vacate its earlier opinion, and instead determined that "there can be no conflict preemption because the FDA's regulations do not conflict with New Jersey's failure to warn laws." McNellis II, 2006 WL 2819046, at *5. The Court held that the interpretation of the FDA was not entitled to the substantial deference accorded by the Pennsylvania District Court, and certified its order to this court for interlocutory appeal. Id. at *10, *13.

The pharmaceutical companies do not seriously argue that this is a case of express preemption[8] or field preemption. We

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[8] Apotex and GSK briefly argue that this is a case of express preemption because the 1962 Amendments to the FDCA stated: "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." Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (Oct. 10, 1962). Of course, the plain language of this provision states that the Amendments do not preempt state law in the absence of a conflict. Thus, to the extent that this provision affects our analysis, it merely states that conflict preemption applies. In other words, this "express preemption" provision simply leads us to a conflict preemption analysis, which

therefore limit our consideration to whether the plaintiffs' state-law claims conflict with the federal scheme.

A.

We consider first whether there is a presumption against preemption applicable in this case. The existence vel non of such a presumption is contested. The Supreme Court has stated: "[i]n all pre-emption cases, and particularly in those in which Congress has legislated in a field which the States have traditionally occupied, we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." Medtronic, Inc. v. Lohr, 518 U.S. 470, 485 (1996) (hereafter referred to as "Lohr") (citation, internal quotation marks, and alterations omitted). Colacicco and McNellis emphasize this "presumption against preemption," and both District Courts recognized the existence of that presumption. See Colacicco, 432 F. Supp. 2d at 524; McNellis I, 2005 WL 3752269, at *3. Although a presumption against preemption is commonly acknowledged, the Supreme Court has made clear that the application of such a presumption is not always appropriate. See Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 347-48 (2001) (declining to apply a presumption against preemption where the plaintiff alleged fraud on the FDA).

Apotex and GSK argue that a presumption against preemption does not apply in the circumstances presented here because the states have not traditionally been involved in the regulation of drug labeling, whereas the federal government has regulated that area for over a hundred years. Pfizer takes an even broader position, arguing that the presumption against preemption does not apply at all in conflict preemption cases.[9]

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may be applied independently of an express preemption analysis.

[9] Pfizer also argues that it has overcome the presumption were it applicable. Where appropriate, we have not hesitated to find a conflict even after applying the presumption against preemption.

The Supreme Court's decision in Hillsborough County undermines both of these arguments. In that case, the Court stated that the "presumption that state or local regulation of matters related to health and safety is not invalidated under the Supremacy Clause," 471 U.S. at 715, and then proceeded to analyze whether local regulations imposed on blood plasma centers "conflict with the federal scheme," id. at 720. The Court concluded that the County's ordinances and regulations, which imposed donor testing and requirements beyond those contained in the federal regulations, and which were designed to protect the health of the donors, to ensure the quality of the plasma, and to protect the recipients of the plasma, id. at 715-16, were not preempted by the federal regulatory scheme because the County's requirements "do not imperil the federal goal of ensuring sufficient plasma," id. at 722.

The Supreme Court later addressed the presumption against preemption in Lohr, where the plaintiff, who was injured by the failure of her pacemaker, filed a "common-law negligence action against the manufacturer of an allegedly defective medical device." 518 U.S. at 474. The manufacturer argued that the claim was preempted by a provision in the MDA that bars state or local requirements different from those applicable under the MDA and which relate to the safety or effectiveness of any device covered by the Act.[10] Id. at 481. The Court referred to the states' police powers to protect the health and safety of their citizens, id. at 485, the premise of the presumption against preemption, in holding that plaintiff's negligence action was not preempted. A plurality of the Court noted that the statutory language precluded any additional "requirement," not any "remedy," under state law, id. at 487, and concluded, by reference to the legislative history, that the statute "was not intended to pre-empt most, let alone all, general common-law duties enforced by damages actions." Id. at 491. We note, however, that the Court did not discuss the

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See Fasano v. Fed. Reserve Bank of New York, 457 F.3d 274, 283, 290 (3d Cir. 2006).

[10] See supra note 7.

presumption against preemption in its recent opinion in Riegel considering the same provision of the MDA at issue in Lohr.

There are, as the pharmaceutical companies argue, relevant Supreme Court decisions where the Court explicitly declined to apply any presumption against preemption. In Buckman, plaintiffs, who claimed injuries from the use of orthopedic bone screws, brought suit against the consultant to the manufacturer on the theory that its statements defrauded the FDA and led the agency to approve a device that caused the plaintiffs' injuries. See 531 U.S. at 343, 347-48. The Supreme Court held that plaintiffs' fraud claims were preempted. It rejected plaintiffs' argument that there was a "virtually irrefutable presumption against implied preemption of private damage remedies predicated on an alleged conflict with a federal remedial scheme." Id. at 351 (internal quotation marks omitted). Because "the relationship between a federal agency and the entity it regulates . . . originates from, is governed by, and terminates according to federal law," the Court concluded that the plaintiffs' claims did not implicate the traditional state interest in the regulation of public health and safety, and thus it did not apply the presumption against preemption. Id. at 347-48.

Similarly, in United States v. Locke, 529 U.S. 89, 94, 108 (2000), the Supreme Court considered whether Washington State laws governing oil tanker operations and designs enacted after the oil spill caused by the Exxon Valdez were preempted by a comprehensive federal regulatory scheme governing oil tankers. The Court declined to apply a presumption against preemption because the case concerned "national and international maritime commerce," a field in which "Congress has legislated . . . from the earliest days of the Republic." Id. The Court noted that "an 'assumption' of nonpre-emption is not triggered when the State regulates in an area where there has been a history of significant federal presence." Id.

While the decisions in Buckman and Locke are distinguishable from the cases before us, they do make clear that it is "the purpose of Congress [as] the ultimate touchstone of pre-emption analysis," Cipollone v. Liggett Group, Inc., 505

U.S. 504, 516 (1992) (citations, internal quotation marks, and alterations omitted), to which we must turn. See also Rice, 331 U.S. at 230; Fasano v. Fed. Reserve Bank of New York, 457 F.3d 274, 284 (3d Cir. 2006). Colacicco and McNellis argue that preemption is inappropriate because Congress has never expressed its intent to preempt state-law tort actions challenging drug labeling. McNellis notes that the New Jersey District Court concluded that it was "unwilling to find . . . that Congress intended to obviate the very state laws that provide remedies to consumers harmed by dangerous products and deceptive marketing in the absence of a clear and compelling Congressional statement." McNellis I, 2005 WL 3752269, at *10 (citing Bates v. Dow Agrosciences LLC, 544 U.S. 431, 450 (2005)).

The pharmaceutical companies respond by quoting the Supreme Court's statement that "in a situation where state law is claimed to be pre-empted by federal regulation, a 'narrow focus on Congress' intent to supersede state law [is] misdirected,' for '[a] pre-emptive regulation's force does not depend on express congressional authorization to displace state law.'" City of New York v. FCC, 486 U.S. 57, 64 (1988) (quoting Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta, 458 U.S. 141, 154 (1982)). In fact, the Supreme Court has found that even where an express preemption saving clause demonstrated Congress' intent to exempt common-law tort actions from preemption, the language of the saving clause did not suggest an intent to "bar the ordinary working of conflict pre-emption principles" or preserve "state-law tort actions that conflict with federal regulations." Geier v. Am. Honda Motor Co., 529 U.S. 861, 869 (2000). The Court held that federal regulations may preempt common-law tort actions under a conflict preemption analysis despite a statutory provision stating that "'[c]ompliance with' a federal safety standard 'does not exempt any person from any liability under common law.'" Id. at 868 (quoting 15 U.S.C. § 1397(k) (1988 ed.)). Thus, the Court concluded that plaintiff's tort action against the automobile manufacturer for failing to install airbags was preempted under conflict preemption principles although expressly saved from preemption by statute. Id. at 881.

It follows that in this case, which is also one of conflict preemption, the lack of a Congressional directive expressly approving or rejecting preemption in the context of drug labeling regulations is not determinative. Rather, the conflict preemption analysis is designed to determine the propriety of preemption where Congress has not explicitly stated its intent. Seen in this light, Pfizer's argument that the presumption against preemption is inapplicable in the context of implied conflict preemption has more force. Although the Supreme Court applied the presumption in Hillsborough County, a decision in which it engaged in a conflict preemption analysis, that analysis followed the Court's consideration of field preemption principles. 471 U.S. at 716-20.[11] Therefore, the extent to which the Court relied on the presumption in the context of its conflict analysis is not clear. Here, we recognize the applicability of the presumption against preemption, but note the tension between such a presumption, which emphasizes the "clear and manifest purpose of Congress," Lohr, 518 U.S. at 485 (internal quotation marks omitted), and implied conflict preemption, which analyzes preemption in the absence of any explicit intent, cf. Geier, 529 U.S. at 885 (failing to formally apply the presumption against preemption, but "assum[ing] that Congress or an agency ordinarily would not intend to permit a significant conflict").

B.

A conflict between state and federal law "arises when compliance with both federal and state regulations is a physical impossibility or when state law stands as an obstacle to the accomplishment and execution of the full purposes and

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[11] Although both field and conflict preemption are generally thought of as forms of implied preemption, a focus on Congressional intent is of greater value in the context of field preemption, where Congress' mere presence in a given field indiscriminately nullifies all state law in the field, than in the context of conflict preemption, which excludes state law only to the extent that it requires individuals to act contrary to conflicting federal obligations.

objectives of Congress." Hillsborough County, 471 U.S. at 713 (citations and internal quotation marks omitted); see also City of New York, 486 U.S. at 64 ("The statutorily authorized regulations of an agency will pre-empt any state or local law that conflicts with such regulations or frustrates the purposes thereof.").

There are not many examples of instances where it is impossible to comply with both federal and state law, presumably because state legislatures and regulators do not readily seek confrontation with federal authority. One such example is provided by the Court's 1913 decision where it considered the effect of a 1907 Wisconsin statute providing that mixtures or syrups offered for sale "shall have upon them no designation or brand . . . other than that required by the state law . . . ." McDermott v. Wisconsin, 228 U.S. 115, 127 (1913). The federal food and drugs act passed in 1906 barred false and misleading labels on product packages. Id. at 127, 129. When the issue came before the Supreme Court, it stated that "the State may not, under the guise of exercising its police power or otherwise, . . . enact legislation in conflict with the statutes of Congress passed for the regulation of the subject . . . ." Id. at 131-32. The Court held that the state statute was invalid because "[t]he legislative means provided in the Federal law for its own enforcement may not be thwarted by state legislation having a direct effect to impair the effectual exercise of such means." Id. at 137.

The scarcity of actual conflict cases has led the Justices to pose hypothetical conflicts. In Florida Lime & Avocado Growers, Inc. v. Paul, 373 U.S. 132, 143 (1963), the Supreme Court hypothesized the existence of an impossibility conflict where "federal orders forbade the picking and marketing of any avocado testing more than 7% oil, while the California test excluded from the State any avocado measuring less than 8% oil content." Under those circumstances, it would be a "physical impossibility" for avocado growers to comply with both federal and state law because California law would require them to do what federal law forbade, that is, pick their avocados after they surpassed the 7% ceiling established by federal law. Id.

In another case, where the issue was whether a federal statute that permits national banks to sell insurance in small towns preempts a state statute that forbids them to do so, Justice Breyer discussed the impossibility situation:

> In this case we must ask whether or not the Federal and State Statutes are in "irreconcilable conflict." The two statutes do not impose directly conflicting duties on national banks-as they would, for example, if the federal law said, "you must sell insurance," while the state law said, "you may not."

Barnett Bank of Marion County, N.A. v. Nelson, 517 U.S. 25, 31 (1996).

Most of the preemption cases falling within the conflict category are cases that present the second scenario discussed in Hillsborough County - when "state law stands as an obstacle to the accomplishment and execution of the full purpose and objectives of Congress." 471 U.S. at 713 (internal quotation marks omitted). In his opinion in Barnett Bank, Justice Breyer continued,

> the Federal Statute authorizes national banks to engage in activities that the State Statute expressly forbids. Thus, the State's prohibition of those activities would seem to "stan[d] as an obstacle to the accomplishment" of one of the Federal Statute's purposes – unless, of course, that federal purpose is to grant the bank only a very limited permission, that is, permission to sell insurance to the extent that state law also grants permission to do so.

517 U.S. at 31 (quoting Hines v. Davidowitz, 312 U.S. 52, 67 (1941)). After deciding that the McCarran-Ferguson Act anti-preeemption rule did not govern the case, id. at 38, the Court held that the federal statute preempted the state statute, id. at 42.

It is not only state statutes that may stand as obstacles to the achievement of federal objectives. It is now established that law suits based on state tort law, as well as on state statutes, may

be viewed as presenting obstacles to the federal objectives and hence barred as preempted. In Geier, the Court held that an action against American Honda based on its failure to provide a driver's side airbag was preempted by a federal regulation. The Court adopted the principle that ordinary preemption principles apply to a state tort action where an actual conflict with a federal objective is at stake. Geier, 529 U.S. at 871-72. The majority stated that in the absence of such a principle:

> state law could impose legal duties that would conflict directly with federal regulatory mandates, say, by premising liability upon the presence of the very windshield retention requirements that federal law requires. See, e.g., 49 CFR § 571.212 (1999). Insofar as petitioners' argument would permit common-law actions that "actually conflict" with federal regulations, it would take from those who would enforce a federal law the very ability to achieve the law's congressionally mandated objectives that the Constitution, through the operation of ordinary pre-emption principles, seeks to protect. To the extent that such an interpretation of the saving provision reads into a particular federal law toleration of a conflict that those principles would otherwise forbid, it permits that law to defeat its own objectives, or potentially, as the Court has put it before, to "'destroy itself.'"

Id. (quoting Am. Tel. & Tel. Co. v. Cent. Office Tel., Inc., 524 U.S. 214, 228 (1998)).

A similar consideration was noted in Lohr where Justice Breyer, in his separate opinion concurring in part and dissenting in part, stated that "ordinarily, insofar as [federal law] pre-empts a state requirement embodied in a state statute, rule, regulation, or other administrative action, it would also pre-empt a similar requirement that takes the form of a standard of care or behavior imposed by a state-law tort action." 518 U.S. at 504-05. In Horn, which dealt with the same express preeemption provision as in Lohr, we quoted from the FDA's letter brief stating, inter alia,

> State common law tort actions threaten the statutory framework for the regulation of medical devices, particularly with regard to FDA's review and approval of product labeling. State actions are not characterized by centralized expert evaluation of device regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the balancing of benefits and risks of a specific device to their intended patient population - the central role of FDA - sometimes on behalf of a single individual or group of individuals.

376 F.3d at 178.

State common-law tort actions based on the manufacturers' failure to warn present the pharmaceutical manufacturers with particular difficulties. State standards of care undoubtedly differ from state to state. Absent a determination that the FDA-approved labeling and the FDA's refusal to require the warnings suggested by plaintiffs in this case preempt state tort actions, the manufacturers may be subjected to considerable liability based on varying standards, with no benchmark that they should follow.

In holding the tort action based on the failure to provide airbags was preempted, the Court in Geier reviewed the history of the consideration of passive restraints by the federal agency, there the Department of Transportation. Similarly, in this case, before we can hold that a federal regulation or, as in Geier, the failure to regulate as extensively as plaintiffs sought, has preemptive force, we must review the record of the FDA's treatment of the desired warning at issue here.

As discussed above, a new drug may not be marketed until it has received FDA approval. The FDA will not approve a drug if its "labeling is false or misleading in any particular." 21 U.S.C. § 355(d)(7). Even after a drug has been approved, a drug will be deemed misbranded if the "labeling is false or misleading in any particular" and the FDA may withdraw approval of that drug and prosecute the manufacturer. See id. §§ 331(b) (prohibition on misbranding), 355(e)(3) (withdrawal authority),

352(a), (f), (j) (definition of misbranding), 332 (injunction proceedings), 333(a) (criminal prosecutions), 334 (seizure). Thus, the FDCA vests the FDA with significant authority over drug labeling. FDA regulations further implement this authority.

Under its regulations, the FDA may withdraw approval of a drug if the manufacturer disregards its obligation to submit periodic reports notifying the FDA of adverse drug experiences and other new information that might affect the drug labeling. 21 C.F.R. §§ 314.80(c), (j), 314.81(b)(2)(i), (d). FDA regulations detail the information that must be included in the warnings section of drug labeling and instruct that such "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug . . . ." Id. § 201.57(e) (2003); id. § 201.80(e) (2007).

There are three distinct procedures by which manufacturers may revise their drugs' labeling, each of which requires the manufacturer to notify the FDA of its proposed revision. See id. § 314.70(a)-(d). Generally, labeling changes require FDA pre-approval. See id. § 314.70(b)(3)(i) (2003). However, changes that "add or strengthen a contraindication, warning, precaution or adverse reaction," may be implemented prior to the manufacturer's receipt of FDA approval. Id. § 314.70(c)(2)(i) (2003); id. § 314.70(c)(6)(iii)(A) (2007).

Colacicco and McNellis argue that because § 314.70(c) allows drug manufacturers to strengthen and augment warnings on drug labeling without prior FDA approval, the FDA labeling requirements constitute mere minimum standards for the information that may be required in their labeling. See, e.g., Sprietsma v. Mercury Marine, 537 U.S. 51, 58-59 (2002). Therefore, they argue that state-law failure-to-warn claims that would require manufacturers to strengthen or augment a warning do not conflict with FDA regulations, and are in fact complementary to those regulations.

The pharmaceutical companies respond that even though labeling changes made pursuant to § 314.70(c) do not require prior approval, the legality of those changes remains within the

FDA's control. They state that because the FDA is directly involved with balancing the benefits and risks of a drug's labeling, see, e.g., 21 C.F.R. § 314.50(d)(5)(viii), and has the statutory authority to order the manufacturer to discontinue distribution of any products incorporating the manufacturer's labeling change, the FDA-approved labeling reflects the FDA's expert judgment about the information that must be included in a drug's labeling.[12]

Of course, in this case we must focus on the effect of the FDA's failure to require a warning that plaintiffs argue was the cause of their injury rather than the effect of a positive regulation. It is always easier to evaluate the effect of a conflict created by a positive regulation than the effect created by inaction. It is difficult to know whether the absence of a regulation may reflect a wait-and-see approach or mere inertia. We are guided to some extent by Geier where the Court held that the failure of the Department of Transportation to require auto manufacturers to equip their 1997 vehicles with a specific form of passive restraint system, i.e. airbags, preempted the state "no airbag" tort suit. 529 U.S. at 874, 881.

In this case we need not speculate on the rationale of the FDA for its failure to require the adult suicidality warnings. Not only has the FDA filed an amicus brief in the Colacicco action but it 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,[13]

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[12] Apotex, for its part, argues that tort actions against generic drug manufacturers are preempted because the Hatch-Waxman Amendments and the FDA's implementing regulations require such manufacturers to maintain labeling identical to that of the innovator drug.

[13] Colacicco, whose complaint was dismissed prior to discovery, argues that the District Court improperly relied on evidence of the FDA's past actions and that we are prohibited from considering that information. This problem does not arise in the

and has concluded that the suicide warnings desired by plaintiffs are without scientific basis and would therefore be false and misleading.

In 1991, after considering whether antidepressants caused or intensified suicidal thoughts, the FDA's Psychopharmacological Drugs Advisory Committee concluded that no such warning should be added to Prozac (an SSRI similar to Paxil and Zoloft) or other antidepressants. The FDA specifically rejected citizen petitions in 1991, 1992, and 1997 which sought to either withdraw approval of Prozac as a result of its asserted association with suicide or to include a suicide warning on the labeling of that drug. In each instance, the FDA concluded that there was insufficient evidence to take the actions requested.

DeAngelis committed suicide on January 22, 2003. The FDA approved the Zoloft suicide precaution seven separate times before and after that date, in each instance requiring Pfizer to market the drug with the precise labeling approved.[14] Further,

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McNellis case, which is before us following summary judgment proceedings. Of course, courts may place limited reliance on public records in the context of a motion to dismiss. See Anspach ex rel. Anspach v. City of Philadelphia, Dep't of Pub. Health, 503 F.3d 256, 273 n.11 (3d Cir. 2007). Thus, in Anspach, we took notice of FDA public records "not for the truth of [their] contents, but rather as evidence of the information provided by the federal government" to the relevant regulated parties. Id. Our recognition of the records contested here, all of which are publicly available, is similarly limited. See also Jean Alexander Cosmetics, Inc. v. L'Oreal USA, Inc., 458 F.3d 244, 256 n.5 (3d Cir. 2006) (recognizing that courts may take judicial notice of prior judicial proceedings).

[14] The FDA first approved Zoloft for the treatment of depression in adults on December 30, 1991, conditioning its approval on Pfizer's incorporation of specifically indicated labeling revisions. In 1996, the FDA approved Zoloft for a new indication, the treatment of obsessive compulsive disorder ("OCD"), with that

just months before DeAngelis' death, the FDA filed an amicus brief in an action before the Court of Appeals for the Ninth Circuit, stating that it had concluded that there was no scientific basis for a warning suggesting that Zoloft causes suicidality. See Brief for the United States as Amicus Curiae, Motus v. Pfizer Inc., 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372, 02-55498), 2002 WL 32303084 (brief submitted September 10, 2002).[15]

The FDA also repeatedly approved the Paxil labeling in effect at the time of Lois Colacicco's prescription of Paxil on October 6, 2003, and her death on October 28, 2003, approving it for a new indication, the treatment of generalized anxiety

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approval again conditioned on Pfizer's incorporation of a series of labeling revisions. The FDA proceeded to approve the use of Zoloft for panic disorder and pediatric OCD in 1997, post-traumatic stress disorder in 1999, premenstrual dysphoric disorder in 2002, and, on February 7, 2003, social anxiety disorder. Each time the FDA approved Zoloft for a new indication, it required that the final printed labeling be identical to the labeling attached to the FDA's approval.

[15] The New Jersey District Court acknowledged the FDA's position in Motus, but decided that it was not appropriate to defer to that litigation position. See McNellis I, 2005 WL 3752269, at *10. However, we distinguish between the agency's legal position in its amicus brief and its factual representations. In the Motus brief, the FDA stated not just its legal conclusions with respect to the applicability of preemption, but it also reported its view of the state of scientific research regarding Zoloft and antidepressants at that time. The FDA's summary of its scientific determinations must be distinguished from the agency's construction of a statute, as the review of scientific information is strictly within its expertise. The FDA asserted facts in support of its legal position, and we take notice of its statement of those facts, rather than its legal position.

disorder, just a year before those events.[16] The FDA approved Apotex's application to market generic paroxetine on June 30, 2003, concluding that "the drug is safe and effective for use as recommended in the submitted labeling," which included the suicide precaution discussed above, rather than a warning. See Letter from Gary Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA, to Apotex Corp. 3 (July 30, 2003), available at http://www.fda.gov/cder/foi/appletter/2003/75356ap.pdf (last visited January 8, 2008). Significantly, on June 19, 2003, the FDA issued a public statement to address reports associating the pediatric use of Paxil with suicidality, in which it stated: "There is no evidence that Paxil is associated with an increased risk of suicidal thinking in adults." FDA Talk Paper, FDA Statement Regarding the Anti-Depressant Paxil for Pediatric Population (June 19, 2003), available at http://www.fda.gov/bbs/topics/answers/2003/ans01230.html (last visited Nov. 8, 2007).

On October 27, 2003, the FDA issued a Public Health Advisory regarding increased suicidality in pediatric users of antidepressants. This advisory was limited to pediatric patients; a warning for adult patients was not issued. In that advisory, the FDA announced that it would continue to research the reports of suicidality in pediatric patients treated with antidepressants, explaining that "[s]uch reports are very difficult to interpret, in the absence of a control group, as these events also occur in untreated patients with depression." FDA, FDA Public Health Advisory (Oct. 27, 2003), available at

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[16] As with its approvals of Zoloft, the FDA approved Paxil for new indications on the condition that the final drug labeling be identical to the labeling approved by the FDA. See, e.g., Letter from Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research, FDA, to GlaxoSmithKline (Oct. 2, 2002), available at http://www.fda.gov/cder/foi/appletter/2002/20031se8-035ltr.pdf (last visited January 8, 2008).

http://www.fda.gov/cder/drug/advisory/mdd.htm (last visited January 8, 2008).

Thus, even when it began to reevaluate its position regarding the association of antidepressants with pediatric and adolescent suicidality, the FDA continued to announce its rejection of adult suicidality warnings for SSRIs as it had for the decade before the prescriptions and deaths at issue in this litigation. Just months prior to Lois Colacicco's death, the FDA publicly stated that Paxil was not associated with a risk of suicidality in adults. Similarly, four months before DeAngelis' death, the FDA filed a public brief stating its position that scientific evidence did not support the addition of a suicide warning on Zoloft's labeling.

Although preemption is commonly thought of in terms of statutes and regulations, a federal agency's action taken pursuant to statutorily granted authority may also have preemptive effect over state law. See Chicago & N. W. Transp. Co. v. Kalo Brick & Tile Co., 450 U.S. 311, 327 (1981) ("These findings by the [Interstate Commerce] Commission, made pursuant to the authority delegated by Congress, simply leave no room for further litigation over the matters respondent seeks to raise in state court."); NCNB Texas Nat'l Bank v. Cowden, 895 F.2d 1488, 1497-99 (5th Cir. 1990) (finding that Federal Deposit Insurance Corporation's action taken pursuant to statutory authority preempted state law); cf. Sprietsma, 537 U.S. at 66-67 (recognizing that an agency's refusal to regulate may be construed as a determination that no such regulation is appropriate and have preemptive force). Because the standard for adding a warning to drug labeling is the existence of "reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.57(e), and the FDCA authorizes the FDA to prohibit false or misleading labeling, a state-law obligation to include a warning asserting the existence of an association between SSRIs and suicidality directly conflicts with the FDA's oft-repeated conclusion that the evidence did not support such an association. Therefore, under the circumstances of this case, the plaintiffs' failure-to-warn claims are preempted by the FDA's actions taken in accordance with its statutory authority.

The FDA clearly and publicly stated its position prior to the prescriptions and deaths at issue here. Therefore, we need not decide whether preemption would be appropriate under different facts--such as where the FDA had not rejected the substance of the warning sought or where the FDA only stated its position after a lawsuit had been initiated--or under the broader theories of preemption argued by the parties. Thus, we do not decide whether the FDA's mere approval of drug labeling is sufficient to preempt state-law claims alleging that the labeling failed to warn of a given danger, whether FDA approval of drug labeling constitutes minimum standards in the absence of the FDA's express rejection of a specific warning, or whether actions against generic drug manufacturers are preempted on the basis of their obligations under the Hatch-Waxman Amendments.[17] Our holding is limited to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires. Cf. Dowhal v. Smithkline Beecham Consumer Healthcare, 88 P.3d 1, 11 (Cal. 2004) (concluding that an FDA "letter established a federal policy prohibiting defendants from giving consumers any warning other than the one approved by the FDA in that letter, and that the use of a [warning required by state law] would conflict with that policy").

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[17] In contrast to our decision, the Supreme Court of Vermont has held that plaintiffs' negligence and failure-to-warn claims alleging inadequate warnings on the labeling of an anti-nausea drug "did not conflict with the FDA's labeling requirements for [the drug] because [Wyeth] could have warned against [the danger alleged by plaintiffs] without prior FDA approval, and because federal labeling regulations create a floor, not a ceiling, for state regulation." Levine v. Wyeth, --- A.2d ----, 2006 WL 3041078, ¶ 6 (Vt. 2006), cert. granted, 128 S. Ct. 1118 (2008). The Vermont Court found that there was "no evidence that the FDA intended to prohibit defendant from strengthening the [drug] label pursuant to [§] 314.70(c)" and thus it was not impossible for Wyeth to comply with both state and federal obligations. Id. ¶ 23. The facts in these cases are otherwise.

The plaintiffs raise two primary objections to this conclusion. First, they argue that nothing less than the FDA's explicit rejection of a drug manufacturer's request to add a contested warning to its drug labeling should suffice to establish conflict preemption. Second, they contend that the pharmaceutical companies failed to provide the FDA with sufficient information for it to make a valid decision regarding the necessity of a suicidality warning. Neither argument is persuasive.

As we previously noted, the FDA is authorized by statute to reject an NDA if the labeling is false or misleading in any particular and may withdraw its approval of a drug upon the same findings. See 21 U.S.C. § 355(d)(7), (e)(3). Plaintiffs argue, however, that the FDA's actions were insufficient to manifest such a rejection here. They ask us to overlook the FDA's various public statements rejecting the existence of an association between SSRIs and adult suicidality because they were not made in the context of the FDA's formal rejection of a CBE supplement submitted by one of the defendant pharmaceutical companies.

We agree that a court could more easily determine the preemption issue if the FDA had formally rejected such a CBE supplement, but we cannot compel the defendant companies to suggest a CBE supplement that they believe is unnecessary. Nor do we favor encouraging regulated parties to submit CBE supplements for the sole purpose of insulating themselves from potential liability. Cf. 44 Fed. Reg. 37,434, 37,435 (June 26, 1979) (cautioning, in the context of medical malpractice liability, that "it would be inappropriate to require statements in drug labeling that do not contribute to the safe and effective use of the drug, but instead are intended solely to influence civil litigation in which the agency has no part"). Thus, we reject the notion that, in order to rise to the level of a conflict in this situation, the FDA's rejection of a warning must be imbued with the formality proposed by the plaintiffs.

Colacicco further argues that the FDA's failure to require an adult suicidality warning cannot be seen as a rejection of the

warning that his lawsuit would require because "GSK manipulated or withheld information from the FDA." Colacicco Reply Br. at 9. This contention borders on the charge that GSK defrauded the FDA by manipulating or withholding such information. Cf. Buckman, 531 U.S. at 346-47. 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.

In the New Jersey action, McNellis opposed Pfizer's motion for summary judgment by submitting copies of research studies that were made public, which McNellis argued showed a link between SSRIs and suicidality. McNellis does not argue that the FDA was unaware of this material. Our focus is on the period before the two deaths that are the subject of the actions before us. We note, however, that the FDA has continued its close scrutiny of the effect of SSRI drugs on suicidality of adults. In March of 2004, the FDA directed GSK and nine other manufacturers of SSRIs to include stronger warnings on drug labels about the need to monitor adult patients for signs of worsening depression or suicidality, but noted that it had "not concluded that these drugs cause worsening depression or suicidality in adult patients."[18] Br. for the United States as Amicus Curiae at 13 (citing FDA Talk Paper, FDA Issues Public Health Advisory on Cautions for Use of Antidepressants in Adults and Children (March 22, 2004), available at http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html).

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[18] In April 2006, GSK, after reviewing studies that disclosed a higher incidence of suicidal behavior in young adults treated with Paxil, modified its Paxil label to include a warning that young adults "especially those with [major depressive disorder], may be at an increased risk of suicidal behavior when treated with" Paxil. Br. for the United States as Amicus Curiae at 14 (citing Paxil Label, available at http://us.gsk.com/products/assets/US_paxil.pdf (last visited Feb. 27, 2008)). It made this change only after filing the proposed change with the FDA and waiting the required 30 days.

More recently, the FDA, after its review of the aggregated data from all SSRI manufacturers, reaffirmed its conclusion that there is insufficient evidence demonstrating that SSRIs are associated with adult suicidality. In its widely distributed notice on Antidepressant Use in Children, Adolescents and Adults dated May 2, 2007, available at http://www.fda.gov/cder/drug/antidepressants/default.htm (last visited Feb. 22, 2008), the FDA incorporated its conclusions that "[s]hort-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24" and that adults ages 65 and older taking antidepressants have a decreased risk of suicidality. Revisions to Product Labeling, available at http://www.fda.gov/cder/drug/antidepressants/antidepressants_label_change_2007.pdf (last visited Feb. 22, 2008); see also FDA News, FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medications, http://www.fda.gov/bbs/topics/NEWS/2007/NEW01624.html (May 2, 2007).[19] The FDA Revisions to Product Labeling directed the drug companies (including manufacturers of Paxil and Zoloft) to make changes in the warnings included at the beginning of the package inserts that confirm that antidepressants increase the risk of suicidality in children, adolescents, and young adults but that the studies did not show an increase in the risk of suicidality in adults older than age 24.[20]

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[19] We may, of course, take judicial notice of this development "which [took] place after the judgment appealed from." Werner v. Werner, 267 F.3d 288, 295 (3d Cir. 2001).

[20] The entire text of the revised warning reads as follows:

> Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-

In light of the FDA's continued review of existing scientific studies, we reject plaintiffs' arguments that the FDA lacked information that would have dissuaded it from rejecting an adult suicidality warning for Zoloft, Paxil, or generic paroxetine in 2003.

The FDA has taken the position, both in the preamble to the 2006 amendments revising the drug labeling regulations and in its amicus brief in the Colacicco case, that plaintiffs' claims are preempted as a result of the actions taken by the FDA pursuant to its regulatory authority. The preamble specifically states that preemption applies to "claims that a [manufacturer]

> 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. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use). Revisions to Product Labeling, available at http://www.fda.gov/cder/drug/antidepressants/antidepressants_label_change_2007.pdf (last visited Feb. 22, 2008).

breached an obligation to warn by failing to include a statement in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the [manufacturer] had an obligation to warn." 71 Fed. Reg. 3922, 3936 (Jan. 24, 2006). The FDA explains in the amicus brief that "the basis for federal preemption is not the [labeling] guidelines themselves . . ., 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 . . . ." Br. for the United States as Amicus Curiae at 28.

We would ordinarily be leery of an agency's view of what is essentially a legal issue, but we note that in Geier the Supreme Court recently addressed the weight to be given to an agency's position on preemption. The Court "place[d] some weight" on a Department of Transportation interpretation, as set forth in an amicus brief, of a rule that it had promulgated. Geier, 529 U.S. at 883. The Court considered that Congress had delegated the agency "authority to implement the statute; the subject matter is technical; and the relevant history and background are complex and extensive." Id. The Court stated that the agency was "'uniquely qualified' to comprehend the likely impact of state requirements." Id. (quoting Lohr, 518 U.S. at 496). The Court also noted the consistency of the agency's position over time, id., and the coherence of the agency's views, id. at 885. Although the Court did not rely solely on the agency's position, it noted that "a specific expression of agency intent to pre-empt, made after notice-and-comment rulemaking" was not necessary to find conflict preemption. Id.

From Geier's discussion of an agency's informal position regarding preemption, we conclude (1) that an agency's position concerning preemption need not be contained in a formal regulation in order to be considered, and (2) that such a position is subject to a level of deference approximating that set forth in Skidmore v. Swift & Co., 323 U.S. 134 (1944). Cf. Christensen v. Harris County, 529 U.S. 576, 587 (2000) (quoting Skidmore, 323 U.S. at 140) (holding that agency interpretations contained

in statements that "lack the force of law" are "'entitled to respect'" only to the extent they have the "'power to persuade'").[21]

"The fair measure of deference to an agency administering its own statute has been understood to vary with circumstances, and courts have looked to the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position." United States v. Mead Corp., 533 U.S. 218, 228 (2001) (alterations omitted) (citing Skidmore, 323 U.S. at 139-40).

It is important to consider the rationale given by the agency for its position that its actions preempt state law in the particular situation. In the case of the SSRI drugs at issue, Paxil, Zoloft, and the generic paroxetine manufactured by Apotex, the FDA has explained that "[u]nder-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." Br. for the United States as Amicus Curiae at 16-17. The FDA's view that "the imposition of liability under state law for defendants' alleged failure to warn would interfere with FDA's accomplishment of regulatory objectives," id. at 22, is in our

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[21] Counsel for GSK suggested that a combination of Skidmore and Auer deference was appropriate. Under Auer v. Robbins, 519 U.S. 452, 461 (1997) (citations and internal quotation marks omitted), an agency's interpretation of its own regulation is "controlling unless plainly erroneous or inconsistent with the regulation." However, because the FDA purports to interpret both the statutory structure and regulatory framework, we believe it more prudent to apply Skidmore deference, which is the weaker of the two. This is also consistent with Geier, wherein the Court considered an agency's interpretation of its own regulation under a less deferential standard than that suggested by Auer. 529 U.S. at 883.

view entitled to at least as much deference, if not more, as the FDA's view of its preemption authority. The Pennsylvania District Court accorded the FDA's views "significant" deference, Colaciccio, 432 U.S. at 529, and we agree that in at least this respect the FDA's view is entitled to some degree of deference.

In light of the circumstances in this case, we agree that the FDA's rejection of the warning plaintiffs proffer preempts a state-law action premising liability on a drug manufacturer's failure to include such a warning in the drug labeling notwithstanding that the agency's view was not subject to notice-and-comment rulemaking.

The Supreme Court has recently acknowledged the FDA's expertise in the context of the medical devices covered by the MDA. It stated, "[b]ecause the FDA is the federal agency to which Congress has delegated its authority to implement the provisions of the Act, the agency is uniquely qualified to determine whether a particular form of state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress,' and, therefore, whether it should be pre-empted." Lohr, 518 U.S. at 496 (citing Hines, 312 U.S. at 67). Justice Breyer, concurring in that decision, also noted that the Court has "suggested that, in the absence of a clear congressional command as to pre-emption, courts may infer that the relevant administrative agency possesses a degree of leeway to determine which rules, regulations, or other administrative actions will have pre-emptive effect." Id. at 505 (Breyer, J., concurring) (emphasis added) (citing cases). Of course, the FDA is equally expert, if not more so, with respect to regulation of drugs, with which it has had a longer experience than with medical devices.

We need not decide whether the FDA's position in this case is inconsistent, as plaintiffs argue, with the FDA's 2000 rule proposal. We see no inconsistency between the FDA's preamble to the 2006 amendments and its long-held position that it has the responsibility to determine whether a warning is required. Compare 44 Fed. Reg. at 37,447 (stating, in 1979, that

"the decision as to whether a warning is legally required for the labeling of a drug must rest with the agency"), with 71 Fed. Reg. at 3934 ("In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act.").

In conclusion, based on our own review of the FDCA, the FDA's regulations, and the FDA's actions taken pursuant to its statutory authority, we conclude that the failure-to-warn claims brought by Colacicco and McNellis conflict with, and are therefore preempted by, the FDA's regulatory actions. It is important to note that we express no view as to the merits of the issue whether SSRIs contribute to adult suicidality. We are not scientists and we do not purport to have any expertise on that issue. That is within the FDA's authority. This decision is based on the record before us.

V.

For the above-stated reasons, we will affirm the judgment of the United States District Court for the Eastern District of Pennsylvania dismissing Colacicco's complaint and we will reverse the order certified by the United States District Court for the District of New Jersey with instructions that judgment be entered in favor of the defendants. In light of our decision with respect to preemption, we need not reach the other issues considered by the District Courts.

AMBRO, Circuit Judge, dissenting

The majority opinion describes these cases as situations calling for preemption: the expert agency, the Food and Drug Administration ("FDA"), consults scientific data to generate the optimal warnings (not too lax, not too alarmist) for drug labels—and state tort lawsuits would disrupt this fine system. But there is an important contrary view that has prevailed until recently: state tort law complements FDA provisions on drug warnings, in part by eliciting more information than the FDA would glean otherwise from pharmaceutical manufacturers. This contrary view has, I believe, the better argument in terms of legal doctrine on preemption, congressional intent, and the history of state tort law alongside federal law. Although the majority opinion is well-crafted and responsibly narrow, I would not move even the short distance my colleagues go toward preemption of state-law torts. I thus respectfully dissent.

I. Presumption Against Preemption

The majority opinion begins its analysis where I would, by examining whether we are to apply a presumption against preemption. State tort law, dealing with failure-to-warn claims (like those brought by the plaintiffs in our cases), addresses health and safety and thus falls within the states' traditional police powers. *See Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (describing the presumption against preemption and asserting "the historic primacy of state regulation of matters of health and safety"). As the majority recognizes, the presumption does not always apply; for example, it does not apply to claims alleging fraud on the FDA. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347–48 (2001). That the presumption there does not apply—where common sense points to federal law

governing exclusively those who seek to defraud a federal agency—is no surprise, and hardly weakens the presumption when it does apply.

The presumption against preemption must inform our analysis of both "whether Congress intended any pre-emption at all" and "the scope of its intended invalidation of state law." *Lohr*, 518 U.S. at 485 (emphasis omitted). When the presumption applies, rebutting it requires a clear expression that Congress intended to preempt. *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) ("In areas of traditional state regulation, we assume that a federal statute has not supplanted state law unless Congress has made such an intention clear and manifest.") (citations and internal quotation marks omitted).

In my view, the majority opinion under-emphasizes congressional intent as the "ultimate touchstone of pre-emption analysis." *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (citations and internal quotations marks omitted). Our inquiry is "guided" by a focus on gaining " 'a fair understanding of *congressional purpose*.' " *Lohr*, 518 U.S. at 485–86 (quoting *Cipollone*, 505 U.S. at 530) (emphasis in original). As the majority opinion rightly recognizes, the defendants in our cases do not make a serious argument that this case involves express preemption or field preemption. But I would place more significance on the fact that the key *conflict* preemption cases that the majority opinion relies on involve express statutory preemption provisions. *Geier v. American Honda Motor Company*, 529 U.S. 861, 864–65 (2000) (evaluating viability of state-tort-law claims in light of a preemption provision, 15 U.S.C. § 1392(d), and a savings provision, *id.* § 1397(k), within the National Traffic and Motor Vehicle Safety Act of 1966); *Lohr*, 518 U.S. at 481 (evaluating viability of state-tort-law claims in light of the preemption provision of the Medical Devices Act, 21 U.S.C. § 360k(a)).

Even when considering a species of implied preemption—as conflict preemption generally is, *see Geier*, 529 U.S. at 884—we should be asking whether Congress intended to preempt. In our cases, we have no statutory preemption provision to interpret that relates to drug labeling in the Food, Drug and Cosmetic Act ("FDCA"). This fact should push us to hold the presumption against preemption in place, as we lack the best kind of evidence of congressional intent: statutory text.

The absence of a relevant preemption provision in the FDCA does not, of course, resolve whether the presumption against preemption is overcome by something else. The Supreme Court has "held repeatedly that state laws can be pre-empted by federal regulations as well as by federal statutes." *Hillsborough County v. Automated Med. Labs.*, 471 U.S. 707, 713 (1985). Although initial approval of drug labeling involves both statutory and regulatory provisions, FDA regulations primarily govern the continuing oversight of drug-label revisions. These regulations, at the time relevant to this litigation, required drug manufacturers to revise labeling "to include a warning as soon as there is reasonable evidence of an assocation of a serious hazard with a drug," 21 C.F.R. § 201.57(e), and to submit supplemental information in the event that they "add or strengthen a contraindication, warning, precaution, or adverse reaction," *id.* § 314.70(c). The defendants in our cases rely primarily on their continuing obligations under these FDA regulations for their conflict-preemption argument.

Yet the mere presence of a comprehensive regulatory scheme such as the FDA's for drug labeling does not itself unseat the presumption against preemption. *Hillsborough County*, 471 U.S. at 717 ("We are even more reluctant to infer pre-emption from the comprehensiveness of regulations than

from the comprehensiveness of statutes.").[22] Because our focus must remain on congressional intent, we should remember in deciding questions of *regulatory* preemption that any inferences regarding congressional purpose typically will be indirect. Congress enacted the FDCA, which in turn enabled the FDA to adopt its regulations regarding continuing (*i.e.*, post-approval) drug labeling. To overcome the presumption against preemption, the defendants in our cases must show that Congress implicitly intended to allow the FDA to adopt regulations that preempt failure-to-warn lawsuits under state law. *Cf. Fidelity Federal Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 162 (1982) (holding that Federal Home Loan Bank Board regulations preempted state law where "the statutory language suggests that Congress expressly contemplated, and approved, the Board's promulgation of regulations superseding state law" after also inquiring into the Board's own intent to preempt).

The majority opinion closes its discussion of the presumption against preemption by describing a "tension" between the presumption as outlined in *Lohr* and some seemingly contrary language in *Geier*. But the *Geier* side of this doctrinal tug-of-war has slippery footing. The quoted language—"[O]ne can assume that Congress or an agency ordinarily would not intend to permit a significant conflict,"

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[22] The majority opinion suggests that, because *Hillsborough County* considered field preemption in analyzing the municipal ordinances at issue, the operation of the Supreme Court's application of the presumption against preemption in that case "is not clear." I disagree with this suggestion. *Hillsborough County*'s discussion of the presumption against preemption appears in Part III of that opinion. 471 U.S. at 714–16. The field-preemption analysis in Sections IV.A and IV.B, and the conflict-preemption analysis in Section IV.C, follow. *Id.* at 716–20. In my view, the Court's purpose in setting out the presumption against preemption in Part III was to indicate that the presumption should guide the analysis in all sections of Part IV.

Geier, 529 U.S. at 885—appears as a *dictum* in the context of a larger discussion of whether an agency must adopt a clear statement of preemptive intent for a conflict between federal regulation and state law to exist.[23] This sentence does not create a counter-presumption in favor of preemption, for the very next sentence in *Geier* states that "a court should not find pre-emption too readily in the absence of clear evidence of a conflict." *Id.* That is a restatement of the presumption against preemption, suggesting that we should not interpret *Geier* to muddy the presumption or to dilute its effect.[24]

When a federal court undertakes a conflict-preemption analysis, a "significant conflict" between federal and state law might be the kind of "clear evidence" that could rebut the presumption against preemption. *Geier*, 529 U.S. at 885. We can assume Congress or the FDA had awareness of products-liability law when legislating or regulating. So if we find a genuine conflict, we may conclude that Congress intended to preempt state law. But in situations involving less obvious conflicts, the presumption against preemption will be more difficult to overcome.

I would apply the presumption against preemption here.

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[23] That discussion in *Geier* settles the issue: an agency need not do so for a conflict to exist. 529 U.S. at 884–85. Even without express statutory preemption or a clear agency statement on preemption, a court may find that state law "actual[ly] conflict[s]" with federal law under the facts of a particular case. *Id.* at 884 (quoting *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990)). I address the broader issue of how much deference we owe an agency's position on preemption below. *See infra* Part II.

[24] In contrast, the majority opinion never again mentions the presumption against preemption after Section IV.A of its opinion, suggesting that the presumption is performing virtually no analytical work.

The plaintiffs' failure-to-warn claims stand near the heart of the states' police powers over matters of health and safety. And the existence and detailed nature of the federal scheme does not change our imperative to require clear congressional intent (whether expressed directly in a preemption provision or implied by an authorizing statute enabling an agency to act) to preempt state tort law.

II. Deference to the FDA's View on Preemption

At the end of its conflict-preemption analysis—even after addressing the plaintiffs' arguments—the majority opinion considers the FDA's own view regarding the preemptive effect of its drug-labeling regulations. In 2006, the preamble to an FDA revision of its drug-labeling regulations stated that failure-to-warn claims are preempted if, at the time of injury, the substance of the alternative warning proposed by plaintiffs (1) had already been submitted to the FDA and (2) had not been adopted. 71 Fed. Reg. 3922, 3936 (Jan. 24, 2006). The FDA also filed an *amicus* brief in the *Colacicco* case before us, arguing that "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." FDA Br. 16. The FDA emphasizes that it strives for the optimal strength of warning. Anything less *or more* than the FDA-approved and FDA-monitored warning, in the agency's view, would be "false or misleading." *See* 21 U.S.C. §§ 331(a)–(b), 352(a); Br. of *Amicus Curiae* United States at 2.

We must decide what weight we should give to these FDA views before analyzing the purported conflict in this case. I agree with the majority opinion that we should apply *Skidmore* deference to the FDA's informal position contained in its 2006 preamble and its *amicus* brief in *Colacicco*. *See Geier,* 529 U.S. at 883 (placing "some weight" on the Department of Transportation's interpretation of its own airbag regulation);

Skidmore v. Swift & Co., 323 U.S. 134, 139 (1944) (giving the Department of Labor's "interpretive bulletin" regarding the calculation of working hours a level of deference based on "all those factors which give it power to persuade, if lacking power to control"). The formulation in *Mead*, which cites *Skidmore* and which the majority opinion quotes, designates the following factors for consideration: "the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position." *United States v. Mead Corp.*, 533 U.S. 218, 228 (2001).

I disagree with the majority opinion, however, in its application of the standards articulated in *Skidmore* and *Mead*. Comparing FDA statements from 1979 and 2006, my colleagues discern "no inconsistency" between them.[25] I suggest a better analysis of inconsistency would take a more detailed view of the FDA's position(s) during the 27 intervening years.[26] For

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[25] Importantly, the majority opinion's quote from the 1979 regulation is taken out of context. Rather than contemplating the FDA's relation to state courts, the quoted sentence discusses the FDA's relation to panels of experts from which the agency seeks advice: "Although FDA often refers questions of whether a warning should be included in the labeling of a drug *to its standing advisory committees*, the decision as to whether a warning is legally required for the labeling of a drug must rest with the agency." 44 Fed. Reg. 37,434, 37,447 (June 26, 1979) (emphasis added). Thus there is no support I can find in the record for the proposition that, in 1979, the FDA viewed its drug-labeling regulations as preemptive of state tort law.

[26] Some Supreme Court cases suggest that inconsistency is no bar to deference. *See, e.g.*, *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29. 42 (1983). But others have language suggesting that inconsistency counts against the agency's position. *See, e.g.*, *Bates*, 544 U.S. at 449 (finding a preemption argument "particularly dubious" in light of the EPA's change in position within five years).

instance, only slightly more than seven years ago the FDA disavowed any "federalism implications" or preemptive effect of changes to its requirements for prescription drug labeling. 65 Fed. Reg. 81,082, 81,103 (Dec. 22, 2000). Rather than maintaining a consistent position, the FDA now undertakes a "180-degree reversal." David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 474 n.59 (2008) (internal quotation marks omitted). Its current position is novel rather than longstanding. *See id.* at 462 ("For most of its seventy-seven-year history [since receiving the name "Food and Drug Administration" in 1930], the [FDA] has regulated the drugs sold in the United States without any significant interaction with the world of state-law damages litigation."). I thus conclude that the FDA's position regarding preemption deserves little deference by way of its inconsistency.

The majority opinion relies on another of the *Skidmore* and *Mead* factors: agency expertise. Undoubtedly, the FDA has special expertise in evaluating the scientific evidence on pharmaceuticals' safety and efficacy. That expertise should contribute to any consideration of the proper mix of legal institutions used to regulate drug labeling. But, as my colleagues note, "[w]e would ordinarily be leery of an agency's view of what is essentially a legal issue." The FDA is not an expert on federalism concerns. Nor is the agency the only Government institution that should bring its perspective to bear on the relationship between the executive branch and state courts; Congress, federal courts, and state courts each have a constitutional responsibility under the Supremacy Clause to evaluate such issues. Thus, I would consider the FDA's expertise only a mild positive in our calculation of how much deference to apply in these cases.

The remaining factors listed in *Mead* weigh against giving the FDA's view on preemption much deference. With

respect to "formality," the FDA has not engaged in notice-and-comment rulemaking on this issue, instead promulgating its views in a preamble to a regulation and a series of *amicus* briefs in cases like these. As the majority notes, notice-and-comment rulemaking is not *required* to find conflict preemption. *See Geier*, 529 U.S. at 885. But the lack of notice-and-comment rulemaking should, all else equal, reduce the level of deference we give the FDA's position. Similarly, the lack of institutional formality suggests a relatively low "degree of care" taken to outline its reasoning.[27] In my view, a high degree of care on issues of preemption would involve scholarly, scientific, and public-health[28] research into the complex matters of law and policy that these cases implicate. I see no evidence in the record that the FDA conducted or commissioned independent research of this nature in preparing the 2006 preamble.

In summary, the *Mead* factors counsel us to give the FDA's position a relatively low level of deference. The ultimate test under *Skidmore* is nonetheless whether the FDA's (and the defendants') view has the "power to persuade," 323 U.S. at 139,

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[27] By making this point I do not mean to criticize FDA counsel's efforts in writing its *amicus* brief in this case or at oral argument. On the contrary, counsel performed admirably in both regards. My focus here is in-depth institutional research on law and policy preceding the recent "about face" on agency preemption.

[28] A group of public health researchers writes that "[i]ndirect regulation of the pharmaceutical industry by tort litigation is an important complement to the regulation of drug safety by the FDA." Br. of *Amicus Curiae* Curt D. Furberg, M.D., Ph.D., *et al.* at 6. This view—based on various scholarly, peer-reviewed articles—does not receive any attention in the 2006 preamble or in the FDA's *amicus* brief. Notice-and-comment rulemaking would provide a forum for such research to be considered, but, as noted, the FDA has not undertaken that administrative process on the issue of preemption of state tort law.

an evaluation I take up in Part III.

III. Conflict Preemption.

The defendants' argument is that labeling that satisfies the FDA is both the minimum and the maximum amount of labeling they may do. Under this view, the FDA believes it has struck the proper balance between safety and efficacy, that is, between avoiding unintended injuries to patients because of insufficient warnings while not deterring too many patients from using drugs that would benefit them because of unjustified over-warnings. Adding additional warnings unsupported by medical evidence would subject the defendants to FDA sanctions for false labeling. Conflict preemption must apply to block state-law claims for failure to warn, according to the defendants, since stronger warnings for Paxil and Zoloft—the drugs within the category of selective seratonin reuptake inhibitors ("SSRIs") involved in these cases—would violate FDA regulations. This makes it impossible, defendants continue, for them to have complied with both state and federal law. Alternatively, imposing an overlay of tort liability would frustrate the federal objective of having the FDA strike the safety-efficacy balance.

For the reasons I describe below, I disagree with this characterization of the interaction of FDA regulation and state tort law. Informed by the presumption against preemption, I see the federal and state constructs as complementary, as they have been since the 1930s. The majority opinion's holding of preemption in these cases, despite an apparently narrow construction, threatens the institutional framework we have for balancing safety and efficacy in the pharmaceutical industry while compensating victims of wrongful injuries.

A. Absence of an Actual Conflict

None of the drug manufacturers in these cases attempted to enhance a warning and received an FDA sanction in response. The majority opinion correctly states that hypothetical conflicts can give rise to conflict preemption. But the hypothetical in question must be convincing for us to allow this. The conflict the defendants raise relies, at its heart, on the FDA punishing drug manufacturers for over-warning. But a heightened warning would likely have its source in new information that the FDA had not previously known. Thus, I find it hard to believe that, if a drug manufacturer augmented its warning in response to or in anticipation of a state tort lawsuit, the FDA would sanction the manufacturer for over-warning consumers under 21 U.S.C. §§ 331(a)–(b) and 352(a).

Indeed, drug manufacturers have authority to strengthen warnings without advance permission from the FDA. The plain language of 21 C.F.R. § 314.70 permits unilateral additions to warnings, subject to subsequent FDA approval: "[T]he holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change," including such changes as "add[ing] or strengthen[ing] a contraindication, warning, precaution, or adverse reaction." 21 C.F.R. §§ 314.70(c)(6), (c)(6)(iii)(A). The motivation for additional warnings, which the regulation does not address, need not come from inside the pharmaceutical company in question or FDA prodding. In particular, that motivation may come from a failure-to-warn lawsuit or the threat of one.

Drug manufacturers have the best information about the safety of their products. The FDA does not conduct its own drug trials and "does not have sufficient authority to require additional clinical trials after drug approval." Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA*, 48 B.C. L. Rev. 1089, 1149 (2007). Thus, to avoid discouraging the party with the best safety information from

coming forward, 21 C.F.R. § 314.70 permits a manufacturer to alter a drug label before the FDA has evaluated and approved the change.

The defendants and the FDA do not cite even one example of the FDA punishing a drug manufacturer for over-warning. *See* Oral Argument Tr. 82, Dec. 10, 2007 (statement of FDA counsel that she was "not aware of any instance" in which the FDA "told a manufacturer who added an increased warning that that warning was unsubstantiated and caused the drug to be misbranded").[29] At oral argument, counsel for GlaxoSmithKline mentioned that, in 2004, the FDA required additional language in response to a strengthened warning by Wyeth Pharmaceuticals in a "changes being effected" supplement under 21 C.F.R. § 314.70. Merely requiring a clarification of or addition to warning language does not strike me as close to being close to a true conflict. On the contrary, the Wyeth example shows that the FDA typically engages in a back-and-forth discussion with drug manufacturers about warnings. In the event of a state tort lawsuit resulting in a warning that conflicted with the FDA's previous judgment, a commonplace dialogue between the manufacturer and the FDA could produce a warning complying with both federal regulations and state tort law.

B. Harmony Between Tort Law and FDA Regulation

Tort law and FDA regulation do not have conflicting

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[29] The majority opinion emphasizes a different fact: that the FDA, in response to citizen petitions and approvals of new uses for existing SSRIs, considered requiring a strengthened warning and declined. I agree that inaction of this kind is a form of agency action. But more important to me is that the FDA may never have sanctioned a drug manufacturer that strengthened a warning without prior FDA approval. This additional example of FDA inaction suggests that the conflict complained of is not an actual conflict.

goals. Both seek to strike a safety–efficacy balance. Under a negligence standard, most state courts balance the cost of care owed to a patient against the prospective harm. *See, e.g.*, *La Russa v. Four Points at Sheraton Hotel*, 821 A.2d 1168, 1173–74 (N.J. Super. Ct. 2003) (quoting Judge Learned Hand's formula from *United States v. Carroll Towing Co.*, 159 F.2d 169, 173, *reh'g denied*, 160 F.2d 482 (2d Cir.1947), which compares the cost of precautions with the expected loss); *cf.* Stephen G. Gilles, *On Determining Negligence: Hand Formula Balancing, The Reasonable Person Standard, and the Jury*, 54 Vand. L. Rev. 813, 816–22 (2001) (describing widespread use of, as well as complications in applying, the Hand formula).

Properly understood, the cost of additional warnings includes the consequences of over-warning that the defendants emphasize and that the FDA similarly takes into account.[30] In reaching its holding of conflict preemption, the majority focuses on the hypothetical scenario of differing (and presumably conflicting) results of the FDA regulatory process and state tort lawsuits. Because we are dealing with hypothetical situations, however, I would focus on the essential harmony of the standards applied by the FDA and state courts rather than the disharmony conjured about the results. Both institutions seek to balance safety and efficacy. If it turns out those results actually conflict, then it is time for Congress to step in or at least for the FDA to propose a rule followed by public comment before

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[30] Advocates of preemption in these cases point to the danger of "over-warning" and imply that over-warning will result from jury decisions biased toward plaintiffs. Br. of *Amicus Curiae* Product Liability Advisory Council, Inc. at 14–23. This argument assumes that juries do not understand that the cost of care, including the cost of taking too much care, is part of determining negligence. I presume, for the purposes of analyzing a hypothetical conflict between federal and state law, that state-court judges will properly instruct juries about the negligence standard.

proclaiming preemption.

Allowing multiple institutions to investigate the difficult question of how strong to make a warning can have important benefits. State courts provide a check on agency power. Our society relies on the FDA to an enormous degree to monitor the safety of pharmaceuticals. But the FDA's toolkit is imperfect and incomplete by design. The FDA relies on the information provided by drug manufacturers (to repeat, it does no independent testing), and will always lack the inside perspective on clinical trials and data analyses stemming from those trials. Moreover, the FDA is limited as to the additional clinical trials it may require post-approval, Davis, *supra*, at 1149 & n.444, and even "the reporting process for postapproval adverse reaction events . . . is too weak," *id.* at 1149 & n.443. Also, as they play their parts in the post-approval process the drug manufacturer and the FDA will not necessarily ask the right questions. The citizen-petition administrative process was used here unsuccessfully to seek an FDA requirement of stronger warnings for SSRIs. Discovery in state tort lawsuits provides a different way for third parties to raise questions about new and existing drugs. Given this context, I would not eliminate the potentially valuable information-gathering tools of state tort law.

To make all this real, I would point out that the regulatory process at the FDA, even if it allows for submission of citizen petitions, does not compensate the families of alleged victims like Lois Colacicco and Theodore DeAngelis. The availability of damages in state tort lawsuits can give injured citizens the incentive to come forward and share potentially valuable information. Even if an injury or death turns out not to have been caused by a drug or an insufficient warning, that information, too, can have social value. And the prospect of paying damages can sharpen drug manufacturers' incentives to place appropriate weight on safety as they strike the safety–efficacy balance. We should not lightly assume this

balance now preempted—and by a single recently adopted preamble at that.

C. Backdoor Federalization

The FDA's position in these cases is an instance of "backdoor federalization," a descriptive term commentators have recently used to describe a trend in the federal courts toward finding state law preempted. On the positive side, centralized federal control can facilitate uniform regulation of a national market (like that for pharmaceuticals) and prevent states from interfering with the affairs of other states. Samuel Issacharoff & Catherine M. Sharkey, *Backdoor Federalization*, 53 UCLA L. Rev. 1353 (2006).

Unfortunately, the trend toward federalization is not fully benign. While the FDA seeks to keep private plaintiffs out of state court (or federal court applying state law in diversity actions), a separate line of jurisprudence has limited private rights of action. There is a "troublesome" contrast in the way courts now tend to "grant agencies expansive discretion to interpret or declare the preemptive scope of the regulations they promulgate, whereas agencies are not given corresponding latitude to infer private rights of action under those same regulations." Catherine M. Sharkey, *Preemption by Preamble: Federal Agencies and the Federalization of Tort Law*, 56 DePaul L. Rev. 227, 258–59 (2007).

Although the FDA should have a strong voice in the debate among government institutions about preemption of state tort law, by executive order it must consult with state and local governments about the consequences of its regulations. *See id.* at 252–55 (citing Exec. Order No. 13,132, 64 Fed. Reg. 43,255, 43,257 (Aug. 10, 1999)). But nothing in the record suggests a dialogue between federal and state officials has occurred regarding preemption of failure-to-warn lawsuits.

I would interpret the absence of an express preemption statute, the text of the actual FDA regulations, and the late arrival of the FDA's statement on preemption in a preamble, as evidence that state tort law is not displaced. Tort lawsuits can generate useful information that the FDA can inject into its regulatory process. And tort damages can aid the FDA in aligning drug manufacturers' incentives to find the right balance between safety and efficacy. In any event, the choice to preempt state tort law is best left to Congress, should it wish to do so. In these cases, I do not see the kind of conflict that implies Congress has made that choice.

IV. Conclusion

The plaintiffs allege that SSRIs increase the risk of patients committing suicide. They further allege that the drug manufacturers knew or should have known this, but failed to label their products appropriately. The defendants would have us halt any inquiry into their alleged negligence before it starts. They contend that, in the area of drug labeling, state tort law renders compliance with federal provisions impossible, or at least stands as an obstacle to federal objectives.

The FDA, which relies on information provided by others, seeks to stop one avenue of information—that gathered from suits under state tort law theories. But should an earlier series of FDA decisions indicating that the previous warnings were adequate, when they might be inadequate, preclude the operation of state tort law? The majority suggests that the plaintiffs' claims border on claiming fraud on the FDA. But the underlying issue in these preemption cases is the structure of federal–state relations. We must decide whether the FDA will be the sole decision-maker. Without a clear statement from Congress or clear evidence that state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines v. Davidowitz*, 312 U.S. 52, 67

(1941), I am reluctant to say that the defendants' claim of a conflict has scaled the presumption against preemption.

A holding of no preemption in these cases would not suggest in any way that the defendant drug manufacturers should be liable for plaintiffs' injuries. Like my majority colleagues, I express no view regarding the relationship between SSRIs and adult suicide. Allowing the plaintiffs' cases to proceed beyond the motion-to-dismiss stage means instead that the state courts and federal district courts applying state tort law may evaluate—provide a check on—whether the FDA struck the right balance in the precautions and warnings it required for SSRIs.

To review the history of this issue, the FDA has for over three-quarters of a century viewed state tort law as complementary to its warning regulations. Only for the last two years has it claimed otherwise. This "sea change," Sharkey, *supra*, at 242, in the FDA's conception of the relationship between federal and state law has not appeared in a regulation subject to notice and comment, but in a preamble to a regulation. With this background, I believe courts should fear to tread where Congress has not given us a clear statement. Because I see sound legal and policy reasons to hold that the presumption against preemption is not overcome, I would allow the plaintiffs' suits to go forward. I respectfully dissent.