**NO. 06-3107**

**IN THE**

# United States Court of Appeals

**FOR THE THIRD CIRCUIT**

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JOSEPH C. COLACICCO,

*Appellant,*

v.

APOTEX, INC. AND GLAXOSMITHKLINE,

*Appellees.*

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On Appeal from the United States District Court
for the Eastern District of Pennsylvania

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## BRIEF OF AMICUS CURIAE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF APPELLEES SEEKING AFFIRMANCE

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Robert N. Weiner
Jeffrey L. Handwerker
Sarah M. Brackney
ARNOLD & PORTER LLP
555 Twelfth Street, NW
Washington, DC 20004
(202) 942-5000

*Counsel for Amicus Curiae Pharmaceutical Research and Manufacturers of America*

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## CORPORATE DISCLOSURE STATEMENT

In accordance with Federal Rule of Appellate Procedure 26.1 and Third Circuit Local Appellate Rule 26.1, Amicus Curiae Pharmaceutical Research and Manufacturers of America ("PhRMA") states that it is a trade association with no parent corporation and with no publicly held company owning 10 percent or more of its stock. PhRMA's member companies are listed below:

- 3M Pharmaceuticals
- Abbott
- Amgen Inc.
- Amylin Pharmaceuticals, Inc.
- Astellas US LLC
- AstraZeneca LP
- Bayer HealthCare - Pharmaceutical Division
- Berlex Laboratories, Inc.
- Boehringer Ingelheim Pharmaceuticals, Inc.
- Bristol-Myers Squibb Company
    - Bristol-Myers Squibb Company Worldwide Medicines Group
- Celgene Corporation
- Cephalon, Inc.
- Daiichi Sankyo, Inc.
- Genzyme Corporation
- GlaxoSmithKline
- Hoffmann-La Roche Inc.
- Johnson & Johnson
    - Advanced Sterilization Products
    - ALZA Corporation
    - Centocor, Inc.
    - Cordis Corporation
    - DePuy Inc.
    - Ethicon Endo-Surgery, Inc.
    - Ethicon Inc.

        - Ethicon Products
        - Gynecare
        - Johnson & Johnson Wound Management
    - Janssen Pharmaceutica Inc.
    - Janssen Research Foundation & R.W. Johnson Pharmaceutical Res. Institute
    - Johnson & Johnson Health Care Systems, Inc.
    - Mitek
    - Ortho Biotech Products, L.P.
    - Ortho-Clinical Diagnostics
    - Ortho-McNeil Pharmaceutical, Inc.
    - OrthoNeutrogena
    - Scios Inc.
    - Therakos, Inc.
    - VistaKon
- Eli Lilly and Company
- Merck & Co., Inc.
    - Merck Human Health Division - U.S. Human Health
    - Merck Research Laboratories
    - Merck Vaccine Division
- Millennium Pharmaceuticals, Inc.
- Novartis Corporation
- Organon USA Inc.
- Otsuka America, Inc.
    - Otsuka America Pharmaceutical, Inc.
    - Otsuka Maryland Research Institute, Inc.
- Pfizer Inc.
- The Proctor & Gamble Company
- Purdue Pharma L.P.
    - The P.F. Laboratories, Inc.
    - The Purdue Frederick Company
- sanofi-aventis U.S.
    - sanofi pasteur
    - sanofi-aventis
- Schering-Plough Corporation
- SCHWARZ PHARMA, INC.
- Sepracor, Inc.
- Serono, Inc.
- Solvay Pharmaceuticals, Inc.

    - Unimed Pharmaceuticals, Inc.
- Valeant Pharmaceuticals International
- Wyeth
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## STATEMENT OF AMICUS CURIAE

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is an association of the country's leading research-based pharmaceutical and biotechnology companies. PhRMA's member companies are devoted to inventing medicines that will allow patients to live longer, healthier, and more productive lives, and they have led the way in the search for new cures. PhRMA members alone invested an estimated $39.4 billion in 2005 in discovering and developing new medicines. PhRMA's mission is to advocate public policies that encourage the discovery of life-saving and life-enhancing new medicines for patients by pharmaceutical and biotechnology research companies.

PhRMA submits this brief in support of Appellees. The Court below properly determined that FDA regulation of pharmaceutical labeling preempts Appellant's state law claims. PhRMA can provide a valuable perspective on this issue. The association has long experience navigating the interrelationship of federal regulation and state law. PhRMA's member companies address daily the obligations and burdens imposed by federal regulation of the products they manufacture. They have confronted conflicting obligations under federal and state law and have been saddled with product liability claims that are at cross-purposes with FDA policies. PhRMA's members have a significant stake in ensuring the proper balance between federal and state interests in this area.

All parties have consented to the filing of this *amicus* brief.

## INTRODUCTION

In the Preamble to its new labeling rules, FDA affirmed that state courts may not require what FDA has forbidden or forbid what FDA has required. In attacking this unremarkable conclusion, Appellant and his *amici* misunderstand both the law of preemption and FDA's statements on the subject. It is not the Preamble that preempts state law. Rather, preemption arises because Appellant's claims conflict with FDA's exercise of the authority delegated by Congress to regulate the labeling of prescription drugs.

In considering whether federal regulations preempt state law, an important first step is to determine what the regulations mean. In the Preamble, FDA interpreted its regulations as imposing optimal, not minimal, safety standards and requiring FDA's approval for all but insignificant labeling changes. *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products ("Preamble"), 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). If FDA standards are not merely minimal, then state lawsuits like this one, seeking warnings FDA rejected, conflict with, rather than supplement, the Agency's regulation. Second, FDA assessed the impact of such discordant state lawsuits on its regulation of prescription drugs. The Agency concluded that these suits impede its efforts to fulfill the responsibilities assigned by Congress for the protection of public health. *See id.*

As a matter of common sense, we would customarily credit the novelist's explanation of her novel, the speaker's commentary on his speech, or the poet's interpretation of her poem. We likewise should credit FDA's interpretation of its

own regulations, issued to implement its statutory mandate. Common sense also dictates that we defer to FDA's assessment of what it needs in order to do its job and what gets in its way. The Supreme Court and this Court have followed this common sense approach, and the District Court did so here. It deferred to FDA's view that state law could not require a warning regarding suicide where the Agency six times had "rejected claims that adult use of [anti-depressants] was associated with increased suicidality because there was no reasonable evidence to support the linkage." *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 527 (E.D. Pa. 2006). The Court, therefore, properly dismissed Appellant's failure-to-warn claims.

## BACKGROUND: THE FDA PREAMBLE

Congress entrusted FDA with the responsibility to "protect the public health by ensuring that . . . drugs are safe and effective" and that product labeling is truthful and not misleading. *See* 21 U.S.C. §§ 393, 352, 355. FDA has fulfilled that responsibility by adopting careful, comprehensive, and complex regulations. Among other things, the regulations require the labeling of a prescription drug to include "any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.100(c)(1). The labeling regulations further require warnings of risks substantiated by reliable scientific evidence. *Id.* §§ 201.56(c), 201.57(c)-(e).

In the Preamble to its new regulation on prescription drug labeling, FDA described the existing labeling rules in detail. *See generally,* 71 Fed. Reg. 3922-3994. The Agency also discussed the process mandated by those rules to change the labeling. *Id.* at 3934. For substantive revisions, the manufacturer must submit a supplement to its approved new drug application explaining the basis for the proposed change. 21 C.F.R. §§ 314.70, 601.12(f). The regulations permit two kinds of labeling supplements: (1) Prior approval supplements, which require FDA approval before a change was made, and (2) "Changes Being Effected" or "CBE" supplements, which can be implemented after FDA is notified of, but before it formally approves, the change. *Id.* FDA explained in the Preamble that "*before* FDA approval" does not mean *without* FDA approval. 71 Fed. Reg. at 3934 (emphasis added). Rather, the Agency emphasized, FDA "reviews all such submissions and may later deny approval of the supplement, and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading." *Id.*

Having applied these regulations to the labeling of tens of thousands of prescription drug products, FDA was unequivocal that its labeling requirements do not establish minimum standards. To the contrary, FDA found, the Food, Drug and Cosmetic Act (FDCA) -- and hence the regulations implementing the Act -- "establish both a 'floor' and a 'ceiling'" *Id.* at 3935. As the Agency explained in its *amicus* brief below:

> Rather than set minimum standards for warnings in drug labeling, FDA seeks to encourage the optimal level of

> use in light of reasonable safety concerns, by requiring scientific evidence of an association between a drug and a particular hazard before warning of that association on a drug's labeling. *See* 21 C.F.R. § 201.57(e).[1]

Br. for *Amicus Curiae* The United States of America, *Colacicco v. Apotex, Inc.*, No. 05-CV-05500-MMB (E.D. Pa.), at 14 (filed May 10, 2006); *see Colacicco*, 432 F. Supp. 2d at 518 (defining issue as "whether regulations of a federal agency, promulgated pursuant to a federal statute, and implementing that statute" preempt state tort suit); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, No. M: 05-1699 CRB, 2006 WL 2374742, at *4 (N.D. Cal. Aug. 16, 2006) (considering FDA's view in the Preamble "of the preemptive effect of its labeling regulations").

FDA also disputed the predicate of the "minimum standards" argument -- the notion that the regulations afford manufacturers the unilateral right to add warnings without FDA approval. *See Bextra*, 2006 WL 2374742, at *4 ("The conclusion that FDA labeling requirements are merely minimum standards is based on the courts' assumption that FDA regulations permit a drug manufacturer to add warnings to its label without prior FDA approval."). In fact, FDA stated, its rules

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[1] Section 201.57(e) requires that labeling include a warning as soon as there is "*reasonable evidence* of an association of a serious hazard with a drug" (emphasis added) (version in effect to June 29, 2006). In its *amicus* brief in *Kallas v. Pfizer Inc*, No. 2:04-cv-00998-PGC (D. Utah), at 9-10 (Sept. 15, 2005), FDA interpreted this regulation to require a warning "where there is reasonable evidence that the drug may have a role in increasing the likelihood of the adverse event," a difficult determination where, as here, "the adverse event in question . . . is known to be a consequence of the disease being treated."

do *not* afford "latitude . . . to revise labeling" without the FDA's permission. 71 Fed. Reg. at 3934. The Agency was unequivocal that "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act." *Id.* In other words, given FDA's veto power, manufacturers -- as a matter of practice and practicality -- must seek the Agency's permission for any material change in drug labeling, even though the regulation allows some changes before FDA can exercise that veto. *Id.*

In addition to interpreting its regulations, FDA addressed its mission under the FDCA to ensure "that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading." *Id.* FDA reiterated that to fulfill this mission, it "carefully controls the content of labeling for a prescription drug," because the labeling is the Agency's "principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use." *Id.* In the Agency's view, state lawsuits challenging approved labeling "can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use." *Id.* at 3935.

## ARGUMENT

FDA in the Preamble provided a logical, coherent analysis of preemption. First, FDA set forth an interpretation of its regulations establishing that they are not minimal requirements and, therefore, can conflict with, rather than merely lay the groundwork for, state requirements. Second, FDA determined that state

lawsuits, like Appellant's, that do conflict with FDA requirements stand as an obstacle to FDA's objectives under the FDCA, resulting in preemption.

With regard to the first point, FDA has authority to promulgate regulations preempting state law. Its reasoned interpretation of its regulations merits substantial deference, including interpretations that result in preemption. FDA is in the best position to know what its own regulations mean. On the second point, FDA's determination that state lawsuits like this one stand as an obstacle to the achievement of its regulatory objectives likewise warrants deference. FDA is best situated to understand its own responsibilities and to know what impediments it has encountered in fulfilling them.

Although consistency is a value in administrative law, rigidity is not. The evolution of FDA's views on these issues reflects a responsible Agency monitoring and adapting to the changing environment it confronts. Indeed, the coherence of FDA's position over time reinforces the case for deference.

## I. FDA HAS AUTHORITY TO PROMULGATE REGULATIONS THAT RESULT IN PREEMPTION OF CONFLICTING STATE LAW

FDA has authority to issue regulations on prescription drug labeling, and those regulations can result in preemption of conflicting state laws. In *City of New York v. FCC*, 486 U.S. 57 (1988), the Supreme Court reaffirmed that the regulations of a federal agency, operating within the scope of its congressionally delegated authority, can preempt state law. The Court further held that where "state law is claimed to be pre-empted by federal regulation, a 'narrow focus on Congress' intent to supersede state law'" -- Appellant's focus here -- "'[is]

misdirected,' for '[a] pre-emptive regulation's force does not depend on express congressional authorization to displace state law.'" 486 U.S. at 64 (quoting *Fid. Fed. Savings & Loan Ass'n v. De la Cuesta,* 458 U.S. 141, 154 (1982)). Instead, the Court stated, "the correct focus is on the federal agency that seeks to displace state law and on the proper bounds of its lawful authority to undertake such action." *Id.* Although *City of New York* involved express preemption by regulation, the Court's directive to focus on what the agency intended encompasses implied preemption as well. Indeed, in the sentence following that directive, the Court specifically invoked the standards for implied preemption, noting that "[t]he statutorily authorized regulations of an agency will pre-empt any state or local law that conflicts with such regulations or frustrates the purposes thereof." *Id.* Thus, the threshold issue here is not whether Congress affirmatively intended that the FDCA preempt state law. It is, rather, whether FDA has statutory authority to regulate the labeling of prescription drugs in a manner that results in preemption of conflicting state requirements.

FDA does have such authority. Congress delegated to the Agency broad responsibility to "protect the public health" by ensuring that prescription drugs are safe and that the label contains appropriate "directions for use and cautionary statements." 21 U.S.C. § 353(b)(2). Among other things, FDA's labeling regulations require warnings that allow physicians to use the drug safely; specify the content, organization, and appearance of labeling; and fashion procedures for changing the labeling. *See* 21 C.F.R. §§ 201.100(c)(1); 201.56; 201.57; 314.70; 601.12. All these requirements fall within the "proper bounds" of FDA's

delegated authority and can preempt state law. *See Hillsborough County, Fla. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 713-18 (1985) (recognizing that FDA regulations could impliedly preempt state law if the Agency intends that they do so).

Appellant and his *amici* argue that the 1962 Amendments to the FDCA restrict FDA's delegated power and bar the Agency from preempting state law here. The argument ignores both the purpose and the language of the very provision they cite:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962). The legislative history shows that this proviso, in the words of its sponsor, merely codified Congressional intent "not to abolish *all State laws* on the same subject *where they are not in conflict* with the Federal law." 108 Cong. Rec. H21083 (daily ed. Sept. 27, 1962) (Rep. Smith) (emphasis added). Thus, while the statute may preclude an argument that federal law fully occupies the field, it plainly envisions preemption where state law conflicts with federal requirements, precisely the situation here.[2]

[2] The Supreme Court, in assessing implied preemption since 1962 has applied the same standards to cases arising under the FDCA as it applied to cases under other statutes. *See, e.g., Buckman v. Pls.' Legal Comm.*, 531 U.S. 341, 347-48 (2001); *Hillsborough*, 471 U.S. at 712-13.

## II. FDA'S INTERPRETATION OF ITS OWN REGULATIONS IS ENTITLED TO DEFERENCE

### A. FDA Can Best Interpret Its Own Regulations

As noted, in the Preamble and in *amicus* briefs filed across the country, FDA interpreted its labeling regulations to mandate the appropriate level of warnings -- warnings that allow doctors to "use the drug safely" -- not the minimum necessary to scrape by. 71 Fed. Reg. at 3935, 3949. In particular, FDA read its regulations as giving it control over prescription drug labeling and not affording manufacturers a unilateral right to make changes. *Id.* at 3934 ("In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act."). That interpretation raised the prospect that state law could in fact conflict with FDA labeling requirements.

Because FDA authors, construes, and enforces its regulations, its interpretation is authoritative. The Supreme Court has held repeatedly that an agency's interpretation of its own rules is "controlling unless plainly erroneous or inconsistent with the regulation." *Auer v. Robbins*, 519 U.S. 452, 461 (1996) (internal quotation marks omitted); *see also, e.g., Lyng v. Payne*, 476 U.S. 926, 939 (1986) ("[A]n agency's construction of its own regulations is entitled to substantial deference."); *Martin v. OSHRC*, 499 U.S. 144, 111 S. Ct. 1171, 1176 (1991) ("[T]he power authoritatively to interpret its own regulations is a component of the agency's delegated lawmaking powers."); *Thomas Jefferson Univ. v. Shalala.*, 512 U.S. 504, 512 (1994) (court must defer to Secretary's interpretation of her regulation unless an alternative reading is "compelled" by its language or history).

Indeed, in *Udall v. Tallman,* 380 U.S. 1, 16 (1965), the Court recognized that "[w]hen the construction of an administrative regulation rather than a statute is in issue, deference is even more clearly in order."[3]

These principles apply with particular force here, where the Agency's rules and the matters it regulates are complicated and call upon specialized expertise. *See Thomas Jefferson Univ.*, 512 U.S. at 512 ("This broad deference is all the more warranted when, as here, the regulation concerns a complex and highly technical regulatory program, in which the identification and classification of relevant criteria necessarily require significant expertise and entail the exercise of judgment grounded in policy concerns." (internal quotations omitted)); *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000) ("Congress has delegated to DOT authority to implement the statute; the subject matter is technical; and the relevant history and background are complex and extensive. The agency is likely to have a thorough understanding of its own regulation and its objectives and is 'uniquely qualified' to comprehend the likely impact of state requirements."). FDA's regulations cover hundreds pages in the Code of Federal Regulations. They are detailed, complicated, and scientifically rigorous. FDA has issued more than 100 guidance documents interpreting its regulations and policies on prescription drugs.

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[3] *Gonzales v. Oregon*, 126 S. Ct. 904 (2006), is not to the contrary. The Court held there that deference under *Auer v. Robbins* did not apply where the regulation at issue merely lifted the words of the statute. In the Court's view, "[a]n agency does not acquire special authority to interpret its own words when, instead of using its expertise and experience to formulate a regulation, it has elected merely to paraphrase the statutory language." 126 S. Ct. at 916. By no stretch of reality can that be said of FDA's labeling regulations.

The Agency provides further explanation of its requirements in Compliance Policy Guides,[4] Regulatory Procedures Manual,[5] letters, speeches, and the innumerable daily interactions that comprise administrative practice. A court that permits state law to override FDA's interpretation of its regulations cannot fully anticipate the ripple effects of its decision through the entire regulatory structure.

### B. FDA's Interpretation Is Consistent with the Language of Its Regulations

Appellant and his *amici* claim that deference is unwarranted here because FDA's interpretations conflict with the language of its regulations. To the contrary, the regulations are consistent with FDA's conclusions that it closely controls the labeling of prescription drugs, that it imposes optimal not minimum standards, and that manufacturers cannot change labeling without FDA approval.

FDA requires that drug labeling include "relevant hazards, contraindications, side effects, and precautions" to enable practitioners to "use the drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.100(c)(1). FDA also requires a warning as soon as "there is reasonable evidence of an association of a serious hazard with a drug." *Id.* § 201.57(e) (prior version). Nothing in this language refers to, much less mandates, minimum standards. And nothing bars FDA from determining that over-warning hinders rather than helps practitioners "use the drug safely." Rather, the reference in the regulation to "reasonable

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[4] *See, e.g.*, Sec. 140.100 Seizure of Books that Constitute Misleading Labeling (CPG 7153.13 (revised Aug. 31, 1989)).

[5] *See* FDA, Regulatory Procedures Manual (Mar. 2004).

evidence of an association" supports FDA's interpretation that parties cannot warn of unsubstantiated hazards. In fact, it is a fair question why an agency charged with protecting the public health would not use its expert judgment to promulgate safety standards that strike the best balance of contending factors.

Similarly, the provision that the Court below identified as the linchpin of the "minimum standards" argument, 21 C.F.R. § 314.70(c), is a narrow exception to the requirement that labeling changes be approved in advance, intended to allow rapid response to urgent new information. What Appellants ignore, however, is that this regulation allows FDA to disapprove a labeling change made without advance approval. The title of the section is "Supplements for changes that may be made *before* FDA approval."[6] The word "before" contemplates that FDA approval or disapproval will follow, not, as Appellant and his *amici* suggest, that FDA's concurrence is unnecessary. Indeed, the very structure of the regulation, dealing with "supplements" to "New Drug Applications" by "applicants," conveys a process in which FDA's permission is sought. Nothing in the language of the regulation conflicts with FDA's conclusion in the Preamble that its veto power, even absent advance approval, affords the Agency practical control over all labeling changes. 71 Fed. Reg. at 3934. *Cf.* 21 U.S.C. § 355(e)(3) (empowering FDA to withdraw NDA absent "substantial evidence that the drug will have the effect it purports or is represented to have").

[6] This citation is to the prior version of the regulation, which was in effect in October 2003.

*Amici* Giles and Dobbs unwittingly substantiate this point. Arguing that drug companies can unilaterally add warnings, they cite the change Wyeth implemented in August 2003, without advance FDA approval, to address pediatric suicide in the labeling for the anti-depressant Effexor. But Giles and Dobbs do not inform the Court that FDA *rejected* that change and directed Wyeth to delete it. In March 2004, FDA told Wyeth, "Because we do not believe that a causal association [with suicidality] has been definitively established, we do not agree with the labeling changes proposed in your August 8, 2003 submission." Letter from Russell Katz, FDA, to Wyeth, March 19, 2004 (attached as Ex. A).[7] FDA warned that if Wyeth was not prepared to make this and other changes, the Agency could "proceed to withdraw these supplemental applications." *Id.* Wyeth acceded, and FDA in response reiterated its view that "it would not be helpful" to include the language Wyeth had proposed regarding "reports of hostility and suicidality." Letter from Russell Katz, FDA, to Wyeth, May 13, 2004 (attached as Ex. B). FDA's responses demonstrate concretely that manufacturers do not have free rein to change the labeling of prescription drugs and that only FDA has authority to determine whether revisions to the labeling are appropriate. They also confirm that the warnings for which plaintiffs argue here directly conflict with the FDA's labeling decision, and thus are preempted.

[7] If the Court considers the argument of *amicus* Vickery that Wyeth used a CBE to change the labeling for Effexor, then -- in the interest of completeness -- the Court should consider FDA's response. In doing so, the Court may take judicial notice of these government records. *See Kos Pharm., Inc. v. Andrx Corp.*, 369 F.3d 700, 705 n.5 (3d Cir. 2004).

## III. THE COURT SHOULD DEFER TO FDA'S DETERMINATION THAT STATE LAWSUITS INTERFERE WITH THE ACHIEVEMENT OF ITS OBJECTIVES

Having interpreted its regulations as imposing optimal not minimal requirements, FDA also assessed whether state lawsuits imposing standards in conflict with those requirements pose an obstacle to the accomplishment of the objectives of Congress. 71 Fed. Reg. at 3935. The Agency concluded that such lawsuits do interfere with its responsibilities. As noted, FDA made clear that it "carefully controls the content of labeling" as the "centerpiece of risk management for prescription drugs." *Id.* In fact, FDA's statement that it "carefully controls" labeling does not capture the exhaustive particularity of its efforts. FDA assigns teams to review each new drug, including:

- chemists, who focus on whether the manufacturing, controls, and packaging are adequate to ensure the identity, strength, quality, and purity of the product;
- pharmacologists and toxicologists, who evaluate the effects of the drug on laboratory animals in the various short and long term studies;
- statisticians, who assess the design and results of each controlled study; and
- clinical pharmacologists and biopharmaceutical experts, who examine the relationship between drug dose and response, as well as the rate and extent to which the drug's active ingredient is distributed in the body, metabolized, and eliminated. [8]

[8] CDER, *2004 Report to the Nation: Improving Public Health Through Human Drugs* (2004 CDER Report) at 34; *see also* CDER, *2001 Report to the Nation: Improving Public Health Through Human Drugs*, at 24.

These team members, along with physicians and other regulatory officials, review the proposed labeling to ensure that it appropriately communicates the relevant information. Their decisions are vetted through advisory committees of recognized experts, established to "advise the Commissioner generally on the safety and effectiveness, including the labeling and advertising, and regulatory control" of prescription drugs.[9] Ultimately, FDA develops the labeling with the manufacturer word by word, and in approving the drug, insists that the labeling be "identical" to the approved version. Particularly given this intense regulatory focus, FDA is well-situated to determine whether state lawsuits requiring different language -- in this case, language the Agency disapproved -- interfere with its regulatory objectives.

The Supreme Court, again, has recognized this point and deferred to FDA's judgment on preemption. In *Hillsborough,* the Court considered whether FDA had impliedly preempted the regulation of blood transfusions when it issued rules on the subject. In the preamble to the rules, FDA had expressly noted that it did not intend to displace state law. The Supreme Court found that "FDA's statement is dispositive on the question of implicit intent to pre-empt unless either the agency's position is inconsistent with clearly expressed congressional intent, or subsequent developments reveal a change in that position." 471 U.S. at 714-15 (citation omitted). Appellant and his *amici*, citing the presumption against preemption,

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[9] Carol Rados, "Advisory Committees: Critical to the FDA's Product Review Process: FDA Consumer (Jan.-Feb. 2004), available at www.fda.gov/fdac/features/2004/104_adv.html; *see* 21 C.F.R. § 14.160(a).

claim that the Court in *Hillsborough* deferred to FDA only because the Agency decided not to preempt state law. But, in fact, the Court did not take such a result-oriented approach. In finding FDA's view determinative, the Court cited *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-845 (1984), the leading case on deference to agencies' interpretation of statutes they enforce. The Court did not invoke any presumption in discussing deference to FDA. Indeed, the Court dealt with the presumption independently, describing it as a "second obstacle in appellee's path." *Id.*

*Amicus* Public Citizen brushes *Hillsborough* aside with the assertion that the preamble there -- accompanying regulations on blood centers -- was within FDA's delegated authority to regulate blood centers. Public Citizen argues that by contrast the Preamble here -- accompanying regulations on prescription drug labeling -- addresses tort suits, a subject purportedly beyond FDA's delegated authority. The asymmetry of this comparison is obvious. FDA in the Preamble to the labeling rule addressed the regulation of prescription drug labeling, just as the FDA in *Hillsborough* addressed the regulation of blood. The discussion of preemption in the Preamble here responded to comments solicited by the Notice of Proposed Rulemaking regarding the product liability impact of the change. Moreover, the suggestion that the discussion of preemption in the Preamble here was beyond FDA's delegated powers highlights a fundamental misconception. The Preamble does not preempt state lawsuits. Rather, *FDA regulation* of prescription drug labeling preempts state lawsuits that conflict with the Agency's exercise of its authority. *All the Preamble does is point out the conflict.* If Public

Citizen were correct, FDA would have to stand mute no matter what obstacle state laws posed to its regulatory functions. Courts have not required such passivity. At least since *Hillsborough,* courts have affirmed repeatedly that the agencies are best situated to identify that obstruction. *See, e.g., Bextra*, 2006 WL 2374742, at *7 ("Congress has delegated the responsibility for administering the FDCA to the FDA; such responsibility implies the authority and expertise to determine which state laws conflict with its regulations."). Thus, in *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996), the Supreme Court reiterated the common sense proposition underlying *Hillsborough* -- that FDA not only has the authority to gauge the preemptive scope of its regulations, but in fact "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 preempted." 518 U.S. at 496 (citation omitted). *Accord, Horn v. Thoratec*, 376 F.3d 163, 171 (3d Cir. 2004) ("FDA's preemption determinations are significant and should inform our interpretation" of Medical Device Amendments).

Appellant's suggestion that this deference is warranted only as to express preemption finds no support in logic or precedent. Logically, the question whether state law obstructs an agency in fulfilling its regulatory mission turns first on the level of interference, and second, on the agency's legislative mandate. Express preemption provisions need not address either, but instead may specify whatever criteria for preemption Congress chooses. As for precedent, *Geier* precludes Appellant's argument. *Geier* involved implied preemption, and the Court echoed

its conclusion in *Medtronic* that a federal agency "is likely to have a thorough understanding of its own regulation and its objectives and is 'uniquely qualified' to comprehend the likely impact of state requirements." *Geier*, 529 U.S. at 883.

Finally, Appellant and his *amici* imply that the Court should not defer to FDA's view of preemption because of various reports suggesting deficiencies and needed improvements in FDA's regulation of drug safety. However, because deference arises from "a sensitivity to the proper roles of the political and judicial branches," *Pauley v. BethEnergy Mines, Inc.*, 501 U.S. 680, 696 (1991), it cannot turn on whether the Court thinks the Agency is doing a good job. Moreover, even assuming the reports were correct that FDA is understaffed and ineffectual, the solution would not be to allow state tort suits that, by FDA's own assessment, obstruct the Agency in performing its assigned role. Indeed, nothing in the cited reports suggests that state tort litigation is a solution to FDA's problems, particularly state litigation that, as here, seeks to impose requirements in conflict with FDA's.

## IV. FDA'S INTERPRETATION OF ITS RULES AND ITS ASSESSMENT OF PREEMPTION HAVE BEEN CONSISTENT

Despite this authority, Appellant and his *amici* contend that FDA's views on preemption merit no respect because they have been inconsistent. In particular, Appellant points to the December 2000 Notice of Proposed Rulemaking for the labeling rule, where the Agency stated that "this proposed rule does not preempt State law." 65 Fed. Reg. 81081, 81103 (Dec. 22, 2000). This argument raises two questions. The first is whether this and other FDA statements are consistent with

FDA's interpretation of its regulations, as set out in the Preamble. They are. FDA has not proffered differing interpretations of its regulations. The second is whether this and other FDA statements are consistent with its finding in the Preamble that state tort suits at odds with FDA requirements interfere with the Agency's regulatory objectives. The answer is that FDA appropriately reached a different overall conclusion in the Preamble than it reached in 2000, based on different facts and circumstances.

### A. FDA Has Been Consistent in Interpreting its Regulations

FDA's general statement in 2000 disclaiming preemption does not purport to interpret the labeling regulations, and in particular, does not characterize them as minimal. Indeed, there is no evidence that FDA even focused on the issue. Nor do Appellant and his *amici* identify any prior statements by FDA interpreting its regulation of the warnings in package inserts for prescription drugs as imposing minimal rather than optimal standards. The one statement they cite on this subject is beside the point. It comes from the preamble to regulations governing "Medication Guides" that are provided directly to patients for certain products. The question arose whether mandating dissemination of such Medication Guides to patients would undermine the learned intermediary defense, which allows drug manufacturers to warn doctors rather than patients. Comments to FDA's proposed rule on this subject urged preemption of state tort claims because otherwise the new rule "would encourage 'failure to warn' claims and challenges to the adequacy of patient labeling, especially compared to the professional labeling." 63 Fed. Reg. 66377, 66383 (Dec. 1, 1998). FDA rejected requests to preempt state law in this

context for several reasons, but in particular because of the specific role it believed federal law accorded states with regard to patient labeling:

> Federal preemption could unduly interfere with the goals and objectives of existing State programs imposed under the Omnibus Budget Reconciliation Act (OBRA) of 1990, which requires that pharmacists offer to counsel Medicaid patients about their prescription drugs. Many States have extended this requirement to all patients who receive prescription drugs, and some States have required that patients receive written medication information. This final rule is intended to complement these State efforts, not replace or hinder them.

*Id.* at 66384. The same considerations do not apply to labeling provided to physicians. Thus, when FDA made the statement Appellant trumpets -- that its "regulations establish the minimal standards necessary, but were not intended to preclude the states from imposing additional labeling requirements" -- the Agency was not speaking of regulations governing the professional labeling at issue here.

Appellant and his *amici* likewise cite no statements by FDA contradicting its conclusion in the Preamble that the decision whether to allow labeling revisions is "squarely and solely FDA's." 71 Fed. Reg. at 3924. Indeed, when it promulgated its labeling regulations in 1979, FDA advanced virtually the same interpretation, stating that "the decision as to whether a warning is legally required for the labeling of a drug must rest with the agency." 44 Fed. Reg. 37434, 37447 (June 26, 1979). Contrary to Appellant's claim, FDA's recent draft guidance on public availability of changes in "Changes Being Effected" Supplements is also consistent with these conclusions. *See* Guidance for Industry: Public Availability of Labeling

Changes in "Changes Being Effected" Supplements (draft Sept. 2006). FDA explained that its decision to make CBE changes public before the Agency approves them:

> should not be construed an endorsement of the revised labeling by the FDA. . . . [A]fter revised labeling is submitted, the FDA carefully reviews the proposed change and then either approves it or sends a letter identifying the deficiencies with the proposed change. Of particular note, the Agency will not permit a labeling change that would misbrand the product.

*Id.* at 1 n.2. Further, FDA reiterated that it "would not allow a change to labeling to add a warning in the absence of reasonable evidence of an association between the product and an adverse event." *Id.* at 2 n.4. This precisely describes the course FDA chose in reviewing and subsequently rejecting Wyeth's August 2003 labeling change for Effexor reporting on an increased risk of suicidality in pediatric patients. *See* p. 14, *supra.*

In short, Appellant and his *amici* cannot evade either the logic or the case law mandating deference to FDA's construction of its own regulations.

### B. FDA Has Consistently Voiced Concern for at Least Five Years that State Tort Suits Interfere with Its Regulatory Duties

As noted, after concluding that its regulations imposed optimal standards, FDA also took the next step to find that state requirements conflicting with those standards interfere with the Agency's authority and thus are preempted. Although that conclusion is different from FDA's statement in 2000, the divergence is entirely appropriate.

Appellant's exaltation of consistency in administrative law improperly conflates different types of agency decisions. To be sure, the rule of law requires that like cases be treated alike and that existing policies be applied evenly. Moreover, where an agency changes its interpretation of unchanged statutory language, courts may consider that inconsistency in gauging the appropriate level of deference afforded the Agency's construction. But where, as here, the Agency's task is to evaluate the effects over time of external factors on the regulatory environment -- specifically, whether state requirements interfere with its statutory mandate -- the standard of consistency cannot be the same. Persistent vacillation or wild swings in the Agency's assessment could undermine its claim to judicial deference. But we would expect that for this type of fact-based appraisal, the Agency's views would evolve over time. Indeed, the Supreme Court in *Hillsborough* articulated just such an expectation. The Court suggested there that the Agency should continually assess whether its initial determination not to preempt state law remained sound. In fact, the Court saw such responsive flexibility as a crucial attribute for an administrative agency:

> [T]he agency can be expected to monitor, on a continuing basis, the effects on the federal program of local requirements. . . . Congress, unlike an agency, normally does not follow, years after the enactment of federal legislation, the effects of external factors on the goals that the federal legislation sought to promote. Moreover, it is more difficult for Congress to make its intentions known -- for example by amending a statute -- than it is for an agency to amend its regulations or to otherwise indicate its position.

471 U.S. at 721.

In this case, the Agency did not vacillate. There were no wild swings in its views. The last "inconsistent" statement on preemption that Appellant and his *amici* cite is in the notice of proposed rulemaking on the labeling rules, issued in December 2000. Since then, FDA did just what the Supreme Court expected. It monitored the effects of local requirements and found ample justification to modify its assessment regarding preemption. The Preamble specifically noted one critical changed circumstance:

> Since the proposed rule was published, FDA has learned of several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act.

71 Fed. Reg. at 3934. FDA cited a number of such lawsuits, including two involving efforts, as in this case, to displace FDA's judgments regarding the labeling of antidepressants. *Id.* at 3934 n.7. FDA had already expressed concern in the Notice of Proposed Rulemaking regarding the impact of state tort suits. 65 Fed. Reg. at 81103. Learning of these additional threats since that time could appropriately magnify FDA's apprehension about "State-law attempts to impose additional warnings [leading] to labeling that does not accurately portray a product's risks" and threatening "FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs." 71 Fed. Reg. at 3935.

Second, as noted, in the Notice of Proposed Rulemaking, FDA requested comments on the product liability implications of the changes it proposed to simplify the labeling. In the Preamble, FDA addressed the comments it received:

> Some comments stated that the new format requirements might have product liability implications for drugs that are not subject to the new requirements. These comments expressed concern that labeling in the old format might be characterized by plaintiffs as inferior to labeling in the new format and, as a result, could be used as evidence that a manufacturer did not provide adequate warnings. They requested that the agency state in the final rule that FDA approval of labeling, whether it be in the old or new format, preempts conflicting or contrary State law, regulations, or decisions of a court of law for purposes of product liability litigation.

*Id.* at 3933-3934. FDA was obligated to consider and address those comments. 5 U.S.C. § 553(c). If, in doing so, the Agency were not permitted to refine or modify its position, then the notice and comment process would be of little value.

Third, beginning before 2000, but more extensively thereafter, FDA has focused with increasing sophistication on risk management for prescription drugs and in particular on the science of risk communication. FDA initiated an advisory committee on risk management in 2002. In 2005, the Agency held a two day conference on "FDA's Communication of Drug Safety Information." At the outset of the conference, the Deputy Commissioner of FDA highlighted FDA's growing expertise and focus:

> At FDA, the task of measuring consumer perception and people's reaction to information and using the scientific information to more finely tune how we speak is becoming a more important part of our work. As the

> amount and complexity of information that we provide continues to mount, a result not only of our desire to speak more openly, but also the increasing complexity of medicine and science itself, we know that we also need to continue to improve how we approach the social sciences of risk communication and the social sciences of measuring consumer perceptions of information.[10]

The Deputy Commissioner recounted FDA's evolving perspective on this issue as recently as September 26, 2006. He observed that the increasing complexity of FDA's work:

> challenges us to find ways to communicate that carefully calibrates the language and the tools we use to speak to the level of risk that we perceive a particular product or piece of information poses. Over warning about risk can be as dangerous as under warning, by discouraging the safe use of medical products that we know have proven benefits.[11]

Just as a scholar's understanding of his or her discipline deepens with study, FDA's approach to risk communication has matured over time. As it learned more, the Agency quite properly could refine its assessment of the impact of state law suits on such communications and escalate its concern about over-warning. To be sure, Appellant and his *amici* deride that concern. Indeed, they dismiss the very concept of over-warning. But they do not have to shoulder the burden of protecting the overall public health. That responsibility falls to FDA.

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[10] http://www.fda.gov/cder/meeting/RiskComm2005/1208fda.pdf, at p. 10-11Dec. 8, 2005, .

[11] Remarks of Dr. Scott Gottlieb, Sept. 26, 2006, at http://www.fda.gov/oc/speeches/2006/CDRH0926.html.

## CONCLUSION

In this case, Appellant claims that the Defendant drug manufacturers should have provided a warning FDA rejected as unsubstantiated and misleading. The District Court properly found that such a claim conflicts with FDA's regulation of prescription drug labeling and therefore is preempted.

In challenging that conclusion, Appellant and his *amici* claim to know better than FDA what FDA's regulations mean and what impedes FDA's work. Congress, however, did not delegate the enforcement of the FDCA to litigants or to courts. That is FDA's mission. There is no basis to second-guess the Agency's reasoned judgments as it seeks to fulfill its statutory mandate.

The District Court's judgment should be affirmed.

Respectfully submitted,

/s/ Robert N. Weiner

Robert N. Weiner
Jeffrey L. Handwerker
Sarah M. Brackney
ARNOLD & PORTER LLP
555 Twelfth Street, N.W.
Washington, DC 20004
(202) 942-5000

*Attorneys for Amicus Curiae Pharmaceutical Research and Manufacturers of America*

December 4, 2006

**CERTIFICATE OF BAR MEMBERSHIP**

Pursuant to Third Circuit Local Appellate Rule 28.3(d), the undersigned hereby certify that they are members of the bar of the United States Court of Appeals for the Third Circuit.

By:

/s/ Robert N. Weiner
Robert N. Weiner

/s/ Jeffrey L. Handwerker
Jeffrey L. Handwerker

*Attorneys for Amicus Curiae*
*Pharmaceutical Research and*
*Manufacturers of America*

## CERTIFICATION PURSUANT TO RULE 32(A)(7)(C)

The undersigned counsel hereby certifies that this brief complies with the type-volume limitation set forth in Federal Rule of Appellate Procedure 32(a)(7)(B). This certification is based upon the word count of the processing system used to prepare this brief. The number of words contained in this brief, excluding the parts of the brief exempted by Rule 32(a)(7)(B)(iii), is 6,910, according to that word processing system.

By:

/s/ Sarah M. Brackney

Sarah M. Brackney

*Attorney for Amicus Curiae Pharmaceutical Research and Manufacturers of America*

**CERTIFICATION PURSUANT TO LOCAL RULE 31.1(C)**

The undersigned counsel hereby certifies that the text of the electronic brief is identical to the text in the paper copies. The undersigned counsel also certifies that a virus check was performed using McAfee Virus Scan Enterprise + Anti-Spyware Module, version 8.0.0, and that no virus was detected.

By:

/s/ Sarah M. Brackney
Sarah M. Brackney

*Attorney for Amicus Curiae Pharmaceutical Research and Manufacturers of America*

## CERTIFICATE OF SERVICE

I, Sarah M. Brackney, hereby certify that two true and correct copies of the foregoing Brief of *Amicus Curiae* Pharmaceutical Research and Manufacturers of America in Support of Appellees Seeking Affirmance were served this 4th day of December, 2006, upon the following, by Federal Express. Ten true and correct copies were dispatched to the Clerk's Office by Federal Express.

Harris L. Pogust
Derek T. Braslow
T. Matthew Leckman
Pogust & Braslow
161 Washington Street
Suite 1520
Conshohocken, PA 19428

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

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

Joseph K. Hetrick
David J. Stanoch
Joshua G. Schiller
Dechert
2929 Arch Street
18th Floor, Cira Centre
Philadephia, PA 19104

Allison Zieve
Public Citizen Litigation Group
1600 20th Street, NW
Washington, DC 20009

Shanin Specter
David J. Caputo
Kline & Specter
1525 Locust Street
19th Floor
Philadelphia, PA 19102

Fred S. Longer
Arnold Levin
Matthew C. Gaughan
Levin, Fishbein, Sedran & Berman
510 Walnut Street
Philadelphia, PA 19106

By:

/s/ Sarah M. Brackney

Sarah M. Brackney

*Attorney for Amicus Curiae Pharmaceutical Research and Manufacturers of America*