S168109

In the

Supreme Court

of the

State of California

CARLYNE McKENNEY,

Plaintiff-Appellant,

v.

PUREPAC PHARMACEUTICAL COMPANY,

Defendant-Respondent.

CALIFORNIA COURT OF APPEAL · FIFTH APPELLATE DISTRICT · NO. F052606
SUPERIOR COURT OF STANISLAUS COUNTY · HON. WILLIAM A. MAYHEW · 343927

ANSWER TO PETITION FOR REVIEW

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I. Issue Presented

Plaintiff Carlyne McKenney maintains that she suffered injuries from use of a prescription generic drug manufactured and sold by defendant Purepac Pharmaceuticals Company. Specifically, she alleges that Purepac failed adequately to warn her of the true association between the drug and her injuries, and that such failure breached a duty under California law, entitling her to an award of damages.

The issue presented is—

Should this Court grant review to consider whether the federal Food and Drug Administration's approval of the labeling for Purepac's drug impliedly preempts Ms. McKenney's state-law claims for damages where

(a) no state or federal appellate court has ever adopted the position advanced by Purepac; and

(b) applicable FDA regulations state that

(i) all prescription drug "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"; and

(ii) all prescription drug manufacturers may, without prior FDA approval, revise an existing drug label "to add or strengthen a contraindication, warning, precaution, or adverse reaction"?

II. Facts and Procedural Background

Plaintiff Carlyne McKenney maintains that she contracted tardive dyskinesia, a severe neurological condition, from overexposure to metoclopramide, a drug manufactured and sold by Purepac. Purepac's product is a generic, medically equivalent version of the name-brand prescription drug Reglan. Specifically, Ms. McKenney claims that Purepac's failure to provide adequate warnings of the true association between metoclopramide and tardive dyskinesia violated California tort

duties. Purepac maintains that Ms. McKenney's claims are preempted by federal law because the label containing the allegedly inadequate warnings was approved by the federal Food and Drug Administration.

The trial court sustained Purepac's demurrer to Ms. McKenney's Fourth Amended Complaint, ruling that federal law preempts her claims under California law. The Court of Appeal reversed, holding that Ms. McKenney's claims do not conflict with, and in fact are consistent with, federal law, and therefore are not preempted. Purepac has now sought review in this Court.

III. Introduction

Purepac's petition for review should be denied because it fails to meet the criteria for review set forth in Rule of Court 8.500(b)(1). Far from evidencing a division among the courts of this state, the Court of Appeal's decision is consistent with all appellate authority regarding whether a state-law failure-to-warn claim seeking damages arising from injuries from a prescription drug are preempted by federal law. As this Court has noted, "numerous courts have concluded [that] Congress evinced no intention of preempting state tort liability for injuries from prescription drugs." *Carlin v. Superior Court* (1996) 13 Cal. 4th 1104, 1113 (citing cases). Indeed, *no appellate decision, state or federal, in the history of American law has agreed with the position advanced by Purepac in its petition for review*: that the federal regulatory scheme for generic prescription drugs preempts a state-law claim for damages arising from an inadequate warning provided on the label of a generic drug.

Purepac does not argue otherwise. Instead, it asserts only that the decision below is wrong on its merits. Even if Purepac were correct, that would not be a reason to grant the petition under the circumstances presented here. To the contrary, in the 70 years since enactment of the

federal Food, Drug, and Cosmetic Act, federal drug regulation and state-law damages liability, against both name-brand and generic manufacturers, have co-existed, with each serving their distinct but complementary purposes and neither interfering with the other—and with the judiciary allowing both schemes to operate.

Put another way, if Purepac's view of the merits were correct, at some point, a serious division among the state's lower courts would develop, in which case this Court's intervention would be appropriate. At this juncture, however, review should be denied, and this case should be allowed to run its course.

But Purepac's view on the merits is not correct, and its petition therefore warrants a response, lest the Court be left with an inaccurate and incomplete discussion of the federal preemption issue. To explain why Purepac's position is wrong, it is necessary, first, to discuss relevant federal drug regulation. Thereafter, we show why Ms. McKenney's claims are not preempted.

IV. Relevant Federal Drug Regulation

A. Marketing Approval

Purepac markets generic metoclopramide, which is a "new drug" under the Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.* *See* 21 U.S.C. § 321(p) (defining "new drug"). The FDCA forbids the distribution of any new drug unless an application to market the drug has been approved by the Food and Drug Administration (FDA). *Id.* § 355.

The FDCA authorizes marketing approval for prescription drugs through two basic pathways. The first, a New Drug Application (NDA), involves a request to FDA by a name-brand manufacturer for permission to market a prescription drug for the first time. *Id.* § 355(a). FDA must approve the NDA unless the proposed new drug fails to meet certain

criteria, including (a) whether clinical testing data and other information show that the drug is safe and effective "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" and (b) whether, 'based on a fair evaluation of all material facts, such labeling is [not] false or misleading in any particular." *Id.* § 355(d).

The second pathway to marketing approval is the Abbreviated New Drug Application (ANDA) established by the 1984 Hatch-Waxman Amendments to the FDCA, Pub. L. No. 98-417, 98 Stat. 1585, which sought to speed generic drugs to market. Under Hatch-Waxman, after a name-brand drug loses patent protection, a manufacturer may file an ANDA, seeking FDA approval to market a generic version of the name-brand drug. *See* 21 U.S.C. § 355(j). A generic manufacturer need not submit independent evidence of the drug's safety and efficacy, but need only establish the generic product's "bioequivalence" to the name-brand drug. *See id.* § 355(j)(8)(B) (defining bioequivalence); 21 C.F.R. § 320.1(e) (same).

B. Generic Drug Labeling

A generic drug's initial labeling must be the same as the labeling for its name-brand equivalent. 21 U.S.C. § 355(j)(2)(A)(v). After FDA approves the ANDA, the generic drug manufacturer is subject to most of the same statutory and regulatory obligations as the name-brand manufacturer, including the obligation to keep its label current, lest its product be deemed misbranded. *Id.* § 352(a); *see also id.* §§ 355(j)(2)(A)(iii)-(iv), (j)(4); 21 C.F.R. §§ 314.105(d), 314.127. Once any new drug—name-brand or generic—is approved by FDA, it generally must be labeled in the approved form. *See id.* § 314.70(b)(2)(v).

Critically, however, the content of an approved drug's label is not set in stone. Indeed, a manufacturer is *required* to amend its labeling in certain

circumstances. FDA regulations provide that approved drug "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.* § 201.80(e) (emphasis added). Necessary label changes are generally made through a "supplement" submitted by the manufacturer to FDA. *See generally id.* §§ 314.70, 314.71, 314.90. And, importantly, manufacturers are permitted to amend their labels, without prior FDA approval, "to add or strengthen a contraindication, warning, precaution, or adverse reaction; [and to] add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product[.]" *Id.* § 314.70(c)(6)(iii)(A), (C);[1] *see also* 44 Fed. Reg. 37434, 37447 (1979) (revised warnings may be made by various means, including label changes and "Dear Doctor" letters). Thus, a manufacturer may revise a label to warn about hazards not on the current label, and, indeed, a manufacturer *must* attempt to do so whenever reasonable evidence exists of an association between a drug and a serious hazard. *See* 21 C.F.R. § 201.80(e). Thus, here, Purepac could have warned of the true association between metoclopramide and tardive dyskinesia without running afoul of, and, indeed, as specifically contemplated by, the FDCA and FDA regulations.

V. Argument

A. Introduction

The federal constitution's Supremacy Clause provides the basic authority for the proposition that conflicts between federal and state law are resolved in favor of federal law. *See McCulloch v. Maryland* (1819) 17 U.S. (4 Wheat.) 316, 427; *Cipollone v. Liggett Group, Inc.* (1992) 505 U.S.

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[1]The regulation authorizing manufacturers to change their labels without FDA pre-approval is known as the "changes being effected," or CBE, regulation.

504, 516. Thus, the question in most preemption disputes, including this one, is whether Congress intended to preempt state law. *See id.* at 516. "Congress's intent may be 'explicitly stated in the statute's language or implicitly contained in its structure and purpose.'" *Id.* (quoting *Jones v. Rath Packing Co.* (1977) 430 U.S. 519, 525).

Federal law impliedly preempts state law only in the rare circumstance where federal law is so comprehensive as to occupy the field, *id.*; *Hillsborough County v. Automated Med. Labs., Inc.* (1985) 471 U.S. 707, 713, 717, or where state law "actually conflicts" with federal law, *Cipollone*, 504 U.S. at 516—that is, where compliance with federal and state law is physically impossible or where allowing state law to operate would stand as an obstacle to the accomplishment of federal objectives. *See Florida Lime & Avocado Growers, Inc. v. Paul* (1963) 373 U.S. 132, 141, 142-43. In this case, it is undisputed that the FDCA does not expressly preempt state-law damages actions, and Purepac does not (and could not) argue that the FDCA occupies the prescription drug field. Thus, Purepac claims only that Ms. McKenney's state-law claims "actually conflict" with federal law.

Where "Congress [has] legislated . . . in a field which the States have traditionally occupied, [involving] the historic police powers of the States," *Rice v. Santa Fe Elevator Corp.* (1947) 331 U.S. 218, 230, there is strong presumption against preemption. *See id.* As this Court has explained, it is "well established that '[c]onsideration of issues arising under the Supremacy Clause "start[s] with the assumption that the historic police powers of the States [are] not to be superseded by ... [the] Federal Act unless that [is] the clear and manifest purpose of Congress." *Jevne v. Superior Court* (2005) 35 Cal. 4th 935, 949 (quoting *Cipollone*, 505 U.S. at 516).

This presumption applies where a defendant is seeking preemption of state tort remedies because, in that situation, preemption would displace the states' longstanding tradition of protecting public health and safety and compensating their injured citizens through the civil justice system. *See, e.g., Bates v. Dow AgroSciences* (2005) 544 U.S. 431, 449; *Medtronic v. Lohr* (1996) 518 U.S. 470, 484-86. And the presumption applies with particular force where the federal scheme claimed to have preemptive effect does not itself provide a damages remedy. *See, e.g., English v. General Electric Co.* (1990) 496 U.S. 72, 87-90; *Silkwood v. Kerr-McGee Corp.* (1984) 464 U.S. 238, 251. Here, with respect to prescription drug regulation, not only did Congress not provide a damages remedy, but it "rejected a provision in a draft of the original FD&C Act providing a federal cause of action for damages [for injuries caused by prescription drugs] because 'a common law right of action [already] exists.'" Robert Adler & Richard Mann, *Preemption and Medical Devices: The Courts Run Amok*, 59 Mo. L. Rev. 895, 924 & n.130 (1995) (quoting Hearings Before a Subcommittee of the Committee on Commerce of the United States Senate on S. 1944, 73d Cong., 2d Sess. 400, 403 (1933)).

B. Damages Claims For Personal-Injury Based On Inadequate Warnings Of Drug Hazards Are Not Preempted.

Purepac does not maintain that state-law failure-to-warn damages actions against the manufacturers of name-brand drugs are preempted. Rather, it asserts that because of the way in which generic drugs are regulated, federal law grants a special immunity to generic manufacturers. As explained below in Part V.C., that argument is wrong, and generic manufacturers have no special preemption protection.

1. First, however, it is important to recognize that Purepac's claim for preemption runs headlong into an overwhelming body of federal and state case law holding that neither the FDCA nor FDA regulations thereunder preempt state-law damages actions seeking compensation for personal injuries caused by FDA-approved drugs. Indeed, every appellate court to have addressed the issue has ruled that FDA approval of the product and its label, or a manufacturer's compliance with FDA regulations, does not preempt any state-law personal-injury claims. *See, e.g., Tobin v. Astra Pharm. Prods., Inc.* (6th Cir. 1993) 993 F.2d 528, 537; *Osburn v. Anchor Labs.* (5th Cir. 1987) 825 F.2d 908, 911-13; *Wells v. Ortho Pharm. Corp.* (11th Cir. 1986) 788 F.2d 741, 746; *Wyeth v. Levine* (Vt. 2006) 944 A.2d 179, *cert. granted*, (2008) 128 S. Ct. 1118; *Feldman v. Lederle Labs.* (N.J. 1991) 592 A.2d 1176, 1185-97; *Kurer v. Parke, Davis & Co.* (Wis. App. 2004) 679 N.W.2d 867, 875 ("As numerous courts have concluded, FDA regulations do not preempt the imposition of state common law liability for failure to warn claims.") (citations omitted). Indeed, as mentioned above, this Court has noted that "numerous courts have concluded [that] Congress evinced no intention of preempting state tort liability for injuries from prescription drugs." *Carlin v. Superior Court* (1996) 13 Cal. 4th 1104, 1113 (citing cases).[2]

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[2]In addition to the unanimity among appellate courts, a large majority of trial courts that have addressed the question have come to the same conclusion. *See, e.g., In re Zyprexa Prods. Liab. Litig.* (E.D.N.Y. 2007) 489 F. Supp. 2d 230, 270-78; *Sarli v. Mylan Bertek Pharmaceuticals, Inc.* (M.D.N.C. July 19, 2007) 2007 WL 2111577; *In re Vioxx Prods. Liab. Litig.* (E.D. La. 2007) 501 F. Supp. 2d 776; *Jackson v. Pfizer, Inc.* (D.Neb. 2006) 432 F. Supp. 2d 964; *Laisure-Radke v. Par Pharm., Inc.* (W.D.Wash. 2006) 426 F. Supp. 2d 1163, 1169; *Peters v. Astrazeneca, LP* (W.D. Wis. 2006) 417 F. Supp. 2d 1051, 1054-57; *Witczak v. Pfizer, Inc.* (D. Minn. 2005) 377 F. Supp. 2d 726, 728-32; *Cartwright v. Pfizer, Inc.*

The prevailing view that the FDCA does not preempt state-law failure-to-warn claims is consistent with the entrenched common-law rule, followed in this jurisdiction, *see id.* at 1113-15; *Stevens v. Parke, Davis & Co.* (1973) 9 Cal.3d 51, 65, that compliance with federal statutes and regulations may be considered by the trier of fact in determining a manufacturer's liability, but is not a complete defense. *See Restatement of Torts (Third)—Products Liability* § 4(b) (Am. Law Inst. 1988); *see also, e.g., McEwen v. Ortho Pharm. Corp.* (Or. 1974) 528 P.2d 522, 534 (citing cases). Thus, it is not the law, nor is it Ms. McKenney's position, that federal regulatory approval may play no role in the trial of this case, but only that it does not provide Purepac a complete defense.

2. Only one appellate court in American history has held preempted a state-law damages claim alleging injury from a prescription drug. In that case, in a split decision, the U.S. Court of Appeals for the Third Circuit found preemption based exclusively on the fact that FDA had conducted extensive post-marketing studies of the drug's claimed side-effects and, thereafter, had specifically and publicly rejected the same warning that the

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(E.D. Tex. 2005) 369 F. Supp. 2d 876, 881-87; *McNellis v. Pfizer, Inc.* (D.N.J. Dec. 29, 2005) 2005 WL 3752269; *Zikis v. Pfizer, Inc.* (N.D. Ill. May 9, 2005) 2005 WL 1126909; *Motus v. Pfizer, Inc.* (C.D. Cal. 2000) 127 F. Supp. 2d 1085, 1091-1100, *aff'g dismissal on other grounds* (9th Cir. 2004) 358 F.3d 659; *In re Paxil Litig.* (C.D. Cal. Oct. 18, 2002) 2002 WL 31375497, *1; *Eve Sandoz Pharm.Corp.* (S.D. Ind. Jan. 28, 2002) 2002 WL 181972; *Caraker v. Sandoz Pharm. Corp.* (S.D. Ill. 2001) 172 F. Supp. 2d 1018, 1029-44; *Globetti v. Sandoz Pharm. Corp.* (N.D. Ala. Mar. 5, 2001) 2001 WL 419160; *Mazur v. Merck & Co.* (E.D. Pa. 1990) 742 F. Supp. 239, 245-48; *Kociemba v. Searle & Co.* (D. Minn. 1988) 680 F. Supp. 1293, 1298-1300; *Graham v. Wyeth Labs.* (D. Kan. 1987) 666 F. Supp. 1483, 1488-93; *Stephens v. G.D. Searle* (E.D. Mich. 1985) 602 F. Supp. 379, 382; *Kelly v. Wyeth* (Mass. Super. Apr. 12, 2007) 22 Mass. L. Rptr. 384, 2007 WL 1302589, *1.

plaintiff maintained would have prevented her injuries. *Colacicco v. Apotex Inc.* (3d Cir. 2008) 521 F.3d 253, 269-72, *cert. pending* (U.S. filed Oct. 2, 2008) No. 08-437; *see id.* at 271-72 ("Our holding is limited to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires."). Here, Purepac does not, and cannot, claim that the FDA has even considered, let alone publicly rejected, the warning about the association between metoclopramide and tardive dyskinesia that Ms. McKenney maintains would have prevented her injuries.

The fundamental difference between this case and the Third Circuit's decision in *Colacicco* also explains why this Court's preemption holding in *Dowhal v. SmithKline Beecham Consumer Healthcare* (Cal. 2004) 32 Cal. 4th 910, relied on by Purepac, is inapposite. In *Dowhal*, the plaintiff sought an injunction under Proposition 65 to add a warning to the actual product label itself, not money damages arising from a personal injury caused by a prescription drug. More importantly, in *Dowhal*, this Court found preemption because FDA had already extensively studied and *rejected* the very warning that the plaintiff sought to add to the label, *id.* at 929-31; in fact, the plaintiff had earlier formally petitioned FDA, and the agency *rejected* the requested label change. *Id.* at 922; *accord Colaccico*, 521 F.2d at 272 (discussing *Dowhal*).

Indeed, *Dowhal's* reasoning strongly supports Ms. McKenney's position. This Court there noted that the matter before it was "an unusual case; in most cases FDA warnings and Proposition 65 warnings would serve the same purpose—informing the consumer of the risks involved in use of the product—and differences in wording *would not call for federal preemption*." *Dowhal*, 32 Cal. 4th at 934 (emphasis added). If, "in most cases," adding prescription drug label warnings under Proposition 65 would

not be preempted, then, *a fortiori*, the same is true here, where the only remedy sought is an award of damages.

3. The overwhelming anti-preemption authority described above should come as no surprise; for 70 years, FDA regulation of prescription drugs and state-law compensation for drug-related injuries have co-existed, with each serving their distinct but complementary purposes and neither interfering with the other. As enacted in 1938, the FDCA did not expressly address preemption of state law at all. And, as noted earlier, Congress declined to provide a federal right of action for damages arising from drug injuries *because state common law already did so*. *See* Hearings Before a Subcommittee of the Committee on Commerce of the United States Senate on S. 1944, 73d Cong., 2d Sess. 400, 403 (1933).

Moreover, in 1962, when enacting FDCA amendments requiring that drugs provide a reasonable assurance of efficacy as well as safety, Congress included the following provision regarding preemption: "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. There is no such conflict between ordinary tort remedies, like those sought by Ms. McKenney, and federal regulation.

As the Vermont Supreme Court held in 2006, no "direct and positive conflict" exists between the FDCA and state law where, as in Ms. McKenney's case, it is possible to comply with both. *See Wyeth v. Levine*, 944 A.2d at 190-91. Or, as the U.S. Court of Appeals for the Fourth Circuit has put it, a federal law that demands a "direct and positive conflict" as a basis for preemption "simply restates the principle that state law is

superseded in cases of an actual conflict with federal law such that 'compliance with both federal and state regulations is a *physical impossibility*.'" *S. Blasting Servs., Inc. v. Wilkes County* (4th Cir. 2002) 288 F.3d 584, 591 (quoting *Hillsborough County*, 471 U.S. at 713) (emphasis added).

No such impossibility exists in this case for two key reasons, both of which are ignored in Purepac's petition for review. **First**, Purepac can comply with both federal labeling requirements and a state-law verdict, which would not require Purepac to alter its label but only to pay damages. As explained in 2005 by the U.S. Supreme Court in *Bates v. Dow Agrosciences*, a "requirement is a rule of law that must be obeyed; an event, such as a jury verdict, that [may] merely motivate[] an optional decision [to revise the product label] is not a requirement." 544 U.S. at 443; *see also In re Zyprexa*, 489 F. Supp. 2d at 277 (FDCA does not preempt state-law duty-to-warn suits because "[j]ury verdicts do not impose mandatory labeling requirements on drug manufacturers; rather, they impose damages for negligence in particular cases. The manufacturer can change its labels through FDA procedure in response to such a verdict, or it can choose to leave the label as-is despite the verdict."); *accord, e.g., Sprietsma v. Mercury Marine* (2002) 537 U.S. 51, 64 (it is "perfectly rational for Congress not to pre-empt common-law claims," even while preempting state regulatory law, because common-law claims "perform an important remedial role in compensating accident victims"); *Goodyear Atomic Corp. v. Miller* (1988) 486 U.S. 174, 185-86.

Second, even if a "direct and positive" conflict could extend beyond situations other than physical impossibility, the duties underlying a state-law inadequate warning claim do not conflict with federal drug regulation, but are fully consistent with them. The possibility of civil liability

encourages companies to enhance product safety and to warn of drug hazards. *See, e.g., In re Zyprexa*, 489 F. Supp. 2d at 277 ("Jury verdicts and adequacy of warning claims serve an important regulatory role in the tort system. State law adequacy-of-warning claims may alert the FDA to potential inadequacies in product labeling."). Such liability is thus in harmony with, and certainly not in conflict with, a regulatory scheme under which manufacturers "shall" update their labeling to warn of all relevant hazards, contraindications, and side effects, 21 C.F.R. § 201.80(e), and with the FDCA, which deems a drug misbranded whenever an FDA-approved label becomes "false or misleading in any particular." 21 U.S.C. § 352(a). *See Bates*, 544 U.S. at 451 (explaining that private damages remedies based on failure to warn tend to aid rather than hinder safety objectives of federal product labeling schemes).

C. There is No Special Preemption Immunity for Generic Drug Manufacturers.

Understanding that the foregoing authorities would doom its preemption defense, Purepac relies on what it claims is a special pro-preemption rule reserved only for *generic* drug manufacturers. Purepac asserts that it is entitled to preemption because generic manufacturers, as opposed to name-brand manufacturers, lack the right to change their drug labels, which must, it says, invariably conform at all times to the FDA-approved label for the name-brand drug. Thus, Purepac says, any state-law claim premised on a generic manufacturer's failure to warn is preempted. For several independent reasons, that assertion is flatly incorrect.

First, for the reasons explained in part V.B. above (at 11-12), under the 1962 amendments to the FDCA, a "direct and positive" conflict between federal and state law is a prerequisite for preemption under the FDCA, and such a conflict does not exist between federal drug regulation and the state-

law damages sought by Ms. McKenney. Thus, any arguments premised solely on some special immunity for generic manufacturers are inapposite.

Second, even assuming (incorrectly) that a generic manufacturer may not employ the CBE regulation, *see* 21 C.F.R. § 314.70(c)(6)(iii), to change a label without FDA pre-approval, Purepac's claim to preemption fails. As noted earlier, FDA regulations obligate the manufacturer—both brand-name *and* generic—to seek to update their labels whenever the evidence requires it: All drug "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.* § 201.80(e) (emphasis added). Indeed, FDA has made clear that generic drug manufacturers, just like name-brand manufacturers, must provide updated safety information to the agency for purposes of revising their labels. As FDA has explained, "[a]fter approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." *See* 57 Fed. Reg. 17950, 17961 (1992).

Thus, even absent a unilateral right to amend a label to protect patient health, manufacturers have an absolute duty to seek FDA approval for such a change when circumstances call for it. Indeed, FDA has made this very point in recent amicus briefs filed in federal appellate and trial courts. *See* Br. of the United States, at 3 n.7, in *Colaccico v. Apotex Corp.*, No. 06-3107 (3d Cir. filed Dec. 4, 2006) ("if the drug manufacturer has 'reasonable evidence of an association of a serious hazard with a drug,' the manufacturer has an obligation to seek FDA approval for a labeling change, in order to add a warning of the new potential hazard.") *See* 21 C.F.R. § 201.80(e)."); FDA Letter Br., at 3, in *Perry v. Novartis Pharmaceuticals*, Civ. No. 05-5350 (E.D. Pa. filed Sept. 22, 2006) ("If a drug manufacturer

has 'reasonable evidence of a causal association' between the use of a drug and a 'clinically significant hazard,' the manufacturer *has an obligation* to seek FDA approval for a labeling change . . .") (quoting FDA regulation).

Purepac relies on 21 C.F.R. § 314.150, which it says prohibits generic manufacturers from making any change to their labels to strengthen warnings "*at all times* throughout the life of the product." Purepac Pet. 8 (emphasis in original). Purepac grossly misrepresents the text and purpose of this regulation. Section 314.150 permits, but does not require, FDA to seek to withdraw approval of an ANDA after a determination that "the labeling for the drug product . . . is no longer consistent with that for the listed drug referred to in the abbreviated new drug application." 21 C.F.R. § 314.150(b)(10). "[T]he purpose of this regulation was not to prevent a generic manufacturer from improving or strengthening its warnings. It was, instead, to ensure that the FDA could require a generic manufacturer 'to modify its labeling to match labeling changes in the reference listed [name-brand] drug.'" *Barnhill v. Teva Pharms. USA, Inc.* (S.D. Ala. Apr. 24, 2007) 2007 U.S. Dist. LEXIS 44718, *8 (quoting 57 Fed. Reg. at 17970). Indeed, as previously noted, in promulgating its ANDA regulations, FDA stated that "[a]fter approval of an ANDA, if an ANDA holder believes that new safety information should be added," the "*FDA will determine whether the labeling for the generic and listed drugs should be revised.*" 57 Fed. Reg. at 17961 (emphasis added). Thus, just as FDA would require generic manufacturers to conform their product labels to labeling changes effectuated by a name-brand manufacturer under section 314.70(c), so, too, would it require name-brand manufacturers to conform to labeling changes originating with a generic manufacturer.

Purepac's acknowledgement that FDA "*may* 'withdraw approval' of [an] ANDA if it finds that the generic's labeling 'is no longer consistent

with that for the listed drug,'" Purepac Pet. 8 (quoting 21 C.F.R. § 314.150(b)(10) (emphasis added)), underscores our point. FDA's authority in this regard is *permissive*, and it would be irrational for FDA to invoke its permissive authority during the temporary transition of all manufacturers' products to a newer, strengthened warning. Tellingly, Purepac does not cite a single instance where FDA has revoked approval of an NDA or ANDA based on strengthened warnings added through the CBE process, and we are aware of none.

In the end, Purepac's real problem is not so much its unfair manipulation of section 314.50, but its failure to confront 21 C.F.R. § 201.80(e), which Purepac's petition does not even cite, but which indisputably provides that both name-brand *and* generic drug 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." In sum, because FDA regulations affirmatively demand that *all* drug manufacturers take steps to revise labels to include warnings of serious drug hazards, a state-law claim premised on a failure to warn of such a hazard—which simply parallels those regulations—cannot be an obstacle to the accomplishment of federal objectives and, thus, cannot be preempted.

Third, Purepak is incorrect that it (as opposed to name-brand manufacturers) may not invoke the CBE regulation, 21 C.F.R. § 314.70(c)(6)(iii)(A), to amend a label to add or strengthen a contraindication, warning, precaution, or adverse reaction. Although not entirely clear (*see* Purepac Pet. 8), Purepac's argument appears to be premised principally on a section of the FDCA, 21 U.S.C. § 355(j)(2)(A)(v), which requires an ANDA *applicant* to submit information showing "that the labeling proposed for the new drug is the same as the labeling approved for the listed [name-brand] drug, and

regulations that reference that statutory requirement." This provision concerns only what "[a]n abbreviated *application* for a drug shall contain," 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added), and, thus, it applies only to the original ANDA submitted to FDA to obtain marketing approval, *not* to post-approval labeling supplements. It says *nothing* about the circumstances under which generic manufacturers may (or must) change their labels once their products are on the market.

The notion that the *original* ANDA may not deviate from the brand-name labeling makes sense. The purpose of the Hatch-Waxman Amendments was to allow generic products to reach the market by showing bioequivalence to the name-brand drug, and, thus, it is rational for FDA to require generic manufacturers—who have not yet observed any post-marketing patient experience or received adverse-event reports regarding use of their drugs—to conform their original labels to the name-brand product at the time their generic products are first marketed. Once a generic drug reaches the market, however, FDA scrutiny to evaluate a proposed warning based on hazardous drug associations, and the generic manufacturer's ability to observe the patient drug experience, are the same as for name-brand manufacturers. That is why drug labels of all manufacturers—name-brand *and* generic—are misbranded unless, "for the protection of users," they bear adequate warnings against any use that endangers human health, 21 U.S.C. § 352(f), and that is why all manufacturers—name-brand *and* generic—"shall" revise their labeling to warn when there is reasonable evidence that a drug is associated with a serious hazard. 21 C.F.R. § 201.80(e).

But the chief flaw in Purepac's argument that the CBE regulation is off-limits to generic manufacturers is that it cannot be squared with the plain language of 21 C.F.R. § 314.70(c)(6), which, as explained above,

expressly authorizes drug manufacturers to strengthen warnings under certain circumstances without FDA pre-approval, *and* 21 C.F.R. § 314.97, a section of the ANDA regulations entitled "Supplements and other changes to an approved abbreviated application," which states that "[t]he applicant *shall* comply with the requirements of §§ *314.70* and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application." (emphasis added). Taken together, these two regulations necessarily mean that the procedures for post-approval supplemental submissions are the same for holders of both NDAs *and* ANDAs—in other words, for name-brand *and* generic manufacturers.[3]

If there had been any doubt on the question whether ANDA holders may employ the CBE regulation to amend a label before obtaining FDA approval, it would now have been resolved by Congress late last year with the enactment of the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) (FDAAA)—yet another authority ignored by Purepac. The FDAAA bolsters FDA's authority to require a manufacturer to change a drug label if the agency becomes aware of information it believes should be included. 121 Stat. at 924 (codified at 21 U.S.C. § 355(o)(4)). To ward off any claim that this expanded FDA

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[3] Once again, Purepac deals with an argument by ignoring it. Its petition omits any citation to, let alone discussion of, 21 C.F.R. § 314.97. Purepac does cite a two-sentence conclusory footnote accompanying a proposed FDA rule, which states that an ANDA holder may not use the CBE regulation to amend its label without prior FDA approval. Purepac Pet. 13 (citing 73 Fed. Reg. 2848, 2849 n.1 (2008)). In that statement, the FDA, like Purepac, ignores 21 C.F.R. § 314.97, which expressly applies the CBE regulation to generic manufacturers. More importantly, FDA does not deny that, aside from the CBE regulation, all manufacturers, name-brand *and* generic, are subject to 21 C.F.R. § 201.80(e), and thus have a duty to seek to update their labeling "as soon as there is reasonable evidence of an association of a serious hazard with a drug."

authority should lead to preemption, Congress included a "rule of construction" in section 901 of the Act: "This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under section 505(j) to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of Title 21, Code of Federal Regulations (or any successor regulations)." 121 Stat. at 925-26 (codified at 21 U.S.C. § 355(o)(4)(I)). The "holder of the approved application under section 505(j)" is *the manufacturer of a generic drug*. Thus, FDAAA's rule of construction affirms Congress's intent that generic manufacturers remain subject to labeling requirements, including in particular the requirement to promptly strengthen label warnings under 21 C.F.R. § 201.80(e) *and* the CBE supplement process under 21 C.F.R. § 314.70(c).[4]

Finally, even assuming (incorrectly) that generic manufacturers are under a federal-law obligation to freeze forever the content of their labels—no matter how inaccurate, misleading, or dangerous—and that obligation preempts a state-law damages claim premised on a failure to warn via the drug label, a state-law damages claim premised on a failure to warn physicians by non-label means would not be preempted.

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[4] In addition to its text, the FDAAA's legislative history underscores that the rule of construction was intended to reaffirm that the FDCA does not preempt state-law damages claims. *See* 153 Cong. Rec. S11832, col. 3 – S11833, cols. 1-2 (Sept. 20, 2007) (Sen. Kennedy); *id.* at S11834, cols. 2-3 (Sen. Leahy); *id.* at S11835, col. 3 (Sen. Durbin). Indeed, even a senator who would have preferred statutory language that would have "occupied the field" of drug labeling and preempted damages suits construed the rule of construction as having anti-preemptive effect, thereby "open[ing] the floodgates" for suits and affording "a definite boon for trial lawyers." *Id.* at S11836, col. 3 – S11837, col. 1 (Sen. Allard).

Under the FDCA, "[t]he term 'labeling' means 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), but does not include other forms of communications, such as "Dear Doctor" letters warning physicians of hazards and contraindications not included in the labeling. Indeed, when FDA promulgated labeling regulations in 1979, it explained that "[t]hese labeling requirements do not prohibit a manufacturer . . . from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered," and thus advised manufacturers that the "issuance of letters directed to health care professionals (*e.g.*, 'Dear Doctor' letters containing such information) is not prohibited by these regulations." 44 Fed. Reg. at 37447; *see Perry v. Novartis Pharma. Corp.* (E.D. Pa. 2006) 456 F. Supp. 2d 678, 686 (state-law damages claims based on warning through any permissible non-label means, "such as letters to health care professionals," are not preempted, relying on 44 Fed. Reg. at 37447). *See also Chemical Specialties Manufacturers Ass'n v. Allenby* (9th Cir. 1992) 958 F.2d 941, 946 (no preemption under provision of federal pesticide law that preempts state law different from or in addition to federal "labeling" because that term does not include point-of-sale signs required under California's Proposition 65); *New York State Pesticide Coalition v. Jorling* (2d Cir. 1989) 874 F.2d 115, 119 (federal pesticide law's preemption of "labeling" does not extend to non-label forms of state regulation).[5]

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[5]Purepac ends its brief with citations to cases that have adopted its position. All are trial court rulings and most are unreported, underscoring that not a single appellate court has ever agreed with Purepac's position.

In fact, only one appellate court has addressed the question whether a generic drug manufacturer may amend its label, and, there, the U.S. Court

* * *

For all of these reasons, state-law damages claims based on a generic drug manufacturer's failure to provide adequate warnings of its product's hazards do not pose an obstacle to the accomplishment of federal regulatory goals. To the contrary, such state-law claims are fully consistent with the objectives of the FDCA. Therefore, the Court of Appeal correctly held that Ms. McKenney's claims are not preempted.

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of Appeals for the Fourth Circuit agreed emphatically with our position that "generic manufacturers . . . [are] permitted to add or strengthen warnings and delete misleading statements on labels, even without prior FDA approval." *Foster v. Am. Home Prod. Corp.* (4th Cir. 1994) 29 F.3d 165, 170. Other courts have come to the same conclusion. *See Kelly*, 22 Mass. L. Rptr. 384, 2007 WL 1302589, *1 ("After name brand and generic manufacturers receive approval from the FDA, they must continue to revise their labels 'to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a casual relationship need not have been established.' 21 C.F.R. §§ 201.80(e), 314.97. Therefore, manufacturers have a continuing obligation to safeguard against misbranding drugs. *See* 21 U.S.C. § 331(a), (b), (k).") (footnote omitted)); *Laisure-Radke*, 2006 WL 901657, *3 ("once the ANDA is approved, generic manufacturers have the same power and duty to add or strengthen their warnings, as do the manufacturers of pioneer drugs, and, therefore, the same liability"); *Sharp v. Leichis* (Fl. Cir. Ct. 2006) 2006 WL 515532, *7; *Block v. Wyeth, Inc.* (N.D. Tex. 2003) 2003 WL 203067, *1 ("A manufacturer of a generic drug may alter a drug's labeling '[t]o add or strengthen a contraindication, warning, precaution or adverse reaction' or '[t]o delete false, misleading or unsupported indications for use or claims for effectiveness' without prior FDA approval.") (relying on 21 C.F.R. §§ 314.70(c)(2), 314.97); *see also Sarli*, 2007 WL 2111577 (rejecting preemption argument made by generic drug manufacturer).

Conclusion

The petition for review should be denied.

Dated: November 24, 2008

Respectfully submitted,

By: _____

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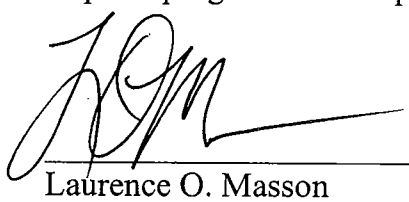
Counsel of Record hereby certifies that pursuant to Rule 8.204(c)(1) of the California Rules of Court, the enclosed brief is produced using 13 point or greater Roman type including footnotes and contains 6,423 words. Counsel relies on the word count of the computer program used to prepare this brief.

Dated: November 24, 2008 By: 

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