Nos. 09-5509, 09-5460, 09-5466

IN THE UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

DENNIS MORRIS,
Plaintiff-Appellant,
v.
WYETH INC., et al.,
Defendants-Appellees.

LALA SMITH,
Plaintiff-Appellant,
v.
WYETH INC., et al.,
Defendants-Appellees.

ALICE WILSON,
Plaintiff-Appellant,
v.
PLIVA INC., et al.,
Defendants-Appellees.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF KENTUCKY

BRIEF FOR AMICUS CURIAE U.S. FOOD AND DRUG ADMINISTRATION

MARK B. CHILDRESS
Acting General Counsel

RALPH S. TYLER
Associate General Counsel,
Food and Drug Division

ERIC M. BLUMBERG
Deputy Chief Counsel, Litigation

WENDY S. VICENTE
Associate Chief Counsel
U.S. Dept. of Health & Human Services
Office of the General Counsel
10903 New Hampshire Avenue
Silver Spring, MD 20993

TONY WEST
Assistant Attorney General

DAVID J. HALE
United States Attorney

DOUGLAS N. LETTER
(202) 514-3602
SHARON SWINGLE
(202) 353-2689
BENJAMIN S. KINGSLEY
(202) 353-8253
Attorneys, Appellate Staff
Civil Division, Room 7252
U.S. Department of Justice
950 Pennsylvania Ave., N.W.
Washington, D.C. 20530

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STATEMENT OF INTEREST

On June 11, 2010, this Court invited the participation of the Food and Drug Administration on the preemption question raised in these cases by plaintiffs' claims against generic pharmaceutical manufacturers. It is the position of the United States that plaintiffs' failure-to-warn claims against manufacturers of

generic drugs are not categorically preempted by federal law, and therefore that the judgments of the district court should be reversed.

STATEMENT OF THE ISSUE

The United States will address the following issue: Whether federal law preempts a tort claim under state law that a generic drug approved by the Food and Drug Administration was inadequately labeled.

STATEMENT OF THE CASE

The Food and Drug Administration ("FDA") regulates the manufacture, sale, and labeling of prescription drug products under the Federal Food, Drug and Cosmetic Act ("FDCA"), as amended, 21 U.S.C. § 301 *et seq.* FDA is charged with ensuring that drugs in commerce are safe and effective under the conditions prescribed, recommended, or suggested in the labeling, 21 U.S.C. §§ 355(d), 393(b)(2)(B), and that they are not misbranded, 21 U.S.C. §§ 321(n), 331(a), (b) and (k), 352. FDA must approve a drug before it is introduced into commerce. 21 U.S.C. § 355(a).

These cases present the consolidated appeal of plaintiffs Lala Smith, Dennis Morris, and Alice Wilson ("plaintiffs"). Each plaintiff alleges that he or she took the generic form of the prescription drug metoclopramide before 2009, and that during this period, the FDA-approved metoclopramide warnings did not warn strongly enough against the risks of developing tardive dyskinesia, a neurological

disorder that causes involuntary movements, from the long-term use of metoclopramide. The district court dismissed all of the claims of each plaintiff, holding that plaintiffs' claims against manufacturers of generic metoclopramide were categorically preempted by the FDCA and its implementing regulations, and that plaintiffs' claims against manufacturers of brand-name metoclopramide could not proceed because they had not taken brand-name metoclopramide. This appeal followed.

STATEMENT OF THE FACTS

I. Statutory and Regulatory Background

A. FDA's Approval Process of Brand-Name and Generic Drugs

To obtain FDA approval to market a new drug, a manufacturer must submit a new drug application ("NDA") to FDA. 21 U.S.C. § 355(b). The NDA must contain, *inter alia*, scientific data and other information demonstrating that the drug is safe and effective, a statement of the drug's components, and specimens of proposed labeling for the drug. 21 U.S.C. § 355(b)(1). To be approved, the NDA must show, *inter alia*, that the "drug is safe for use," and "will have the effect it purports or is represented to have[,] under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof[.]" 21 U.S.C. § 355(d)(1) and (5). Thus, "[d]rug labeling serves as the standard under which FDA determines whether a product is safe and effective[,]" because to be

marketed, a drug must be safe and effective as labeled. 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985). A drug approved under the NDA process is often referred to as a "brand-name" drug.

Once a brand-name drug's NDA has been approved and officially listed by FDA, *see* 21 U.S.C. § 355(j)(7), any manufacturer may seek approval for a generic version under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 ("Hatch-Waxman Amendments"). That law prescribes a process for submitting an abbreviated new drug application ("ANDA") for a generic drug. 21 U.S.C. § 355(j). The ANDA approval process for a generic drug does not require the manufacturer to provide independent clinical evidence of safety and efficacy. Instead, the ANDA must generally show, *inter alia*, that the generic drug has the same active ingredient(s) as, and is bioequivalent to, a reference listed drug, *i.e.*, the brand-name drug to which the proposed generic will be equivalent. 21 U.S.C. § 355(j)(2)(A)(ii) and (iv). The manufacturer must also show that the "labeling proposed for the [generic] drug is the same as the labeling approved for" the reference listed drug. 21 U.S.C. § 355(j)(2)(A)(v).[1]

[1] The statutory and regulatory scheme permits some limited differences in the labeling, *see* 21 C.F.R. § 314.94(a)(8)(iv), but we do not discuss them here given that they are not relevant on the facts alleged.

B. FDCA Labeling Requirements

A drug is "misbranded" in violation of the FDCA when its labeling is false or misleading, or does not provide adequate directions for use and adequate warnings. *See* 21 U.S.C. §§ 321(n), 331(a), (b) and (k), 352(a), (f), (j) and (n). The term "labeling" under the FDCA is expansive: It embraces "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). Under that definition, "[o]ne article or thing is accompanied by another when it supplements or explains it . . . . No physical attachment one to the other is necessary." *Kordel v. United States*, 335 U.S. 345, 350 (1948); *see also* 21 C.F.R. § 202.1(*l*)(2).

The labeling of a prescription drug satisfies federal requirements if it gives physicians and pharmacists sufficient information—including indications for use and "any relevant hazards, contraindications, side effects, and precautions"—to allow those medical professionals to "use the drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.100(c)(1). FDA regulations further establish specific requirements for prescription drug labeling that "purports to furnish information for use," "whether or not [the information] is on or within a package from which the drug is to be dispensed [or] distributed." 21 C.F.R. § 201.100(d). Among those specific requirements is warning language that "shall

describe serious adverse reactions and potential safety hazards [and] limitations in use imposed by them[.]" 21 C.F.R. § 201.57(e) (2002); *see also* 21 C.F.R. § 201.100(d)(3).[2] In reviewing an NDA, FDA considers evidence submitted by the applicant, and other relevant scientific information, to determine whether the proposed labeling is accurate, truthful, not misleading, and adequate. Thus, FDA's approval of an NDA includes approval of the proposed drug labeling. *See* 21 U.S.C. § 355(b)(1)(F) and (d); 21 C.F.R. § 314.105(c).

The Hatch-Waxman Amendments require "the labeling . . . for [a generic] drug [to be] the same as the labeling approved for the [reference listed drug]." 21 U.S.C. § 355(j)(4)(G). This requirement reflects the fundamental premise of

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[2] As is noted below, each plaintiff took generic metoclopramide for a different time period. These time periods ranged from 1993 through 2006. This Court should be aware that, between 1993 and 2006, the labeling regulations were revised several times. For example, in 2006, the updated warning standards for older drugs—including metoclopramide— were moved to a different part of the regulation, and now appear at 21 C.F.R. §§ 201.56(e) and 201.80. *See* 71 Fed. Reg. 3922, 3996 (Jan. 24, 2006).

These various revisions are not generally relevant to the government's position in this brief—that plaintiffs' claims are not categorically preempted by federal law. That position, as explained below, is based in part on the preamble to the 1992 regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992), and the 1992 regulations were promulgated before any of the plaintiffs began taking metoclopramide. Therefore, for convenience, this brief will reference the standards for older drugs under the regulations that were in place in 2002, because those regulations governed a significant portion of the time period during which two of the plaintiffs were using metoclopramide. However, given the preliminary stage of this litigation, it is difficult to say whether the amendments to the regulations would affect each plaintiff's particular case in some way.

the ANDA process that a generic drug can be relied upon as a therapeutic equivalent of its reference listed drug. *See* 54 Fed. Reg. 28,872, 28,884 (Jul. 10, 1989) ("[T]he purpose of [21 U.S.C. § 355(j)] . . . is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts."). Accordingly, FDA places "a very high priority [on] assuring consistency in labeling," so as "to minimize any cause for confusion among health care professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name products." Division of Generic Drugs, FDA, *Policy and Procedure Guide* 37 (1989) (see appendix); *see also* 57 Fed. Reg. 17,961 (Apr. 28, 1992).

Correspondingly, the submission and approval provisions for ANDAs are different from those that apply to NDAs. An ANDA must include not only the drug's proposed labeling, *see* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(ii), but also a comparison of the proposed labeling to the reference listed drug's labeling, 21 C.F.R. § 314.94(a)(8)(iv), and a "statement that the applicant's proposed labeling . . . is the same as the labeling of the [reference listed drug]," 21 C.F.R. § 314.94(a)(8)(iii). In evaluating an ANDA, FDA's review of labeling focuses on whether the generic drug's labeling "is the same as the labeling approved for the [reference listed drug]." 21 U.S.C. § 355(j)(4)(G); *see also* 21 C.F.R. § 314.105.

C. Manufacturers' Procedures and Duties to Update Warnings

Information on the risks and benefits associated with a drug accumulates over time. Accordingly, NDA and ANDA holders must keep records of clinical experiences and ensure that their products remain safe and effective as labeled. *See* 21 U.S.C. § 355(k). In particular, implementing regulations provide that a manufacturer must record and report certain adverse events to FDA. 21 C.F.R. § 314.80(a) and (c) (NDA holders); 21 C.F.R. § 314.98(a) (ANDA holders). A drug's "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." 21 C.F.R. § 201.57(e) (2002). And manufacturers must submit annual reports that include, *inter alia*, a "summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product" and a "description of actions the applicant has taken or intends to take as a result of this new information." 21 C.F.R. § 314.81(b)(2)(i).

A manufacturer may change its approved labeling by filing a "supplemental application" (also known as a "supplement"). *See* 21 C.F.R. § 314.70 (2002).[3] ANDA holders must "comply with the requirements [applicable to NDA holders]

[3] The supplemental application regulations at 21 C.F.R. § 314.70 were revised in 2004, 69 Fed. Reg. 18,728, 18,764 (Apr. 8, 2004), but, as noted in the prior footnote, this brief will describe the regulations in place in 2002.

regarding the submission of supplemental applications." 21 C.F.R. § 314.97. Supplements are by regulatory definition part of the application. *See* 21 C.F.R. § 314.3(b). Accordingly, any supplement must be approved by FDA, and that approval in general requires that the application as supplemented satisfy the requirements of the FDCA and FDA's regulations.

Certain changes to a drug's approved labeling require FDA's prior approval, which a manufacturer seeks by submitting a prior approval supplement to its approved NDA or ANDA. 21 C.F.R. § 314.70(b) and (b)(3) (2002). Certain other changes—including changes to approved labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction"—are brought to FDA's attention through a "changes being effected" supplement. 21 C.F.R. § 314.70(c) and (c)(2)(i) (2002); *see also Wyeth v. Levine*, 129 S. Ct. 1187, 1196 (2009).

Besides changing the approved labeling, manufacturers from time to time disseminate information about their drugs—including updated warnings—through correspondence to health care providers, known as "Dear Health Care Professional" letters. *See* 21 C.F.R. § 200.5 (setting standards for such correspondence); Center for Drug Evaluation & Research, *Manual of Policies & Procedures* 6020.10 (July 2, 2003) ("*MAPP*") (establishing protocols for internal FDA review and monitoring of such correspondence).

II. Facts and Proceedings Below

Plaintiff Dennis Morris alleges that he took generic metoclopramide from March 1993 until October 2005. Morris Complaint, 09-5509 RE 1, ¶ 12. Plaintiff Lala Smith alleges that she took generic metoclopramide from June 2002 until May 2005. Smith Complaint, 09-5460 RE 1, ¶ 26. Plaintiff Alice Wilson alleges that she took generic metoclopramide from March 2006 until July 2006. Wilson Complaint, 09-5466 RE 1, ¶¶ 9, 11. All plaintiffs allege that their use of generic metoclopramide caused them to develop tardive dyskinesia. Morris Complaint, 09-5509 RE 1, ¶ 19; Smith Complaint, 09-5460 RE 1, ¶ 27; Wilson Complaint, 09-5466 RE 1, ¶ 15.

Metoclopramide is the generic version of the brand-name drug Reglan, and until 2004, Reglan's approved labeling stated that "[t]herapy longer than 12 weeks has not been evaluated and cannot be recommended," and it warned that there was a risk of tardive dyskinesia that was "believed to increase with the duration of treatment and the total cumulative dose." In 2004, FDA approved a request (made by the then-holder of the Reglan NDA) to add a bold-type sentence to the labeling stating, "Therapy should not exceed 12 weeks in duration." In 2009, FDA approved a boxed warning, *see* 21 C.F.R. 201.80(e), that "[t]reatment with

metoclopramide for longer than 12 weeks should be avoided in all but rare cases" because of the risk of tardive dyskinesia.[4]

All three plaintiffs separately sued the various defendants in these cases, alleging that the metoclopramide they took was defective because both the generic and brand-name manufacturers failed to adequately warn of the risks of long-term use. Morris Complaint, 09-5509 RE 1; Smith Complaint, 09-5460 RE 1; Wilson Complaint, 09-5466 RE 1. As is relevant to the government's interest, the district court dismissed each plaintiff's claims against the generic manufacturers separately, holding in each case that the plaintiff's failure-to-warn claims were preempted by federal law. Morris Opinion, 09-5509 RE 93; Smith Opinion, 09-5460 RE 98; Wilson Opinion, 09-5466 RE 83. Each plaintiff filed a motion for reconsideration, which the district court rejected. Morris Denial of Reconsideration, 09-5509 RE 110; Smith Denial of Reconsideration, 09-5460 RE 113; Wilson Denial of Reconsideration, 09-5466 RE 98. Following the Supreme Court's decision in *Wyeth v. Levine*, the district court again reaffirmed its ruling.

[4] The quoted language is drawn from the approved package inserts, which can be found at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/18821-S018_Reglan.pdf at 10 (1999 insert); http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/17854s047lbl.pdf at 6 (2004 insert); http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017854s051,021793s004lbl.pdf at 1 (2009 insert).

Morris Notice, 09-5509 RE 113; Smith Notice, 09-5460 RE 117; Wilson Notice, 09-5466 RE 101.

Each plaintiff appealed to this Court. Following briefing and oral argument, on June 11, 2010, this Court invited the government to address whether plaintiffs' claims against generic pharmaceutical manufacturers were preempted by federal law.

SUMMARY OF THE ARGUMENT

The district court incorrectly held that plaintiffs' failure-to-warn claims against generic drug manufacturers are categorically preempted by the FDCA and FDA's regulations. The district court's decision is inconsistent with the decisions of the only courts of appeals to address the question since *Wyeth v. Levine*, 129 S. Ct. 1187, 1196 (2009). *Demahy v. Actavis*, 593 F.3d 428, 449 (5th Cir. 2010); *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 612 (8th Cir. 2009).[5] Though federal law may circumscribe the possible theories of recovery by plaintiffs, it does not present an outright bar to recovery.

[5] Defendants in *Demahy* and *Mensing* have filed petitions for writs of certiorari with the Supreme Court in both cases. *See Actavis, Inc. v. Demahy* (Sup. Ct. 09-1501); *PLIVA, Inc., et al. v. Mensing* (Sup. Ct. 09-993); *Actavis Elizabeth, LLC v. Mensing* (Sup. Ct. 09-1039). On November 2, 2010, at the Supreme Court's invitation, the United States filed an amicus brief in the *Mensing* cases recommending that certiorari be denied, reflecting the same position on the preemption question as this brief.

Plaintiffs' failure-to-warn claims are not categorically preempted, because a generic pharmaceutical manufacturer, like a brand-name manufacturer, can (and indeed, must) inform FDA of new information about risks that may require a change in the labeling of its drug. Furthermore, though the "changes being effected" and prior approval supplement processes were not expressly available to generic manufacturers, the defendants could have asked FDA to coordinate appropriate "Dear Health Care Professional" letters or to take other action with respect to labeling. Moreover, holding a generic pharmaceutical manufacturer liable on a failure-to-warn theory would not unacceptably frustrate the purposes of the Hatch-Waxman Amendments.

STANDARD OF REVIEW

This Court reviews de novo a district court ruling that federal law preempts state law. *GTE Mobilnet of Ohio v. Johnson*, 111 F.3d 469, 475 (6th Cir. 1997).

ARGUMENT

I. Plaintiffs' Claims Are Not Categorically Preempted by Federal Law.

A. Impossibility Preemption

A state tort claim is preempted if it is impossible for a defendant to comply with both the state law duty underlying the claim and federal regulatory requirements. *Wyeth*, 129 S. Ct. at 1196; *Geier v. American Honda Motor Co.*, 529 U.S. 861, 873 (2000). The generic manufacturer defendants contend that,

because federal law requires generic manufacturers to maintain labeling for their generic drugs that is the same as the labeling of the reference listed drug, it was impossible for them to warn plaintiffs about risks posed by the long-term use of metoclopramide (beyond the warnings already approved for the reference listed drug). *See, e.g*, PLIVA et al. Br., 09-5509, at 12–13 ("PLIVA et al. Br."). The defendants' premise is correct, but does not support their conclusion.

1. Plaintiffs do not contend that state law required the generic manufacturer defendants to withdraw their products altogether from the market. Rather, their claims rest on the products' labeling, and allege that defendants failed to satisfy FDA's requirements related to proper labeling. Accordingly, the federal laws and regulations governing the approved labeling of generic pharmaceuticals supply the appropriate frame of reference for the preemption question here.

A pharmaceutical product is unlawfully misbranded under the FDCA when its labeling is false or misleading, or does not provide adequate directions for use or adequate warnings against any use dangerous to health. 21 U.S.C. §§ 321(n), 331(a), (b) and (k), 352(a), (f), (j) and (n). As *Wyeth* explains, a central premise of federal drug regulation is that the manufacturer bears responsibility for the content of its labeling at all times. 129 S. Ct. at 1197–98. In that regard, "state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Id.* at 1202–03. At a minimum, when federal law

requires a manufacturer to take steps to update its labeling, a state may impose a similar duty and consequent damages liability for failing to meet that duty. *Cf. Riegel v. Medtronic, Inc.*, 552 U.S. 312, 330 (2008); *Bates v. Dow Agroscis. LLC*, 544 U.S. 431, 447–48 (2005); *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996).

2. The parties dispute the federal duties incumbent on defendants and the methods available to them under the FDCA to affect the labeling of their products. As explained above, the holder of an approved ANDA is not free to change its approved labeling at will. *See* 21 C.F.R. § 314.70(a) (2002). At the time of the events in these cases, FDA's interpretation of the FDCA and its regulations was that: (1) an ANDA holder in defendants' position could not unilaterally change its approved labeling under the "changes being effected" process; (2) the prior approval supplement process was not expressly available to any manufacturer to change approved labeling to add or strengthen a warning; (3) ANDA holders were nonetheless required to provide FDA with new information about risks, and FDA would have acted on such information if appropriate; and (4) an ANDA holder unilaterally sending "Dear Health Care Professional" letters of the kind plaintiffs seem to envision could have resulted in misbranding the drug. Those FDA interpretations are entitled to deference. *See Auer v. Robbins*, 519 U.S. 452, 462 (1997); *Chevron U.S.A. Inc. v. NRDC*, 467 U.S. 837, 842–43 (1984); *Huffman v.*

Comm'r, 518 F.3d 357, 367–68 (6th Cir. 2008); *Estate of Gerson v. Comm'r of Internal Revenue*, 507 F.3d 435, 438 (6th Cir. 2007).

i. Defendants correctly contend that the "changes being effected" process was not available to them to unilaterally change their drugs' approved labeling. It is true, as plaintiffs contend, that FDA's CBE regulation applies to ANDA holders. *See* 21 C.F.R. 314.97. However, supplements are subject to the substantive standards governing applications, so the "changes being effected" regulation must be read in conjunction with regulations pertaining specifically to generic labeling. Those regulations require a generic drug's labeling to be "the same as the labeling of the reference listed drug." 21 C.F.R § 314.94(a)(8)(iii); *see* 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. § 314.150(b)(10) (providing that ANDA approval may be withdrawn if the drug's labeling "is no longer consistent with that for the [reference listed drug]").

In light of the substantive limitations on generic labeling, FDA has consistently taken the position that an ANDA holder may not unilaterally change its approved labeling. In promulgating its final rule implementing labeling requirements for ANDAs, FDA responded to comments suggesting that the labeling regulations should permit generic manufacturers to deviate from the brand-name labeling "to add contraindications, warnings, precautions, adverse reactions, and other safety-related information." 57 Fed. Reg. 17,950, 17,961

(Apr. 28, 1992). FDA disagreed, explaining that "the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval." *Id*. FDA stated that an ANDA holder wishing to add a warning to approved labeling should furnish adequate supporting information to FDA, which would then determine whether the labeling for all products should be modified. *Id*. FDA's guidance on labeling changes reiterated that substantive limitation on changes to an ANDA. Center for Drug Evaluation & Research, *Guidance for Industry: Changes to an Approved NDA or ANDA* 24 (Apr. 2004), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077097.pdf ("All labeling changes for ANDA products must be consistent with [21 U.S.C. 355(j)].").[6]

ii. The prior approval supplement process also was not expressly available to the generic manufacturer defendants to make the labeling change plaintiffs seem to envision. As relevant here, the prior approval supplement process applied to "change[s] in labeling, except one described in paragraph[] (c)(2) . . . of this section." 21 C.F.R. § 314.70(b)(3)(i) (2002). That exception is a cross-reference

[6] The "changes being effected" process was available for an ANDA holder to conform its approved labeling to updated reference listed drug approved labeling because, under those circumstances, the change would be consistent with the substantive requirements for generic labeling.

to the "changes being effected" provision for added or strengthened warnings, which plaintiffs say describes the precise labeling change that defendants should have made here. *See, e.g.*, Morris Opening Br., 09-5509, at 23–32 ("Morris Br."). Such changes were therefore not intended to be made through the prior approval supplement process.

iii. Although no formal supplement process under 21 C.F.R. § 314.70 (2002) was expressly available to the generic manufacturer defendants, they were obligated to provide FDA with information about labeling concerns. To implement the FDCA's prohibition of misbranded products, FDA requires that 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." 21 C.F.R. § 201.57(e) (2002); *see* 21 U.S.C. § 352(a), (f), (j) and (n). Moreover, defendants had a duty to inform FDA of certain adverse events, 21 C.F.R. §§ 314.80(a) and (c), 314.98(a), and annually to report "information . . . that might affect the safety, effectiveness, or labeling of the drug product," 21 C.F.R. § 314.81(b)(2)(i).

In the preamble to the final rule implementing the ANDA application process, FDA explained how ANDA holders should discharge their duty to provide adequate warnings:

> If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether

> the labeling for the generic and listed drugs should be revised. After 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.

57 Fed. Reg. at 17,961.[7] This orderly process reconciles what could otherwise be conflicting statutory mandates that a generic drug not be misbranded, 21 U.S.C. § 352, yet also bear labeling "the same as the labeling approved for the [reference listed drug]," 21 U.S.C. § 355(j)(4)(G).

Such situations arise infrequently, and when they do, there tend to be unique, fact-specific considerations at issue. For that and other reasons, FDA has not promulgated a formal regulation for this process. Instead, it has chosen to make available to generic manufacturers points of contact in FDA's Office of Generic Drugs. FDA's internal procedures recognize that "some labeling reviews" will require the Office of Generic Drugs to consult other FDA components with particular expertise, such as the Office of Review Management (now known as the Office of New Drugs). *MAPP* 5200.6, at 1 (May 9, 2001); *see id.* at 5 (FDA

[7] At the time of the events in these cases, FDA could have requested—though not directly required—a manufacturer to make appropriate changes to its approved labeling. Had the manufacturer refused, FDA could have withdrawn approval of the application under 21 U.S.C. § 355(e). FDA now has authority under the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, to require such changes based on new information from a variety of sources. *See* 21 U.S.C. § 355(o)(4) (Supp. II 2008). FDA is currently developing guidance on how that authority will be exercised for changes to NDA and ANDA approved labeling.

request-for-consultation form applicable to "labeling revision"). In that process, intra-agency consultations regarding "ANDAs with possible serious safety concerns" are assigned the highest priority. *Id.* at 3. Thus, had a metoclopramide ANDA holder provided information to FDA at the time of the events in these cases, FDA would have used intra-agency consultations to subject any serious safety concerns to a substantive evaluation like that for a supplement under 21 C.F.R. § 314.70.

iv. With respect to "Dear Health Care Professional" letters, nothing in the FDCA or FDA's regulations categorically forbids an ANDA holder from unilaterally sending such correspondence. Rather, much like promotional material, "Dear Health Care Professional" letters may be reviewed by FDA for compliance with the FDCA and FDA regulations governing matters such as misbranding. *See MAPP* 6020.10 (July 2, 2003).

Nonetheless, ANDA holders do not customarily send "Dear Health Care Professional" letters without coordinating with FDA. Apart from the practical benefits to coordinating with FDA, ANDA holders also operate under a regulatory constraint. "Dear Health Care Professional" letters sent by a generic manufacturer could potentially affect the perceived therapeutic equivalence of the generic drug and its reference listed drug counterpart. Thus, because "Dear Health Care Professional" letters are "labeling," they implicate 21 C.F.R.

§ 314.150(b)(3). Under that provision, FDA may withdraw approval of an ANDA if "the labeling of the drug, based on a fair evaluation of all material facts, is . . . misleading in any particular." Depending on its content, a "Dear Health Care Professional" letter from an ANDA holder could inaccurately imply therapeutic differences between the generic drug and its reference listed drug that do not exist, and therefore be misleading. For example, an ANDA holder's letter notifying providers about a manufacturing defect in a particular production lot would not be misleading with respect to the therapeutic equivalence of the generic drug and the reference listed drug. By contrast, an ANDA holder's unilateral letter warning about risks of that are not specific to the generic product could mislead consumers and providers into believing that the generic drug and reference listed drug were not therapeutic equivalents.[8]

Plaintiffs seem to envision "Dear Health Care Professional" correspondence of the latter sort, *see, e.g.*, Morris. Br. at 35, which would likely be misleading. State law may not impose liability on an ANDA holder for failing to send such a letter unilaterally. But an ANDA holder certainly may provide FDA with any information it believes warrants such a letter. Indeed, there may be

[8] Such a scenario is necessarily hypothetical because FDA has never found circumstances warranting such an exercise of its authority under 21 C.F.R. § 314.150(b)(3).

little practical difference for purposes of these tort suits between proposing a "Dear Health Care Professional" letter and proposing a change to approved labeling: either would have involved bringing the relevant information to FDA's attention with a view to providing consistent warnings for the reference listed drug and its generic equivalents.

3. In short, FDA mediates the channels available to an ANDA holder under federal law for disseminating strengthened warnings. Defendants argue that state tort law conflicts with that regime because, "[n]ot only is the outcome of any proposed labeling change pure speculation, but also there is no support for the proposition that 'proposing a label change' would satisfy any state-imposed duty of providing adequate warnings for the product." PLIVA et al. Br. at 37.

We may assume, *arguendo*, that defendants are correct that state law would be preempted to the extent it would hold them liable without regard to how FDA would have acted on a hypothetical warning proposal.[9] For absent FDA's assent, defendants could not lawfully have disseminated their product with the sort of warning plaintiff seems to propose. But that does not foreclose liability, as

[9] A fully informed, actual decision by FDA that a particular warning would be inconsistent with the FDCA or FDA's regulations would presumably preempt a state law claim predicated on the necessity of such a warning. *See Wyeth*, 129 S. Ct. at 1203 & n.14; *id.* at 1204 (Breyer, J., concurring); *cf. Chicago & N.W. Transp. Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311 (1981). Defendants do not contend FDA made such a decision here.

plaintiffs' theory of recovery does not necessarily depend on defendants' failure to communicate warnings to their customers (something ultimately in FDA's control). Rather, their theory alternatively rests on defendants' failure *to take steps* to warn their customers. *See, e.g.*, Morris Br. at 32–33 ("[T]he generic appellees cannot show, nor is there any reason to believe, that the FDA would not have approved a stronger warning, for both generic metoclopramide and Reglan, before Dennis Morris's prescription was written. The generic appellees' failure even to seek such approval was both negligent and actionable."). We express no view on whether such a theory is viable as a matter of state law.

Additionally, the parties can litigate on remand the question of what action FDA would have taken in response to a hypothetical warning proposal from defendants. Upon remand, a burden allocation in such a situation ultimately turns on litigation considerations, not an interpretation of the FDCA or FDA's regulations. However, it would be reasonable for the defendants to bear the burden of showing the likelihood of FDA inaction on a proposed warning. Whether understood as a defense of federal preemption or a state law defense of justification, a tort defendant ordinarily bears the burden of proving the circumstances supporting its defense. *See Wyeth*, 129 S. Ct. at 1196; *CSX Transp., Inc. v. Easterwood*, 507 U.S. 658, 670 (1993) ("[The tort defendant] has failed to establish that the regulations apply to these cases, and hence we find [plaintiff's

claim] is not pre-empted."); *Koch v. Southern Pac. Transp. Co.*, 547 P.2d 589, 593 (Or. 1976) ("The constraint of governmental authority properly relates to circumstances giving rise to justification," which "must be proven by the asserting party.").

In any event, the precise character of further proceedings in the district court was not the focus of the defendants' dispositive motions, which argued that plaintiffs' claims could not proceed at all. And with respect to that issue, the district court incorrectly held that plaintiffs' claims are categorically preempted.

B. Frustration of Purposes Preemption

Even if compliance with both state and federal law is not impossible, the state law duty underlying a tort claim is preempted if it would frustrate the purposes and objectives of federal law. *See Wyeth*, 129 S. Ct. at 1199; *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). The generic manufacturer defendants contend that Congress's purpose in enacting the Hatch-Waxman Amendments was to bring low-cost generic drugs quickly to market; they argue that state law duties to warn would obstruct that purpose because generic manufacturers would be forced, at great expense, to acquire and maintain extensive scientific data on their drugs. PLIVA et al. Br. at 48–49, 53–55.

That argument is wrong. The Hatch-Waxman Amendments do not pursue the objective of low-cost generic drugs without limitation. Certainly, those

Amendments were intended in part to accelerate the availability of low-cost generic drugs. *See* H.R. Rep. No. 857, 98th Cong., 2d Sess. Pt. 1, at 14–15 (1984). "But no legislation pursues its purposes at all costs." *Dolan v. United States*, 130 S. Ct. 2533, 2547 (2010) (internal quotation marks omitted). That principle is particularly apt here because the Hatch-Waxman Amendments *amend*, and thus must be read in tandem with, the rest of the FDCA. As *Wyeth* explains, the FDCA's purpose is to "bolster consumer protection against harmful products," and it reflects Congress's "determin[ation] that widely available state rights of action provide[] appropriate [compensatory] relief for injured consumers." 129 S. Ct. at 1199. Nothing in the Hatch-Waxman Amendments suggests that Congress intended to abandon those principles in the case of generic drugs.

Moreover, the Supreme Court reasoned in *Wyeth* that, given Congress's 1976 enactment of an express preemption provision for medical devices and its "certain awareness of the prevalence of state tort litigation," Congress "surely would have enacted an express pre-emption provision" if it believed that all "state-law suits posed an obstacle to its objectives." 129 S. Ct. at 1200. That reasoning applies here as well. Indeed, if it did not, individuals harmed by inadequately labeled generic drugs would (on defendants' view) have no remedy, while individuals who took the same drug with the same labeling in its brand-name form would (by virtue of *Wyeth*) have a state tort remedy. "If Congress had intended to

deprive injured parties of a long available form of compensation"—and to do so in such an inconsistent manner—"it surely would have expressed that intent more clearly." *Bates*, 544 U.S. at 449.

Finally, defendants overstate the costs involved, and hence the effect of allowing state tort failure-to-warn suits on the market for generic pharmaceuticals. Plaintiffs allege that defendants could have obtained sufficient grounds for a labeling change simply from published literature on metoclopramide and adverse event reports. Morris Reply Br., 09-5509, at 9–10. Defendants disagree with that as a factual matter, suggesting a far broader knowledge base would have been necessary. PLIVA et al. Br. at 53–55. And indeed, imposing on a generic manufacturer a state law duty not to market its product without developing for itself knowledge as comprehensive as FDA's or the NDA holder's could pose preemption questions different from the ones plaintiffs' complaints raise. But the modest duty actually posited in plaintiffs' complaints seems unlikely to affect the availability of generic pharmaceuticals.

C. Court of Appeals Decisions Supporting the Government's Position

The only courts of appeals to address the question presented in these cases since the Supreme Court's decision in *Wyeth* have held that a state law tort plaintiff's failure-to-warn claims against a manufacturer of a generic drug are not categorically preempted by federal law. *Demahy v. Actavis*, 593 F.3d 428, 449

(5th Cir. 2010); *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 612 (8th Cir. 2009). Both courts held that: (1) because there are options available to a generic manufacturer to take steps to change its label, it is not categorically impossible for generic manufacturers to warn their customers about risks beyond those described on the approved labeling of a drug; and (2) imposing such an obligation on manufacturers through a state law tort duty does not conflict with the purposes and objectives of the FDCA. *Demahy*, 593 F.3d at 449; *Mensing*, 588 F.3d at 612.

The government agrees with the fundamental holdings of these courts, but endorses a slightly different approach for generic manufacturers to initiate a labeling change. In *Demahy*, the Fifth Circuit held that the "changes being effected" process was available to an ANDA holder to make a unilateral change in its approved labeling. 593 F.3d at 439–44. In *Mensing*, the Eighth Circuit made no holding with respect to the "changes being effected" process, but held that the prior approval supplement process was available to an ANDA holder to initiate changes in approved labeling. *Mensing*, 588 F.3d at 610. Those holdings misunderstand FDA's regulations, as neither the "changes being effected" or prior approval supplement process was intended for use by a generic manufacturer in the ways contemplated by those courts. Instead, as explained above, generic manufacturers can request a labeling review directly with FDA without proceeding through either formal supplement process.

However, those Fifth and Eighth Circuit holdings are consistent with the appropriate preemption analysis. Underpinning the preemption holdings in both *Demahy* and *Mensing* was the recognition that there are ways for a generic manufacturer to take steps to warn its customers about risks that are not adequately described on a label, and that manufacturers are obligated to bring information about such risks to the attention of FDA. *Demahy*, 593 F.3d at 445; *Mensing*, 588 F.3d at 609. The precise method through which a manufacturer can initiate such changes was not relevant to either court. *See Demahy*, 593 F.3d at 445 ("Of the three avenues for complying with both state and federal law . . . each shares the same fundamental attributes: the manufacturer bears primary responsibility for maintaining its label consistent with safe and effective use of its product; when reports indicate that a label requires revision, the manufacturer must alert the FDA and provide supporting scientific data; and the FDA then makes the decision whether such a labeling change is supported by science."); *Mensing*, 588 F.3d at 609 ("The availability of one particular procedure [the CBE process] is immaterial to the preemption analysis in light of this clear directive to generic manufacturers and the availability of the prior approval process.").

Ultimately, FDA would apply the same standards to evaluate a request for a label change under the informal labeling review process described above as it would normally apply in the prior approval supplement or "changes being

effected" processes. Therefore, in practical terms, the misunderstandings of the courts of appeals in *Demahy* and *Mensing* only affect how a generic manufacturer can begin to take steps to change its label and how quickly such changes can be implemented, but not whether it can take such steps or the standards by which any requests for a labeling change would be evaluated by FDA. Thus, this Court can adopt the positions expressed by FDA in this brief without creating any significant split of authority with its sister courts of appeals.

CONCLUSION

For the foregoing reasons, the judgments of the district court should be reversed.

Respectfully submitted,

MARK B. CHILDRESS
Acting General Counsel

RALPH S. TYLER
Associate General Counsel,
Food and Drug Division

ERIC M. BLUMBERG
Deputy Chief Counsel, Litigation

WENDY S. VICENTE
Associate Chief Counsel
U.S. Dept. of Health & Human Services
Office of the General Counsel
10903 New Hampshire Avenue
Silver Spring, MD 20993

TONY WEST
Assistant Attorney General

DAVID J. HALE
United States Attorney

/s/ Douglas N. Letter
DOUGLAS N. LETTER
(202) 514-3602
/s/ Sharon Swingle
SHARON SWINGLE
(202) 353-2689
/s/ Benjamin S. Kingsley
BENJAMIN S. KINGSLEY
(202) 353-8253
Attorneys, Appellate Staff

Civil Division, Room 7252
U.S. Department of Justice
950 Pennsylvania Ave., N.W.
Washington, D.C. 20530

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CERTIFICATE OF COMPLIANCE

I certify that this brief complies with the typeface and style requirements of Federal Rule of Appellate Procedure 29(c) because it has been prepared in a proportionally spaced typeface using Corel WordPerfect 12 in 14-point Times New Roman font. I further certify that, pursuant to Federal Rule of Appellate Procedure 29(d), the brief contains 6,395 words according to the count of Corel WordPerfect 12.

/s/ Benjamin S. Kingsley
Benjamin S. Kingsley
Benjamin.S.Kingsley@usdoj.gov
Attorney, Appellate Staff
Civil Division, Room 7261
U.S. Department of Justice
950 Pennsylvania Ave., N.W.
Washington, DC 20530-0001

CERTIFICATE OF SERVICE

I certify that on November 16, 2010, I filed the foregoing brief with the Court by using the appellate CM/ECF system. I further certify that all participants in the case are registered CM/ECF users and will be served by the appellate CM/ECF system.

/s/ Benjamin S. Kingsley
Benjamin S. Kingsley
Benjamin.S.Kingsley@usdoj.gov
Attorney, Appellate Staff
Civil Division, Room 7261
U.S. Department of Justice
950 Pennsylvania Ave., N.W.
Washington, DC 20530-0001

Appendix

Division of Generic Drugs, FDA, *Policy and Procedure Guide* (1989)

Division of Generic Drugs
Policy and Procedure Guide

Guide # 8-89
Date: 8/21/89

Subject: Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling.

PURPOSE: To state the policy of the Labeling Review Branch concerning the handling of ANDAs currently under review when the labeling of the innovator product has or soon will change.

BACKGROUND: For many innovator drug products, package insert labeling is the subject of frequent revisions and updating. This impacts heavily on the Labeling Review Branch since each time there is a change in the innovator's labeling it could necessitate similar changes in the labeling of as many as 20 or 30 generic drug products. A change in any section of the package insert of the innovator's product, particularly an important change, e.g., in WARNINGS, PRECAUTIONS, CONTRAINDICATIONS or DOSAGE AND ADMINISTRATION, triggers action by the Labeling Review Branch to request submission of a supplemental application providing for the labeling revisions from all generic manufacturers of that drug product. Prompt accomplishment of the revision process is important to assure that consistency is found in the labeling of all similar drug products.

POLICY:

1) It is the policy of the Division to associate a very high priority with assuring consistency in labeling and to see to minimize the time between changes in the innovator's labeling and similar revision in the labeling of the generics. This is done to minimize any cause for confusion among health care professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name drug products.

In pursuing this goal, it is important to remain mindful of such factors as the administrative costs associated with frequent labeling changes, varying priorities among different reasons for changes in labeling and any avoidable delays in the approval of new generic drug products. While the goal will be complete and timely comparability between innovator and generic labeling, in actuality some lag time will occur.

2) In terms of priority among requests for labeling changes, the following will apply:

A) FIRST PRIORITY - dictating full effort to accomplish changes as soon as possible.

Changes important enough to warrant widespread professional notification, i.e., through issuance of a "Dear Doctor Letter".

B) SECOND PRIORITY - dictating effort to accomplish changes in a timely manner - (i.e., ± 90 days)

Important* changes in or additions to Contraindications, Warnings or Dosage and Administration.

C) THIRD PRIORITY - dictating routine notification and permitting considerable flexibility in implementation, i.e., time of next printing or 180 days.

PROCEDURE:

The following table describes the operational approach to dealing with updating final printed generic labeling in response to changes in that of the innovator product. The time frames are usual and customary. Special circumstances may result in a different time frame:

a) Pertaining to Approved ANDAs

1) FIRST PRIORITY changes - allow 60 to 120 days after notification by FDA for submission by application holders.

2) SECOND AND THIRD PRIORITY changes - permit enough time to permit incorporation of the change in the next printing or 180 days; whichever is sooner.

b) Pertaining to Applications Pending Approval

	Approval Imminent (15 days)	Not Ready to Approve Within 15 day
Innovator Already Made Changes	FIRST PRIORITY: Revision will be required prior to approval, however an application may be approved with a commitment to use only the updated labeling in all marketed packages. SECOND AND THIRD PRIORITIES: Firm will be permitted to make the revision within 180 days post-approval.	ALL PRIORITIES: Firm must revise before approval.
We Anticipate Changes	ALL PRIORITIES: Applicant(s) cautioned that further revision is imminent. No specific timetable for change dictated.	ALL PRIORITIES: Applicant(s) cautioned that further revision is imminent, and that revision may be requested prior to approval.

*Judgement of the importance of labeling changes is usually determined among the members of the Labeling Branch and the Deputy Director of the Division, with the benefit of consultation with the appropriate ODE I or ODE II reviewing Division if necessary.

Acting Director, Division of Generic Drugs

8/20/89
Date