Nos. 09-993 and 09-1039

In the Supreme Court of the United States

PLIVA, INC., ET AL., PETITIONERS

v.

GLADYS MENSING

ACTAVIS ELIZABETH, LLC, PETITIONER

v.

GLADYS MENSING

ON PETITIONS FOR WRITS OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE EIGHTH CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

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QUESTION PRESENTED

Whether federal law preempts a tort claim under state law that a generic drug approved by the Food and Drug Administration was inadequately labeled.

TABLE OF CONTENTS

Page

Statement 1
Discussion 10
A. The court of appeals correctly held that respondent's claims are not categorically preempted 11
B. There is no conflict in the courts of appeals 22
C. The interlocutory posture of this case makes it unsuitable for review 23
Conclusion 24
Appendix – Center for Drug Evaluation and Research, Guidance for Industry: Changes to an Approved NDA or ANDA (Nov. 1999) 1a

TABLE OF AUTHORITIES

Cases:

Auer v. *Robbins*, 519 U.S. 452 (1997) 13
Bates v. *Dow Agroscis. LLC*, 544 U.S. 431 (2005) 12, 21
Chevron U.S.A. Inc. v. *NRDC*, 467 U.S. 837 (1984) 13
CSX Transp., Inc. v. *Easterwood*, 507 U.S. 658 (1993) 19
Chicago & N.W. Transp. Co. v. *Kalo Brick & Tile Co.*, 450 U.S. 311 (1981) 19
Demahy v. *Actavis, Inc.*, 593 F.3d 428 (5th Cir.), petition for cert. pending, No. 09-1501 (filed June 7, 2010) 22
Dolan v. *United States*, 130 S. Ct. 2533 (2010) 21
Geier v. *American Honda Motor Co.*, 529 U.S. 861 (2000) 11
Hines v. *Davidowitz*, 312 U.S. 52 (1941) 20
Koch v. *Southern Pac. Transp. Co.*, 547 P.2d 589 (Or. 1976) 20
Kordel v. *United States*, 335 U.S. 345 (1948) 4

Cases—Continued: Page

Medtronic, Inc. v. *Lohr*, 518 U.S. 470 (2005) 12
Riegel v. *Medtronic, Inc.*, 552 U.S. 312 (2008) 11
Wyeth v. *Levine*, 129 S. Ct. 1187 (2009) . . . . . *passim*

Statutes and regulations:

Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 3
Federal Food, Drug and Cosmetic Act, 21 U.S.C. 301 *et seq.* 2
21 U.S.C. 321(m) 3, 17
21 U.S.C. 321(n) 2, 3
21 U.S.C. 331(a) 2, 3
21 U.S.C. 331(b) 2, 3
21 U.S.C. 331(k) 2, 3
21 U.S.C. 352 . . . . . 2, 16
21 U.S.C. 352(a) 3, 15
21 U.S.C. 352(f) 3, 15
21 U.S.C. 352(j) 3, 15
21 U.S.C. 352(n) 3, 15
21 U.S.C. 355(a) 2
21 U.S.C. 355(b) 2
21 U.S.C. 355(b)(1) 2
21 U.S.C. 355(b)(1)(F) 4
21 U.S.C. 355(d) 2, 4
21 U.S.C. 355(d)(1) 2
21 U.S.C. 355(d)(5) 2
21 U.S.C. 355(e) 16
21 U.S.C. 355(j) 3, 5, 14
21 U.S.C. 355(j)(2)(A)(ii) 3
21 U.S.C. 355(j)(2)(A)(iv) 3

Statutes and regulations—Continued: Page

21 U.S.C. 355(j)(2)(A)(v) 3, 5
21 U.S.C. 355(j)(4)(G) 4, 13, 16
21 U.S.C. 355(j)(7) 3
21 U.S.C. 355(k) 5
21 U.S.C. 355(o)(4) (Supp. II 2008) 16
21 U.S.C. 393(b)(2)(B) 2
Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 16
21 C.F.R.:
Section 200.5 7
Section 201.56(e) 4
Section 201.57(e) (2001) 4, 6, 15
Section 201.80 4
Section 201.100(c)(1) 4
Section 201.100(d) 4
Section 201.100(d)(3) 4
Section 202.1(*l*)(2) 4, 17
Section 314.3(b) 6
Section 314.70 . . . . . 6, 17
Section 314.70 (2001) 6, 15
Section 314.70(a) (2001) 12
Section 314.70(b) (2001) 6
Section 314.70(b)(3) (2001) 6
Section 314.70(b)(3) (2005) 23
Section 314.70(b)(3)(i) (2001) 14
Section 314.70(c) (2001) 7
Section 314.70(c)(2)(i) (2001) 7
Section 314.70(c)(4) (2005) 23
Section 314.71(c) (2001) 23

Regulations—Continued: Page

Section 314.80(a) 6, 15
Section 314.80(c) 6, 15
Section 314.81(b)(2)(i) 6, 15
Section 314.94(a)(8)(ii) 5
Section 314.94(a)(8)(iii) 5, 13
Section 314.94(a)(8)(iv) 3, 5
Section 314.97 . . . . . 6, 13
Section 314.98(a) 6, 15
Section 314.105(c) 4, 5
Section 314.150(b)(3) 17, 18
Section 314.150(b)(10) 13

Miscellaneous:

Center for Drug Evaluation and Research:
Guidance for Industry: Changes to an Approved NDA or ANDA (Nov. 1999) 14
Manual of Policies and Procedures:
(May 9, 2001) 16
(July 2, 2003) 7, 17
Division of Generic Drugs, FDA, Policy and Procedure Guide (1989) 5
50 Fed. Reg. 7470 (1985) 2
54 Fed. Reg. 28,884 (1989) 5
57 Fed. Reg. 17,961 (1992) 5, 14, 16
69 Fed. Reg. 18,764 (2004) 6
71 Fed. Reg. (2006):
p. 3988 4
p. 3996 4
H.R. Rep. No. 857, 98th Cong., 2d Sess. Pt. 1 (1984) 20

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BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

This brief is submitted in response to the Court's order inviting the Solicitor General to express the views of the United States. In the view of the United States, the petitions for writs of certiorari should be denied.

STATEMENT

Petitioners manufactured the generic pharmaceutical metoclopramide. These petitions arise from respondent's suit alleging, *inter alia*, that she was injured because petitioners failed to adequately warn that long-term use of that prescription drug could cause tardive dyskinesia.

The question presented is whether federal law governing generic drugs and drug labeling preempts respondent's failure-to-warn claims under Minnesota law.

1. 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).

a. To obtain FDA approval to market a new drug, a manufacturer may 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. 7470 (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 of 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 referenced listed drug (RLD), *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 RLD. 21 U.S.C. 355(j)(2)(A)(v).[1]

b. 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

[1] This brief omits discussion of the limited permitted differences, see 21 C.F.R. 314.94(a)(8)(iv), because they are not relevant on the facts alleged here.

one to the other is necessary." *Kordel* v. *United States*, 335 U.S. 345, 350 (1948); see 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) (2001); see 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 [RLD]." 21 U.S.C.

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[2] After the events in this case, the labeling regulations were revised. The standards for older drugs—including metoclopramide—are (as relevant here) essentially unchanged, but now appear at 21 C.F.R. 201.56(e) and 201.80. See 71 Fed. Reg. 3988, 3996 (2006). This brief discusses only older drugs and cites the standards as codified in 2001.

355(j)(4)(G). This requirement reflects the fundamental premise of the ANDA process that a generic drug can be relied upon as a therapeutic equivalent of its RLD. See 54 Fed. Reg. 28,884 (1989) ("[T]he purpose of [21 U.S.C. 355(j)] * * * is to ensure 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 57 Fed. Reg. 17,961 (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 RLD'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 [RLD]," 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 [RLD]." 21 U.S.C. 355(j)(4)(G); see 21 C.F.R. 314.105(c).

c. 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) (2001). 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 proceed to change its approved labeling by filing a "supplemental application" (also known as a "supplement"). See 21 C.F.R. 314.70 (2001).[3] ANDA holders must "comply with the requirements [applicable to NDA holders] 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 (PAS) to its approved NDA or ANDA. 21 C.F.R. 314.70(b) and (b)(3) (2001). Certain other changes—including changes to ap-

[3] Because the events in this case occurred before the supplemental application regulations at 21 C.F.R. 314.70 were revised in 2004, 69 Fed. Reg. 18,764, this brief discusses only the pre-2004 regulations and agency guidance.

proved labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction"—are brought to FDA's attention "at the time the applicant makes [the] change" through a "changes being effected" (CBE) supplement. 21 C.F.R. 314.70(c) and (c)(2)(i) (2001); see *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" (DHCP) 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).

2. According to the allegations in respondent's complaint, in March 2001, her physician prescribed Reglan, the brand-name version of metoclopramide, to treat her diabetic gastroparesis. Respondent's pharmacist filled this prescription with generic metoclopramide sold by petitioners. Respondent took metoclopramide for four years and developed tardive dyskinesia. Pet. App. 3a.[4]

When respondent first took metoclopramide, 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

[4] All references are to the petition appendix in No. 09-993.

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 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.[5]

3. Respondent sued petitioners and others alleging, as relevant here, that the metoclopramide she took was defective because petitioners failed to adequately warn of the risks of long-term use. Respondent contended that "despite mounting evidence [before and during her period of metoclopramide use] that long term metoclopramide use carries a risk of tardive dyskinesia far greater than indicated on the label, no metoclopramide manufacturer took steps to change the label warnings." Pet. App. 3a. Respondent's amended complaint alleges that petitioners "[f]ailed to [a]ct as [r]equired by the FDA" with respect to the labeling of their products. Dkt. 48 at 13.

As relevant here, petitioners moved to dismiss or for summary judgment. The district court granted the motions, holding that respondent's failure-to-warn claims were preempted. Pet. App. 24a-48a, 55a-58a. Respondent offered three mechanisms by which petitioners could have satisfied their state law duty to warn consistent with the FDCA and FDA regulations. Respondent first argued that petitioners could have changed their approved labeling using the CBE process. The district court rejected that argument because it concluded that the CBE process was unavailable to generic manufactur-

[5] The quoted language is drawn from the approved Reglan tablet package inserts, available through http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

ers, and any change would have contravened the Hatch-Waxman Amendments' requirement that the generic labeling be the "same as" the brand-name drug's label. *Id.* at 36a-46a. Respondent also argued that petitioners could have sent DHCP letters or sought FDA's approval to change their approved labeling using the PAS process. The district court rejected those arguments as well. *Id.* at 46a-47a.

4. The court of appeals reversed in relevant part. Pet. App. 1a-23a. It declined to decide whether the CBE process was available to petitioners, concluding that the PAS process was available to petitioners, so they "could have at least *proposed* a label change that the FDA could receive and impose uniformly on all metoclopramide manufacturers if approved." *Id.* at 11a. The court pointed to a variety of FDA regulations and statements expressing "FDA's expectation that generic manufacturers will initiate label changes other than those made to mirror changes to the name brand label." *Id.* at 13a. Similarly, with respect to DHCP letters, the court concluded that petitioners "could have suggested that the FDA send out a warning letter," although it determined that "Congress did not intend that generic manufacturers send out [DHCP] letters uncoordinated with other manufacturers." *Id.* at 14a & n.5.

The court of appeals rejected the district court's conclusion that uncertainty about what action FDA might have taken in response to such a request was a reason to bar liability. The court explained that *Wyeth* "made it clear * * * that uncertainty about the FDA's response * * * makes federal preemption less likely," because "[petitioners] must show the likelihood of FDA *in*action." Pet. App. 15a, 16a. The court found no evidence in the

record suggesting FDA would have rejected a labeling proposal from petitioners. *Id.* at 16a.

The court of appeals also rejected petitioners' argument that permitting state failure-to-warn claims would unacceptably frustrate the Hatch-Waxman Amendments' purpose of encouraging development of low-cost generic drugs. The court of appeals explained that Congress did not intend those Amendments to override "the fundamental requirement of the FDCA that all marketed drugs remain safe." Pet. App. 19a. In that regard, the court continued, "Congress and the FDA have long viewed state tort law as complementing, not obstructing, the goals of the FDCA." *Ibid.* (citing *Wyeth*, 129 S. Ct. at 1197, 1199-1200).

DISCUSSION

The court of appeals correctly rejected petitioners' contention that respondent's failure-to-warn claims are categorically preempted by the FDCA, and its decision is consistent with the decision of the only other court of appeals to address the question since *Wyeth* v. *Levine*, 129 S. Ct. 1187, 1196 (2009). The court of appeals misunderstood FDA's regulations in some respects, but its decision correctly reflects the essential point that federal law may circumscribe, but does not outright bar, possible theories of recovery by respondent. Moreover, because those theories are at present undeveloped, this case's interlocutory posture makes it an unsuitable vehicle for considering the preemption questions petitioners raise. Accordingly, the Court should deny review.

A. The Court Of Appeals Correctly Held That Respondent's Claims Are Not Categorically Preempted

The court of appeals correctly held that respondent's 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. The court of appeals also correctly concluded that petitioners could have asked FDA to coordinate appropriate DHCP letters (or, by extension, to take other action with respect to labeling). Furthermore, the district court correctly concluded that the CBE process was unavailable to petitioners, and that holding was undisturbed by the court of appeals. The court of appeals incorrectly concluded that the PAS process was intended for petitioners' use, but that error is unlikely to affect future proceedings. Finally, the court of appeals correctly concluded that holding a generic pharmaceutical manufacturer liable on a failure-to-warn theory would not unacceptably frustrate the purposes of the Hatch-Waxman Amendments.

1. 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). Petitioners contend that because federal law required them to maintain labeling for their generic drugs that was the same as the labeling of the RLD, it was impossible for them to warn respondent about risks posed by the long-term use of metoclopramide (beyond the warnings already approved for the RLD). 09-993 Pet. 23; 09-1039 Pet. 10-11.

Petitioners' premise is correct, but it does not support their conclusion.

a. Respondent does not contend that state law required petitioners to withdraw their products altogether from the market. Rather, her claims rest on the products' labeling, and she alleges that petitioners 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. See pp. 3-4, *supra*. 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 1197-1198. In that regard, "state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Id.* at 1202-1203. 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, 447-448 (2005); *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 495 (1996).

b. The parties dispute the federal duties incumbent on petitioners and the methods available to petitioners under the FDCA to affect the labeling of their products. The holder of an approved ANDA is not free to change its approved labeling at will. See 21 C.F.R. 314.70(a)

(2001). At the time of the events in this case: (1) an ANDA holder in petitioners' position could not unilaterally change its approved labeling under the CBE process; (2) the PAS 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 DHCP letters of the kind respondent seems 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, 842-843 (1984).

i. The district court correctly concluded that the CBE process was not available to petitioners to unilaterally change their drugs' approved labeling, and the court of appeals did not disturb that holding, see Pet. App. 11a. FDA's CBE regulation applies to ANDA holders. See 21 C.F.R. 314.97. But supplements are subject to the substantive standards governing applications, so the CBE 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 [RLD]." 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) (ANDA approval may be withdrawn if the drug's labeling "is no longer consistent with that for the [RLD]").

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. at 17,961. 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." *Ibid.* 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. *Ibid.*; see pp. 15-17, *infra*. 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 (Nov. 1999) ("All labeling changes for ANDA products must be consistent with [21 U.S.C. 355(j)]."") (reproduced at App., *infra*, 1a-4a).[6]

ii. The PAS process also was not expressly available to petitioners to make the labeling change respondent seems to envision. As relevant here, the PAS 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) (2001). That exception is a cross-reference to the CBE provision for added or strengthened warnings, which respondent says describes the labeling change that petitioners should have made here. See

[6] The CBE process was available for an ANDA holder to conform its approved labeling to updated RLD approved labeling because, under those circumstances, the change would be consistent with the substantive requirements for generic labeling.

Resp. C.A. Br. 23-26. Such changes were therefore not intended to be made through the PAS process.

iii. Although no formal supplement process under 21 C.F.R. 314.70 (2001) was expressly available to petitioners, 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) (2001); see 21 U.S.C. 352(a), (f), (j) and (n). Moreover, petitioners had a duty to inform FDA of certain adverse events (see 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 [RLD]," 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 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 this case, FDA would have used intra-agency consultations to sub-

[7] At the time of the events in this case, 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.

ject any serious safety concerns to a substantive evaluation like that for a supplement under 21 C.F.R. 314.70.

iv. The court of appeals misunderstood the status of DHCP letters under the FDCA and FDA's regulations, but nonetheless reached the correct result in this case. Contrary to the court of appeals' view, nothing in the FDCA or FDA's regulations categorically forbids an ANDA holder from unilaterally sending such correspondence. Rather, much like promotional material, DHCP letters may be reviewed by FDA for compliance with the FDCA and FDA regulations governing matters such as misbranding. See *MAPP* 6020.10 (July 3, 2003).

Nonetheless, ANDA holders do not customarily send DHCP letters without coordinating with FDA. Apart from the practical benefits to coordinating with FDA, ANDA holders also operate under a regulatory constraint. DHCP letters sent by a generic manufacturer could potentially affect the perceived therapeutic equivalence of the generic drug and its RLD counterpart. See p. 5, *supra*. Thus, because DHCP letters are "labeling," see pp. 3-4, *supra*, 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 DHCP letter from an ANDA holder could inaccurately imply therapeutic differences between the generic drug and its RLD 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 RLD. By contrast, an ANDA holder's letter warning about risks seemingly

unique to its product could mislead consumers and providers into believing that the generic drug and RLD were not therapeutic equivalents.[8]

Respondent seems to envision DHCP correspondence of the latter sort, 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 little practical difference for purposes of this tort suit between proposing a DHCP 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 RLD and its generic equivalents.

c. In short, the court of appeals correctly held that FDA mediates the channels available to an ANDA holder under federal law for disseminating strengthened warnings (though the court misunderstood precisely which processes were appropriate). Petitioners argue that state tort law conflicts with that regime because proposing a warning to FDA "would not make the labeling for metoclopramide any more adequate under Minnesota common law"; "[o]nly a *change* in the labeling would satisfy the state law duty." 09-1039 Pet. 13; see 09-993 Pet. 20.

We may assume, *arguendo*, that petitioners are correct that state law would be preempted to the extent it would hold them liable without regard to how FDA would

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[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).

have acted on a hypothetical warning proposal.[9] For absent FDA's assent, petitioners could not lawfully have disseminated their product with the sort of warning respondent seems to propose. But the court of appeals did not suggest otherwise: It did not describe respondent's theory as resting on petitioners' failure to communicate warnings to their customers (something ultimately in FDA's control). Rather, it described her theory as resting on "[petitioners'] failure *to take steps* to warn their customers." Pet. App. 17a (emphasis added); see *id.* at 3a, 11a. Moreover, in observing that the record before it did not "suggest the FDA would have rejected a labeling proposal from [petitioners]," the court of appeals appeared to anticipate that the parties could litigate on remand the question of what action FDA would have taken in response to a hypothetical warning proposal from petitioners. *Id.* at 16a.

The court concluded that petitioners would bear the burden of "show[ing] the likelihood of FDA *in*action." Pet. App. 16a. That allocation—which ultimately turns on litigation considerations, not an interpretation of the FDCA or FDA's regulations—is reasonable. 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*

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[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). Petitioners do not contend FDA made such a decision here.

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 proceedings on remand to the district court is not the focus of the questions presented in the petitions, which contend instead that respondent's claims may not proceed at all. See 09-993 Pet. i; 09-1039 Pet. i. And with respect to that issue, the court of appeals correctly held that respondent's claims are not categorically preempted.

2. 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). Petitioners contend that Congress's "primary 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. 09-993 Pet. 20-22; 09-1039 Pet. 10-11.

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, this 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 preemption 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 petitioners' 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, petitioners overstate the costs involved, and hence the effect of the court of appeals' decision on the market for generic pharmaceuticals. The court of ap-

peals understood respondent to allege that petitioners could have obtained sufficient grounds for a labeling change simply from published literature on metoclopramide and adverse event reports. See Pet. App. 18a. Petitioners disagree with that as a factual matter, suggesting a far broader knowledge base would have been necessary. See 09-993 Pet. 21. 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 respondent's complaint raises. But the modest duty actually posited in respondent's complaint seems unlikely to affect the availability of generic pharmaceuticals.

B. There Is No Conflict In The Courts Of Appeals

Petitioners do not contend there is any conflict among the courts of appeals on the question presented. Since this Court's decision in *Wyeth*, both courts of appeals to decide the question presented have concluded that state law failure-to-warn claims against generic pharmaceutical manufacturers are not preempted, because the manufacturers could have sought FDA approval of added or strengthened warnings. See Pet. App. 11a-17a; *Demahy* v. *Actavis, Inc.*, 593 F.3d 428, 436-439, 444-445 (5th Cir.), petition for cert. pending, No. 09-1501 (filed June 7, 2010).[10]

[10] In *Demahy*, the Fifth Circuit held that the CBE process was available to an ANDA holder to make a unilateral change in its approved labeling. 593 F.3d at 439-444. Although that holding misunderstands FDA's regulations, see pp. 13-14, *supra*, it is nonetheless compatible with the court of appeals' decision below, which did not resolve whether the CBE process was available, see Pet. App. 11a. Moreover, FDA applies the same standards to evaluate both PAS and CBE supple-

The Sixth Circuit has heard oral argument on the issue, and invited FDA to submit its views. See *Smith* v. *Wyeth, Inc.*, No. 09-5460; *Wilson* v. *Pliva, Inc.*, No. 09-5466; *Morris* v. *Wyeth, Inc.*, No. 09-5509. And the Ninth Circuit recently heard argument in *Gaeta* v. *Perrigo Pharms. Co.*, No. 09-15001, which raises the same question, but in the context of an over-the-counter drug. Should one of those cases result in a split of authority, this Court would likely have another opportunity to address the question presented. But given the current agreement in the courts of appeals, review is unwarranted at this time.

C. The Interlocutory Posture Of This Case Makes It Unsuitable For Review

Unlike *Wyeth*, which arose after a jury verdict, this case is interlocutory and arose on early motions to dismiss or for summary judgment. Consequently, the record here is underdeveloped on several legal and factual issues that could materially affect this Court's examination of issues relevant to preemption. For example, the scope of petitioners' duty under state law seems disputed (see pp. 18-19, *supra*); it is unclear whether the disagreement between the Fifth Circuit in *Demahy* and the district court below—over whether the CBE process was available to ANDA holders—will be outcome-determinative (see note 10, *supra*); respondent has not articulated precisely what warning she contends petitioners should

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ments, see 21 C.F.R. 314.70(b)(3) and (c)(4) (2005), 314.71(c) (2001), and would have applied a similar standard to evaluate whether new information submitted by an ANDA holder warranted a change to approved labeling, see pp. 16-17, *supra*. Thus, in practical terms, the Fifth Circuit's CBE holding bears principally on how quickly the defendant manufacturer could have put a hypothetical change into effect.

have proposed to FDA; and there is no evidence of how FDA would have responded to such a proposal (see Pet. App. 16a). Those many uncertainties further counsel against review at this time.

CONCLUSION

The petitions for writs of certiorari should be denied.

Respectfully submitted.

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NOVEMBER 2010

APPENDIX

Guidance for Industry

Changes to an Approved NDA or ANDA

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
November 1999
CMC #

(1a)

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[24]

X. LABELING

A. General Considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. An applicant should promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations. All labeling changes for ANDA products must be consistent with section 505(j) of the Act.

B. Major Changes (Prior Approval Supplement)

Any proposed change in the labeling, except those that are designated as moderate or minor changes by regulation or guidance, should be submitted as a prior approval supplement. The following list contains some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.

4. Changes based on data from preclinical studies.

5. Revision (expansion or contraction) of population based on data.

6. Claims of superiority to another product.

7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

C. Moderate Changes (Supplement—Changes Being Effected)

[25]

A changes being effected supplement should be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product, (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness, or (5) is specifically requested by FDA. The submission should include 12 copies of final printed labeling. The following list includes some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.

2. Addition of a precaution arising out of a postmarketing study.

3. Clarification of the administration statement to ensure proper administration of the product.

4. Labeling changes, normally classified as major changes, that FDA specifically requests be implemented using a changes being effected supplement.

D. Minor Changes (Annual Report)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report. The following list includes some examples that are currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201), without a change in the content of the labeling.

2. Editorial changes, such as adding a distributor's name.

3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.

4. Labeling changes made to comply with an official compendium.

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