

Nos. 09-993, 09-1039 and 09-1501

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**In the Supreme Court of the United States**

PLIVA, INC., ET AL., PETITIONERS

*v.*

GLADYS MENSING

ACTAVIS ELIZABETH, LLC, PETITIONER

*v.*

GLADYS MENSING

ACTAVIS, INC., PETITIONER

*v.*

JULIE DEMAHY

*ON WRITS OF CERTIORARI  
TO THE UNITED STATES COURTS OF APPEALS  
FOR THE FIFTH AND EIGHTH CIRCUITS*

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**BRIEF FOR THE UNITED STATES  
AS AMICUS CURIAE SUPPORTING RESPONDENTS**

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**QUESTION PRESENTED**

Whether federal law preempts state law causes of action based on a claim that a generic drug approved by the Food and Drug Administration was inadequately labeled.

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**INTEREST OF THE UNITED STATES**

These cases concern the circumstances in which state law may hold the manufacturer of a generic drug approved by the Food and Drug Administration (FDA) liable for failing to warn of hazards associated with the drug. At the Court's invitation, the United States filed a brief at the petition stage of two of these cases.

## STATEMENT

Petitioners manufactured the generic prescription drug metoclopramide. Respondents sued petitioners alleging, *inter alia*, that they were injured because petitioners failed to adequately warn that long-term use of that drug could cause tardive dyskinesia. The question presented is whether federal law governing generic drug labeling preempts respondents' failure-to-warn claims under state law.

1. FDA regulates the manufacture, sale, and labeling of prescription drugs 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 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). Moreover, 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 labeling. See 21 U.S.C. 355(b)(1)(F) and (d); 21 C.F.R. 314.105(c) and .125(b)(8). 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 as such by FDA (see 21 U.S.C. 355(j)(7)), and subject to certain periods of NDA exclusivity (see 21 U.S.C. 355(j)(5)(F)), any manufacturer may seek approval to market a generic version under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, known as the Hatch-Waxman Amendments. Those Amendments prescribe 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 or 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 (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 FDCA requires a manufacturer to 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); see also 21 U.S.C. 355(j)(4)(G). An ANDA therefore must include 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); see 21 C.F.R. 314.105(c). 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) (Section 355(j) is intended “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).

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) and (j). 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 21 C.F.R. 202.1(l)(2). Some labeling—for example, the package insert and other proposed labeling submitted in an NDA under 21 U.S.C. 355(b)(1)—requires FDA’s approval and is thus referred to as “approved labeling.” Other labeling—for example,

promotional materials and some communications by manufacturers to physicians—does not require such approval, although it must be consistent with the drug’s approved labeling, 21 C.F.R. 201.100(d)(1), and a copy must be supplied to FDA for review, 21 C.F.R. 314.81(b)(3)(i).

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 professionals to “use the drug safely and for the purposes for which it is intended.” 21 C.F.R. 201.100(e)(1). FDA regulations further establish specific requirements for any 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 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).<sup>1</sup>

c. Information on the risks and benefits associated with a drug may accumulate over time. Accordingly, NDA and ANDA holders must keep records of clinical experiences and ensure that their drugs remain safe and

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<sup>1</sup> In 2006—after the events in *Mensing* (see J.A. 180-181) and very late in the events in *Demahy* (see J.A. 434-435)—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 .80. See 71 Fed. Reg. 3988, 3996 (2006). This brief discusses only older drugs and cites the standards as codified in 2001 and 2002, which is when respondents allege they were first prescribed metoclopramide (J.A. 180, 434).

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),<sup>2</sup> and must also annually report 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 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). That regulation implements the FDCA’s provision that a drug that lacks “adequate warnings” is misbranded. 21 U.S.C. 352(f)(2); see 44 Fed. Reg. 37,447 (1979) (citing 39 Fed. Reg. 33,229 (1974)).

A manufacturer may proceed to change its approved labeling by filing a “supplemental application” (also

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<sup>2</sup> FDA interprets 21 C.F.R. 314.80, “Postmarketing reporting of adverse drug experiences,” to impose requirements upon all sponsors, including ANDA holders. Those requirements cannot be viewed in isolation or selectively applied to ANDA holders, as the PLIVA petitioners assert (Br. 19). To comply with Section 314.80(c)’s reporting requirements, sponsors determine which adverse drug experiences meet the definitions in Section 314.80(a) and should be reported—an exercise that involves some measure of “review” as described in Section 314.80(b). The “scientific literature” and “postmarketing study” provisions in Section 314.80(d) and (e) are not freestanding obligations, but rather specific rules for reporting adverse drug experience information acquired through those channels.

known as a “supplement”). See 21 C.F.R. 314.70 (2001).<sup>3</sup> 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 all the requirements of the FDCA and FDA’s regulations that apply to original applications.

All changes to a drug’s approved labeling require FDA’s assent. Certain changes require FDA’s prior approval, which a manufacturer seeks by submitting a prior approval supplement (PAS). 21 C.F.R. 314.70(b) and (b)(3) (2001). 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 “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). Manufacturers sometimes also 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

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<sup>3</sup> The bulk of the events in these cases (see J.A. 180-181, 434-435) occurred before the 2004 revision of the supplemental application regulations at 21 C.F.R. 314.70 (see 69 Fed. Reg. 18,764). Accordingly, this brief discusses only the pre-2004 regulations and agency guidance. The parties have not suggested, and we have not identified, anything in the 2004 revision that would materially affect these cases.

for such correspondence). DHCP letters are “labeling” under 21 U.S.C. 321(m) and 21 C.F.R. 202.1(l)(2).<sup>4</sup>

2. According to the allegations in respondents’ operative complaints, their physicians prescribed Reglan, the brand-name version of metoclopramide, in March 2001 to treat Mensing’s diabetic gastroparesis, and in October 2002 to treat Demahy’s gastroesophageal reflux disease. Respondents’ pharmacists filled those prescriptions with generic metoclopramide sold by one or more petitioners. Respondents each took metoclopramide for several years, and each developed tardive dyskinesia. J.A. 179-182, 433-435.

When respondents 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 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.<sup>5</sup>

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<sup>4</sup> Manufacturers also supply information about their drugs for compilations such as the *Physicians’ Desk Reference*, a publication mentioned in Demahy’s complaint, J.A. 438-439. Such submissions are also labeling, see 21 C.F.R. 202.1(l)(2), but because respondents’ brief does not discuss them, this brief discusses only DHCP letters.

<sup>5</sup> The quoted language is drawn from the approved Reglan tablet package inserts, available through <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. See also Actavis Br. 8-12 & nn.3-8.

3. Respondents separately sued certain manufacturers of metoclopramide (some of whom are petitioners here) alleging that the metoclopramide each took was defective because petitioners failed to adequately warn of the risks of long-term use. Mensing 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.” J.A. 402 (court of appeals’ opinion). Her amended complaint alleges that petitioners “[f]ailed to [a]ct as [r]equired by the FDA” with respect to the labeling of their drugs, and that “the package insert for \* \* \* metoclopramide substantially understated the prevalence of acute and long term side effects of ingesting the drug,” J.A. 192, 194.

Similarly, Demahy contended that Actavis, Inc. “ignored scientific and medical literature establishing a higher risk of developing tardive dyskinesia [than suggested by its drug’s labeling], failed to request a labeling revision from the FDA, failed to change the label itself \* \* \*, and failed to report safety information directly to the medical community.” J.A. 522 (court of appeals’ opinion). Her amended complaint alleges Actavis, Inc. “failed to fully, truthfully and accurately disclose \* \* \* metoclopramide data to the FDA,” and that “the package insert \* \* \* for Reglan did not adequately inform physicians about the risks associated with \* \* \* metoclopramide,” J.A. 437, 439.

As relevant here, petitioners moved to dismiss or for summary judgment. The *Mensing* district court granted the motions, holding that failure-to-warn claims

were preempted. J.A. 364-399. The *Demahy* district court denied the motion, holding that failure-to-warn claims could proceed, except “to the extent [they] constitute[] a fraud-on-the-FDA claim” preempted under *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 348 (2001). J.A. 477-519. It certified its order for interlocutory appeal under 28 U.S.C. 1292(b). J.A. 424.

4. The courts of appeals, addressing largely identical preemption arguments advanced by petitioners, held that respondents’ failure-to-warn claims could proceed.<sup>6</sup> J.A. 400-421, 520-563.

Countering petitioners’ defense that federal law made it impossible for them to alter their drugs’ labeling, respondents offered three mechanisms by which petitioners could have satisfied their state law duty to warn consistent with the FDCA and FDA regulations. Respondents first argued that petitioners could have changed their approved labeling using the CBE process. The *Demahy* court concluded that the CBE process was available to Actavis, Inc., just as it was to the NDA holder in *Wyeth*, based on the court’s belief that FDA’s regulations requiring “that a generic’s label initially conform to the [RLD’s label] \* \* \* do not address post-approval modifications at all.” J.A. 535; see J.A. 542-551. The *Mensing* court declined to decide whether the CBE process was available to petitioners. See J.A. 412.

Respondents also argued that petitioners could have sent warning DHCP letters or sought FDA’s approval to change their approved labeling using the PAS pro-

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<sup>6</sup> *Demahy* did not appeal the district court’s decision regarding the fraud-on-the-FDA aspect of her claim, so that determination is not before this Court.

cess. Both courts of appeals agreed that petitioners could have sought a change through the PAS process, see J.A. 412, 551-552, or asked FDA to coordinate a DHCP letter, see J.A. 413 & n.5, 552-553, while recognizing it would have been inappropriate for petitioners to send such letters on their own, *ibid.* Both courts of appeals also rejected petitioners' argument that uncertainty about what action FDA might have taken in response to such requests was a reason to bar liability. In their view, *Wyeth* "made it clear \* \* \* that uncertainty about the FDA's response \* \* \* makes federal preemption less likely," because "[t]o support preemption [petitioners] must show the likelihood of FDA *inaction.*" J.A. 414-415; accord J.A. 555-556. Each court found no evidence in the record before it suggesting FDA would have rejected a labeling proposal from petitioners. J.A. 415, 556.

The courts of appeals also rejected petitioners' arguments that permitting state law failure-to-warn claims would unacceptably frustrate the Hatch-Waxman Amendments' purpose of encouraging development of low-cost generic drugs. J.A. 416-418, 557-562. The courts explained that Congress did not intend the Hatch-Waxman Amendments to override "the fundamental requirement of the FDCA that all marketed drugs remain safe." J.A. 417; accord J.A. 561.

#### SUMMARY OF ARGUMENT

Petitioners contend they could not deliver whatever additional warnings state law required while remaining faithful to FDA's labeling regulations and the Hatch-Waxman Amendments' requirement that a generic drug's approved labeling be the "same as" the brand-name drug's approved labeling. They further claim that

any approach that reconciles state and federal law would impermissibly intrude on FDA's authority. They therefore conclude that respondents' claims must be pre-empted.

That reasoning is incorrect. FDA regulations require NDA holders and ANDA holders alike to act upon new safety information that warrants added or strengthened warnings. Petitioners are correct that, in meeting that federal duty, they could not properly have invoked the CBE or PAS process, or sent the sort of DHCP letter respondents envision. But ANDA holders nonetheless "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.

In particular, a drug is misbranded under the FDCA if "its labeling [does not] bear[] \* \* \* adequate warnings \* \* \* against unsafe dosage or methods or duration of administration or application." 21 U.S.C. 352(f)(2). FDA in turn imposes on manufacturers a duty that a prescription drug's approved "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). This reflects the "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Wyeth*, 129 S. Ct. at 1197-1198. When Section 201.57(e) obligates an applicant to revise its label, and both generic and brand-name drugs are affected, it is appropriate to assume that FDA (once informed of the relevant new information) will pursue an orderly process to ensure appropriate changes are made.

The question for preemption purposes, therefore, is whether the generic drugs respondents took were misbranded under 21 U.S.C. 352(f)(2) and the standard in 21 C.F.R. 201.57(e) (2001). That approach reconciles the Hatch-Waxman Amendments’ “same as” requirement with the FDCA’s misbranding standard and FDA’s implementing regulation. It fulfills Congress’s intention that failure-to-warn suits would “provide[] appropriate [compensatory] relief for injured consumers” and “motiv[at]e manufacturers \* \* \* to give adequate warnings. *Wyeth*, 129 S. Ct. at 1199-1200. And it avoids the inconsistency in petitioners’ position, under which individuals harmed by inadequately labeled generic drugs would have no remedy against the manufacturer, while individuals who took the same drug with the same labeling in its brand-name form would (by virtue of *Wyeth*) have such a remedy.

Those considerations lose force, however, if the drugs were not misbranded under federal law. Moreover, even if an ANDA holder had proposed a labeling change in that situation, FDA would not have engaged with the RLD sponsor to revise its labeling. At this stage of the case, however, assuming the truth of respondents’ allegations—which effectively plead that petitioners’ drugs were misbranded and that the Section 201.57(e) duty was triggered—respondents’ cases should be allowed to proceed.

#### ARGUMENT

#### **RESPONDENTS’ FAILURE-TO-WARN CLAIMS ARE NOT CATEGORICALLY PREEMPTED**

A state tort claim is preempted if it is impossible for a plaintiff to comply with both the state law duty underlying the claim and federal regulatory requirements.

*Wyeth*, 129 S. Ct. at 1196. 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 statutes and regulations. See *Williamson v. Mazda Motor of Am., Inc.*, No. 08-1314, slip op. 5 (Feb. 23, 2011); *Wyeth*, 129 S. Ct. at 1199. “[T]he purpose of Congress is the ultimate touchstone in every pre-emption case.” *Wyeth*, 129 S. Ct. at 1194 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)).

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, they cannot be held liable for failing to warn respondents about the risks of long-term metoclopramide use (beyond the warnings already approved for the RLD). Petitioners’ argument fails to take account of the substantive and procedural framework under the FDCA and FDA’s implementing provisions for revising labeling to reflect associations between a drug and a serious hazard. ANDA holders, like NDA holders, have a duty under federal law to propose appropriate changes to approved labeling to communicate warnings about serious drug hazards. When that duty is triggered, and the ANDA holder does not act upon it, the plaintiff’s claim is not preempted.

**A. Petitioners Could Have Sought Changes To Their Drugs’ Approved Labeling Under The Circumstances Alleged By Respondents**

As respondents point out (Br. 22), petitioners now “concede that they could have asked FDA to approve stronger warnings for both Reglan and generic metoclopramide.” Respondents continue to suggest, however,

that petitioners could also have used certain FDA regulations to revised their approved labeling in ways the agency does not recognize as permissible. The courts below similarly offered their own interpretations of FDA’s regulations that FDA has since informed this Court are mistaken. See Gov’t Pet. Stage Amicus Br. 12-18, 22 n.10. In summary, petitioners could not properly have invoked the CBE or PAS process, or sent the sort of DHCP letter respondents envision. But an ANDA holder nonetheless should have provided FDA with new information about risks. This Court will “defer to [FDA’s] interpretation of its own regulation[s] \* \* \* unless that interpretation is ‘plainly erroneous or inconsistent with the regulation[s].’” *Chase Bank USA, N.A. v. McCoy*, 131 S. Ct. 871, 880 (2011) (citing *Auer v. Robbins*, 519 U.S. 452, 461 (1997)); see *Chevron U.S.A. Inc. v. NRDC*, 467 U.S. 837, 842-843 (1984).

a. The CBE process was not available to petitioners to unilaterally change their drugs’ approved labeling. FDA’s CBE regulation does apply to ANDA holders. See 21 C.F.R. 314.97. But ANDA supplements are subject to the substantive standards governing ANDAs, so the CBE regulation must be read in conjunction with FDA’s regulations pertaining specifically to ANDAs. Those regulations require a generic drug’s proposed 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 approved labeling “is no longer consistent with that for the [RLD]”). As a result, the CBE supplement that respondents say petitioners should have filed—to revise the approved labeling on their products alone—would not have satisfied 21 C.F.R.

314.94(a)(8)(iii)'s "same as" requirement, and therefore would not have been approvable.<sup>7</sup>

The Fifth Circuit's error in *Demahy* with respect to CBE changes traces to its mistaken belief that FDA's regulations requiring "that a generic's label initially conform to the [RLD's label] \* \* \* do not address post-approval modifications at all." J.A. 535; see J.A. 542-551. That is incorrect; supplements are by definition part of the application, see 21 C.F.R. 314.3(b), and therefore must (in combination with the application) satisfy the substantive standards for applications.<sup>8</sup>

Indeed, FDA has consistently taken the position that an ANDA holder may not unilaterally change its approved labeling. For example, in promulgating its final rule implementing labeling requirements for ANDAs, FDA rejected the suggestion that the 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.

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<sup>7</sup> Contrary to respondents' contention (Br. 33-34), the neighboring exception in 21 C.F.R. 314.94(a)(8)(iv) permitting proposed ANDA labeling to differ from the RLD's approved labeling "to comply with current FDA labeling guidelines or other guidance" does not apply on the facts alleged here. That regulation addresses the narrow situation where FDA itself has specifically "require[d] a change in the labeling of a drug product to make available important new information about the safe use of a drug product, but the [RLD's] labeling has not yet been updated to reflect this change." 54 Fed. Reg. at 28,884. There was no such action on FDA's initiative in the period relevant to these cases.

<sup>8</sup> By contrast a CBE supplement is the appropriate process 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.

FDA explained that “[e]xcept for labeling differences due to [issues not relevant here], 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 instead that an ANDA holder wishing to add a warning should furnish adequate supporting information to FDA, which would then determine whether the labeling for all drugs should be modified. *Ibid.*; see pp. 19-21, *infra*. FDA’s guidance on labeling changes reiterates that limitation on changes to an ANDA. Center for Drug Evaluation & Research, *Guidance for Industry: Changes to an Approved NDA or ANDA* 24 (Nov. 1999).

b. The PAS process also was not available to petitioners to make the labeling change respondents 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 respondents say describes the labeling change that petitioners should have made here. See, *e.g.*, Resp. Br. 31. Such changes could therefore not appropriately be made through the PAS process. Moreover, 21 C.F.R. 314.94(a)(8)(iii)’s “same as” requirement would prevent approval of a PAS proposing labeling that would diverge from the RLD’s approved labeling.

Respondents’ reading (Br. 32) of 21 C.F.R. 314.70(b)(3)(i) (2001)—that it simply acknowledges the possibility of a CBE change without ruling out the possibility of a PAS change—may also be linguistically plausible. But FDA does not interpret its regulation that way; rather, FDA’s stated approach (see pp. 19-21, *in-*

*fra*) is that ANDA holders should contact FDA under a less formalized process so that it can pursue orderly changes for all affected drugs. That said, FDA would not have ignored the substantive labeling changes proposed in such a PAS on procedural grounds. Rather, FDA would have construed such a supplement as a request to determine whether the labeling for the RLD and all generic equivalents should be revised.

c. Respondents also argue (Br. 36-37) that petitioners could have sent a DHCP letter to respondents' physicians warning of risks greater than those described in petitioners' drugs' approved labeling. To be sure, nothing in the FDCA or FDA's regulations categorically forbids an ANDA holder from unilaterally sending a DHCP letter. And a DHCP letter can be an appropriate way to bring new information to the attention of medical professionals. But the particular letter respondents envision would only be appropriate in tandem with a corresponding change to the drug's approved labeling. A DHCP letter was not the freestanding option respondents portray it to be.

A DHCP letter is "labeling" under the FDCA and FDA's regulations, 21 C.F.R. 202.1(l)(2), so the manufacturer must provide a copy to FDA, 21 C.F.R. 314.81(b)(3), which will review the letter for compliance with the FDCA and FDA regulations governing matters such as misbranding. See 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).

The DHCP letter respondents envision would have been subject to 21 C.F.R. 201.100(d), which addresses

prescription drug labeling “that furnishes \* \* \* information for use” of the drug. Such labeling must be “consistent with and not contrary to [the drug’s] approved \* \* \* labeling.” 21 C.F.R. 201.100(d)(1). The DHCP letter respondents envision would have violated that provision because its very purpose would have been to depart from what respondents allege was an insufficiently serious warning in the approved labeling about metoclopramide’s long-term risks. Cf. *FDA, Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion 2* n.5 (Draft May 2009) (strongly advising against issuing promotional labeling that includes risk information “not in the product’s approved labeling or appropriate for inclusion in the labeling”).<sup>9</sup>

In addition, under 21 C.F.R. 314.150(b)(3), FDA may withdraw approval of an ANDA if “the labeling of the drug”—which, again, includes DHCP letters—“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.

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<sup>9</sup> Strictly speaking, 21 C.F.R. 201.100 establishes not absolute requirements for prescription drugs, but rather an exemption from otherwise-applicable statutory requirements. It implements 21 U.S.C. 352(f), which provides that a drug is misbranded “[u]nless its labeling bears \* \* \* adequate directions for use,” but further provides that FDA shall exempt a drug from that condition when it is “not necessary for the protection of the public health.” Prescription drugs (for which directions for use are supplied by physicians and pharmacists) are exempted, provided they meet the conditions of 21 C.F.R. 201.100.

d. Even though pursuing the avenues described above would not have been appropriate, petitioners were nonetheless obligated (accepting respondents' allegations as true) to seek to revise their labeling and provide FDA with supporting information about risks. FDA contemplated this situation. In the preamble to the final rule implementing the ANDA application process, it 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. This approach gives FDA the opportunity to use its authority to pursue an orderly process to reconcile 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).<sup>10</sup>

Situations where an ANDA holder alone has a basis to believe stronger warnings should be added to its

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<sup>10</sup> Respondents suggest (Br. 35-36) the same result could be accomplished by filing a citizen petition under 21 C.F.R. 10.30. Although not FDA's preferred procedure, FDA would not refuse to entertain such a petition.

drug's approved labeling have not been known to arise frequently. And when one does, there tend to be unique, fact-specific considerations; as the parties and several amici point out, the Hatch-Waxman Amendments have fostered a diverse marketplace for generic drugs. For that and other reasons, FDA has not promulgated a formal regulation for this process. Instead, the agency has chosen to make available to generic manufacturers points of contact in FDA's Office of Generic Drugs, just as it does for any number of potential issues not specifically provided for by formal regulation. 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 subject any serious safety concerns to a substantive evaluation like that for a supplement under 21 C.F.R. 314.70, and taken action as appropriate. At the time of the events in this case, FDA could have requested (though not directly required) the NDA holder to make appropriate changes to its approved labeling. Had the NDA holder refused, FDA could have withdrawn approval of the application, see 21 U.S.C. 355(e); 21 C.F.R. 314.150(a)(2)—most obviously because the NDA holder's

approved labeling, like the ANDA holder's, would have been inadequate in light of the new information.<sup>11</sup>

**B. A State Failure-To-Warn Claim Is Not Preempted When A Manufacturer Has A Federal Duty To Propose A Corresponding Change To Approved Labeling But Fails To Do So**

In *Wyeth*, the plaintiff contended (and a state jury agreed) that she sustained injuries caused by Phenergan, a brand-name drug sold by the defendant manufacturer (Wyeth), and that her injuries were proximately caused by inadequate warnings in Phenergan's approved labeling. See 129 S. Ct. 1192-1193. This Court rejected Wyeth's impossibility preemption defense. It read the record to reflect newly acquired information on Wyeth's part regarding the risk of gangrene from administration of Phenergan. *Id.* at 1196-1197. That understanding of the record was the basis for two conclusions: First, Wyeth could have appropriately invoked the CBE process to change Phenergan's approved labeling. See *id.* at 1197. Second, in light of Wyeth's duty "to revise its label 'to include a warning as soon as there is reasonable evidence of an association of a serious hazard with [its] drug,'" the Court concluded that "when the [gangrene] risk \* \* \* became apparent, Wyeth had a duty to provide a warning that adequately described

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<sup>11</sup> FDA now has authority under the Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823, to require labeling changes based on new information from a variety of sources. See 21 U.S.C. 355(o)(4) (Supp. III 2009). FDA is currently developing guidance on how that authority will be exercised for changes to NDA and ANDA approved labeling. The existence of that authority and FDA's implementation of it could affect the preemption analysis of cases like these arising from events occurring after FDAAA's enactment.

that risk.” *Id.* at 1198 (quoting 21 C.F.R. 201.80(e) (formerly 21 C.F.R. 201.57(e) (2001))).

Taking respondents’ allegations as true, petitioners were under the same duty as Wyeth “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 they had been directed to “provide adequate supporting information” for FDA to “determine whether the labeling for the generic and listed drugs should be revised.” 57 Fed. Reg. at 17,961.

***1. A generic drug manufacturer must seek to revise its drug’s approved labeling to include a warning as soon as there is reasonable evidence of an association of a serious hazard with the drug***

A drug is misbranded under the FDCA if, *inter alia*, “its labeling [does not] bear[] \* \* \* adequate warnings \* \* \* against unsafe dosage or methods or duration of administration or application.” 21 U.S.C. 352(f)(2). As a corollary, a drug is also misbranded if “it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling.” 21 U.S.C. 352(j). A misbranded drug may not be introduced into commerce. See 21 U.S.C. 331(a).

To implement Section 352, FDA requires that a section of a prescription drug’s approved labeling headed “Warnings” describe “serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.” 21 C.F.R. 201.57(e) (2001); see 44 Fed. Reg. at 37,447 (citing 39 Fed. Reg. at 33,229) (describing authority for 21 C.F.R. 201.57(e) (2001)). That same regulation imposes a duty to keep warnings current: “The labeling

shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.” 21 C.F.R. 201.57(e) (2001). This duty applies to NDA holders and ANDA holders alike. “Reasonable evidence” under the regulation, FDA has explained, is evidence “on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug.” 44 Fed. Reg. at 37,447. An “association” between a drug and a serious hazard exists “when there is significant medical evidence of a possible health hazard”; labeling must be revised “without waiting for a causal relationship to be established by definitive studies.” 39 Fed. Reg. at 33,231 (referenced by 44 Fed. Reg. at 37,447).

As this Court recognized in *Wyeth*, that duty to keep warnings current reflects the “central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain accurate.” 129 S. Ct. at 1197-1198 (citing, *inter alia*, 21 C.F.R. 201.80(e) (formerly 21 C.F.R. 201.57(e) (2001))).

When Section 201.57(e) obligates an applicant to revise its label, it may properly be assumed that FDA will permit an appropriate change to discharge that duty.<sup>12</sup>

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<sup>12</sup> There are, infrequently, situations where a revision arguably called for by the standard in Section 201.57(e) must be reconciled with other risk communication considerations. Cf. *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004) (addressing FDA’s decision regarding labeling of nicotine-containing smoking-cessation products, which required balancing warnings to pregnant women about the products’ potential reproductive hazards against, *inter alia*, the risk that such warnings would misleadingly suggest that continuing to

Indeed, it would be both paradoxical and contrary to FDA’s statutory responsibilities for FDA to insist upon a labeling revision under a certain standard—“reasonable evidence of an association of a serious hazard with a drug,” *ibid.*—and then fail to respond positively to a warning proposed in conformity with that standard.<sup>13</sup>

**2. *A generic drug manufacturer’s federal duty to seek a labeling revision supplies the appropriate standard for the preemption inquiry here***

Drugs with FDA approval are presumptively lawful to sell in commerce. Respondents do not contend otherwise or suggest that petitioners’ drugs simply should not have been available on the market. Because respondents’ claims are directed only to the labeling of petition-

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smoke was a safer course). The parties do not suggest these cases raise such a situation.

<sup>13</sup> *Wyeth* addressed both the manufacturer’s duty to revise its approved labeling and FDA’s hypothetical response to a proposed revision, but it treated them as distinct issues. See 129 S. Ct. 1198-1199. The issue of FDA’s hypothetical response was the subject of minimal briefing—it was raised only in *Wyeth*’s reply brief. See Pet. Reply Br. at 12, *Wyeth, supra*, No. 06-1249. Nonetheless, this Court’s discrete discussion of FDA’s hypothetical response has led many lower courts to take the question of preemption in this context to turn on whether “FDA would not have approved a change to [the drug’s] label.” *E.g.*, J.A. 556 (brackets in original) (quoting *Wyeth*, 129 S. Ct. at 1198).

The circumstances of *Wyeth* did not, however, require a direct focus on the likelihood of FDA disapproval. If under FDA regulations “*Wyeth* had a duty to provide a warning that adequately described [the relevant] risk,” *Wyeth*, 129 S. Ct. at 1198, then those facts required it to act on the duty and FDA’s procedures gave *Wyeth* the means to do so. *Wyeth*, therefore, did not find itself in an impossible situation calling for preemption. In those circumstances, the Court understandably insisted upon “clear evidence” before it could “credit *Wyeth*’s contention that the FDA would have prevented it from adding a stronger warning.” *Id.* at 1198-1199.

ers' drugs, the preemption question presented turns on the extent to which state law may impose a duty to warn without conflicting with federal law.

At the most basic level, there is no reason to suppose a conflict between federal and state law if both demand the same conduct from the defendant. When, as here, federal law requires a manufacturer to act 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) (analogous conclusion in context of an express preemption clause); *Bates v. Dow Agroscis. LLC*, 544 U.S. 431, 447-448 (2005) (same); *Lohr*, 518 U.S. at 495 (same).

That framework for generic drugs is in harmony with *Wyeth's* rule for brand-name drugs: Irrespective of whether a drug is approved under an NDA or an ANDA, if the drug was misbranded due to new safety information not reflected in its labeling, then the plaintiff's claims are not preempted. The manufacturer was under a federal duty to revise its federally approved labeling and FDA gave it the ability to seek such changes. Petitioners, by contrast, argue that they enjoy a free pass accorded to virtually no other manufacturer regarding product labeling—in the field of drugs or otherwise. Individuals harmed by inadequately labeled generic drugs would (on petitioners' view) have no remedy against the manufacturer, while individuals who took the same drug with the same labeling in its brand-name form would (by virtue of *Wyeth*) have such a 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 ex-

pressed that intent more clearly.” *Bates*, 544 U.S. at 449.

Focusing the preemption inquiry on the standard in 21 C.F.R. 201.57(e) (2001) to avoid misbranding accommodates a number of potentially contradictory commands from the FDCA, FDA’s regulations, and this Court’s decisions:

- It respects both the Hatch-Waxman Amendments’ requirement that the approved labeling of a generic drug be the “same as” the RLD’s labeling, 21 U.S.C. 355(j)(2)(A)(v), and FDA’s regulation that implements the FDCA’s misbranding provision by requiring approved labeling to be revised “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).
- It appropriately presumes that FDA, if confronted with new safety information triggering the duty FDA itself set out in Section 201.57(e), would act on that information in the way FDA itself indicated it would in its 1992 preamble, see 57 Fed. Reg. at 17,961. See *United States v. Chemical Found.*, 272 U.S. 1, 14 (1926) (“The presumption of regularity supports the official acts of public officers.”).
- It remains faithful to the principle that “[f]ailure-to-warn actions, in particular, lend force to the FDCA’s premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times,” and thus “state law offers an additional, and important, layer of consumer

protection that complements FDA regulation.” *Wyeth*, 129 S. Ct. at 1202-1203.

- It preserves an appropriate ambit for “widely available state rights of action [to] provide[] appropriate relief for injured consumers,” because there is generally no “federal [compensatory] remedy for consumers harmed by unsafe or ineffective drugs.” *Wyeth*, 129 S. Ct. at 1199.
- It functions as a measured incentive for drug manufacturers to bring new safety information to FDA’s attention. See *Wyeth*, 129 S. Ct. at 1200 (“[S]tate-law remedies further consumer protection by motivating manufacturers \* \* \* to give adequate warnings.”).<sup>14</sup>

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<sup>14</sup> Some of petitioners’ amici (Apotex Amicus Br. 26-30; Generic Pharm. Ass’n Amicus Br. 10-15; Morton Grove Amicus Br. 28-31), and even some petitioners at the petition stage (see 09-993 Pet. 20-22; 09-1039 Pet. 10-11) have touched on a distinct but related preemption question: to what extent do the Hatch-Waxman Amendments permit state law to impose a duty on a generic manufacturer to acquire or develop safety information about its drugs? In the extreme (*e.g.*, by requiring clinical trials), such a duty could undermine the viability of the generic pharmaceutical market the Hatch-Waxman Amendments sought to foster. But that would pose preemption questions different from the ones respondents’ complaints more directly raise. Respondents’ primary theory appears to be that information already in petitioners’ possession (see J.A. 198-199, 438-439, 441, 444) or readily available in published scientific literature (see J.A. 193, 439, 441) showed that the labeling was inadequate. Petitioners (see 09-993 Pet. 21) and their amici (see Morton Grove Amicus Br. 28-29) disagree with that as a factual matter, suggesting a far broader knowledge base would have been necessary. Even respondents’ complaints could be read to support that view. See J.A. 193 (alleging petitioners “failed to investigate”); J.A. 439 (referring to petitioners’ “ability to review data from clinical studies”). But given these cases’ interlocutory posture, this

Those principles lose force, however, if the generic drug is not misbranded and the duty in Section 201.57(e) is not triggered. In that event, there is no federal policy against selling the drug and no call to change its label (let alone for FDA to orchestrate a change to the RLD's label). There is diminished value, from the perspective of federal law, to the incentives created by a state tort duty for a manufacturer to propose a warning that federal law would not require. And if the generic drug and RLD are not misbranded, then petitioners' plea to impossibility becomes more substantial: Even if the ANDA holder proposed a labeling change, FDA would not engage with the RLD sponsor to revise its labeling; yet without such a change, the ANDA holder would be obliged to maintain approved labeling the "same as" the RLD's approved labeling.<sup>15</sup>

***3. Accepting respondents' allegations as true, petitioners were under a federal duty to revise their approved labeling***

In the posture of these cases, this Court must accept respondents' allegations as true. They contend that accumulating scientific evidence established that the risk of tardive dyskinesia (unquestionably a serious hazard) associated with long-term use of metoclopramide was significantly greater than what was reflected in petition-

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Court should accept as true respondents' allegations that information known by or readily available to petitioners warranted a labeling change.

<sup>15</sup> Because this case concerns only generic drugs, it is not necessary to consider whether the preemption analysis would be different in a case brought (like *Wyeth*) against an NDA holder with access to the CBE process, but involving (unlike *Wyeth*) a drug for which a revised warning was not required by Section 201.57(e) to avoid misbranding.

ers' drug's approved labeling. See p. 9, *supra*. In addition to whatever claim those allegations state under state law, they would also establish that petitioners' metoclopramide products were misbranded under 21 U.S.C. 352(f)(2) because those drugs would lack adequate warnings, and petitioners would have failed to discharge their duty under Section 201.57(e) to seek a revision to their approved labeling in light of newly acquired information not previously considered by FDA. Accordingly, petitioners' preemption defense cannot prevail at the pleadings stage—though, of course, it may ultimately succeed if petitioners can show the true facts are otherwise.

***4. Petitioners' arguments for preemption of respondents' claims are not persuasive***

Petitioners offer several arguments why FDA's role in mediating ANDA-initiated changes to approved labeling supports their position that failure-to-warn claims against ANDA holders are either categorically preempted or impose a special burden on plaintiffs. None is persuasive.

a. The PLIVA petitioners' primary submission is that "speculation about how FDA would have responded to a hypothetical submission seeking warning changes" would "usurp[] a function that Congress has assigned to a federal regulatory body." PLIVA Br. 49-50 (quoting *Arkansas La. Gas Co. v. Hall*, 453 U.S. 571, 580-582 (1981) (*Arkla*), and citing *Nantahala Power & Light Co. v. Thornburg*, 476 U.S. 953 (1986); *Chicago & N.W. Transp. Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311 (1981)). The PLIVA petitioners err because the decisions they cite rest on the extraordinarily comprehensive authority the agencies in question had in their re-

spective fields: “[The Federal Energy Regulatory Commission has] plenary authority over interstate wholesale rates, and \* \* \* the States [may] not interfere with this authority.” *Nantahala*, 476 U.S. at 966; accord *Arkla*, 453 U.S. at 580; see *Kalo Brick & Tile*, 450 U.S. at 326 (“Because Congress granted the exclusive discretion \* \* \* to the [Interstate Commerce] Commission, there is no further role that the state court could play.”). A central “consideration[] underlying the [filed rate] doctrine” applied in those cases is “preservation of the agency’s primary jurisdiction over reasonableness of rates.” *Arkla*, 453 U.S. at 577-578 (citation omitted); accord *Kalo Brick & Tile*, 450 U.S. at 325. By contrast, “Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.” *Wyeth*, 129 S. Ct. at 1200. Rather, “the FDCA’s premise [is] that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times,” and thus “state law offers an additional, and important, layer of consumer protection that complements FDA regulation.” *Id.* at 1202-1203.

The PLIVA petitioners further contend (Br. 5) that their reading of *Arkla*, *Nantahala*, and *Kalo Brick & Tile* mirrors the United States’ reading of those cases in a prior submission to this Court. See U.S. Br. at 20-21, *Warner-Lambert Co. v. Kent*, 552 U.S. 440 (2008) (U.S. *Warner-Lambert* Br.). That brief was, however, filed without the benefit of this Court’s decision in *Wyeth*. Moreover, the fraud-on-the-FDA issues in *Warner-Lambert* and *Buckman*, *supra*, impermissibly intruded on federal law because they constituted a collateral attack on a decision actually made by FDA in the past—thus they entailed “second-guessing \* \* \*

FDA’s decisionmaking” on an issue actually presented to it and “a difficult inquiry into [the] counterfactual situation” that would have existed absent the alleged fraud. U.S. *Warner-Lambert* Br. 20 (internal quotation marks omitted). By contrast, the appropriate inquiry here addresses whether petitioners’ drugs violated substantive misbranding and regulatory standards based on new information not presented to FDA.

If FDA had actually rejected a labeling change proposed by an ANDA holder, the cases petitioners cite might well operate to bar a jury from revisiting FDA’s decision. But because here the matter was not even presented to FDA, and “the statute contemplates that federal juries will resolve most misbranding claims,” *Wyeth*, 129 S. Ct. at 1197, a court and jury should not be prevented from deciding an issue of misbranding in the course of adjudicating a tort suit.<sup>16</sup>

b. Petitioners also contend (PLIVA Br. 50-53; Actavis Br. 28-29) that FDA’s response to a hypothetical warning proposal would be part of the causal chain respondents would have the burden of establishing in their cases-in-chief under state law. Respondents disagree. Br. 41-44. This Court need not, and should not, resolve that issue of state law because the lower courts did not pass upon it, and because it is beyond the scope of the question presented, which addresses only the extent of federal preemption.

Federal law demands only that the ANDA holder be allowed to raise as an affirmative defense under federal law the issue of whether its drug was not misbranded. That approach comports with settled federal preemption

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<sup>16</sup> A misbranding determination in a private tort suit would not, of course, bind FDA in the exercise of its regulatory authority.

law and background tort principles. A defendant ordinarily bears the burden of proving the circumstances supporting its preemption 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.”).

This approach is also practical. A tort plaintiff’s failure-to-warn claim necessarily entails some showing of deficiency in labeling—an unreasonable warning in a negligence claim, or an inadequate warning in a strict liability claim. The thrust of such claims is likely to resemble the FDCA’s standard for misbranding and FDA’s interpretation of that standard, see pp. 23-25, *supra*. Thus, if a plaintiff succeeds in proving her claim under state law, there is at least some reason to believe the drug was misbranded and federal law demanded revised labeling—and the defendant can fairly be tasked with showing otherwise.

c. The Actavis petitioners also criticize (Br. 29-31) as impermissibly speculative any approach that would attempt to account for how FDA would have responded to a hypothetical warning proposal. Other petitioners express concern (PLIVA Br. 55-61) that allowing litigation over FDA’s response to a hypothetical warning proposal would overburden FDA with requests for documents and testimony, or encourage excessive defensive submissions by ANDA holders to FDA. But the approach to preemption in this brief turns on whether the substantive standard in Section 201.57(e) and the FDCA’s misbranding provisions were violated, not on what FDA would have done in response to a proposed

labeling change—although evidence of the latter could be relevant. The concerns about speculation over FDA’s response and burdens on FDA’s resources are therefore significantly diminished.

In addition, the United States’ position is that records and employees of the federal government are immune from third-party subpoenas issued in private litigation, and that such records and testimony must be sought under an agency’s Touhy regulations, see generally *United States ex rel. Touhy v. Ragen*, 340 U.S. 462 (1951), subject only to deferential judicial review under the Administrative Procedure Act, 5 U.S.C. 706(2)(A). That is, to be sure, no guarantee against intrusion. See U.S. *Warner-Lambert Br.* at 22-23. But the United States expressed that concern in *Wyeth*, see U.S. *Wyeth Br.* at 24, and this Court evidently rejected it. Moreover, this Office has been informed that, in the two years since *Wyeth* was decided, FDA has actually seen *fewer* attempts to obtain its records through third-party subpoenas. In light of that experience, FDA would expect a similarly modest burden from an inquiry in tort litigation into misbranding.

FDA is likewise not prepared to predict that a ruling in respondents’ favor would unreasonably encourage ANDA holders to inundate the agency with proposed warning revisions with the expectation that FDA would reject them, perhaps with preemptive effect. Naturally, FDA would not condone that practice. *Wyeth* created a similar incentive for NDA holders, but in FDA’s experience thus far it has not unleashed a surge of defensive CBE supplements.<sup>17</sup> As a practical matter, genuinely

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<sup>17</sup> Under current regulations a CBE change to strengthen a warning need not be effected prior to FDA’s approval of the supplement. See

new information about drugs in long use (as generic drugs typically are) appears infrequently, so the risk of overwhelming FDA seems attenuated in this setting. And if trivial submissions became a problem, FDA could promulgate regulations to manage the information flow.

**CONCLUSION**

The judgments of the courts of appeals should be affirmed.

Respectfully submitted.

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21 C.F.R. 314.70(c)(6) (2010). Thus, neither an NDA holder nor an ANDA holder need ever invest in implementing an unapproved change.