

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

In the Supreme Court of the United States

PLIVA, INC., ET AL., PETITIONERS

v.

GLADYS MENSING, RESPONDENT

ACTAVIS ELIZABETH, LLC, PETITIONER

v.

GLADYS MENSING, RESPONDENT

ACTAVIS INC., PETITIONER

v.

JULIE DEMAHY, RESPONDENT

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

**BRIEF FOR MORTON GROVE PHARMACEUTI-
CALS, INC. AND IMPAX LABORATORIES, INC. AS
AMICI CURIAE IN SUPPORT OF PETITIONERS**

W. GORDON DOBIE
JAMES F. HURST
MAUREEN L. RURKA
WILLIAM P. FERRANTI
Winston & Strawn LLP
35 W. Wacker Drive
Chicago, IL 60601
(312) 558-5600

STEFFEN N. JOHNSON*
Winston & Strawn LLP
1700 K Street, N.W.
Washington, DC 20006
(202) 282-5000
sjohnson@winston.com

**Counsel of Record*

Counsel for Amici Curiae

QUESTION PRESENTED

The Drug Price Competition and Patent Term Restoration Act (the “Hatch-Waxman Act”) allows for the approval of low-cost generic drug products through an abbreviated process that hinges on the requirement that generic drug products—and their warnings—must in all material respects be “the same as” their FDA-approved brand-name equivalents.

Does the Hatch-Waxman Act preempt state-law failure-to-warn claims against the manufacturer of a generic drug whose warnings were, as the Hatch-Waxman Act and the FDA’s implementing regulations expressly require, “the same as” those the FDA approved for the product’s brand-name equivalent?

TABLE OF CONTENTS

| | Page |
|--|-------------|
| QUESTION PRESENTED | i |
| TABLE OF AUTHORITIES | iv |
| INTRODUCTION AND INTERESTS OF <i>AMICI CURIAE</i> | 1 |
| STATEMENT OF THE CASE..... | 3 |
| A. Approval of ANDA and NDA products | 3 |
| B. Post-approval label-change and reporting requirements | 6 |
| C. Proceedings below..... | 8 |
| SUMMARY OF ARGUMENT | 9 |
| ARGUMENT | 13 |
| I. Federal Law Preempts Claims That A Generic Manufacturer Should Have Changed Its Label..... | 13 |
| A. Generic labeling must be “the same as” the name-brand equivalent. | 14 |
| B. Generic manufacturers may not unilaterally change their product labeling..... | 15 |
| 1. CBE process | 15 |
| 2. PAS process..... | 16 |
| 3. DHCP letters..... | 17 |
| II. Under <i>Buckman</i> , Federal Law Preempts Claims That A Generic Manufacturer Should Have Warned Or Provided Additional Information To The FDA..... | 18 |

| | | |
|----|--|----|
| A. | There is no presumption against preemption of claims that a generic manufacturer should have warned the FDA. | 18 |
| B. | Under <i>Buckman</i> , States may not police communications between a generic manufacturer and the FDA—and claims based on label change <i>proposals</i> require such policing. | 20 |
| 1. | The legal context of these cases is strikingly similar to what the Court evaluated in <i>Buckman</i> | 21 |
| 2. | The United States alone has authority to enforce the FDCA, and to decide whether generic labels should be changed. | 23 |
| 3. | State regulation is an added burden on generic manufacturers and, as such, conflicts with the federal regime. | 28 |
| 4. | Allowing state regulation will impose substantial costs on the FDA. | 32 |
| | CONCLUSION | 35 |

TABLE OF AUTHORITIES

| | Page(s) |
|--|-----------------------------|
| CASES | |
| <i>Arkansas La. Gas Co. v. Hall</i> , 453 U.S. 571 (1981) | 26, 28 |
| <i>BMW, Inc. v. Gore</i> , 517 U.S. 559 (1996) | 25 |
| <i>Bonito Boats, Inc. v. Thunder Craft Boats, Inc.</i> , 489 U.S. 141 (1989) | 31 |
| <i>Boyle v. United Techs. Corp.</i> , 487 U.S. 500 (1988) | 20, 25 |
| <i>Buckman Co. v. Plaintiffs' Legal Comm.</i> , 531 U.S. 341 (2001) | 1-2, 7, 10-13, 18-28, 31-32 |
| <i>Carroll v. Otis Elevator Co.</i> , 896 F.2d 210 (7th Cir. 1990) | 35 |
| <i>Chicago & North Western Transp. Co. v.</i> <i>Kalo Brick & Tile Co.</i> , 450 U.S. 311 (1981) | 26 |
| <i>Crosby v. Nat'l Foreign Trade Council</i> , 530 U.S. 363 (2000) | 24 |
| <i>Exxon Shipping Co. v.</i> <i>United States Dep't of Interior</i> , 34 F.3d 774 (9th Cir. 1994) | 34 |
| <i>Gaeta v. Perrigo Pharm. Co.</i> , No. 09-15001, 2011 WL 198420 (9th Cir. Jan. 24, 2011) | 26 |

| | |
|--|------------|
| <i>Garner v. Teamsters</i> , 346 U.S. 485 (1953) | 25 |
| <i>Geier v. Am. Honda Motor Co.</i> , 529 U.S. 861 (2000) | 19, 31, 32 |
| <i>Heckler v. Chaney</i> , 470 U.S. 821 (1985) | 7, 24 |
| <i>In re Barr Labs., Inc.</i> , 930 F.2d 72 (D.C. Cir. 1991) | 5, 22 |
| <i>Int'l Paper Co. v. Ouellette</i> , 479 U.S. 481 (1987) | 24 |
| <i>Medtronic, Inc. v. Lohr</i> , 518 U.S. 470 (1996) | 22 |
| <i>Pennsylvania R.R. v. Public Serv. Comm'n</i> , 250 U.S. 566 (1919) | 25 |
| <i>Pennsylvania v. Nelson</i> , 350 U.S. 497 (1956) | 24 |
| <i>San Diego Bldg. Trades Council v. Garmon</i> , 359 U.S. 236 (1959) | 24 |
| <i>U.S. Bancorp Mortg. Co. v. Bonner Mall P'ship</i> , 513 U.S. 18 (1994) | 27 |
| <i>United States ex rel. Touhy v. Ragen</i> , 340 U.S. 462 (1951) | 34 |
| <i>United States v. Locke</i> , 529 U.S. 89 (2000) | 20 |
| <i>Watters v. Wachovia Bank, N.A.</i> , 550 U.S. 1 (2007) | 19 |

Wyeth v. Levine,
129 S. Ct. 1187 (2009) 9-10, 13, 15, 17-20, 26, 27, 30

**CONSTITUTIONAL PROVISIONS, STATUTES, AND
REGULATIONS**

21 C.F.R.:

| | |
|----------------------------|-------|
| §20.1 | 34 |
| §20.2(a)..... | 34 |
| §202.1(l)(2) | 6, 17 |
| §312.2 | 4 |
| §312.20 | 4 |
| §314.50 | 3 |
| §314.50(d)..... | 3 |
| §314.50(e)..... | 3 |
| §314.50(f) | 3 |
| §314.70(b)..... | 6 |
| §314.70(b)(2)(v)(A) | 6, 16 |
| §314.70(c) | 15 |
| §314.70(c)(6)(iii)(A)..... | 6, 15 |
| §314.70(c)(6)(iii)(C)..... | 15 |
| §314.80(c) | 7 |
| §314.80(j)..... | 7 |

21 C.F.R.—Continued:

| | |
|--------------------------|----------|
| §314.81 | 7 |
| §314.92(a)(1) | 4 |
| §314.93 | 4 |
| §314.94(a)..... | 4 |
| §314.94(a)(8)(iii) | 15 |
| §314.94(a)(8)(iv)..... | 5 |
| §314.98..... | 7 |
| §314.127 | 5 |
| §314.150(b)(1) | 7 |
| §314.150(b)(3) | 7, 17 |
| §314.150(b)(10) | 7, 15-16 |
| §807.87(e)..... | 22 |

21 U.S.C.:

| | |
|-----------------------|-------|
| §312(m) | 6, 17 |
| §331(e)..... | 7 |
| §332(a)..... | 7 |
| §333(a)..... | 7 |
| §333(f) | 8 |
| §333(f)(3)(A)(7)..... | 7 |

21 U.S.C.—Continued:

| | |
|-----------------------|-------|
| §334(a)..... | 7 |
| §336..... | 7 |
| §337(a)..... | 7, 23 |
| §355(b)..... | 3 |
| §355(b)(1) | 3 |
| §355(e)..... | 7 |
| §355(i) | 4 |
| §355(j) | 4 |
| §355(j)(2)(A) | 4 |
| §355(j)(2)(A)(i)..... | 4 |
| §355(j)(2)(A)(v)..... | 5, 14 |
| §355(j)(2)(C) | 4, 5 |
| §355(j)(4)(G)..... | 15 |
| §355(k) | 7 |
| §355(n) | 34 |
| §355(o)..... | 8 |
| §355(o)(4) | 8 |
| §355-1(g) | 8 |
| §375(b)..... | 7 |

| | |
|--|----------|
| Food And Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823..... | 8 |
| U.S. Const. Art. IV, Cl. 2 | 3, 19 |
| OTHER AUTHORITIES | |
| 2 McCormick on Evid. §337 (6th ed. 2009) | 27 |
| 50 Fed. Reg. 7452 (Feb. 22, 1985) | 4 |
| 57 Fed. Reg. 17950 (April 28, 1992) | 4, 7, 14 |
| 73 Fed. Reg. 2848 (Jan. 16, 2008) | 16 |
| Adverse Drug Reaction Reporting Regulations Working Group, Center for Drug Evaluation & Research, <i>Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drug & Licensed Biological Products: Clarification of What to Report</i> (Aug. 1997), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071981.pdf | 32, 33 |
| ASPE Issue Brief: Office of the Assistant Secretary for Planning & Evaluation, Office of Science and Data Policy–U.S. Department of Health and Human Services, <i>Expanding the Use of Generic Drugs</i> (Dec. 2010), available at http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml | 2, 30-31 |

| | |
|---|----|
| Center for Drug Evaluation & Research, <i>Manual of Policies & Procedures</i> 5240.3 (Oct. 18, 2006), available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079787.pdf | 33 |
| Joseph A. DiMasi, et al., <i>The Price of Innovation: New Estimates of Drug Development Costs</i> ,” 22 <i>J. Health Economics</i> 151 (2003) | 30 |
| Division of Generic Drugs, FDA, <i>Policy & Procedure Guide</i> (1989) | 14 |
| Drug Price Competition and Patent Term Restoration Act of 1984, Committee Notes, 130 Cong. Rec. 24416, H.R. 3605 (Sept. 6, 1984)..... | 5 |
| Drug Price Competition and Patent Term Restoration Act, Committee Notes, 130 Cong. Rec. 24970, S. 1538 (Sept. 12, 1984) | 5 |
| FDA, Generic Drug Prices, available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm | 31 |
| GAO, <i>New Drug Development, Report to Congressional Committees</i> , 26 <i>Biotech. L. Rep.</i> 82 (2007) | 4 |
| New Drug Application: Hearings on H.R. 3605 Before the Subcomm. On Health and the Environment of the House Comm. on Energy and Commerce, 98th Cong., 1st Sess. (1983) | 5 |

“P.L. 98-417, Drug Price Competition and
Patent Term Restoration Act,” H.R. Rep.
No. 857(I), 98th Cong., 2d Sess. (1984),
reprinted in 1984 U.S.C.C.A.N. 2647 5

Restatement (Second) of Torts §433B(1) (1965) 27

INTRODUCTION AND INTERESTS OF *AMICI CURIAE**

There are two types of duties that state failure-to-warn law might attempt to impose on a generic drug manufacturer: One is to change its label; the other is to provide additional information to the FDA. Petitioners and the Government explain why the first duty is preempted—that is, why any claim that a generic manufacturer failed to change its label cannot be squared with federal law. We agree with their arguments.

We file this brief, however, to explain why federal law preempts not only claims directly seeking a change in generic labeling, but also claims premised on a generic manufacturer’s alleged failure to provide sufficient information to the FDA, or to request the FDA’s permission to change its label. As this Court recognized in *Buckman Co. v. Plaintiffs’ Legal Committee*, 531 U.S. 341 (2001), “the relationship between a federal agency and the entity it regulates is inherently federal in character”; it “originates from, is governed by, and terminates according to federal law.” *Id.* at 347. Thus, enforcement of the FDCA is “exclusively” the FDA’s prerogative; and the “delicate balance” that Congress struck between keeping unsafe products off the market and making efficacious products available may not be “skewed” by allowing “un-

* The parties have consented to the filing of this brief, and their letters of consent are on file with the Clerk. In accordance with Rule 37.6, *amici* state that no counsel for any party has authored this brief in whole or in part, and no person or entity, other than the *amici*, has contributed monetarily to the preparation or submission of this brief.

predictable civil liability” under state tort law to piggyback on the federal regime. *Id.* at 348, 350, 352.

Amici are manufacturers of generic drugs, and defendants in a slew of similar cases. Indeed, Morton Grove Pharmaceuticals has been a named defendant in more than 500 metoclopramide cases. *Amici*’s concern is that, unless these state failure-to-warn claims are held categorically preempted, this type of liability will put generic manufacturers in an impossible situation, raise the price of generic drugs, and impose costs on the FDA—all in violation of federal law.

These suits are particularly hard on smaller generic companies like *amicus* Morton Grove, which can stay in business only because of the lower costs of generic drug development. “While estimates of the cost to bring a new branded drug to market are in excess of a billion dollars, the research and development costs for a new generic drug are only 1 to 2 million dollars.”¹ Moreover, “[t]he relatively low costs to entry for generic drugs lead to increased competition, which drive prices for generic drugs down dramatically.” *Id.* at 5. Indeed, “growth in the use of generic drugs has generated substantial savings for American consumers”—savings estimated to be \$139.6 billion *in 2009 alone*. *Id.* at 2, 6. But if generics must undertake their own research to determine whether to propose label changes to the FDA, these savings will be greatly reduced if not eliminated. Indeed, claims like those sanctioned by the courts below

¹ ASPE Issue Brief: Office of the Assistant Secretary for Planning & Evaluation, Office of Science and Data Policy—U.S. Department of Health and Human Services, *Expanding the Use of Generic Drugs* 4-5 (Dec. 2010), available at <http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml>.

threaten to put smaller generics out of business—a problem with which those courts were none too concerned. JA416 (*Mensing*) (suggesting that generic manufacturers “could * * * simply stop[] selling the[ir] product[s]”).

At a minimum, the rulings below threaten to work fundamental changes in the way generics do business—multiplying their costs, to the ultimate detriment of consumers and the nation’s health care system. That result would be squarely at odds with the Hatch-Waxman Act, which gave birth to the modern generic pharmaceutical industry and ushered in an era of low-cost drugs. That Act is “the supreme law of the land”; “anything in the constitution or laws of any state to the contrary” must yield. U.S. Const. Art. IV, Cl. 2. The rulings below must therefore be reversed.

STATEMENT OF THE CASE

A. Approval of ANDA and NDA products

For drugs sold in the United States, there are two tracks to FDA approval.

1. First, for new drugs—typically sold, following approval, under a name brand—a manufacturer must submit a new drug application (NDA) establishing that the drug is safe and effective when used as labeled. 21 U.S.C. §355(b); 21 C.F.R. §314.50. To that end, an NDA must include data demonstrating that the drug is safe and effective; analysis of the drug’s composition; explanation of the methods and controls used for manufacturing, processing, and packing the drug; and proposed labels. 21 U.S.C. §355(b)(1)(A)-(F); 21 C.F.R. §314.50(d)-(f). Further, before filing an NDA, the manufacturer must obtain authorization to conduct clinical trials to establish the drug’s safety

and efficacy to treat a specific condition. 21 U.S.C. §355(i); 21 C.F.R. §§ 312.2, 312.20.

The NDA process is intensive. A typical NDA spans thousands of pages and is grounded in clinical trials conducted, on average, over seven years. GAO, *New Drug Development, Report to Congressional Committees*, 26 Biotech. L. Rep. 82, 94 (2007). On average, the FDA spends some 442 days evaluating NDA submissions. *Id.* at 86.

2. Whereas NDA approval turns on establishing that a drug is safe and effective, the second track to FDA approval—an abbreviated new drug application (ANDA)—turns on establishing that the drug is “the same as” an FDA-approved NDA drug. 21 U.S.C. §355(j); 57 Fed. Reg. 17950, 17953 (April 28, 1992). These “generic” drugs must be identical to an approved NDA drug with respect to active ingredient, route of administration, dosage form, strength, and conditions of use. 21 U.S.C. §355(j)(2)(A)(i); 21 C.F.R. §314.92(a)(1).² Moreover, an ANDA must establish that the generic drug is therapeutically equivalent or “bioequivalent” to, and will be given the same labeling as, the name-brand drug. 21 U.S.C. §355(j)(2)(A); 21 C.F.R. §314.94(a). Use of the same label is critical because “[d]rug labeling serves as the standard under which FDA determines whether a product is safe and effective.” 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985).

² At FDA’s discretion, the ANDA process may also be used for a drug with one different active ingredient, or whose route of administration, dosage form, or strength differs from the NDA product. 21 U.S.C. §355(j)(2)(C); 21 C.F.R. §314.93; see generally 57 Fed. Reg. at 17951-17952.

Generic manufacturers need not (and do not) provide clinical evidence of safety or efficacy. The point of Hatch-Waxman, after all, was “to get generic drugs into the hands of patients at reasonable prices—fast.” *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991).³ Accordingly, Congress directed the FDA to approve any product that is a true generic—*i.e.*, bioequivalent to the branded drug and sold with identical labeling. The FDA will reject any ANDA drug that flunks these criteria. 21 C.F.R. §314.127.

The requirement that a generic label be “the same as” the brand-name equivalent has only two statutory exceptions: a generic label may reflect a difference in active ingredient, dosage form, strength, or route of administration that has been vetted and approved under 21 U.S.C. §355(j)(2)(C) (see *supra* n.2), and it may reflect the fact that the generic and name-brand products “are produced or distributed by different manufacturers.” 21 U.S.C. §355(j)(2)(A)(v). This second exception encompasses “omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under * * * the act.” 21 C.F.R.

³ See also, *e.g.*, “P.L. 98-417, Drug Price Competition and Patent Term Restoration Act,” H.R. Rep. No. 857(I), 98th Cong., 2d Sess. (1984), reprinted in 1984 U.S.C.C.A.N. 2647, Pet. App. 122; New Drug Application: Hearings on H.R. 3605 Before the Subcomm. On Health and the Environment of the House Comm. on Energy and Commerce, 98th Cong., 1st Sess. (1983), Pet. App. 114a; Drug Price Competition and Patent Term Restoration Act of 1984, Committee Notes, 130 Cong. Rec. 24416, H.R. 3605 (Sept. 6, 1984), Pet. App. 136a; Drug Price Competition and Patent Term Restoration Act, Committee Notes, 130 Cong. Rec. 24970, S. 1538 (Sept. 12, 1984).

§314.94(a)(8)(iv). These exceptions are not at issue here.

B. Post-approval label-change and reporting requirements

1. The rules governing modification of generic product labeling are simple. Indeed, there is only one: The generic label must at all times remain “the same as” the FDA-approved label for the name-brand equivalent. If the FDA approves changes to a brand’s label, all generics must change their labels too. Otherwise, the generic label may not be modified.

For example, the FDA’s “changes being effected” (CBE) rule allows manufacturers to revise name-brand drug labels to “add” or “strengthen” a “contraindication, warning, precaution, or adverse reaction,” where warranted by newly discovered information. 21 C.F.R. §314.70(c)(6)(iii)(A). As discussed below (at 15), however, generics may not use the CBE process to make a label change resulting in a label that differs from the brand’s.

FDA regulations also provide for a “prior approval supplement” (PAS) process for making “major” label changes. 21 C.F.R. §314.70(b). This process, however, is not available for strengthening warnings—which changes must be made through the CBE process. 21 C.F.R. §314.70(b)(2)(v)(A).

Manufacturers may also provide information regarding their products, including warnings, through “Dear Health Care Professional” (DHCP) letters. Such letters, however, are “labeling” under federal law. 21 U.S.C. §312(m); 21 C.F.R. §202.1(l)(2). Accordingly, generic manufacturers may not send DHCP letters unilaterally, because doing so could create the misimpression that there is a difference

between generic and name-brand drugs—which would constitute misbranding. See CVSG Br. 17-18. DHCP letters therefore require FDA approval.

If a generic manufacturer deviates from the FDA-approved labeling for the branded drug—including by failing to modify its label to match changes made to the brand’s—the FDA may withdraw approval. 21 C.F.R. §314.150(b)(10); 21 C.F.R. §314.150(b)(3); see also 57 Fed. Reg. at 17961, 17970.

2. All manufacturers, including generics, must report adverse reactions to the FDA. 21 U.S.C. §355(e), (k); 21 C.F.R. §§ 314.80(c), 314.81, 314.98; see also 21 U.S.C. §331(e). The FDA may investigate and punish non-compliance with a wide range of sanctions, including withdrawal of approval (21 U.S.C. §355(e); 21 C.F.R. §§ 314.80(j), 314.81(d), 314.150(b)(1)); injunctions (21 U.S.C. §332(a)); criminal penalties (*id.* §333(a)); civil monetary penalties (*id.* §333(f)(3)(A)); seizure (*id.* §334(a)); and enforcement proceedings (*id.* §337(a)). The FDCA also preserves the FDA’s discretion to take less stringent action where appropriate. 21 U.S.C. §§ 336, 375(b).

The FDA “thus has at its disposal a variety of enforcement options.” *Buckman*, 531 U.S. at 349 (footnote omitted). It uses this authority “to punish and deter fraud against the Administration, and * * * to achieve a somewhat delicate balance of statutory objectives.” *Id.* at 348. In deciding how best to enforce the FDCA, the FDA enjoys unreviewable discretion (*Heckler v. Chaney*, 470 U.S. 821, 837-838 (1985)), and “all * * * proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States” (21 U.S.C. §337(a)).

3. The Food And Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823, gave the FDA additional tools to regulate prescription drugs. Most notably, the FDA may require post-approval studies of drugs; demand labeling changes; require changes in the risk evaluation and mitigation strategy now required for many drugs; and impose substantial civil penalties for non-compliance. 21 U.S.C. §§ 355(o), 355-1(g), 333(f).

Significantly, in 21 U.S.C. §355(o)(4), Congress directed the FDA to provide notice of label changes to the NDA holder. Manufacturers of generic drugs under approved ANDAs are given notification—and the burden of responding to FDA-proposed changes—only when the NDA holder is no longer marketing the product. *Ibid.*

C. Proceedings below

Respondents developed tardive dyskinesia, a neurological disorder, after long-term use of metoclopramide. They were prescribed the name-brand version of that drug, Reglan, and their prescriptions were filled with generic metoclopramide manufactured by Petitioners. At the time, the FDA-approved label for Reglan warned of the risk of developing tardive dyskinesia. As required, Petitioners' labels for generic metoclopramide provided identical warnings.

Respondents nevertheless filed suit, claiming that Petitioners violated state law by failing to label their products with warnings different from those mandated by the FDA. Misinterpreting federal law and giving short shrift to the requirement that generic products at all times be labeled “the same as” their branded equivalents, the Eighth and Fifth Circuits authorized Respondents to assert not only that Peti-

tioners ought to have departed from their FDA-approved label, but also that they ought to have provided additional warnings *to the FDA*. JA409-416 (*Mensing*); JA554-556 (*Demahy*).

Indeed, according to the Eighth Circuit it matters not whether a generic manufacturer may avail itself of the CBE procedure that was so critical to this Court's decision in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), because state law may require the manufacturer to “take steps” to provide a new warning—*i.e.*, to “propose[] a label change that the FDA could receive and impose uniformly on all metoclopramide manufacturers.” JA409-410 (*Mensing*). The Fifth Circuit similarly concluded that, without regard to the CBE process, state law may require a generic manufacturer to “alert the FDA and provide supporting scientific data; and the FDA then makes the decision whether such a labeling change is supported by science.” JA554 (*Demahy*).

SUMMARY OF ARGUMENT

The decisions below rest on two premises: first, that generic manufacturers may unilaterally initiate changes to their product labels via means such as the CBE process, the PAS process, and DHCP letters; and second, that even apart from the availability of these processes, state tort law may regulate generic drug manufacturers' relationship with the FDA, by imposing hefty damage awards on perceived failures to provide the agency with sufficient information. Neither premise, however, can be reconciled with the text, structure, or purpose of the Hatch-Waxman Act—or with this Court's precedents.

I. State law may not hold manufacturers liable for selling generic drugs with labeling that is “the same as” the brand-name equivalent. This is not a generic manufacturer’s choice; it is a mandate of federal law. It is thus *impossible* for generic manufacturers to comply with any duty under state tort law requiring a warning different from, or in addition to, what the FDA has approved for the brand-name drug. And the fact that generic manufacturers may not unilaterally alter, add to, or otherwise depart from FDA-approved labels distinguishes these cases from *Wyeth v. Levine*, 129 S. Ct. 1187 (2009). This is not even a close question.

II. In addition, however, States may not hold generic manufacturers liable in tort for failing to provide information to the FDA that supposedly *would have* (according to a lay jury) led the agency to order label changes. The courts below approved state tort claims premised on the notion that a manufacturer has a duty to “provide adequate supporting information to FDA,” and thus “could * * * at least *propose*] a label change that the FDA could receive and impose uniformly.” JA410 (*Mensing*); JA554-556 (*Demahy*). But such claims cannot be reconciled with *Buckman Co. v. Plaintiffs’ Legal Committee*, 531 U.S. 341 (2001), which held that the FDA alone is responsible for policing communication between the agency and the manufacturers it regulates. There, as here, lower courts had recognized state tort liability premised “solely [on] the violation of * * * the FDCA disclosure requirements.” *Id.* at 352-353. But as the Court recognized, such litigation “would exert an extraneous pull on the scheme established by Congress,” and is therefore preempted. *Id.* at 353.

A. As a threshold matter, no presumption against preemption applies to state tort claims that hinge on a generic company's failure to warn the FDA. Such a claim has never been part of traditional state regulation of health and safety; it is a newly devised overlay, premised on and arising solely out of *federal* law. As *Buckman* explained, "the relationship between a federal agency and the entity it regulates is inherently federal in character because the relationship originates from, is governed by, and terminates according to federal law." 531 U.S. at 347. Indeed, even the concurring Justices in *Buckman* would have found preempted state tort law theories that "depend upon speculation as to the FDA's behavior in a counterfactual situation." *Id.* at 354 (Stevens and Thomas, JJ., concurring in judgment).

B. Even apart from application of a presumption against preemption, *Buckman* confirms that state law cannot be allowed to police manufacturers' relationship with the FDA.

The ANDA process, even more so than the §510(k) process at issue in *Buckman*, "sets forth a comprehensive scheme for determining whether an applicant has demonstrated that a product is * * * equivalent to a predicate [drug]." *Id.* at 348. Moreover, enforcing the FDCA is the FDA's "exclusive[]" prerogative, and the agency may prefer a "measured response" to a generic's alleged failure to submit "additional necessary information." *Id.* at 348, 349, 352. That is because the FDA is charged with striking "a somewhat delicate balance" between keeping unsafe products off the market and making efficacious products available to patients. *Id.* at 348. That balance may not be "skewed" by allowing "unpredictable civil liability" under state law to piggyback on the federal regime.

Id. at 348, 350. Such a result would raise the stakes exponentially for generics, working wholesale changes in the way such companies do business and ultimately discouraging development of needed low-cost drugs. See *id.* at 348, 350.

Indeed, unless generic manufacturers do exactly what Hatch-Waxman was designed to prevent—*i.e.*, spend time and money replicating the brand’s studies and creating a knowledge base for evaluating new data that might warrant revisiting the scientific and practical trade-offs embodied in the FDA-approved label—they cannot comply with the duties imposed by the decisions below. If the point of Hatch-Waxman was to affirmatively encourage low-cost generic drugs, then surely federal law will not countenance state regulation that multiplies the cost of generic drugs by purporting to oversee the *federal* regulatory scheme. *Buckman*, 531 U.S. at 350.

Finally, such potential state liability gives regulated entities “an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA[.]” *Buckman*, 531 U.S. at 351. *Amici* have an interest in an FDA that operates quickly and efficiently—goals quite consistent with the best interests of patients, who need safe and effective drugs sooner rather than later. What no one needs is a generic pharmaceutical industry that cannot protect itself from state tort liability unless it inundates the FDA with information, suggestions, cautions, and incessant proposals to reconsider drug labels.

Yet, under the decisions below, if the FDA has not rejected the most risk-averse label clever minds can devise—and every variation short of it—then injured

plaintiffs can ask lay juries whether a manufacturer should have made a particular pitch, and whether, had that pitch been made, the FDA would have acted. The parties will be forced to seek both written discovery regarding the agency’s internal decision-making process and testimony concerning how agency personnel would have responded to various hypothetical scenarios. The result will be precisely what the Court warned against in *Buckman*: serious interference with the FDA’s resources and enforcement of the FDCA.

For all these reasons, the decisions below should be reversed, and state law failure-to-warn claims against manufacturers of generic drugs held categorically preempted.

ARGUMENT

I. Federal Law Preempts Claims That A Generic Manufacturer Should Have Changed Its Label.

As Petitioners and the Government explain, federal law dictates that generic drug labels be “the same as” the FDA-approved label for the name-brand equivalent—both before and after the ANDA’s approval. And since federal law requires generic drug labels to contain a specific set of cautions—and none other—it is *impossible* for generic manufacturers to comply with state law requirements to provide additional warnings. If a warning is not part of the FDA-approved label, generic manufacturers may not give it. For generic drugs, federal labeling requirements “serve as a ceiling as well as a floor.” *Wyeth*, 129 S. Ct. at 1204 (Breyer, J., concurring).

**A. Generic labeling must be “the same as”
the name-brand equivalent.**

To prevent consumers from erroneously thinking a name-brand drug is somehow better (or worse) than its generic copies, and to decrease the cost of generic drugs, Congress mandated that generic drugs have “the same” labels as their name-brand equivalents. 21 U.S.C. §355(j)(2)(A)(v). This is a condition of FDA approval, and a manufacturer may no more ignore this requirement post-approval than it could change the drug’s active ingredient. Federal law places “a very high priority [on] assuring consistency in labeling * * * to minimize the cause for confusion among health care professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name drug products.” Division of Generic Drugs, FDA, *Policy & Procedure Guide* 37 (1989).

As discussed above (at 5), there are only two statutory exceptions to this requirement—and neither includes stronger safety warnings. Indeed, in adopting final ANDA regulations in 1992, the FDA rejected proposals that “FDA accept ANDA’s with warnings or precautions in addition to those on the reference listed drug’s label.” 57 Fed. Reg. at 17953; accord *id.* at 17957. As detailed by Petitioners PLIVA, Inc., et al. (at 19-20, 38-40), the FDA has maintained this position for decades. But according to Respondents, generic manufacturers may unilaterally revise their labels via the CBE process, initiate label changes via the PAS process, and provide information to doctors via DHCP letters. Respondents are wrong on every count.

B. Generic manufacturers may not unilaterally change their product labeling.

1. CBE process

The “changes being effected” (CBE) process, 21 C.F.R. §314.70(c), was central to this Court’s holding in *Wyeth*. See 129 S. Ct. at 1196, 1199 (impossibility analysis literally starting and ending with the CBE regulation). That process allows brands to alter drug labels to “add or strengthen a contraindication, warning, precaution, or adverse reaction,” or to “add or strengthen an instruction about dosage and administration that is intended to increase the [drug’s] safe use,” where warranted by newly discovered information. *Id.* at 1196 (quoting 21 C.F.R. §314.70(c)(6)(iii)-(A), (C)).

By the Fifth Circuit’s reasoning, the FDA’s CBE regulation “does not, on its face, distinguish between generic and name brand drug manufacturers,” and thus “does not forbid a generic manufacturer from using the CBE process to unilaterally change a label.” JA543 (*Demahy*). The Eighth Circuit took a similar view. JA412-413, 414-415 (*Mensing*). But as the Government explains (CVSG Br. 13-14), generics may use this process *only* to make changes already approved for the brand’s label. The CBE regulation must be read in conjunction with the substantive standards governing generic labeling—including the rule that ANDAs will not be approved unless the generic’s proposed labeling *is* “the same as” the name-brand equivalent, and the rule that approval will be withdrawn unless that labeling *stays* “the same as” the brand’s. 21 U.S.C. §355(j)(4)(G); 21 C.F.R. §314.94(a)(8)(iii); 21 C.F.R. §314.150(b)(10).

Given that ANDA approval may be withdrawn if “the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug” (21 C.F.R. §314.150(b)(10)), it makes no sense to read the “same as” limitation as applying during the approval stage, but not afterwards. Accord Proposed Rule, 73 Fed. Reg. 2848, 2849 n.1 (Jan. 16, 2008). Rather, generic manufacturers are required to conform to the approved labeling for the listed drug *at all times*.

For generic products, therefore, the CBE process provides nothing more than a mechanism to maintain consistency with the brand’s labeling *if* that labeling changes. It does not permit complying with rules of state tort law providing that generic drugs ought to carry more fulsome warnings. If the brand’s label changes, so too must the generic’s; but if the brand’s label has not changed, neither may the generic’s.

2. PAS process

Nor may generic manufacturers use the PAS process to add or strengthen warnings on their labels.

The text of the FDA’s PAS regulations is dispositive: “[C]hanges [requiring pre-approval] include, but are not limited to * * * the following label changes: Changes in labeling, except those described in paragraph[] (c)(6)(iii) * * * of this section.” See 21 C.F.R. §314.70(b)(2)(v)(A). That exception is a cross-reference to the CBE provision quoted above, which governs strengthened warnings. And as we have shown, the CBE process is unavailable to generics seeking to implement labels that differ from the brand’s.

3. DHCP letters

Finally, Respondents propose that generic manufacturers can provide warnings to doctors and patients, above-and-beyond FDA-approved labeling, by sending “Dear Health Care Professional” (DHCP) letters. Not so.

Because DHCP letters are “labeling” under federal law, they implicate the federal prohibition on misbranding. 21 U.S.C. §312(m); 21 C.F.R. §202.1(l)(2). If a generic manufacturer were to unilaterally send a DHCP letter warning of additional risks associated with its product, that would tend to suggest—wrongly—that there is a difference between the generic and brand-name drug. Accordingly, DHCP letters can be sent only with FDA approval or coordination—something the Eighth Circuit recognized. JA413 n.5 (*Mensing*) (“FDA sends [DHCP] letters out on behalf of ANDA holders if it determines that such a letter is * * * necessary”). Generic manufacturers who unilaterally send letters risk having approval for their products revoked. 21 C.F.R. §314.150(b)(3).

* * * * *

The federal regime requires generic drugs to bear “the same” label as their brand-name equivalents—at all times, and in all relevant particulars. In assessing the viability of failure-to-warn suits against manufacturers of name-brand products, the Court in *Wyeth* reasoned that such manufacturers are responsible for the content of their labels, and that federal law provides a mechanism to unilaterally update safety information without prior FDA approval. 129 S. Ct. at 1196-1199. Neither conclusion is true of generic manufacturers. It is therefore impossible for generic

manufacturers to comply with any state tort law requirement to use labeling not mandated by the FDA.

II. Under *Buckman*, Federal Law Preempts Claims That A Generic Manufacturer Should Have Warned Or Provided Additional Information To The FDA.

Although federal law precludes generic manufacturers from unilaterally providing additional, non-FDA-approved warnings to consumers, the courts below concluded that such manufacturers could be held liable for “failing to take steps to change the label”—either by providing the FDA with information as to “additional risks” of their products, or by “*propos[ing]* a label change that the FDA could receive and impose uniformly.” See JA534 (Demahy); JA410 (*Mensing*); see also CVSG Br. 11 (suggesting that failure-to-warn claims are not “categorically preempted” because generics must report adverse events to FDA, and may request label changes). But this attempt to carve-out a role for state tort regulation is flatly inconsistent with *Buckman*, and with the text, structure, and purposes of the Hatch-Waxman Act.

A. There is no presumption against preemption of claims that a generic manufacturer should have warned the FDA.

At the outset, we emphasize that these are not cases in which the Court should apply a “presumption against preemption.” Cf. *Wyeth*, 129 S. Ct. at 1195 n.3.

1. To begin with, any such presumption is difficult to reconcile with the text and structure of the Constitution itself. The Supremacy Clause provides that all federal law “shall be the supreme law of the land; and the judges in every state shall be bound thereby, any-

thing in the constitution or laws of any state to the contrary notwithstanding.” U.S. Const. Art. IV, Cl. 2. This language does not suggest a reticence on the part of the Framers to preempt state law. Rather, they specifically contemplated that rulings of state courts and judges might interfere with the operation of federal law, and made clear that federal law should take precedence “notwithstanding” “*anything* in the constitution or laws of any state *to the contrary*.” If anything, this language *undercuts* any presumption against preemption. And as a matter of constitutional structure, limits on federal power should be effectuated by proper interpretation of enumerated federal powers, not by tipping the scales against preemption where Congress validly acted. Cf. *Watters v. Wachovia Bank, N.A.*, 550 U.S. 1, 22 (2007).

2. Even if a presumption against preemption were appropriate in other contexts, no such presumption applies in *conflict* preemption cases, much less here. In analyzing whether there is a conflict between federal and state law, it makes no sense—as a matter of logic or common sense—to *presume* that Congress would tolerate such a conflict. Either there is a conflict or there isn’t. That, in part, is why “neither an express pre-emption provision nor a saving clause bars the ordinary working of conflict preemption principles.” *Buckman*, 531 U.S. at 352 (internal quotation and alteration marks omitted); accord *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 869 (2000).

3. In any case, “policing” manufacturers’ “dealings with the FDA”—dealings “prompted by the [FDCA], and the very subject matter of [which] [is] dictated by that statute’s provisions”—“is hardly ‘a field which the States have traditionally occupied.’” *Buckman*, 531 U.S. at 347-348 (citation omitted). *Wyeth* held

that garden-variety failure-to-warn claims fell within States' historic concern with health and safety regulation, notwithstanding a 100-year history of federal pharmaceutical regulation. 129 S. Ct. at 1195 n.3; but cf. *United States v. Locke*, 529 U.S. 89, 108 (2000) (presumption against preemption "is not triggered when the State regulates in an area where there has been a history of significant federal presence"). But claims that generic manufacturers should have provided the FDA with "additional necessary information"—on which the agency allegedly would have acted—do not "implicat[e] federalism concerns and the historic primacy of state regulation of matters of health and safety." *Buckman*, 531 U.S. at 347-348 (citation omitted); cf. *Boyle v. United Techs. Corp.*, 487 U.S. 500, 504-505 (1988) (no presumption against preemption where the interests at stake are "uniquely federal" in nature). Accordingly, "no presumption against pre-emption obtains in this case." *Buckman*, 531 U.S. at 348.

B. Under *Buckman*, States may not police communications between a generic manufacturer and the FDA—and claims based on label change *proposals* require such policing.

Even apart from the absence of any presumption against preemption, several parallels between these cases and *Buckman* confirm that the "taking steps" liability contemplated by the courts below "would exert an extraneous pull on the scheme established by Congress." 531 U.S. at 353. Indeed, the legal context in which these cases arise is strikingly similar.

1. The legal context of these cases is strikingly similar to what the Court evaluated in *Buckman*.

a. The duty at issue here is the same as that alleged in *Buckman*. According to the courts below, even if federal law prohibits generics from unilaterally changing their labels (which it does), such companies may nonetheless be subjected to state tort liability for failing to “take steps” to “alert the FDA” of the need for “a label change that the FDA could * * * impose uniformly.” See JA534, 547, 554-556 (*Demahy*); JA410 (*Mensing*). To be sure, the courts did not call this a “fraud” theory. But the central allegation is the same—namely, that the manufacturer breached a duty to disclose “adequate supporting information to FDA” concerning the risks of a product. JA547 (*Demahy*) (citation omitted). And in both cases the lower courts recognized state tort liability premised “solely [on] the violation of * * * the FDCA disclosure requirements.” 531 U.S. at 352-353. As *Buckman* confirmed, however, federal law preempts claims that a manufacturer failed to submit “additional necessary information” in its “dealings with the FDA.” *Id.* at 347, 348.

b. The FDA approval processes at issue here and in *Buckman* are closely analogous. *Buckman* involved the FDA’s abbreviated (§510(k)) process for approving “substantially equivalent” medical devices. These cases involve the FDA’s abbreviated (ANDA) process for approving “bioequivalent” generic drugs. In both contexts, approval rests on a showing that the applicant’s product is similar or identical to a predicate product—one subjected to more rigorous, “time consuming,” and “thorough review.” 531 U.S. at 344-345. And in both contexts, the purpose of abbreviated

approval is to get the later product “on the market within a relatively short period of time.” *Id.* at 350; see *Barr Labs.*, 930 F.2d at 76 (Hatch-Waxman’s fundamental goal is “to get generic drugs into the hands of patients at reasonable prices—fast”).

Although the “[Section] 510(k) notification requires little information, rarely elicits a negative response from the FDA, and gets processed very quickly” (*Medtronic, Inc. v. Lohr*, 518 U.S. 470, 478-479 (1996) (citation omitted)), this Court found that process to have preemptive effect because, “to achieve its limited purpose, [it] imposes upon applicants a variety of requirements that are designed to enable the FDA to make its statutorily required judgment as to whether the device qualifies” (*Buckman*, 531 U.S. at 348-349). Thus, the fact that an FDA-regulated product relies on safety or efficacy data submitted for a predicate product—and is subject to review “lack[ing] the [earlier] review’s rigor”—does *not* make the relationship between the FDA and the manufacturer any less “inherently federal.” *Id.* at 347, 348.

Indeed, ANDA products are far more closely tied to NDA drugs than are §510(k) devices to their Class III counterparts. Both the labeling and active ingredient of an ANDA product must be “the same as” the NDA drug’s. Manufacturers of §510(k) devices are subject to no comparable requirements. See 21 C.F.R. §807.87(e). Moreover, as discussed below, the FDA enjoys the same enforcement options whether the manufacturer simply failed to provide required information or made affirmative misstatements to the agency. These cases therefore present an even stronger case for preemption than did the facts of *Buckman*.

2. The United States alone has authority to enforce the FDCA, and to decide whether generic labels should be changed.

a. Preemption of failure-to-inform-the-FDA claims is also warranted because, as in *Buckman*, the authority and discretion to take action against a generic manufacturer for noncompliance with federal law rests “exclusively [with] the Federal Government.” 531 U.S. at 352. As the Court there explained, “[t]he FDCA leaves no doubt that it is the Federal Government rather than private litigants who are authorized to file suit for noncompliance with the medical device provisions: ‘[A]ll such proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States.’” *Id.* at 349 n.4 (quoting 21 U.S.C. §337(a)). This is equally true of the reporting requirements at issue here. And the FDA may well prefer a more “measured response” than that of a lay jury hearing one case in isolation. *Id.* at 349.

The Fifth Circuit noted that, because there is no private federal cause-of-action for the failure to warn, consumers of generic drugs have no remedy if state actions are preempted. JA532 (*Demahy*). But this lack of a private damages remedy is by design. As detailed above (at 7-8), the FDA has several means of regulating the conduct of generic manufacturers. The availability of this range of regulatory options “is a critical component of the statutory and regulatory framework under which the FDA pursues difficult (and often competing) objectives.” *Buckman*, 531 U.S. at 349. Further, when it determines that the FDCA has been violated, the FDA has “complete dis-

cretion” to pursue the remedy that, in its judgment, best fits the violation. *Chaney*, 470 U.S. at 835.

State tort law policing of communications between regulated entities and the FDA, by contrast, would operate in a vacuum, divorced from any obligation or incentive to balance the goal of full disclosure against other worthy (sometimes competing) policy objectives—such as patients’ interest in access to live-saving medicines with significant side effects. Even if state and federal law share the same ultimate goal, “[t]he fact of a common end hardly neutralizes conflicting means.” *Crosby v. Nat’l Foreign Trade Council*, 530 U.S. 363, 379 (2000). Accordingly, state law is still preempted if it “interferes with the methods by which the federal statute was designed to reach this goal.” *Int’l Paper Co. v. Ouellette*, 479 U.S. 481, 494 (1987). And since violating one’s duties to the FDA “is not a local offense,” but an offense against the United States, it is “vital” that enforcement “should be exclusively within the control of the Federal Government.” *Pennsylvania v. Nelson*, 350 U.S. 497, 505 (1956).

And make no mistake: State tort liability is a form of additional regulation. “The obligation to pay compensation” is “a potent method of governing conduct and controlling policy.” *San Diego Bldg. Trades Council v. Garmon*, 359 U.S. 236, 247 (1959). Unlike name-brand drugs, generic drugs typically have a thin profit margin—which means these hefty damage awards can be company killers. Just as the Court in *Buckman* recognized that the “fear” of “expos[ing] the manufacturer * * * to unpredictable civil liability” might “discourage [applicants] from seeking §510(k) approval of devices” (531 U.S. at 350), so too may the prospect of liability for an alleged failure to inform

the FDA deter the development of needed low-cost generic medicines.

Allowing failure-to-inform-FDA claims would also allow juries in 50 different States to reach judgments that differ from the FDA's—and from each other's. See *Garner v. Teamsters*, 346 U.S. 485, 490-491 (1953) (“A multiplicity of tribunals and a diversity of procedures are quite as apt to produce incompatible or conflicting adjudications as are different rules of substantive law.”). Citing this danger, *Buckman* explained that allowing liability under “50 States’ tort regimes will dramatically increase the burdens facing potential applicants—burdens not contemplated by Congress.” 531 U.S. at 350. The effect was an “inevitable conflict with the FDA’s responsibility to police fraud consistently with the Administration’s judgment and objectives.” *Ibid.* The same is true of the failure-to-inform-the-FDA claims here.

Indeed, because drugs cross state lines, the rulings below effectively allow the most warning-happy State to set policy for the whole nation, undermining the Act’s goal of promoting uniform labels. But “one State’s power to impose burdens on the interstate market” is “constrained by the need to respect the interests of other States.” *BMW, Inc. v. Gore*, 517 U.S. 559, 571 (1996). And where “[t]he subject-matter * * * peculiarly * * * calls for uniform law,” States may not “supplement” federal mandates. *Pennsylvania R.R. v. Public Serv. Comm’n*, 250 U.S. 566, 569 (1919); see also *Boyle*, 487 U.S. at 507-508.

b. A further problem is that the failure-to-inform-the-FDA claims approved below would allow state law to establish and enforce a labeling standard other than that which was adopted by the FDA and in force

at the relevant time. As even the concurring Justices in *Buckman* recognized, state tort liability should not “depend upon speculation as to the FDA’s behavior in a counterfactual situation”; it should be “grounded in the agency’s explicit actions.” See 531 U.S. at 354 (Stevens, J., concurring). Indeed, States generally may not provide causes of action that fail to give effect to federal administrative decisions that have neither been rescinded by the agency nor set aside by the federal courts. *Arkansas La. Gas Co. v. Hall*, 453 U.S. 571 (1981) (*Arkla*); *Chicago & North Western Transp. Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311 (1981). The claims here, however, would proceed on the theory that Respondents should receive damages as if marketing a drug approved by the FDA—under a label it mandated—was unlawful.

c. Incredibly, the decisions below would go so far as to put the burden on *defendants* to adduce “clear evidence” that FDA would have *rejected* a labeling proposal. JA409-416 (*Mensing*); JA554-556 (*Demahy*); see also *Gaeta v. Perrigo Pharm. Co.*, No. 09-15001, 2011 WL 198420, *10 (9th Cir. Jan. 24, 2011) (reasoning that the FDA’s conclusion that there was “no need” to add a hepatotoxicity warning “at this time” did *not* amount to “clear evidence that the FDA would have rejected the [plaintiffs’] proposed hepatotoxicity warning *two years later*”) (emphasis added).

Misunderstanding *Wyeth*, the courts below reasoned that *Petitioners* bear the burden of proving how FDA would have responded in a counterfactual situation of Respondents’ devise. JA415 (*Mensing*); JA555-556 (*Demahy*); see also CVSG Br. 19. As an initial matter, this makes no sense. If a plaintiff’s claim is that she was injured by a failure to warn—or, more precisely, that the generic manufacturer

should have provided additional information to the FDA, which would have approved further warnings—then FDA *action* is “an essential link in the chain of causation.” See *Buckman*, 531 U.S. at 353 (Stevens, J., concurring). Quite apart from the fatal problems with claims that depend on “speculation as to the FDA’s behavior in a counterfactual situation” (*ibid.*), *all* elements of such claims, including causation, are Respondents’ burden to prove. Restatement (Second) of Torts §433B(1) (1965).

Furthermore, requiring generic manufacturers to “show the likelihood of FDA *inaction*” (JA415 (*Mensing*)) is contrary to the usual rule that those seeking relief from the status quo bear the burden of proof. Cf. *U.S. Bancorp Mortg. Co. v. Bonner Mall P’ship*, 513 U.S. 18, 26 (1994); 2 McCormick on Evid. §337 (6th ed. 2009). In *Wyeth*, the Court reasoned that nothing barred name-brand manufacturers from unilaterally strengthening warnings via the CBE process. 129 S. Ct. at 1196-1197. Thus, to establish a conflict between state and federal law, it was necessary to show that the FDA would have acted after the fact to reject a label change made by the brand—a burden that falls on the manufacturer. *Id.* at 1198.

The situation here is fundamentally different. The *starting point* is a conflict between state and federal law: Petitioners must use the FDA-approved label; unlike the defendants in *Wyeth*, they may not unilaterally provide any enhanced warning state law might require; and a conflict thus exists *unless and until the FDA acts*. Here, as in *Wyeth*, one party must show FDA *action* to prevail; that party bears the burden.

Wherever the burden is placed, however, the conflict between state and federal law is not averted by a

jury's conclusion that the FDA would have required a different label had the manufacturer only proposed it. The FDA "alone is empowered" to decide whether generic labels should be altered, and by seeking damages based on assumptions concerning what the FDA "might have done," Respondents seek to "usurp[] a function that Congress has assigned to a federal regulatory body." *Arkla*, 453 U.S. at 581-582.

3. State regulation is an added burden on generic manufacturers and, as such, conflicts with the federal regime.

Allowing state tort claims here would also thwart federal policy favoring inexpensive, widely-available generic drugs, as it would force generic manufacturers to undertake burdens—collecting and analyzing scientific data, and making risk-assessment decisions on pain of substantial liability—that Congress never intended. Cf. *Buckman*, 531 U.S. at 350. Such costs are particularly problematic under Hatch-Waxman, which was enacted to *increase* the availability, and *lower* the cost, of generic drugs.

First, Congress exempted generics from safety and efficacy mandates applicable to brands, replacing those burdens with a lighter burden—to be "the same as" an NDA drug. It would thwart the federal scheme, therefore, to impose on generics the burdens that Congress imposed on brands.

The Government asserts that "petitioners could have asked FDA to coordinate appropriate DHCP letters (or, by extension, to take other action with respect to labeling)." CVSG Br. 11. But Congress made brands—*not* generics—responsible for maintaining labeling. Moreover, the practical reality is that name-brand manufacturers possess the proprietary

information and experience with respect to safety that was necessary to obtain approval in the first place—and can analyze new information against that backdrop.

Generic manufacturers, by contrast, do not have the same proprietary data, experience, or other knowledge, except with respect to bioequivalence. As discussed above, the central and immutable federal obligation imposed on generic manufacturers is to maintain a label “the same as” a branded equivalent. To be sure, federal law does not *forbid* generic manufacturers (or anyone else) from making labeling suggestions to the FDA. But it puts the *obligation* to do so on companies able to make informed suggestions. If generics must attempt to fulfill this role, such companies will be obliged to err on the side of overly stringent warnings—to the detriment of patients who need generic drugs—to avoid being perceived as “soft” on the risks of their products. That would be a perverse system of incentives.

Furthermore, creating the knowledge base necessary to propose label changes has a cost. Indeed, contrary to the courts below (JA416-417 (*Mensing*); JA558-560 (*Demahy*)), generic manufacturers of metoclopramide could not have requested—much less triggered—a label change based simply on articles in the medical literature or their own individual experiences with adverse events. Label changes require fuller scientific substantiation. Such substantiation can be obtained only through analysis of the proprietary clinical studies conducted to obtain approval of the branded drug—information to which generics lack access—or by post-approval studies, which ge-

nerics are not authorized to perform consistent with Hatch-Waxman.⁴

In fact, the decisions below are surprisingly oblivious of the history underlying Hatch-Waxman. Under the old regime, generics had to be priced to reflect the fact that all would-be generic manufacturers had to independently establish safety and efficacy. Allowing the civil liability contemplated by the decisions below would re-impose these costs—which are not small. One calculation put the cost for pre-approval clinical studies for a branded drug at \$176.5 million (in 2000 dollars), and the *post-approval* research and development cost for a new drug brought to market at \$140 million. Joseph A. DiMasi, et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 *J. Health Economics* 151, 172, 173 (2003). That is a several hundred-fold increase over the post-Hatch-Waxman cost of researching generic drugs, as “the [current] research and development costs for a new generic drug are only 1 to 2 million dollars.” ASPE Issue Brief, *supra*, at 4-5.

These costs would be borne by consumers—in the form of increased prices, decreased availability as manufacturers exit the market, or both. Not only does increased generic substitution drive down the price of the *brand* (ASPE Issue Brief, *supra*, at 3), but “[t]he relatively low costs to entry for generic drugs lead to increased competition, which drive prices for

⁴ Only in 2009, and based on a four-year review, did the FDA order a stronger warning regarding the risk of prolonged metoclopramide use. *Br. of Petitioners Actavis Inc. et al.* 11-12; *Br. of Amicus Curiae, Morris v. Wyeth, Inc.*, Doc. 00618908446, No. 09-5509 (6th Cir.) (filed Feb. 5, 2010), and exhibits thereto.

generic drugs down dramatically” too (*id.* at 5). As the FDA has found, “the first [generic] entrant has a relatively small effect on price, but subsequent entrants dramatically reduce the average relative price.” *Ibid.* More precisely, “the appearance of a second generic manufacturer reduces the average generic price to nearly half the brand name price. * * * For products that attract a large number of generic manufacturers, the average generic price falls to 20% of the branded price and lower.”⁵ In short, these plaintiffs do not represent the interest of consumers generally.

Even indulging the assumption that allowing state tort liability might make drugs safer (which is doubtful), Congress has already struck a balance between safety and cost. And where federal law reconciles competing objectives, “that is not a judgment the States may second-guess.” *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989). Rather, state regulation “must yield to the extent that it clashes with the balance struck by Congress.” *Ibid.*; accord *Geier*, 529 U.S. at 874-881 (state tort law was preempted insofar as it balanced competing policy objectives—including issues of cost and safety—differently from federal law).

Here, state common law regulation would impose substantial costs on generic manufacturers. These costs cannot be brushed aside as extra incentive to comply with federal law; instead, they “would exert an extraneous pull on the scheme established by Congress,” and “[are] therefore pre-empted.” *Buckman*, 531 U.S. at 353.

⁵ FDA, Generic Drug Prices, <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm>.

4. Allowing state regulation will impose substantial costs on the FDA.

Finally, from the FDA's side as well, allowing state failure-to-inform-the-FDA claims would impose substantial new costs and create practical problems.

First, due to the risk of second-guessing by juries, companies must “fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court.” *Buckman*, 531 U.S. at 351; see *Geier*, 529 U.S. at 882 (“this Court’s pre-emption cases ordinarily *assume* compliance with the state law duty”). And this fear in turn creates “an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA’s evaluation of an [ANDA].” *Buckman*, 531 U.S. at 351.

More information is not necessarily better. Indeed, the FDA asks drug companies *not* to submit adverse event reports unless there is an identifiable patient and reporter, a suspect drug, and an adverse event—all four—“because reports without such information make interpretation of their significance difficult, at best, and impossible, in most instances.”⁶ The FDA likewise discourages reporting of adverse events derived from “planned contacts and active solicitation” unless they are “serious” *and* “unexpected”

⁶ Adverse Drug Reaction Reporting Regulations Working Group, Center for Drug Evaluation & Research, *Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drug & Licensed Biological Products: Clarification of What to Report 1-2* (Aug. 1997), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071981.pdf>.

and “there is a reasonable possibility that the drug or biological product caused the adverse experience.” *Id.* at 3-4. The agency even “encourage[s] * * * manufacturers to submit requests to the Agency * * * to waive the requirement to submit [forms] to the FDA for each adverse experience that is determined to be both nonserious and labeled.” *Id.* at 4. If state tort law may punish them on a failure-to-inform-the-FDA theory, generic manufacturers are unlikely to comply with such agency requests.

A related problem is that, if the FDA is flooded with unneeded information, then its decision-making will slow down—and it will take even longer for generic drugs to reach consumers. That would be directly contrary to the animating purpose of Hatch-Waxman. Yet delay is already a problem: “Since 2002, the number of ANDAs submitted has continued to grow. [The Office of Generic Drugs] expects that the increased number of ANDAs, plus additional workload from citizen petitions and the submission of ANDAs for more complex drug products, could potentially cause delays in the approval of ANDAs, including ANDAs for drug products that are particularly important to the public health.” Center for Drug Evaluation & Research, *Manual of Policies & Procedures* 5240.3, at 1 (Oct. 18, 2006).⁷ If allowed to stand, the rulings below will exacerbate this problem.

Further, if state tort liability hinges on hypothetical decisions FDA *might have made*, then FDA will be burdened by demands for discovery regarding internal deliberations and how agency personnel might have responded under various hypothetical scenarios.

⁷ <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079787.pdf>.

Existing regulations suggest that the FDA is not inclined to accommodate such demands. See 21 C.F.R. §§20.1, 20.2(a). But while the Government can resist, parties may challenge any refusal to testify under the APA. *United States ex rel. Touhy v. Ragen*, 340 U.S. 462 (1951); *Exxon Shipping Co. v. United States Dep't of Interior*, 34 F.3d 774, 778-780 (9th Cir. 1994). Further, if the FDA becomes the gatekeeper for private tort liability, it can anticipate myriad petitions from prospective plaintiffs urging the agency to find unlawful nondisclosures—which would be every bit as burdensome as testifying.

Insofar as the FDA succeeds in beating back such burdens, its reward will be lay juries forced to speculate, without FDA guidance, as to whether the agency would have approved label changes championed after the fact by injured plaintiffs. That is, if state tort liability is allowed to depend on a jury's assessment of what the FDA would have done, the FDA must either submit to the burdens of assessing hypotheticals and participating in private litigation, or we can have no confidence that the jury will reach the right result.

Indeed, while juries will be charged with evaluating the materiality of information not submitted to the FDA, they cannot replicate the FDA process. Congress has directed the agency, in making safety and efficacy determinations, to rely on experts from several scientific disciplines. 21 U.S.C. §355(n). Moreover, juries are ill-equipped to discern how the FDA implements its policies, why certain types of information may be probative (or not probative), or how the agency's institutional expertise affects its evaluation. Thus, while it is questionable whether juries can accurately determine the propriety of warnings at

all,⁸ it is frankly absurd to think they can accurately predict what FDA “would have” done.

Finally, the inevitable disconnect between state law and FDA requirements poses serious practical difficulties for generic manufacturers. What is a manufacturer to do if, for example, a jury rules that that it should have provided a new warning that the FDA has not vetted, much less approved? Submit the proposal, to be sure—and pull its product from the market in the meantime? Submit the proposal and ask the FDA to deny it, to preclude liability in other States? And what if the FDA rejects the proposal? It is cold comfort indeed if, in the aftermath of a crippling verdict, the FDA declines to act as the verdict assumes it would have.

CONCLUSION

The decisions below should be reversed and state law failure-to-warn claims against generic drug manufacturers held categorically preempted.

⁸ Fact-finders lack perspective beyond the injured patient in the case before them. See *Carroll v. Otis Elevator Co.*, 896 F.2d 210, 215-216 (7th Cir. 1990) (Easterbrook, J., concurring) (jurors in product liability cases tend to focus on “today’s injury” rather than probabilities, rendering “invisible” those who would have been harmed had the allegedly defective product *not* been on the market).

Respectfully submitted.

W. GORDON DOBIE
JAMES F. HURST
MAUREEN L. RURKA
WILLIAM P. FERRANTI
Winston & Strawn LLP
35 W. Wacker Drive
Chicago, IL 60601
(312) 558-5600

STEFFEN N. JOHNSON*
Winston & Strawn LLP
1700 K Street, N.W.
Washington, DC 20006
(202) 282-5000
sjohnson@winston.com

** Counsel of Record*

Counsel for Amici Curiae

JANUARY 2011