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

IN THE
Supreme Court of the United States

PLIVA, INC., *et al.*, 09-993 *vide* 09-1039, *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, 09-1039 *vide* 09-993, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS INC., 09-1501, *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eights Circuits

BRIEF OF THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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QUESTION PRESENTED

The Drug Price Competition and Patent Terms 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 product warnings were, as the Hatch-Waxman Act and FDA implementing regulations expressly require, "the same as" those FDA approved for the product's brand-name equivalent?

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INTEREST OF *AMICUS CURIAE* AND SUMMARY OF ARGUMENT

The Generic Pharmaceutical Association ("GPhA") is a non-profit, voluntary association[1] comprised of more

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[1] All parties have consented to the filing of this brief, and letters evincing such consent have been filed with the Clerk. Pursuant to

than 140 manufacturers and distributors in the generic pharmaceutical industry. GPhA members provide American consumers with generic pharmaceutical medications that are just as safe and efficacious as their brand-name counterparts, but at a fraction of the cost. Generic drugs today account for nearly 70% of all prescription pharmaceuticals dispensed in the United States each year, providing access to safe and affordable medicines for more Americans, including the poor and elderly, than ever before.

The matters now before the Court are representative of thousands of product liability lawsuits currently pending against GPhA members across the country. The essential thrust of those suits is to misapply this Court's recent decision in *Wyeth* v. *Levine*, 129 S.Ct. 1187 (2009), to subject generic drug manufacturers to the same post-marketing surveillance and labeling requirements applicable to brand-name manufacturers without regard to the ruinous costs this would impose on the generic pharmaceutical industry—costs that Congress explicitly sought to eliminate for the express purpose of increasing the availability of low-cost generic drugs.

The generic pharmaceutical industry has been shaped by congressional and regulatory oversight for specific public purposes—to make medicines available to as many people as possible at the lowest possible costs without introducing additional safety risks. Those purposes have been achieved. Generic drugs are required to be no more than exact copies of brand-name drugs that already have been subjected to the thorough testing process required

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this Court's Rule 37.6, *amicus* states that no counsel for a party authored any part of this brief and that neither such counsel, nor any party, nor any person or entity other than *amicus*, its members, or its counsel made a monetary contribution intended to fund the preparation or submission of this brief.

by the Food and Drug Administration ("FDA"). Generic manufacturers *cannot* change their labeling under federal law; only FDA can do that. Nor can generic manufacturers reinvent the expensive research and testing FDA required to approve the brand drug, all of which was complete many years before the generic version could even be produced. Recreating that wheel would eliminate the key benefit of generic drugs—that they are low cost without new risk.

This is common sense, but it is not only that. It is the regulatory regime purposefully adopted by Congress and FDA. Upsetting that regulatory balance by exposing generic manufacturers to state tort liability will adversely affect the industry, drive up costs for no salutary purpose, and contravene the intent of the political branches of government. It would return the generic pharmaceutical industry to its condition *before* Congress specifically authorized abbreviated approval conditioned on the "sameness" between the brand drug and the generic drug. That would also return the United States to a time when producing low-cost alternatives to brand drugs was economically unfeasible. It would, in short, threaten the continued availability of affordable generic drugs in America.

ARGUMENT

I. Divesting Generic Drug Manufacturers of Labeling Authority and Responsibility Is an Integral Part of a Carefully Calibrated Congressional Policy to Make Generic Drugs Widely Available by Ensuring that Generic Drugs Are Identical to Branded Drugs

Contemporary regulation of generic drugs has developed along a trajectory steeped in experience. Generic drugs are not simply "cheaper" drugs, in the sense that they are lesser in quality or in any other meaningful way.

Rather, they are cheaper—and intentionally so—precisely because they are *the same* as the name-brand drugs which have been subjected to the extraordinarily intensive testing required in the United States. To be a generic drug, the key requirement is that it be *identical* to the brand drug in all material respects. Generics rely on the intensive testing and approval process for the brand drug; in exchange, they forfeit any ability to modify the contents of the brand drug or the labeling that must accompany it. A brief survey of how Congress established the current regulatory regime, which divides brand-name drugs from their generic equivalents, demonstrates why it makes no sense to hold generic drug manufacturers liable in tort for actions that are beyond their control.

A. Congress has determined that generic drugs must be identical to the brand drugs they duplicate

Congress laid the foundation for the modern pharmaceutical regulatory scheme in 1962 by amending the Food, Drug and Cosmetic Act ("FDCA") to require that *all* drugs marketed in the United States must be approved by FDA as both safe and effective. H.R. Rep. No. 98-857(I) (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2649 (hereinafter "H.R. Rep."), Pet. App. 124a.[2] Every manufacturer of a drug first marketed after 1962 was required to conduct clinical studies to demonstrate safety and efficacy. *Id.* at 124a-125a. This costly and time-consuming testing requirement applied equally to both branded drugs and generic versions. *Ibid.*

FDA mitigated the inefficiencies in this regime by developing an abbreviated procedure for "duplicate" ver-

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[2] All references to "Pet. App." are to Appendix accompanying the petition for a writ of certiorari in No. 09-993, *Pliva, Inc., et al.* v. *Mensing*, No. 09-993.

sions of previously approved branded drugs. If the "duplicate" was bioequivalent to, or the "same as," the branded drug, the abbreviated process dispensed with duplicative clinical studies. "FDA considers such retesting to be unnecessary and wasteful because the drug already had been determined to be safe and effective" through testing submitted by the brand manufacturer. *Id.* at 124a.

In 1984, Congress explicitly adopted—and expanded upon—this common-sense approach. The Hatch-Waxman Amendments to the FDCA ("Hatch-Waxman") codified FDA's abbreviated procedure for approval of duplicate drugs and authorized its use for all generic drugs. See generally 21 U.S.C. § 355(j); Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,873 (proposed July 10, 1989). Hatch-Waxman exempts generic drug manufacturers from the extensive and costly testing and reporting requirements applicable to manufacturers of new, and therefore untested, drugs. It authorizes FDA to approve a proposed generic drug if its manufacturer can demonstrate that the generic product is bioequivalent to a branded drug previously approved by FDA as safe and effective. See 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.92(a)(1). Specifically, the generic manufacturer must show that its drug is the *same as* the branded drug with respect to active ingredient, route of administration, dosage form, strength, conditions of use and—most importantly here—labeling. See 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.92(a)(1).

B. Congress' purpose was to decrease healthcare costs—and it has succeeded, beyond Congress' wildest expectations

The intended consequence of precluding any variation between generic drugs and the approved brand drug was to foster vigorous price competition among generics. Hatch-Waxman had a clear and overriding purpose—to

increase the availability of low-cost generic drugs, with the twin benefits of decreasing healthcare costs for everyone and increasing access to quality medical care for millions of poor and elderly Americans. Simply stated, the essential point of Hatch-Waxman was "to get generic drugs into the hands of patients at reasonable prices—fast." *Andrx Pharms., Inc.* v. *Biovail Corp. Int'l*, 256 F.3d 799, 809 (D.C. Cir. 2001) (internal quotation omitted).

Congress estimated that Hatch-Waxman would "make available almost immediately nearly twice as many low-cost, generic drugs as are now available." 130 Cong. Rec. H24456 (daily ed. Sept. 6, 1984) (statement of Rep. Douglas Walgren), Pet. App. 142a. Further, the increased availability of affordable generic drugs "would save American consumers $920 million over the next 12 years." H.R. Rep., Pet. App. 125a. Congress further projected that federal and state governments both would reap the benefits of increased generic competition through substantial savings in government assistance programs, noting that the federal government alone spent approximately $2.4 billion for drugs in 1983 in Medicaid and Veterans Administration programs. *Id.* at 127a.

Beyond the significant overall cost savings, Congress also recognized that increasing the availability of affordable generic drugs would materially improve the quality of medical care available to poor and elderly Americans.

> [T]here are many post-1962 drugs that are off patent for which there is no generic competition. Drugs in this category, taken from a list of the top 100 prescribed drugs, have a drugstore market value of $500 million * * * Who is hurt by delay? The elderly, the 11 percent of the population who purchase 25 percent of all drugs.

New Drug Application: Hearing on H.R. 3605 Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce, 98th Cong. 43 (1983) (statement of Kenneth Larsen, chairman of the Generic Pharmaceutical Industry Association). Evidence presented during committee hearings revealed:

> in stark human terms what it means to pay high prices for drugs, when FDA-approved identical generics could be available at a fraction of the price * * * The choice, for them, is horrendous. Do you stop taking drugs at the end of the month, or do you skip some meals, or do you fail to heat your house and wait out the month in the cold? Those are the realities. Unless Congress provides an effective procedure for approving post-1962 drugs, consumers, particularly the elderly, are left with the hard choices.

Id. at 44. "For these older Americans this bill will ease the Hobson's choice between spending fixed incomes on pharmaceuticals or other necessities." Pet. App. 115. As President Reagan said at the time, Hatch-Waxman would assure that "the American people will save money, and yet receive the best medicine that pharmaceutical science can provide." Presidential Statement on Signing S. 1538 Into Law, 20 Weekly Comp. Pres. Doc. 1359, 1360 (Sept. 24, 1984) (quoted in *Glaxo, Inc.* v. *Novopharm, Ltd.*, 110 F.3d 1562, 1568 (Fed. Cir. 1997)).

The reality of Hatch-Waxman has far exceeded the projections of even its most optimistic proponents. The Congressional Budget Office (CBO) reported in 1998 that savings realized from the substitution of generic for brand-name drugs saved consumers between $8 billion and $10 billion in 1994 alone, the tenth year after the enactment of Hatch-Waxman. Congressional Budget Office, How Increased Competition From Generic Drugs

Has Affected Prices and Returns in the Pharmaceutical Industry 13 (1998) (hereinafter "CBO 1998").[3]

Since then, annual savings have grown exponentially. A second study by the CBO revealed that generic drug use in 2007 saved seniors and the federal government $33 billion just on Medicare Part D prescription drug costs. Congressional Budget Office, Effects of Using Generic Drugs on Medicare's Prescription Drug Spending 7-8 (2010) (hereinafter "CBO 2010").[4] Another recent study of prescription drug use in the U.S. found that dispensing generic versions of brand name drugs saved the American healthcare system more than *$824 billion* over the past decade (2000-2009) and *$139.6 billion in 2009 alone*. Generic Pharmaceutical Association, Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009 1-2 (2010) (hereinafter "GPhA 2010").[5] The savings projected by the proponents of Hatch-Waxman—$920 million over the first 12 years—are now being achieved *every three days.*

The impact of generic competition on overall drug prices is dramatic and escalating. By 1998, the average retail price of a prescription for a generic drug had fallen to half the cost of a multi-source brand-name drug ($17.40 vs. $37.40).[6] *See* CBO 1998 at 31. Today, the average generic drug costs barely a quarter of its branded counterpart. CBO 2010 at 8-9. A 2009 IMS National

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[3] Available at http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf.

[4] Available at http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15-PrescriptionDrugs.pdf.

[5] Available at http://www.gphaonline.org/sites/default/files/GPhA%20Savings%20Study%20Book%20Updated%20Web%20FINAL%20Jul23%2010_0.pdf

[6] A multi-source brand refers to a drug that is sold under a brand name but is also available in generic versions from other manufacturers. CBO 1998 at 31.

Prescription Audit demonstrated this dramatic difference by comparing what the typical insurance or government formulary charges today:

- $6 for generic medications;
- $29 for preferred brand drugs; and
- $40 for non-preferred brand drugs.[7]

Aitken et al., Prescription Drug Spending Trends in the United States: Looking Beyond the Turning Point, 28 Health Affairs, no. 1, w151, w155 (2009).

The increased availability of low-cost generic drugs also has fulfilled Hatch-Waxman's second, and perhaps most important, goal: increased access to quality medical care for millions of Americans, particularly the poor and elderly. As the CBO noted in its 1998 study:

> The Hatch-Waxman Act has increased the likelihood that generic copies will become available once the patent on a brand-name drug expires. Before the act (in 1983), only 35 percent of the top-selling drugs no longer under patent had generic copies available. Today, nearly all do.

CBO 1998 at xii. Affordable generic alternatives are available today in virtually every important therapeutic class, including such drugs as oncology and cardiovascular medicines that were once priced far beyond the means of many Americans. GPhA 2010 at 3. For many Americans, the increased availability of affordable generic alternatives literally can mean the difference between receiving quality medical care or receiving none, as

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[7] A preferred drug refers to a drug that is authorized for use under an insurance or government plan and thus may dispensed without additional approvals. A non-preferred drug, on the other hand, may be dispensed to a patient only after special approval is obtained. See, *e.g.*, Texas Health and Human Services Commission, Texas Medicaid/CHIP Vendor Program, Prior Authorization Program, available at http://www.hhsc/state.tx.us/hcf/vdp/pt/pa_program.html.

shown by a recent AARP survey in which fully a quarter of seniors reported not being able to afford a prescription drug when no generic was available. See FDA, Greater Access to Generic Drugs: Special Report From the FDA Consumer Magazine and the FDA Center for Drug Evaluation and Research (4th ed. 2006).[8] Moreover, government assistance programs, such as Medicaid, now can help more Americans at lower cost.

> Data from the federal Centers for Medicare and Medicaid Services (CMS) show that in 2009 about 290 million prescriptions were purchased through the Medicaid program at a total cost of $23 billion. The availability of generics enabled Medicaid to purchase 64% of these prescriptions (186 million) by using just $3.9 billion of the $23 billion spent for drugs. *In other words, Medicaid met nearly two-thirds of its prescription drug need with less than one-fifth of its prescription dollars.*

GPhA 2010 at 4 (emphasis added). Similarly, the CBO found that although generics constituted fully 65% of prescriptions dispensed under Medicare Part D in 2007, they accounted for only 25% of total prescription drug costs. CBO 2010 at 12.

C. The low generic prices Congress desires depend upon the low costs of market entry made possible by Hatch-Waxman

The savings described above result from a system in which a new drug is rigorously scrutinized through exacting FDA requirements, given a profit-making period of patent exclusivity, and then—once the regulatory approval is set and the patent has expired—allowing replication of that drug by manufacturers who must certify that the generic version is identical to the name-brand

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[8] Available at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143545.htm

version. This system treats generic manufacturers as just that—manufacturers, not inventors or testers—and thereby keeps their market-entry costs low.

The prices for generic drugs are linked directly to the costs of market entry, and several features of Hatch-Waxman work together to reduce the market entry costs for new generic drugs. First, the ANDA process eliminates the duplicative, unethical[9] and expensive testing requirements that formerly were necessary to obtain approval for a generic copy of a previously approved innovator drug. H.R. Rep., Pet. App. 124a. As the CBO put it:

> The Hatch-Waxman Act streamlined the process for approving generic drugs by requiring only that manufacturers demonstrate "bioequivalence" to an already-approved innovator drug. (Bioequivalence means that the active ingredient is absorbed at the same rate and to the same extent for the generic drug as for the innovator drug.) The tests necessary to prove bioequivalence are much less costly than those required to prove safety and efficacy.

CBO 1998 at xii.

Second, Congress required that a generic drug be "the same as" the branded drug with respect to active ingredient, route of administration, dosage form, strength and conditions of use recommended in the label. 21 U.S.C. § 355(j)(2)(A). And in codifying FDA's streamlined ANDA scheme, Congress expressly adopted FDA's policy of using the term "same as" for the equivalency required for generic drug approval:

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[9] In exempting generic manufacturers from the need to perform duplicative clinical trials, Congress recognized that "such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective." H. R. Rep., Pet. App. at 124a.

> The committee has adopted the FDA's policy of utilizing the terms "same" except that the bill permits an ANDA to be approved for less that all of the indications for which the listed drug has been approved as explained below.

H.R. Rep., Pet. App. 131a. Of particular relevance here, Congress likewise preserved the "same as" requirement for the labeling of the generic drug by requiring that an ANDA must contain adequate information "to show that the labeling proposed for the [generic] drug is the same as the labeling approved for the listed drug * * * ." 21 U.S.C. § 355(j)(4)(G).

The streamlined testing and labeling requirements for generic medications have dramatically reduced the costs of market entry. For the average new drug that was first tested in humans during the 1970s and early 1980s, its producer had spent $114 million (in 1987 dollars) on development and testing. DiMasi, Cost of Innovation in the Pharmaceutical Industry, 10 J. of Health Econ. 107, 132 (1991). Today, the cost to bring a new branded drug to market typically exceeds a billion dollars. U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, Office of Science and Data Policy, ASPE Issue Brief, Expanding Use of Generic Drugs 4-5 (2010) (hereinafter "ASPE Issue Brief").[10] By contrast, the research and development costs for a generic drug are about *one-tenth of one percent* as much—only 1 to 2 million dollars (although those costs have risen significantly as well).[11] *Ibid.*

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[10] Available at http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml.

[11] The costs of entry for generics, while still dramatically lower than for brand-name entrants, have also increased substantially over time. The average research and development costs for a new generic

The explanation for this thousand-fold difference in preliminary costs is obvious:

> Because they can reverse-engineer an innovator drug, and need not repeat safety and effectiveness studies, generic manufacturers can bypass the time and costs to develop a new drug and bring a drug to market with a much smaller investment.
>
> * * *
>
> The relatively low costs to entry for generic drugs lead to increased competition, which drives prices for generic drugs down dramatically.

ASPE Issue Brief at 3, 5.

Low cost of entry affects generic prices in another important way—it increases competition. The price difference between brand and generic drugs is directly related to the number of generic entrants to the market. When FDA analyzed the impact of generic drug entry on average prices for generics (as a percentage of the price for the brand drug) in 2005, it found that the first generic entrant has a relatively small effect on price, but subsequent entrants dramatically reduce the average relative price. ASPE Issue Brief at 5; Figure 1, *infra*. With only one entrant, the generic price averaged fully 94% of the brand price, but even a single additional generic competitor cut the price in half. The entry of four more dropped the generic price to only a quarter of the brand. *Id.* The low cost of generic drugs is dependent upon robust competition created by the low cost of market entry.

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drug were approximately $338,000 in the period immediately following passage of the Act but grew to approximately $603,000 a decade later. See Reiffen & Ward, Generic Drug Industry Dynamics 4 (Fed. Trade Comm'n, Working Paper, 2003), available at http://www.uta.edu/faculty/mikeward/GenericDynamics.pdf.

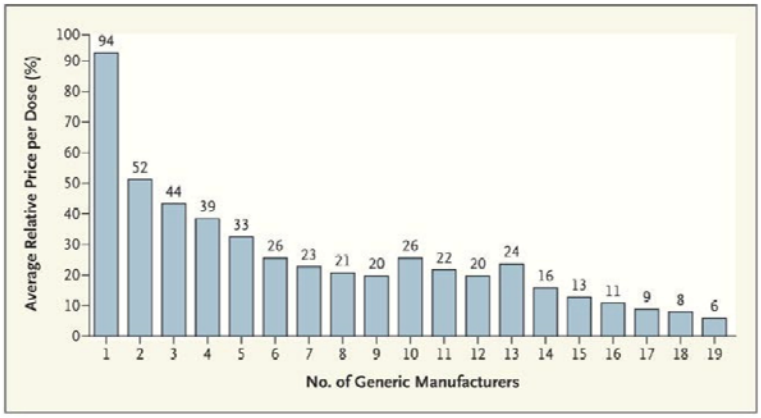

Figure 1: Change in the Average Relative Price of a Drug as the Number of Generic Versions Increases. The average relative price is the average price of a generic version divided by the price of the brand-name drug. Data are from an FDA analysis of retail sales data from IMS Health. Frank, Perspective: The Ongoing Regulation of Generic Drugs, 357 New Eng. J. Med. 1993, 1995 (2007).

The streamlined regulatory scheme for generic drugs established by Hatch-Waxman is central to this economic model. America has already seen the consequences of imposing the full regulatory and economic burden on generics:

> Before 1984, generic-drug makers were obliged to conduct the same safety and efficacy tests that had been required of the original brand-name manufacturers to receive Food and Drug Administration (FDA) approval for marketing. These provisions often rendered it noneconomical to bring a generic to market. The Hatch–Waxman Act changed all that.

Frank, Perspective: The Ongoing Regulation of Generic Drugs, 357 New Eng. J. Med. 1993, 1993-1994 (2007).[12]

[12] Available at http://www.nejm.org/doi/full/10.1056/NEJMp078193.

In enacting this statutory scheme, Congress in effect created the modern generic pharmaceutical industry. Congress enhanced the availability of generic medications by eliminating unnecessary costs of entry. And—as described in greater detail below—it did so without any threat to public health (because the "same as" requirement ensures that generics are precisely the same as medicines already fully approved for public use, and which would be used by all patients but for cost). Generics introduce no new risks to the public, but they substantially expand the availability of affordable drugs to those who need them most.

D. The statutory requirement that a generic drug be the "same as" its brand counterpart provides adequate assurances of safety

The central requirement of "sameness" not only provides the generic manufacturer with a clear blueprint for development but also assures FDA and the public that the generic drug is safe and effective. "In the case of drugs which are the same as the listed drug, the focus of the bill is to provide * * * FDA with sufficient information to assure that the generic drug is the same as the listed drug that has previously been determined to be safe and effective." H.R. Rep., Pet. App. 130a. See also 57 Fed. Reg. 17,950, 17,951 (April 28, 1992) (establishing procedures for duplicates of post-1962 drugs). As the Fifth Circuit noted in *Demahy*, FDA's own guidelines for generic drug labeling are premised on the policy that "[c]onsistency among generic and name brand manufacturers not only avoids redundant research and monitoring efforts, it also assures consumers and physicians that the generic product is safe and effective." JA561.

The *Demahy* Court certainly was correct when it noted that "Congress did not consider the Hatch-Waxman Amendments in a vacuum." JA561. Indeed, Congress recognized that to achieve the goal of increas-

ing the availability of prescription drugs that are *both* safe and effective *and* low-cost, the ANDA scheme had to reflect the fact that brand and generic manufacturers play fundamentally different roles in the drug development process. A new brand-name drug enters the market under the protection of a period of patent exclusivity during which it constitutes the entirety of the market. The brand drug reaches the market in the first instance only after FDA concludes that it is safe and effective based on an extensive program of animal toxicology and human clinical trials. The brand manufacturer thereafter maintains market approval for its drug by complying with any post-approval requirements of FDA, which often include additional clinical trials to support new indications or formulations of the drug or to satisfy additional safety or efficacy concerns raised by FDA. See 21 C.F.R. § 314.510; FDA, Center for Drug Evaluation and Research, Guidance for Industry: Postmarketing Studies and Clinical Trials—Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act 2-3 & nn. 3-4 (2009) (describing FDA authority to require post-marketing studies).

The brand manufacturer also must conduct extensive post-marketing surveillance that encompasses review and analysis of reported adverse events and published medical and scientific literature—an analysis that is conducted against the backdrop of knowledge obtained through the clinical trials and other research conducted to obtain approval in the first place. See 21 U.S.C. § 355(k); 21 C.F.R. § 314.80. During this period of patent exclusivity, the brand manufacturer thus effectively has a monopoly, not only on the market for the drug, but also on the accumulated medical and scientific knowledge of its safety and efficacy, which it shares with FDA pursuant to the comprehensive federal scheme of post-marketing surveillance and reporting regulations.

It is only after the expiration of this period of market exclusivity for the brand—which typically can last as long as 14 years[13]—that the first generic manufacturer can apply for FDA approval to enter the market. Generic entry thus begins only after the therapeutic and safety profile of the drug is well understood by the brand manufacturer and FDA—and, perhaps more importantly, by the medical community and consumers—based on many years of study, regulation and use. As the *Demahy* court recognized:

> In the world of prescription drugs, a pharmaceutical company manufactures, and the FDA approves, a branded drug only after extensive research and testing. Pioneer drug manufacturers thus develop superior knowledge of their product * * * Conversely, generic manufacturers undertake limited research efforts thanks to Hatch-Waxman. They can obtain approval for their copycat drug and label with the limited showing that their product is the "same as" a branded drug * * * That difference in initial regulatory burdens marks a *stark tension between Hatch-Waxman's quest to quickly and cheaply place generic drugs on the market and a state law tort regime* that represents the lone remedy for individuals harmed by inadequate labeling of generic drugs.

JA560-61 (emphasis added).

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[13] As the APSE Issue Brief put it, "[p]atents are issued by the U.S. Patent Office and offer 20 years of protection from competition. However, sponsors typically apply for a patent early in the drug development process and so many of the years of patent protection will be expended before the drug reaches the market. The Hatch-Waxman Act offers restoration of some of the years of patent protection expended during clinical testing and FDA review. Up to five years of patent term may be restored, with the total patent time after FDA approval limited to 14 years." APSE Issue Brief at 9.

Moreover, unlike the branded regime, which contemplates a market restricted to one drug, the Hatch-Waxman scheme is designed to encourage the market entry of as many generic competitors as is economically feasible. See *infra* Part I.C. The generic market that emerges following the expiration of the branded monopoly thus is, by design, highly fragmented. Although the overall generic market share will grow relative to the brand as more generic competitors enter the market, no single generic manufacturer will ever achieve anything approaching the market dominance initially enjoyed by the brand. Indeed, it is the essential fungibility between generic and brand, and among generics, that provides the assurance of consistency of safety and efficacy across the entire market.

Just as any one generic manufacturer can capture only a portion of the market for a drug, so too can any one manufacturer accumulate only a piece of the safety data for the drug. For example, generic drug manufacturers receive relatively few adverse event reports ("AERs") following approval of their products—far fewer, certainly, than are received by the brand manufacturer and FDA. See FDA, Center for Drug Evaluation and Research, Office of Generic Drugs, Manual of Policies and Procedures, Handling of Adverse Experience Reports and Other Generic Drug Postmarketing Reports 1 (2005)[14] (noting Office of Generic Drugs receives few AERs since the reports frequently do not identify a generic manufacturer for the drug and because the safety profile of a drug is well-known before generic versions are approved). Further, because generic manufacturers do not have the comprehensive scientific data necessary to perform a meaningful analysis of reported adverse

[14] Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079791.pdf.

events, FDA requires only that they submit to the agency the limited post-approval reports they actually receive and maintain adequate records. See 21 C.F.R. § 314.94. Moreover, FDA does not require generic drug manufacturers to affirmatively survey scientific literature. See 21 C.F.R. § 314.80(b).[15] After all, such a requirement would only increase costs to no meaningful end.

II. HATCH-WAXMAN PREEMPTS STATE TORT LIABILITY FOR LABELING

FDA has implemented a comprehensive regulatory scheme for generic drugs that is carefully designed to achieve the goal of Hatch-Waxman: to allow the generic industry to produce medicines with the same therapeutic benefits as brand-name drugs, but at a fraction of the cost. At its core is the unerring policy that generic drug products and their warnings must be "the same as" their brand-name equivalents. By misapplying this Court's recent decision in *Wyeth*—a decision construing FDA's regulations for *branded* drugs, which reflect an entirely different set of public health objectives—the decisions of the courts below undermine the very foundation of Hatch-Waxman by subjecting generic manufacturers to the threat of state tort liability unless they do what federal law expressly prohibits them from doing.

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[15] 21 C.F.R. § 314.80(b) requires "applicants" to promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, post-marketing clinical investigations, post-marketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. But such "applicants" are only those under § 314.50 or § 505(b)(2)—both of which sections apply only to *branded* NDA applicants.

A. State tort liability is inconsistent with Hatch-Waxman's "same as" requirement, under which only FDA may regulate the content of generic drug labeling

It would be something of a Catch-22 for a manufacturer to be held liable under state law for inadequate labeling, given that it would be a violation of federal law for the manufacturer to tinker with the label (and contrary to the principles described above for a generic manufacturer to undertake the sort of duplicative research even to generate data that *might* result in modification of a label). But that would be the consequence of affirming the judgments below.

1. FDA has, in fact, made clear that the labeling for generic drugs is controlled by the agency, not by the generic manufacturers. For example, FDA issued a "Policy and Procedure Guide" shortly after the adoption of Hatch-Waxman, which provides that generic manufacturers cannot unilaterally revise their product labels but instead must await instruction from the agency before making any change to warnings, precautions, or similar labeling. See FDA, Division of Generic Drugs, Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling, Policy and Procedure Guide No. 8-89 (1989).

That this is the law governing manufacturers should be dispositive, but FDA's approach also makes good sense. FDA has recognized that the fragmented nature of the generics market, where multiple competitors each possess only a portion of the accumulated safety data for a drug, makes unilateral labeling changes both impractical and counterproductive:

> [E]ach time there is a change in the innovator's labeling, it could necessitate similar changes in the labeling of as many as 20 or 30 generic drug prod-

> ucts. A change in any section of the package insert of the innovator's product, particularly an important change, e.g., in WARNINGS, PRECAUTIONS, CONTRAINDICATIONS OR DOSAGE AND ADMINISTRATION, triggers action by the Labeling Review Branch to request submission from all generic manufacturers of that drug product. Prompt accomplishment of the revision process is important to assure that consistency is found in the labeling of all similar drug products.

Id. at 1. FDA has recognized that uniformity of brand and generic labeling is essential "to minimize any cause for confusion among healthcare professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name drug products."[16] *Ibid.* And FDA has since reiterated this requirement of strict uniformity of labeling many times—in its 1992 Final Rule[17] and its response to public comments thereto,[18] in its 1999 guidance for industry,[19]

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[16] This latter concern—the prospect that labeling variation might undermine public confidence in generic drugs—is a very real and serious concern. Perhaps the greatest barrier to the adoption of generic drugs is the persistent misconception that generic drugs are somehow inferior to their brand-name equivalents, and both FDA and the generics industry spend millions of dollars each year to reassure consumers that affordable generic drugs really are—as federal law requires them to be—the *same as* their more expensive brand-name counterparts. See, *e.g.*, FDA, Facts and Myths About Generic Drugs (2009), available at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ ucm167991.htm

[17] See 21 C.F.R. §§ 314.93(a), 314.94(a)(8), 314.127(a)(7).

[18] See, e.g., 57 Fed. Reg. 17,961, cmt. 40 ("FDA disagrees with the comments [suggesting that ANDA applicants be permitted to deviate from the labeling for the reference listed drug] * * *. [T]he ANDA product's labeling must [be] the same as the listed product's

and in its response to public comments on its 2006 Final Rule.[20]

2. As clear as FDA has been about these principles, the Brief for the United States as *amicus curiae* filed at the petition stage in this case articulates them at least as clearly (cited hereinafter as "U.S. Br."). Indeed, the brief of the United States not only confirms unequivocally that the content of generic drug labeling is a matter within the exclusive regulatory authority of FDA but also highlights the folly of injecting state tort law into that determination.

In reviewing the labeling regulations applicable to generic manufacturers, the United States first confirms the fundamental principle that "[t]he holder of an approved ANDA is not free to change its approved labeling at will." U.S. Br. 12. The United States then acknowledges that "no formal supplement process under 21 C.F.R. 314.70 (2001) [is] expressly available" to generic drug manufacturers to unilaterally change their product labeling. *Id.* at 15. Specifically, the United States confirms two key limits:

- The Changes Being Effected ("CBE") process of 21 C.F.R. § 314.97 is not available to generic manufacturers because that provision must be read in conjunction with the many regulations that

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labeling because the listed drug product is the basis for ANDA approval.")

[19] See FDA, Center for Drug Evaluation and Research, Guidance for Industry, Changes to an Approved NDA or ANDA at 20 (1999) (requiring that all labeling changes for ANDA drugs must be consistent with section 505(j) [21 U.S.C. § 355(j)(4)(G)], which requires generic labeling to be the "same as" that of the brand).

[20] See 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006) (revising certain labeling format requirements and directing that a generic manufacturer must adhere to the format of the labeling of the brand drug, even if that format does not comply with the new formatting requirements).

require generic drug labeling to be the "same as" that of the brand drug. U.S. Br. 13 (citing 21 C.F.R. § 314.94(a)(8)(iii), 21 U.S.C. § 355(j)(4)(G) and 21 C.F.R. § 314.150(b)(10)).

- The Prior Approval Supplement ("PAS") procedure "also was not expressly available to petitioners to make the labeling change respondent seems to envision," because the CBE process is the exclusive procedure applicable to added or strengthened warnings. U.S. Br. 14.

Next, the United States refutes respondents' assertion that generic drug manufacturers may unilaterally send Dear Health Care Provider ("DHCP") letters warning of product risks inconsistent with those reflected in the labeling for the brand product. U.S. Br. 17. After noting that nothing in the regulations categorically forbids sending such correspondence, the United States observes:

> Nonetheless, ANDA holders do not customarily send DHCP letters without coordinating with FDA. Apart from the practical benefits to coordinating with FDA, *ANDA holders also operate under a regulatory constraint*. DHCP letters sent by a generic manufacturer could potentially affect perceived therapeutic equivalence of the generic drug and its RLD [branded] counterpart * * * *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.*

Ibid. (emphasis added). Contrasting a letter advising of a manufacturing defect with another letter warning about health risks, the United States observes that the former would not be misleading with respect to the therapeutic equivalence of the generic drug to the brand, while the

latter correspondence could be misleading: "[A]n ANDA holder's letter warning about risks seemingly unique to its product could mislead consumers and providers into believing that the generic drug and RLD were not therapeutic equivalents." *Id.* at 17-18. The United States notes finally:

> Respondent seems to envision DHCP correspondence of the latter sort, which would likely be misleading. *State law may not impose liability on an ANDA holder for failing to send such a letter unilaterally.*

Id. at 18 (emphasis added).

The United States concludes that "FDA mediates the channels available to an ANDA holder under federal law for disseminating strengthened warnings." U.S. Br. 18. This, of course, has been FDA's position from the outset: "After approval of an ANDA, if an ANDA holder believes that new safety information should be provided, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." *Id.* at 15-16 (quoting 57 Fed. Reg. 17,961, the preamble to FDA's final rule implementing the ANDA application process). That means in the instant case, in the words of the United States, that "*absent FDA's assent, petitioners could not lawfully have disseminated their product with the sort of warning respondent seems to propose.*" *Id.* at 19 (emphasis added).

The Court should spare generic manufacturers (and the American people, who ultimately absorb the transaction costs foisted upon the industry) the Catch-22 that respondents would gladly impose upon them. Generic labeling is the province of FDA, not state courts, and for the reasons expressed in Part I, it is essential to the ful-

fillment of Hatch-Waxman's purposes that it stay that way.

B. The consequences of finding no preemption of tort liability would undo the very structure of the industry that Congress has carefully created

Given the statutory and regulatory background, and the inconsistency between state supervision of labeling (as respondents demand) and exclusive federal control of labeling (as federal law requires), members of GPhA can reasonably ask this question: Where does this leave us when faced with precisely the sort of state tort law claim respondents assert here, and what role can state tort law play in regulating the content of a generic drug label consistent with Congress' intent in adopting Hatch-Waxman and FDA's purpose in implementing it?

1. Unfortunately, on this point, the courts below, and the United States here, are all over the map. All of their answers would distort the industry without warrant from the Act and without any salutary gain for the public. None of these answers recognizes that the question is simply preempted, leaving no role for state courts:

- The Fifth Circuit's opinion in *Demahy* concludes that generic and branded products must be "the same" *only* on the date FDA first approves the generic product; that, thereafter, the generic manufacturer is free to change the label at will. JA534-35. That conclusion is plainly wrong, at least if one assumes that the United States and FDA understand their own regulations. Certainly, it flies in the face of everything FDA has ever said on the subject and what the United States says here, and FDA's implementing regulations are entitled to substantial deference. See

Chevron U.S.A., Inc. v. *Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984).

- The Eighth Circuit's opinion in *Mensing* correctly acknowledges that "generic labels must be substantively identical to the name-brand label even after they enter the market," and that generic manufacturers thus may not unilaterally change their labeling. JA409. But apart from the singularly unhelpful suggestion that the generic manufacturers simply quit the business altogether,[21] the court posits only that manufacturers could at least *propose* a label change, which the FDA could approve or not at its sole discretion. JA409-10.
- Perhaps recognizing that the ability of a generic manufacturer to propose a label change is a far cry from the power to actually make the change, especially since the latter authority rests exclusively with FDA, the United States suggests a scheme, governed by state tort law, which would ignore the product labeling altogether. Under this scheme, the question of state tort liability would turn, not on the manufacturer's "failure to communicate warnings to their customers (something ultimately in FDA's control)," but rather on their "failure to *take steps* to warn their customers." U.S. Br. 19 (emphasis original). The question thus would be, not what the labeling said, but "what action FDA would have taken in response to a *hypothetical* warning proposal" from the manufacturer.

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[21] It is difficult to conceive a pronouncement more at odds with the clear intent of Congress in adopting Hatch-Waxman to encourage the availability of affordable generic drugs than the *Mensing* court's suggestion that "if [the generic manufacturers] realized their label was insufficient but did not believe they could even propose a label change, they could have stopped selling the product." JA416.

> *Ibid.* (emphasis original). Moreover, the United States contends that in proving this purely hypothetical question, the *manufacturer* "would bear the burden of 'show[ing] the likelihood of FDA *in*action.'" *Ibid.* (quoting JA414-15 (emphasis original)).

The problem with this last approach, of course, is that the pivotal liability question to be decided under state tort law—namely, what FDA would have done in response to a hypothetical warning proposal—is fundamentally not one of fact, but rather one of federal regulatory law and public healthcare policy. In a conventional product liability action, the jury is asked to resolve the factual question of what the consumer would have done, under the particular circumstances attending his use of the product, had the manufacturer provided adequate warnings of the product's dangers. In the case of a prescription drug, the fact inquiry shifts under the learned intermediary doctrine to the prescribing physician, but the essential question remains the same: What would the prescribing physician have done, under the particular circumstances of his treatment of this particular patient, had the manufacturer provided adequate warnings of the product's dangers? In each instance, the operative question is one of fact determinable from evidence of the particular circumstances existing as between that particular plaintiff and that particular defendant at that particular point in time.

The liability question posited here—the hypothetical inquiry into the mind of FDA—is a fundamentally different endeavor, one for which lay juries and state tort law are wholly unsuited. The generic pharmaceutical market is, by congressional design, highly fragmented, with many competitors, any one of whom can possess only a small piece of the overall safety and therapeutic puzzle for a given drug. Only FDA can see the entire picture—

indeed, that is why the agency insists so steadfastly that it, and only it, can dictate the content of a generic product label. In considering whether to adopt a label change, FDA is not limited to information from a single manufacturer in isolation, but rather has access to data from all manufacturers and from wholly independent sources as well, much of which will not be available, or even known, to any single generic manufacturer. FDA may have to consider the potential impact of a proposed label change across an entire therapeutic class, as where there exist multiple brand-name drugs, each with multiple generic equivalents, that present safety or efficacy concerns common to the class. FDA also may have to consider issues that transcend any one drug or even class of drug, as where a change in the manner of use of one drug or class may impact the manner of use of another drug or class.

The hypothetical question of what would FDA do will rarely, if ever, turns solely on factual considerations unique to a single drug product; rather, the inquiry invariably will hinge on broader concerns of FDA regulatory policy. For example, suppose a generic manufacturer were to propose a change to strengthen the suicide warning for its antipsychotic medication. That proposal would affect not only the labeling of the brand-name reference drug and every generic version of that drug, but also every brand-name antipsychotic in the same therapeutic class, together with every generic version of those brands; and the proposal to change the labeling for the antipsychotic class could also impact the labeling of the antidepressant, sedative and anti-anxiety classes as well. In short, a suggested label change for a single drug that may seem entirely reasonable to a lay jury may, in fact, be fundamentally inconsistent with FDA's broader regulatory and public health objectives.

State tort law is well-equipped to resolve factual disputes arising out of particular transactions, events or relationships, but it is ill-suited to answer speculative questions of federal regulatory policy. Indeed, this Court has long held that federal law preempts state-law claims that depend on speculation about what a federal agency would have done in hypothetical regulatory proceedings. *Arkansas La. Gas Co.* v. *Hall*, 453 U.S. 571, 578-79 (1981); see also *Nantahala Power & Light Co.* v. *Thornburg*, 476 U.S. 953, 963-964 (1986); *Chicago & N.W. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311, 324-27 (1981).

2. Moreover, attempting to adjudicate hypothetical questions of federal healthcare policy under state tort law would impose extraordinary burdens on FDA, and therefore indirectly on the industry and on the public. First, imposition of a state-law duty to "take steps" to prompt FDA to change product labeling inevitably would lead to the agency being inundated with "proposals" from generic manufacturers, driven by the advice of attorneys, not scientists. This is a situation the Court has addressed before, in upholding federal preemption in a similar context, where it observed that such a scheme would:

> cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court. Applicants would then have an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA.

Buckman Co. v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001).

Worse still, most of these proposals inevitably would be counterproductive, since individual generic manufacturers lack access to all the safety data relevant to the drug or class, and thus lack the perspective to appreciate

fully the implications of their requests. The scheme would run up costs for generics, which would be passed on to consumers; would result in a deluge to FDA as a preemptive measure against litigation; and because of the volume and likelihood of irrelevance, would subject FDA to searching for needles in haystacks, diverting resources from the agency's public health mission where they are best used. The current approach, where manufacturers submit incidents as they become aware of them, and FDA evaluates them with the benefit of all the accumulated safety data, avoids each of these ills.

Third, such a scheme would thrust FDA into the middle of private litigation. The pivotal question in every "take steps" trial—what FDA would have done in response to a hypothetical proposal—necessarily would depend on evidence beyond the control of the litigants themselves. To delve into the regulatory mind of FDA, litigants, courts, and juries would require access to the regulatory record and thinking of FDA. The agency, and its documents and personnel, would become the central evidence in every trial. FDA understandably has resisted such intrusion in the past; in 2008, for instance, the United States told this Court:

> In one recent products liability class action, *Walson* v. *Merck & Co.*, No. 3:04-cv-00027-GPM-DGW (S.D. Ill.), FDA devoted approximately 1,300 employee hours to producing approximately 40,000 pages of documents in response to a third-party subpoena. Private litigation such as this would divert FDA's resources and create a substantial potential for distorting its mission.

Br. for the United States as *Amicus Curiae* Supporting Petitioners 7-8, *Warner-Lambert* v. *Kent*, 552 U.S. 440 (2008) (No. 06-1498), 2007 WL 4218889. Even with FDA involvement, the accuracy of any answer to the speculative question is doubtful; without FDA involvement, inac-

curacy would be certain. And depriving the parties of such essential evidence would raise serious due-process concerns—especially under a scheme, such as that proposed here, where the *defendant* would bear the burden of *disproving* the likelihood of FDA action.[22]

Finally, by far the most pernicious consequence of the proposed "take steps" scheme is that it would shift the essential regulatory question—what is a generic manufacturer to do with the information it receives about its drug—from the exclusive province of FDA to the vagaries of fifty varying systems of state tort law. Would a lay jury, guided by a state-law "ordinary care" standard, be allowed to hold a generic manufacturer liable for failing to conduct duplicative clinical testing, notwithstanding FDA's clear and long-standing policy against such a requirement? Or that a generic manufacturer who faithfully collected and reported its safety data to FDA could be liable nonetheless for failing to collect and analyze the safety data of its generic competitors, or even of the brand? Could a jury find that a prudent manufacturer should, as the *Mensing* court suggests, better quit the business altogether than market its drug in the face of regulatory uncertainty?

Indeed, the struggles of the courts below in interpreting and applying FDA labeling regulations only highlight the folly of transferring the regulatory mantel to lay juries guided by state tort law. And the fact that their struggles lead them to concoct a state remedy that is so

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[22] Even were it appropriate for state courts to embark on "take steps" regulatory trials, a notion GPhA vigorously contests, the burden of proof would have to be the reverse of that proposed by the *Mensing* court and the United States. The plaintiff would be required to prove, as part of his or her *prima facie* case, that the defendant manufacturer failed to "take steps" to propose labeling changes that FDA likely would have adopted.

wholly unlike any cause of action traditionally recognized under conventional state tort law is, by itself, sufficient indicia that such a state law claim is inconsistent with the historic police powers of the States and thus preempted by federal law.

The vague injunction to "do something" can easily become, under state tort law, an obligation to do *anything* without regard to its impact on the fundamental Hatch-Waxman goal of "get[ting] generic drugs into the hands of patients at reasonable prices—fast." See *Andrx Pharms.*, 256 F.3d at 809 (internal quotation omitted).[23]

CONCLUSION

The notion that manufacturers of generic drugs may change their product labels without FDA consent is plainly wrong. Federal law forecloses that option. The alternative notion that generic manufacturers can "take steps" to change their labels—the sufficiency of which will be adjudicated piecemeal by lay juries under state tort law, rather than through comprehensive and dispassionate regulation by the federal agency specially charged and equipped for that purpose—is just as plainly wrong. The Court should reverse the judgments below because these questions are preempted by federal law.

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[23] This formulation of the syllogism appeared in a recent article about a different topic: "We must do something; this is something; therefore we must do it." Scrap the Cap, The Economist, Nov. 20, 2010, p. 15. This is no way to manage a healthcare system that is an increasingly substantial part of the national economy. But it is the formula that would govern the proposed "take steps" scheme if the opinions below are affirmed.

Respectfully submitted.

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