No. 17-290

IN THE
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,
v.
DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to the
United States Court of Appeals for the Third Circuit

BRIEF OF AMICI CURIAE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AND BIOTECHNOLOGY INNOVATION ORGANIZATION IN SUPPORT OF PETITIONER

Robert A. Long, Jr.
Counsel of Record
Michael X. Imbroscio
Paul W. Schmidt
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
rlong@cov.com
(202) 662-6000

September 2018 *Counsel for Amici Curiae*

TABLE OF CONTENTS

Page

INTEREST OF AMICI CURIAE 1

INTRODUCTION AND SUMMARY OF ARGUMENT 3

ARGUMENT 6

I. The FDAAA Materially Affects the *Levine* Preemption Calculus. 6

A. The Current Statutory Regime Governing Labeling for Prescription Medicines. 7

1. The FDA Is the Final Arbiter of the Contents of a Medicine's Labeling. 7

2. The FDA Now Has an Affirmative Duty to Amend Labeling When It Concludes New Safety Information Should Be Conveyed. 9

B. The FDA's Additional Statutory Obligations Under the FDAAA Materially Affect the Preemption Analysis Where the FDA Expressly Considers the Safety Information at Issue. 15

C. The Third Circuit Misapplied the *Wyeth v. Levine* Framework in a Clear-Cut Case of Preemption. 18

II. The Court of Appeals Disregarded the Realities of the FDA's Labeling Review, Thereby Threatening Its Effectiveness. 21

A. Prescription Medicine Labeling Must Contain the Essential, Scientifically-Grounded Safety Information. 22

B. The Third Circuit's Standard Threatens to Overwhelm the FDA's Review Capabilities. 25

C. The Third Circuit's Decision Will Discourage Innovation and Harm Public Health. 27

CONCLUSION 35

TABLE OF AUTHORITIES

Page(s)

Cases

Buckman Co. v. Plaintiffs' Legal Committee, 531 U.S. 341 (2001) 26, 27

Dowhal v. SmithKline Beecham Consumer Healthcare, 88 P.3d 1 (Cal. 2004) 23

Lofton v. McNeil Consumer & Specialty Pharm., 672 F.3d 372 (5th Cir. 2012) 27

Mason v. SmithKline Beecham Corp., 596 F.3d 387 (7th Cir. 2010) 23

Mutual Pharm. Co., Inc. v. Bartlett, 570 U.S. 472 (2013) 27

PLIVA, Inc. v. Mensing, 564 U.S. 604 (2011) 28

Riegel v. Medtronic, Inc., 552 U.S. 312 (2008) 34

Robinson v. McNeil Consumer Healthcare, 615 F.3d 861 (7th Cir. 2010) 22

Thomas v. Hoffman-LaRoche, Inc., 949 F.2d 806 (5th Cir. 1992) 22

Wyeth v. Levine, 555 U.S. 555 (2009) ..... *passim*

Statutes

21 U.S.C. § 352(a) 12

21 U.S.C. § 355(b)(1) 28, 29

21 U.S.C. § 355(e) 12

21 U.S.C. § 355(i)(2) 28

21 U.S.C. § 355(o)(3)(A) 29

21 U.S.C. § 355(o)(4) ..... *passim*

Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110–85, 121 Stat. 823 3

Other Authorities

21 C.F.R. § 201.56 7

21 C.F.R. § 201.57 7

21 C.F.R. § 201.66 7

21 C.F.R. § 201.80 7

21 C.F.R. § 312.20(a)–(b) 28

21 C.F.R. § 312.21 28

21 C.F.R. § 312.23(a)(8) 28

21 C.F.R. § 314.70(b)(2)(v) 7

21 C.F.R. § 314.70(c) 7, 8

21 C.F.R. § 314.80 10

150 Cong. Rec. S8657 (daily ed. July 22, 2004) 34

153 Cong. Rec. S5628 (daily ed. May 7, 2007) 13

153 Cong. Rec. S10136 (daily ed. July 26, 2007) 12, 13

153 Cong. Rec. S11831 (daily ed. Sept. 20, 2007) 13, 14, 25

71 Fed. Reg. 3922 (Jan. 24, 2006) 27

73 Fed. Reg. 49,603 (Aug. 22, 2008) 8, 22, 23

Admin. Office of the U.S. Courts, *U.S. District Courts — Civil Cases Commenced, by Nature of Suit, During the 12-Month Periods Ending September 30, 2012 Through 2017*, http://www.uscourts.gov/sites/default/files/data_tables/jb_c2a_0930.2016.pdf 31

David E. Bernstein, *The Breast Implant Fiasco*, 87 Calif. L. Rev. 457 (1999) 32

Robert Brent, *Medical, Social, and Legal Implications of Treating Nausea and Vomiting of Pregnancy*, 186 Am. J. Obstetrics & Gynecology S262 (2002) 32

Jane Brody, *A Perfect Storm for Broken Bones*, N.Y. Times (Feb. 12, 2018) 23, 24

Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20 (2016) 29

Carl Djerassi, *The Future of Birth Control*, Wash. Post (Sept. 10, 1989) 33

Richard A. Epstein, *Legal Liability for Medical Innovation*, 8 Cardozo L. Rev. 1139 (1987) 30

Lisa Girion, *State Vioxx Trial Is Set as Drug Suits Boom*, L.A. Times, June 27, 2006 31

Guidance for Industry: Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act, FDA (July 2013), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf 10, 11, 20

Deborah R. Hensler, *Has the Fat Lady Sung? The Future of Mass Toxic Torts*, 26 Rev. Litig. 883 (2007) 31

Jared S. Hopkins & Michelle Cortez, *Lilly's Alzheimer's Disease Drug Fails in Final-Stage Trial*, Bloomberg (Nov. 23, 2016, 6:52 AM), https://www.bloomberg.com/news/articles/2016-11-23/lilly-s-alzheimer-s-disease-drug-fails-in-final-stage-trial 30

H.R. Rep. No. 110–225 (2007) 12, 13

Gina Kolata, *Fearing Drugs' Rare Side Effects, Millions Take Their Chances with Osteoporosis*, N.Y. Times (June 1, 2016) 24

E. Michael Lewiecki et al., *Hip fracture trends in the United States, 2002 to 2015*, 29 Osteoporosis Int'l 717 (2018) 24

MedWatch: The FDA Safety Information and Adverse Event Reporting Program, FDA, https://www.fda.gov/Safety/MedWatch/default.htm (last updated Aug. 29, 2018) 10

Nat'l Research Council, Comm. on Contraceptive Dev., & Inst. of Med., Div. of Int'l Health, *Developing New Contraceptives: Obstacles and Opportunities* (Luidi Mastroianni et al. eds., 1990), https://www.nap.edu/read/1450 33

News Release, FDA, *FDA Approves Diclegis for Pregnant Women Experiencing Nausea and Vomiting* (Apr. 8, 2013) 32

Lars Noah, *Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs*, 54 S.C. L. Rev. 371 (2002) 32

Nina Nuangchamnong & Jennifer Niebyl, *Doxylamine Succinate–Pyridoxine Hydrochloride (Diclegis) for the Management of Nausea and Vomiting in Pregnancy: An Overview*, 6 Int'l J. Women's Health 401 (2014) 32

PhRMA, *Annual Membership Survey* (2017), http://phrma-docs.phrma.org/files/dmfile/PhRMA_membership-survey_2017.pdf.....29

PhRMA, *Biopharmaceutical Research & Development: The Process Behind New Medicines* (2015), http://www.phrma.org/sites/ 29

PhRMA, *Biopharmaceuticals in Perspective: Spring 2017* (2017), http://phrma-docs.phrma.org/files/dmfile/Biopharmaceuticals-in-Perspective-2017.pdf 1, 29, 30

PhRMA, *Modernizing Drug Discovery, Development and Approval* (2016), http://phrma-docs.phrma.org/sites/default/files/pdf/proactive-policy-drug-discovery.pdf.....28

Press Release, PhRMA, PhRMA Statement Regarding Benefits of New Medicines (Apr. 30, 2013), https://www.phrma.org/press-release/.....30

S. Ct. Rule 37.6.....1

S. Rep. No. 104-69 (1995).....33

Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases*, 46 Stan. L. Rev. 1 (1993).....32

Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 Food & Drug L.J. 295 (2006) 29

U.S. Judicial Panel on Multidistrict Litig., MDL Statistics Report — Docket Type Summary (Sept. 17, 2018), http://www.jpml.uscourts.gov/sites/jpml/files/Pending_MDL_Dockets_By_Type-September-17-2018.pdf 31

W. Kip Viscusi et al., *A Statistical Profile of Pharmaceutical Industry Liability, 1976-1989*, 24 Seton Hall L. Rev. 1418 (1994) 30

What We Do, FDA, https://www.fda.gov/aboutfda/whatwedo/default.htm# 7

INTEREST OF AMICI CURIAE

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies.[1] PhRMA advocates in support of public policies that encourage the discovery of life-saving and life-enhancing new medicines. PhRMA members produce innovative medicines, treatments, and vaccines that save and improve the lives of countless individuals every day. PhRMA members have invested more than half a trillion dollars in R&D since 2000, and in 2017 alone invested an estimated $71.4 billion in discovering and developing new medicines. PhRMA, *Biopharmaceuticals in Perspective: Spring 2017*, at 35 (2017), http://phrma-docs.phrma.org/files/dmfile/Biopharmaceuticals-in-Perspective-2017.pdf [hereinafter *Biopharmaceuticals in Perspective*]; *About*, PhRMA, https://www.phrma.org/about#key (last visited September 17, 2018).

The Biotechnology Innovation Organization ("BIO") is the world's largest biotechnology

[1] Pursuant to Rule 37.6, *amici* affirm that no counsel for a party authored this brief in whole or in part and that no person other than *amici*, their members, or their counsel made any monetary contributions intended to fund the preparation or submission of this brief. A list of PhRMA members is available at http://www.phrma.org/about/members. A list of BIO members is available at https://www.bio.org/bio-member-directory. Merck & Co. is a member of PhRMA, but did not contribute financially to the preparation of this brief. The parties have consented in writing to the filing of all timely *amicus* briefs.

organization, providing advocacy, business developments, and communications services for its members worldwide. BIO's mission is to champion biotechnology and advocate for its member organizations, both large and small. BIO members are involved in research and development of innovative healthcare technologies, and corporate members range from entrepreneurial companies developing a first product to Fortune 500 multinationals. BIO also represents state and regional biotechnology associations, service providers to the industry, and academic centers.

This case presents a question of critical importance for members of PhRMA and BIO: whether, after the Food and Drug Administration ("FDA") considers a potential safety issue but ultimately decides after reviewing the relevant scientific data that no warning is justified, a jury may nonetheless hold the company liable under state law for failing to provide the warning the FDA rejected. The burdens of product liability litigation are already substantial for life sciences companies, and a regime that permits these companies to be held liable under state law for failure to include warnings expressly deemed inappropriate or unwarranted by the FDA would greatly compound that liability in a manner that both is unfair and could deter innovation. The Court should reverse the Third Circuit's judgment and establish clear, consistent, and fair preemption rules for FDA-rejected warnings.

INTRODUCTION AND SUMMARY OF ARGUMENT

The FDA brings its extensive scientific expertise to bear in approving medically-appropriate labeling for prescription medicines, both before and after they are brought to market. Congress granted the FDA authority to review and approve labeling in recognition of the agency's institutional capacity to assess how best to communicate complex risk and benefit information, including evaluating the scientific basis for proposed warnings. In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court considered the FDA's role and held that state-law tort claims are preempted when it is clear that the FDA would have rejected the labeling that a plaintiff asserts was required by state law.

After the events at issue in *Levine*, Congress gave the FDA additional authority over labeling in the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110–85, 121 Stat. 823. The FDAAA adopted Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act ("Section 505(o)(4)"), codified at 21 U.S.C. § 355(o)(4), which *requires* the FDA to add safety information to a medicine's labeling when the agency recognizes a new serious safety risk, and grants the FDA express authority to require such labeling changes. Under Section 505(o)(4), when the FDA becomes aware of a new serious safety issue that it determines should be reflected in labeling, the FDA *must* engage with a drug's sponsor to add appropriate labeling. Neither quibbles over language nor sponsor recalcitrance can stand in the way of updating the

label to reflect this new safety information. Under the revised statutory regime, when the FDA has considered a potential new safety issue and exercised its scientific judgment to conclude that no new labeling is required, the agency's decision not to adopt such labeling provides dispositive evidence that the FDA would have rejected *any* warning for that particular safety risk, regardless of the language used.

The FDA's new affirmative obligations under Section 505(o)(4) thus modify the preemption equation presented in *Levine*. *Levine* focused on a sponsor's duty to update labeling unilaterally under the FDA's "Changes Being Effected" regulations, and left open the possibility that the FDA might have accepted a sponsor's proposal to amend its warning in a manner that subsequent litigation adversaries argue was required by state law. In this case, however, after considering the available scientific evidence addressing the potential new serious safety issue, the FDA rejected Merck's proposal to include such a warning. There is no basis for thinking that the FDA's decision was driven by dissatisfaction with the specific language of Merck's proposal. If the FDA had believed that the safety issue needed to be reflected in the label, it was under a statutory obligation to propose alternative language to address that safety issue. The FDA's flat rejection was not accompanied by any counter-proposal, and thus reflected the agency's considered judgment that no additional labeling was justified. Unlike the pre-Section 505(o)(4) situation in *Levine*, the FDA's decision not to adopt the proposed labeling constitutes

precisely the "clear" rejection that the Court envisioned in *Levine*.

The Third Circuit disagreed, holding that preemption of state-law claims is a factual determination reserved for jury resolution absent a "'smoking gun' rejection letter" laying out the FDA's rationale for rejecting the warnings sought. Pet. App. 55. The Third Circuit's approach cannot be reconciled with the FDA's statutory duties under the FDAAA. The Third Circuit's preemption standard will also hinder the FDA's ability to ensure that labeling contains essential, scientifically-based information, and it will give manufacturers an incentive to inundate the FDA with linguistic variants of labeling requests in an effort to attain a level of clarity sufficient to trigger preemption. In addition, the regime endorsed by the Third Circuit could discourage innovation and pose a threat to public health.

Section 505(o)(4) now requires that the FDA must act whenever it identifies a new potential serious safety issue, and this Court should clarify that the Third Circuit's preemption analysis cannot be reconciled with the current federal regulatory regime. The decision of the Third Circuit should be reversed.

ARGUMENT

I. The FDAAA Materially Affects the *Levine* Preemption Calculus.

Given the statutory framework in which the FDA and drug manufacturers operate, the Third Circuit erred in its interpretation and application of *Wyeth v. Levine*. The Third Circuit's decision does not take proper account of the complexities of drug labeling or the obligations of the FDA and manufacturers throughout the labeling process, particularly following the enactment of the FDAAA and the FDA's duty to amend a drug's labeling if it identifies an unlabeled serious safety risk that requires a warning. 21 U.S.C. § 355(o)(4). In light of that affirmative statutory obligation, where the FDA considers a potential new safety issue but ultimately concludes that the new safety information does not warrant new labeling, that regulatory decision necessarily provides the requisite verification that the FDA would have rejected a labeling proposal from a sponsor containing such information. In this case, the situation is even more stark, because the FDA expressly rejected Merck's specific request for such labeling. Because Section 505(o)(4) places a duty on the FDA to amend labeling if it deems it necessary once presented with a potential serious safety issue, it is no answer to say Merck did not use the right words or did not press hard enough for the change. Because the FDA rejected Merck's proposed labeling without pursuing additional communications regarding labeling language, the FDA's rejection was necessarily grounded in science, not in language quibbles.

A. The Current Statutory Regime Governing Labeling for Prescription Medicines.

1. The FDA Is the Final Arbiter of the Contents of a Medicine's Labeling.

To ensure that "the public get[s] the accurate, science-based information they need," the FDA tightly regulates the labeling for all prescription medicines. *What We Do*, FDA, https://www.fda.gov/aboutfda/whatwedo/default.htm# mission (last updated Mar. 28, 2018). FDA regulations set out detailed labeling requirements, specifying required categories, precise information each category should include, and, in many cases, exact formatting standards. *See* 21 C.F.R. §§ 201.56-57, 201.66, 201.80. As relevant here, medicine labeling must warn about any serious hazard for which there is "reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6).

The FDA must approve labeling before a medicine can be marketed, and the agency continues to scrutinize labeling for as long as the medicine remains on the market. While the manufacturer bears responsibility for its labeling, the FDA is the final authority on its contents. Before a manufacturer can amend its labeling, it generally must obtain FDA approval through the submission of a "prior approval supplement" ("PAS") to its New Drug Application. *See* 21 C.F.R. § 314.70(b)(2)(v). Manufacturers can, in some circumstances, add or strengthen a warning to reflect "newly acquired information." *See id.*

§ 314.70(c)(6)(iii). Even then, however, a manufacturer cannot distribute the new labeling until it submits a "changes being effected" ("CBE") supplement to the FDA. *See id.* § 314.70(c)(3)–(6). Once a CBE supplement is submitted, the FDA must review the contents of the amended labeling, and if the FDA does not find that "the evidence of a causal association satisfies the standard for inclusion in the labeling," *id.* § 314.70(c)(6)(iii)(A), it must retroactively reject the change and may order the manufacturer to stop distributing products with the new labeling, *see id.* § 314.70(c)(6)–(7); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,603, 49,608 (Aug. 22, 2008) ("[A] CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug . . . ."). In all circumstances, then, the FDA is the final arbiter of the contents of new and amended drug labeling.

In exercising its authority, the FDA frequently communicates with drug manufacturers regarding new and amended labeling. As the Solicitor General's brief confirms, the FDA engages with manufacturers with regard to "scientific, medical, and procedural issues that arise" throughout the "iterative" labeling process. U.S. Cert. Br. at 5 (citations omitted). Notably, the FDA may communicate with manufacturers to address "minor" or "editorial" issues involved in proposed labeling:

> If FDA reviewers identify "easily correctable deficiencies" in a supplement, they will "make every reasonable effort to communicate [them] promptly to applicants." 21 C.F.R. 314.102(b). And if only "editorial or similar minor deficiencies in the [proposed] labeling" exist, FDA may approve the supplement on the condition that the applicant makes appropriate corrections and submits a copy of the final labeling before marketing the drug with that labeling. 21 C.F.R. 314.105(b).

Id. at 5–6. The dynamics of the FDA-manufacturer relationship thus involve frequent communications throughout a tightly-regulated labeling process.

2. The FDA Now Has an Affirmative Duty to Amend Labeling When It Concludes New Safety Information Should Be Conveyed.

The FDA's role in medicine labeling includes a duty to ensure labeling remains adequate after medicines are marketed. If the FDA becomes aware of a safety concern that requires a warning — either from a manufacturer's submission or through the FDA's own continuous monitoring of adverse event

reports[2] — the FDA must ensure the necessary labeling changes are adopted.

Legislative changes enacted in 2007 expanded the FDA's authority and affirmative obligation to amend labeling. Once the FDA "becomes aware of new safety information that [it] believes should be included in the labeling of the drug," Section 505(o)(4) requires the FDA to "promptly" engage the drug's sponsor to amend the drug's labeling. *See* 21 U.S.C. § 355(o)(4)(A).[3] In its notification, the FDA details the source of the new safety information, a description of the safety information, proposed labeling changes, and instructions for the manufacturer. *See FDA Guidance for Industry*, *supra*, at 6.[4]

---

[2] Manufacturers are required to report "serious and unexpected" adverse events to the FDA within 15 days of receipt and to periodically report all other adverse events. 21 C.F.R. § 314.80. The FDA also receives adverse event reports through a voluntary reporting system, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, FDA, https://www.fda.gov/Safety/MedWatch/default.htm (last updated Aug. 29, 2018).

[3] The FDA has compiled a non-exhaustive list of sources of new safety information in guidance it issued regarding Section 505(o)(4). *See Guidance for Industry: Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act*, FDA (July 2013) at 16, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf [hereinafter "*FDA Guidance for Industry*"].

[4] Notification letters that apply to a single manufacturer "are considered confidential commercial information and are not posted" on the FDA's website. The "resulting supplement is

After receiving a notification letter, a manufacturer must submit a "supplement proposing changes to the approved labeling to reflect the new safety information," or notify the FDA that it "does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted." *See* 21 U.S.C. § 355(o)(4)(B). After receiving a manufacturer's response, Section 505(o)(4) requires the FDA to:

> promptly review and act upon such supplement. If the [FDA] disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the [FDA] shall initiate discussions to reach an agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

See id. § 355(o)(4)(C).

Section 505(o)(4) also grants the FDA express authority to "issue an order directing the [manufacturer] to make such a labeling change as the [FDA] deems appropriate to address the new safety information." *See id.* § 355(o)(4)(E). Following such an order, a manufacturer is required to submit labeling changes within 15 days. *See id.*

---

approved and posted," however. *See FDA Guidance for Industry*, *supra*, at 13.

§ 355(o)(4)(E). Section 505(o)(4) gives the FDA authority to "accelerate the timelines" where it "concludes that such a labeling change is necessary to protect the public health." *See id.* § 355(o)(4)(H).

The FDAAA thus marked a significant increase in the FDA's authority and responsibility to ensure a medicine's labeling remains scientifically accurate during its marketing. To be sure, prior to 2007 the FDA possessed considerable practical ability to generate labeling changes through its authority to (1) withdraw approval of a medicine if its labeling was "false or misleading in any particular," 21 U.S.C. § 355(e), and (2) bring an enforcement action against the manufacturer for misbranding, *see id.* § 352(a). Under the former statutory scheme, however, the FDA lacked express statutory authority to order a labeling change after the approval of a medicine. *See Levine*, 555 U.S. at 571 ("Indeed, prior to 2007, the FDA lacked the authority to order manufacturers to revise their labels."). Following enactment of the FDAAA, the FDA has both the authority and the *affirmative duty* to add safety information to labeling to address an unlabeled safety concern.

The legislative record surrounding the FDAAA reflects Congress's intent to increase the FDA's authority and responsibilities in order to better protect public health. *See, e.g.*, 153 Cong. Rec. S10136–37 (daily ed. July 26, 2007) (statement of Sen. Grassley). The House report notes that the FDAAA "strengthens FDA's postmarket drug safety authority" by "provid[ing] FDA with the authority to require labeling changes under appropriate

circumstances." H.R. Rep. No. 110–225, at 4 (2007). Moreover, Senator Grassley, a co-sponsor of the bill, noted, "[Congress] need[ed] to make sure that we're giving FDA, the watchdog, some bite to go with the bark." 153 Cong. Rec. S10137 (daily ed. July 26, 2007) (statement of Sen. Grassley). A bipartisan group of lawmakers observed that once the FDA has identified potential safety issues, it "needs to be empowered . . . to take action to address those questions and to ensure timely notice to doctors and consumers of new safety risks that they are already taking." 153 Cong. Rec. S5628 (daily ed. May 7, 2007) (statement of Sen. Grassley); 153 Cong. Rec. S11832 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy) ("This legislation will give FDA the authority, for the first time, to compel a drug company to add warnings of newly discovered risks on the drug label."); 153 Cong. Rec. S11835 (daily ed. Sept. 20, 2007) (statement of Sen. Durbin) (noting "[t]he bill gives the FDA more tools to detect the safety problems of drugs after they are available to consumers[]" and "the FDA is given greater authority to require drug companies to add warning labels[.]").

Indeed, the FDAAA reflected both an effort to strengthen the FDA's authority and responsibility to oversee labeling and to confirm that manufacturers retain responsibility if they fail to update their labeling with new safety information. *See* 21 U.S.C. § 355(o)(4)(I) ("This paragraph shall not be construed to affect the responsibility of the [sponsor] to maintain its label in accordance with existing requirements [including the CBE regulations]"); *see also Levine*, 555 U.S. at 567–68 (citing 121 Stat. 925–926) (noting that

Congress "adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels"). The legislative history of the FDAAA confirms these joint goals. *See* 153 Cong. Rec. S11839–40 (daily ed. Sept. 20, 2007) (statement of Sen. Coburn) (noting "the newly expanded role of the FDA does and should preempt State law when it comes to drug safety and labeling," and maintaining that long-standing preemption principles remain following the FDAAA "because there is an overriding Federal interest in ensuring that the FDA, as the public health body charged with making these complex and difficult scientific judgments, be the final arbiter of how safety information is conveyed."); *see also* 153 Cong. Rec. S11832 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy) (noting that "[b]y enacting this legislation, we do not intend to alter existing state law duties imposed on a drug manufacturer to obtain and disclose information regarding drug safety hazards either before or after a drug receives FDA approval or labeling," but also stating, "[w]e do not believe that the regulatory scheme embodied in this act is *comprehensive enough to preempt the field or every aspect of state law*.") (emphasis added). Thus, while manufacturers retain responsibility for labeling, the FDAAA unmistakably increased the FDA's authority to change labeling. Accordingly, the FDAAA marked a meaningful change to the FDA's obligations and authority.

B. The FDA's Additional Statutory Obligations Under the FDAAA Materially Affect the Preemption Analysis Where the FDA Expressly Considers the Safety Information at Issue.

Because the FDAAA was enacted after the events in *Levine,* this Court did not consider the effect of that statute on the preemption analysis. *See Levine*, 555 U.S. at 567 (citation omitted) ("In 2007, after Levine's injury and lawsuit, Congress again amended the FDCA. For the first time, it granted the FDA statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval."). The Court held in *Levine* that if "the FDA would not have approved" a label required by state law, then the state law claim would be preempted. *Id.* at 571. In *Levine*, the Court held that Wyeth had presented no "clear evidence" that the FDA would not have approved a change to Phenergan's label and emphasized that the FDA had never given "more than passing attention" to the safety issue alleged in the lawsuit. *Id.* at 571–72.

In this case, the Third Circuit, interpreting *Levine*, held that preemption is a factual determination reserved for jury resolution absent a "'smoking gun' rejection letter" laying out the FDA's rationale for rejecting the warnings sought. Pet. App. 55. The Third Circuit's conclusion does not take

proper account of the FDA's affirmative obligations under the FDAAA.

As explained above, where the FDA has determined, considering the scientifically-based evidence at its disposal, that new safety information warrants a warning, it has an affirmative duty to add information to the labeling about that risk using Section 505(o)(4). Under Section 505(o)(4), the FDA may take one of three paths when it has determined that an unlabeled safety risk should be reflected in labeling. First, a manufacturer may submit proposed labeling in response to the FDA's notification that amended labeling is required. 21 U.S.C. § 355(o)(4)(B). The FDA is then required to act on the manufacturer's proposal, and either accept the proposed labeling or work with the manufacturer to determine the contents of the labeling through an iterative process. *Id.* § 355(o)(4)(C). Second, the manufacturer may disagree that a labeling change is necessary. *Id.* § 355(o)(4)(B). In that case, the FDA must continue to work with the manufacturer to reach agreement as to the necessity of a labeling change, and, if the FDA still feels a labeling change is required, to determine the contents of the labeling. *Id.* § 355(o)(4)(C). Third, if cooperative efforts between the FDA and the manufacturer are not successful, the FDA may issue an order compelling the manufacturer to submit labeling changes. *Id.* § 355(o)(4)(E). In all three scenarios, the FDA must fulfill its statutory obligations where it has determined a warning is required. In no circumstance can the FDA determine that an unlabeled safety risk

requires a warning, yet do nothing. To do so would violate the FDA's duty under Section 505(o)(4).

Alternatively, where the FDA has made the considered scientific judgment that no additional labeling is required regarding a potential new safety issue, that ends the inquiry. The FDA has no obligation to continue working with a manufacturer on labeling language where the FDA has concluded that no new labeling language is warranted.

As a consequence of this statutory framework, when the FDA duly considers a potential safety issue and rejects the addition of new safety labeling, that considered rejection provides precisely the clear evidence that supports preemption of state-law claims under *Levine*. While the manufacturer retains ultimate responsibility for the content of the labeling of its medicine, including responsibility for failing to update labeling with new safety information not duly considered by the FDA, the FDA's additional obligations under Section 505(o)(4) require the agency to work with a medicine's sponsor to get the labeling language right if the FDA has determined that a warning should be added. Conversely, if the FDA determines that no new labeling is required, that conclusion by necessity reflects the FDA's assessment that such labeling is not scientifically warranted. Otherwise, the FDA would be in direct violation of its statutory obligations. That decision by the FDA demonstrates, in turn, that the agency would have rejected any effort by the manufacturer to make such a change unilaterally under the CBE provisions — the very inquiry *Levine* instructs the courts to undertake

in determining whether a civil claim would be preempted.

C. The Third Circuit Misapplied the *Wyeth v. Levine* Framework in a Clear-Cut Case of Preemption.

In this case, the FDA considered the new safety information at issue and determined, consistent with its obligations under Section 505(o)(4), that no new safety labeling was warranted. But the FDA did not stop there. It went further by expressly rejecting the sponsor's proposal to add such a warning. As the Solicitor General has pointed out, the Third Circuit's preemption analysis ignores the implication of the FDA's actual rejection of the sponsor's proposed labeling update. *See* U.S. Cert. Br. at 16, 19. Even more fundamentally, the court overlooked the import of the FDA's substantive scientific determination that no new warning was warranted. No rational preemption framework should presume a dereliction of agency duty. But the Third Circuit adopted precisely such a framework in this case. By allowing a jury to attribute the FDA's dispositive rejection to linguistic disagreements, the Third Circuit disregarded the FDA's affirmative obligations under Section 505(o)(4).

Because the Third Circuit did not take proper account of the FDA's affirmative duties, it erroneously concluded that there was insufficient evidence that the FDA would have rejected alternate labeling language regarding atypical femoral fractures. But here there is no dispute that the FDA concluded that

the scientific data on femoral fractures did not support a warning in the labeling, and thus declined to adopt a change to Fosamax's warnings discussing this risk. *See* U.S. Cert. Br. at 16, 19. The FDA's substantive rejection cannot be viewed as simply the FDA's failure to agree with Merck's proposed language. The proposition that the FDA might have accepted a differently-worded warning on atypical femoral fractures assumes that the FDA violated its statutory duties. The FDA considered and rejected the warning at issue without pursuing linguistic negotiations with Merck, thus confirming that the FDA was concerned with the underdeveloped science, not with the language used in the labeling.

If the FDA had determined in 2009 that additional labeling for femoral fractures was needed in the Warnings and Precautions section of the Fosamax label, it would have been obligated *at that time* to work with Merck to determine the contents of that labeling. *See* 21 U.S.C. § 355(o)(4)(C); U.S. Cert. Br. at 22. Indeed, the FDA did exactly that in approving new Adverse Reaction language for Fosamax, which was modified from the proposal that Merck had submitted. Had the FDA determined that an atypical femoral fracture warning was appropriate for the Warnings and Precautions section, it would have similarly initiated similar conversations with Merck to come to an agreement on labeling language.[5]

[5] In guidance to the industry, the FDA notes, "FDA expects that information that results in changes made only to the ADVERSE

The FDA's subsequent actions further confirm that its rejection of Merck's proposed labeling was not due to a disagreement with Merck's proposed language, but was instead rooted in the FDA's belief that a warning was not appropriate or necessary at that time. After reviewing the evidence Merck submitted in support of its labeling change, the FDA instructed Merck to "hold off" on adding a warning while a task force considered whether any warning was "warranted." Pet. App. 17–18. Only after receiving the task force's recommendation did the FDA conclude that atypical femoral fractures were "'potentially more closely related to'" Fosamax use than it had previously appreciated. Pet. App. 21. At that time, the FDA began working with Merck consistent with its Section 505(o)(4) authority to amend the Fosamax label to include a warning that was backed by adequate science.

The FDA's substantive determination in 2009 that the scientific record did not warrant a labeling change provides the conclusive verification *Levine* envisions that the FDA would have rejected a request by Merck to make such a labeling change. That the FDA actually rejected Merck's labeling submission

---

REACTIONS section, but does not warrant inclusion of other sections (such as WARNINGS AND PRECAUTIONS), would not normally trigger safety labeling changes under section 505(o)(4)." *FDA Guidance for Industry*, *supra*, at 6. This guidance confirms that had the risk of atypical femoral fracture been serious enough to warrant a change in the Warnings and Precautions section, the FDA would have worked with Merck to make those changes using its Section 505(o)(4) authority.

only confirms that result. The Third Circuit's speculation that the FDA might have permitted such a change had Merck asked in some different manner — and its direction that a lay jury should decide the question — cannot be squared with the FDA's statutory obligations. The FDA's rejection of Merck's labeling supplement without initiating labeling discussion provides dispositive confirmation that the FDA did not believe any additional warning was appropriate at that juncture. Because Merck could not have complied with the FDA's federal directives while also including the warning Plaintiffs claim is required under state law, Plaintiffs' claim is preempted.

II. The Court of Appeals Disregarded the Realities of the FDA's Labeling Review, Thereby Threatening Its Effectiveness.

In addition to disregarding the FDAAA's impact on the *Wyeth v. Levine* preemption framework, the Third Circuit also failed to consider the practical implications of its preemption rule. The Third Circuit's standard gives insufficient deference to the policy rationale behind the FDA's extensive labeling authority, particularly following the FDAAA. The Third Circuit's decision also creates conditions under which the FDA's review capabilities could be overwhelmed by labeling submissions, thus hampering its ability to ensure accurate and appropriate labeling. Lastly, the Third Circuit's preemption standard could disincentivize innovation and harm public health.

A. Prescription Medicine Labeling Must Contain the Essential, Scientifically-Grounded Safety Information.

Pharmaceutical labeling strikes a delicate balance. Labeling conveys a wealth of information necessary for the safe and effective use of a medicine. But this information must be communicated in a manner that is useful to healthcare professionals. One way in which labeling achieves this balance is by providing information only when it is scientifically-based.

Striking this balance is critically important because patients may be harmed when labeling communicates unfounded safety information. First, physicians may disregard lengthy labeling if it is weighted down with speculative warnings, causing them to overlook important, scientifically-founded safety information. *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 869 (7th Cir. 2010) ("The resulting information overload [from describing every remote risk] would make label warnings worthless to consumers."); *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 816 n.40 (5th Cir. 1992) (noting that if manufacturers were required to clutter their warnings with "every possible risk," then "physicians [would] begin to ignore or discount the warnings"); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. at 49,605–06 (unfounded statements in FDA labeling may cause "more important warnings" to be "overshadow[ed]").

Second, warnings that are not grounded in science can discourage the beneficial use of medicines. *See, e.g.*, *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010) ("[O]verwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted . . . ."); *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1, 14 (Cal. 2004) ("[A] truthful warning of an uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently making a medically unwise decision."); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. at 49,605–06 ("[O]verwarning . . . may deter appropriate use of medical products . . . ."). All medicines have risks, and all prescribing decisions are based on balancing those risks against potential benefits. Distorting the true nature of that balance, by overstating unfounded or speculative risks, inhibits medical professionals from making optimal prescribing decisions.

The case of bisphosphonates like Fosamax provides a dramatic example of this phenomenon. With an aging U.S. population, the societal risks of decreased bone health are substantial. For instance, looking only at hip fractures, direct medical costs in the first six months after a fracture can be more than $50,000. *See* Jane Brody, *A Perfect Storm for Broken Bones*, N.Y. Times (Feb. 12, 2018), https://www.nytimes.com/2018/02/12/well/bone-fractures-broken-hip-osteoporosis-drugs-treatment-diagnosis.html. With the advent of new medicines like bisphosphonates, Americans experienced a

striking reduction in hip fractures in the 10-year period from 2002 to 2012, but then that reduction suddenly leveled off in 2012. E. Michael Lewiecki et al., *Hip fracture trends in the United States, 2002 to 2015*, 29 Osteoporosis Int'l 717, 717 (2018) ("We found that hip fracture rates declined each year from 2002 to 2012 and then plateaued at levels higher than projected for years 2013, 2014, and 2015."). That leveling off had a real public health impact. *Id.* ("The plateau in age-adjusted hip fracture incidence rate resulted in more than 11,000 additional estimated hip fractures over the time periods 2013, 2014, and 2015."). And this decline in usage can be traced directly to the impact of high-profile litigation and adverse media focusing on the potential rare side effects of bisphosphonates. *See* Gina Kolata, *Fearing Drugs' Rare Side Effects, Millions Take Their Chances with Osteoporosis*, N.Y. Times (June 1, 2016), https://www.nytimes.com/2016/06/02/health/osteoporosis-drugs-bones.html (describing impact of lawsuits and media in dissuading patients from using bisphosphonates); Brody, *supra* ("Currently, many people at risk of a fracture – and often their doctors – are failing to properly weigh the benefits of treating fragile bones against the very rare but widely publicized hazards of bone-preserving drugs, experts say.").

The consequences of getting this critical balance wrong are high, which is exactly why the FDA and manufacturers interact throughout a tightly-regulated process to ensure that labeling appropriately and accurately conveys the risks and benefits associated with all medicines. Through this

process, the FDA brings to bear its expert judgment about whether a risk should appear in a medicine's label and, if so, how best to convey that information without diluting the labeling by including speculative or scientifically-unfounded warnings. The Third Circuit's standard disregards the FDA's expertise by allowing a jury to speculate as to the FDA's reasoning for rejecting labeling. Juries that are not well-versed in the complex duties and responsibilities of the FDA — including its affirmative obligations under the FDAAA — cannot provide the same assurances for consumer safety as the FDA.[6]

B. The Third Circuit's Standard Threatens to Overwhelm the FDA's Review Capabilities.

The Third Circuit's decision also creates perverse incentives that threaten to undermine the FDA's review process. As interpreted by the Third Circuit, "clear evidence" requires a "'smoking gun' rejection letter." Pet. App. 55. That requirement misunderstands the nature of FDA review by assuming that review is limited to the precise verbiage submitted, when in fact, the FDA cannot let linguistic disagreements stand in the way of

[6] Senator Coburn noted during debate on the FDAAA that, "[o]verwarning, just like underwarning, can similarly have negative effect on public safety and public health.[] In this bill, we have created a clear labeling pathway between the FDA and a drug sponsor in this bill to ensure that consumers get scientifically accurate and appropriate warning of drug safety risks." 153 Cong. Rec. S11840 (daily ed. Sept. 20, 2007) (statement of Sen. Coburn).

medically-warranted warnings. *See* 21 U.S.C. § 355(o)(4)(C). More problematic, the need for a "smoking gun" rejection letter will create an incentive for manufacturers to submit multiple iterations of a warning to maximize the prospect that some future jury will find the FDA's rejection sufficiently clear.

The FDA routinely makes scientific judgments regarding medicine safety. As this case demonstrates, it often makes those judgments without delaying its future work by stopping to issue formal public statements on every judgment that it makes, particularly in those instances where it makes judgments that warnings are not scientifically appropriate. Given that reality, companies facing potentially massive product liability risks will have an incentive to press for definitive rejections of all conceivable labeling variations.

Creating a regime that incentivizes manufactures to inundate the FDA with serial labeling submissions could materially impair the FDA's ability to carry out its mission. In *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), this Court held that state law "fraud-on-the-FDA" claims are preempted, reasoning that such claims incentivize manufacturers "to submit a deluge of information that the [FDA] neither wants nor needs" out of "fear that their disclosures . . . will later be judged insufficient in state court," thereby creating "additional burdens on the FDA[]." *Id.* at 351. The Third Circuit's preemption standard creates the same incentives that *Buckman* found impermissible.

Diverting the attention of the FDA toward litigation-defensive submissions would be an exercise fraught with peril. *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) ("FDA reviews all [CBE] submissions . . . ."); *Lofton v. McNeil Consumer & Specialty Pharm.*, 672 F.3d 372, 380 (5th Cir. 2012) (when manufacturers are compelled "to flood the FDA with information" to protect against liability, the FDA "loses control over its ability, based on scientific expertise, to prescribe — and intelligently limit — the scope of disclosures necessary for its work"); Br. for the United States as Amicus Curiae Supporting Pet'r at 25, *Wyeth v. Levine*, 555 U.S. 555 (2009) (No. 06-1249) ("[The FDA] could not reasonably be expected to *expressly* reject every possible variant of approved labeling as part of its decisional process. Indeed, it would underestimate the post hoc imagination of lawyers to think such an exhaustion of potential variants by the manufacturer or the agency is even possible."). The Third Circuit's misguided standard, however, would produce such results. As in *Buckman*, the Court should find these incentives impermissible and reverse the Third Circuit's flawed interpretation of *Wyeth v. Levine*.

C. The Third Circuit's Decision Will Discourage Innovation and Harm Public Health.

Bringing a new medicine to market is a lengthy and expensive process. *See Mutual Pharm. Co., Inc. v. Bartlett*, 570 U.S. 472, 476 (2013) ("The process of submitting an NDA is both onerous and lengthy.");

PLIVA, Inc. v. Mensing, 564 U.S. 604, 612 (2011) (citations omitted) ("[A] manufacturer seeking federal approval to market a new drug must prove that it is safe and effective and that the proposed label is accurate and adequate. . . . Meeting those requirements involves costly and lengthy clinical testing."). Before studying a new medicine in humans, a pharmaceutical company must conduct a broad range of laboratory and animal studies to test how the medicine works and assess its safety. 21 C.F.R. § 312.23(a)(8). If the results are promising, the company submits an Investigational New Drug application ("IND") to the FDA, outlining the preclinical study results and offering a plan for clinical trials in humans. 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)–(b). Only after an IND is submitted to the FDA and goes into effect can a company begin to study the prospective medicine in humans.

Human clinical trials generally occur in three phases, each of which typically must be completed before the potential new medicine may undergo FDA review and approval. 21 C.F.R. § 312.21. On average, the clinical trial phase takes six to seven years. PhRMA, *Modernizing Drug Discovery, Development and Approval* 1 (2016), http://phrma-docs.phrma.org/sites/default/files/pdf/proactive-policy-drug-discovery.pdf.

Following the satisfactory completion of clinical trials, a company can seek the FDA's approval to market the medicine by submitting a New Drug Application ("NDA"). 21 U.S.C. § 355(b)(1). The NDA,

which must contain, among other things, the results of the clinical and pre-clinical testing, proposals for manufacturing, and proposed labeling for the new medicine, *id.*, often exceeds 100,000 pages in length, PhRMA, *Biopharmaceutical Research & Development: The Process Behind New Medicines* 14 (2015), http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.

This process is tremendously expensive. On average, developing and obtaining FDA approval of a new medicine takes ten to fifteen years and costs $2.6 billion. *Biopharmaceuticals in Perspective*, *supra*, at 29; *see also* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20 (2016).[7] PhRMA's member companies invest approximately one quarter of their total annual domestic sales on research and development — an estimated $65.5 billion in 2016. *Biopharmaceuticals in Perspective, supra*, at 35. The

[7] These estimates actually understate the cost of approval, as the FDA frequently requires that a sponsor undertake additional clinical studies after approval. *See* 21 U.S.C. § 355(o)(3)(A). According to one estimate, more than three quarters of all new medicine approvals are accompanied by a commitment from the sponsor to conduct one or more post-marketing, or "Phase IV," studies. Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 Food & Drug L.J. 295, 300 (2006). PhRMA's member companies spent more than $7.4 billion in 2016 conducting these studies. PhRMA, *Annual Membership Survey* 6 tbl.4 (2017), http://phrma-docs.phrma.org/files/dmfile/PhRMA_membership-survey_2017.pdf.

biopharmaceutical industry as a whole invested $75.3 billion in research and development in 2015. *Id.* at 31.

These research efforts also involve tremendous risk, as most compounds invented never attain FDA approval. Only one out of every 5,000 to 10,000 compounds under development, and less than 12 percent of medicines entering clinical trials, obtains FDA approval. Press Release, PhRMA, PhRMA Statement Regarding Benefits of New Medicines (Apr. 30, 2013), https://www.phrma.org/press-release/phrma-statement-regarding-benefits-of-new-medicines; *Biopharmaceuticals in Perspective*, *supra*, at 29; *see also, e.g.*, Jared S. Hopkins & Michelle Cortez, *Lilly's Alzheimer's Disease Drug Fails in Final-Stage Trial*, Bloomberg (Nov. 23, 2016, 6:52 AM), https://www.bloomberg.com/news/articles/2016-11-23/lilly-s-alzheimer-s-disease-drug-fails-in-final-stage-trial (discussing an innovator's $3 billion investment in an Alzheimer's treatment medication that failed at the final stage of clinical testing).

Given the enormous costs associated with researching and developing new medicines, the scope of litigation risk has a significant effect on a company's decision to invest in innovation. *See* W. Kip Viscusi et al., *A Statistical Profile of Pharmaceutical Industry Liability, 1976-1989*, 24 Seton Hall L. Rev. 1418, 1419 (1994) ("[T]he net effect of the surge in liability costs ha[s] been to discourage innovation in the pharmaceutical industry . . . ."); Richard A. Epstein, *Legal Liability for Medical Innovation*, 8 Cardozo L. Rev. 1139, 1153 (1987) ("If in the aggregate the net gains are wiped out by the liability costs, then

the product will no longer be made."). The scope of litigation against pharmaceutical companies is already immense and rapidly expanding. Last year, 21,335 product liability lawsuits were filed against pharmaceutical companies in federal courts alone, up from 6,791 lawsuits in 2012 and just 2,700 lawsuits in 2001.[8] Today, out of sixty-nine pending product liability multidistrict litigation proceedings, twenty-eight involve pharmaceuticals.[9] By comparison, between 1960 and 1999, there were only five MDL product liability actions involving FDA-approved medicines.[10]

The anti-nausea drug Bendectin, used to treat severe morning sickness in pregnant women, illustrates how unpredictable and unfounded litigation risks influence a company's decision to invest in innovation. After Bendectin was alleged to be the cause of birth defects in thousands of lawsuits, its manufacturer withdrew the medicine from the

---

[8] *See* Admin. Office of the U.S. Courts, Table C-2A: *U.S. District Courts — Civil Cases Commenced, by Nature of Suit, During the 12-Month Periods Ending September 30, 2012 Through 2017*, http://www.uscourts.gov/sites/default/files/data_tables/jb_c2a_0930.2016.pdf; Lisa Girion, *State Vioxx Trial Is Set as Drug Suits Boom*, L.A. Times, June 27, 2006, at C1.

[9] *See* U.S. Judicial Panel on Multidistrict Litig., MDL Statistics Report — Docket Type Summary (Sept. 17, 2018), http://www.jpml.uscourts.gov/sites/jpml/files/Pending_MDL_Dockets_By_Type-September-17-2018.pdf.

[10] *See* Deborah R. Hensler, *Has the Fat Lady Sung? The Future of Mass Toxic Torts*, 26 Rev. Litig. 883, 897–902 tbl.1 (2007).

market in 1983. Only later was it vindicated by scientific studies showing that Bendectin posed no maternal fetal risk.[11] In 2013, after nearly thirty years off the market, Bendectin returned under a new name.[12] In the interim, hospital admissions for excessive vomiting during pregnancy had doubled, costing the U.S. economy $1.7 billion annually in time lost from work, caregiver time, and hospital expenses apart from the avoidable human suffering.[13]

The development of medicines for high-risk and vulnerable populations is especially subject to this phenomenon. By 1990, for example, eight of the nine major U.S. pharmaceutical companies that had been involved in researching and developing new

---

[11] *See* Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases*, 46 Stan. L. Rev. 1, 7 (1993); Robert Brent, *Medical, Social, and Legal Implications of Treating Nausea and Vomiting of Pregnancy*, 186 Am. J. Obstetrics & Gynecology S262, S262–63 (2002); *see also* David E. Bernstein, *The Breast Implant Fiasco*, 87 Calif. L. Rev. 457, 460 (1999); Lars Noah, *Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs*, 54 S.C. L. Rev. 371, 392 (2002).

[12] *See* News Release, FDA, *FDA Approves Diclegis for Pregnant Women Experiencing Nausea and Vomiting* (Apr. 8, 2013).

[13] *See* Nina Nuangchamnong & Jennifer Niebyl, *Doxylamine Succinate–Pyridoxine Hydrochloride (Diclegis) for the Management of Nausea and Vomiting in Pregnancy: An Overview*, 6 Int'l J. Women's Health 401, 401–02 (2014).

contraceptives had abandoned their efforts.[14] According to a contemporaneous report from the National Research Council and the Institute of Medicine, "recent products liability litigation and the impact of that litigation on the cost and availability of liability insurance have contributed significantly to the climate of disincentives for the development of contraceptive products." *Id.* at 141. In 1989, the inventor of the birth control pill, Carl Djerassi, recommended changes to the product liability regime, commenting that "[t]he United States is the only country other than Iran in which the birth-control clock has been set backward during the past decade."[15] The executive director of the Society for the Advancement of Women's Health Research similarly testified before Congress that "the current liability climate is preventing women from receiving the full benefits that science and medicine can provide." S. Rep. No. 104-69, at 7 (1995).

In *Levine*, the Court accepted the argument that diminished incentives for research and production of medicines might be offset by the possibility of uncovering "unknown drug hazards" and "incentives for drug manufacturers to disclose safety risks

---

[14] Nat'l Research Council, Comm. on Contraceptive Dev., & Inst. of Med., Div. of Int'l Health, *Developing New Contraceptives: Obstacles and Opportunities* 59 (Luidi Mastroianni et al. eds., 1990), https://www.nap.edu/read/1450.

[15] Carl Djerassi, *The Future of Birth Control*, Wash. Post (Sept. 10, 1989), https://www.washingtonpost.com/archive/opinions/1989/09/10/the-future-of-birth-control/7e25f2cc-ae35-4a79-8daf-031db02f81be/?utm_term=.c627032fecdb.

promptly." 555 U.S. at 579. But where the FDA has identified a potential safety risk and rejected the need for a warning, or where a manufacturer brings proposed labeling for a safety risk to the FDA and the agency disagrees about the necessity of a warning, subsequent civil litigation is unlikely to have offsetting health benefits. *See Levine,* 555 U.S. at 582 ("But it is also possible that state tort law will sometimes interfere with the FDA's desire to create a drug label containing a specific set of cautions and instructions.") (Breyer, J., concurring); *see also Riegel v. Medtronic, Inc.*, 552 U.S. 312, 325 (2008) (whereas "the experts at the FDA" apply a "cost-benefit analysis," a jury "sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court"); 150 Cong. Rec. S8657 (daily ed. July 22, 2004) (statement of former FDA Chief Counsels) ("If every state judge and jury could fashion their own labeling requirements for drugs and medical devices, . . . FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information would be seriously eroded."). By discounting the rigorous FDA-supervised process manufacturers undertake to bring a medicine to market and encouraging civil litigation, the Third Circuit's decision hampers innovation and harms public health.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted,

Robert A. Long, Jr.
Counsel of Record
Michael X. Imbroscio
Paul W. Schmidt
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
rlong@cov.com
(202) 662-6000

September 2018 *Counsel for Amici Curiae*