No. 19-1444

IN THE
Supreme Court of the United States

GLAXOSMITHKLINE LLC,

Petitioner,

v.

UNITED FOOD AND COMMERCIAL WORKERS LOCAL 1776 AND PARTICIPATING EMPLOYERS HEALTH AND WELFARE FUND, ET AL.,

Respondents.

On Petition For a Writ of Certiorari
To the United States Court of Appeals
For the Third Circuit

BRIEF OF AMICUS CURIAE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF PETITIONER

Paul W. Schmidt
Gregory L. Halperin
COVINGTON & BURLING LLP
The New York Times Building
620 Eighth Avenue
New York, NY 10018

Michael X. Imbroscio
Counsel of Record
Emily Ullman
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
mimbroscio@cov.com
(202) 662-6000

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Counsel for Amicus Curiae

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INTEREST OF AMICUS 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's members produce innovative medicines, treatments, and vaccines that save and improve the lives of countless individuals every day. Since 2000, PhRMA's members have invested more than $900 billion into discovering and developing new medicines, including an estimated $79.6 billion in 2018 alone. *About*, PhRMA, https://www.phrma.org/About. PhRMA's members are leading the way in developing new vaccines and treatments for COVID-19, with nearly half of all clinical trials using products invented by PhRMA's members. *See PhRMA COVID-19 Treatment Progress*, PhRMA, https://phrma.org/Coronavirus/Activity-Tracker (last updated July 20, 2020) [hereinafter *COVID-19 Tracker*].

This case presents a question of critical importance to PhRMA's members: whether, after the Food and Drug Administration ("FDA") considers a

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[1] Pursuant to Rule 37.6, *amicus* affirms that no counsel for a party authored this brief in whole or in part and that no person other than *amicus*, its members, or its counsel made any monetary contributions intended to fund the preparation or submission of this brief. A list of PhRMA's members is available at https://www.phrma.org/en/About/Members. GlaxoSmithKline ("GSK") is a member of PhRMA but did not contribute financially to the preparation of this brief. The parties were timely notified of *amicus*'s intent to file this brief and consented to its filing.

potential safety issue and decides that the available science is inadequate to justify a warning, a jury may nonetheless be allowed to hold a company liable under state law for failing to provide that same warning, based on (a) science that accumulates after FDA's consideration and after the time in which the labeling is alleged to be deficient, or (b) information that shows no greater risk than the information FDA considered. The burdens of product liability litigation are already substantial for life sciences companies, and a regime that permits these companies to be held liable for omitting warnings deemed unwarranted by FDA under the existing science would unfairly compound that liability in a manner that could deter development of new medicines and impede post-approval safety research. The Court should reverse the Third Circuit's judgment.

INTRODUCTION AND SUMMARY OF ARGUMENT

FDA brings extensive scientific expertise to bear in approving medically-appropriate labeling for prescription medicines, both before and after they come to market. Congress granted FDA authority to review and approve labeling because of the agency's unique institutional capacity to assess how best to communicate complex risk and benefit information, including by determining whether the available science justifies a warning at all. In recognition of that authority, this Court held in *Wyeth v. Levine*, 555 U.S. 555, 571 (2009), that state-law tort claims are preempted whenever there is "clear evidence" that FDA would have rejected the labeling that a plaintiff asserts state law requires. And in *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672, 1680

(2019), the Court explained that "clear evidence" exists when a company "fully inform[s] the FDA of the justifications for the warning" by submitting "all material information," with FDA informing the company that it "would not approve a change to the drug's label to include that warning."[2]

In this case, after considering all material information addressing a potential new safety issue, FDA rejected GSK's proposed warning based on the agency's considered judgment that the existing science was "inadequate" to support it. Pet. App. 64. That rejection provides clear evidence that FDA would have likewise rejected any earlier labeling change reflecting the same rejected warning, including one submitted under the Changes Being Effected ("CBE") regulation, especially given that the science was even less developed at earlier points in time.

Yet the Third Circuit rejected GSK's preemption defense by re-casting what it means for FDA to be "fully informed" in ways that disregard this Court's precedents and FDA regulations. Rather than assess whether FDA was "fully informed" of all existing "material information" at the time FDA issued its rejection, the Third Circuit engaged in a retrospective

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[2] Although FDA's formal rejection of a warning upon receipt of full information constitutes clear evidence, such evidence can also be established through other means. *See, e.g.*, *Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882, 890–91 (7th Cir. 2020) (*Albrecht* does not require showing that a company "actually requested a change for the label and that the FDA rejected it"); *Cerveny v. Aventis, Inc.*, 783 F. App'x 804, 808 n.9 (10th Cir. 2019) (rejecting argument that "*Albrecht* 'dictates that only labeling changes sought by the manufacturer can lead to preemption'").

analysis of whether additional support for the warning emerged after FDA's disapproval. The Third Circuit further suggested that FDA is not "fully informed" of the justifications for a warning whenever it requests additional information, regardless of whether that requested information shows anything different than what FDA already knows or whether it could even support a labeling change.

The Third Circuit's decision places life sciences companies in the impossible position of facing civil liability for not adopting warnings that FDA prohibited after evaluating all material, state-of-the-art information bearing on the potential safety issue. Because scientific knowledge is ever-changing, the Third Circuit's unrealistic preemption standard will hamper innovation and endanger public health by potentially exposing life sciences companies to liability when scientific knowledge accumulates after FDA's rejection of proposed labeling and after the time in which the labeling is alleged to be deficient. Making matters worse, the holding below irrationally penalizes companies for undertaking post-approval studies that advance scientific knowledge. The Court should grant the Petition.

ARGUMENT

I. Given the Massive Costs Associated with Developing New Medicines, Preemption of Failure-to-Warn Claims that Conflict with FDA Determinations Is Critical for Innovation and Public Health

Bringing a new medicine to market is a lengthy and expensive process. On average, developing a new

medicine and obtaining FDA approval takes ten to fifteen years and costs $2.6 billion.[3] These research efforts involve tremendous risk, as just one out of every 5,000 to 10,000 compounds under development, and just one out of every eight medicines entering clinical trials, obtains FDA approval.[4] For example, just four out of 150 medicines developed since 1998 to treat Alzheimer's disease have secured FDA approval, with one medication recently failing at the final stage of clinical testing after a company had invested $3 billion into its development.[5]

Due to the high risk of failure, life sciences companies necessarily develop multiple medications in parallel, each at great expense. Today, approximately 8,000 potential new medicines are under study, with

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[3] PhRMA, *Biopharmaceuticals in Perspective: Summer 2019*, at 33 (2019), https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMA_2019_ChartPack_Final.pdf [hereinafter *Biopharmaceuticals in Perspective*]; *see also* Joseph DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20 (2016).

[4] *Clinical Trials—So Necessary but More Complex than Ever*, PhRMA (Mar. 3, 2011), https://catalyst.phrma.org/clinical-trials-so-necessary-but-more-complex-than-ever; *Biopharmaceuticals in Perspective*, *supra* note 3, at 33.

[5] *Biopharmaceuticals in Perspective*, *supra* note 3, at 43; *see also, e.g.*, Michelle Cortez & Jared Hopkins, *Lilly's Alzheimer's Disease Drug Fails in Final-Stage Trial*, Bloomberg (Nov. 23, 2016), https://www.bloomberg.com/news/articles/2016-11-23/lilly-s-alzheimer-s-disease-drug-fails-in-final-stage-trial.

PhRMA's members investing an estimated $79.6 billion—nearly one-quarter of their total annual domestic sales—in research and development.[6]

In light of the enormous cost and risk associated with bringing a medicine to market, the prospect of litigation bears heavily on a company's decision to invest in innovation. The current COVID-19 health crisis demonstrates how protections from unpredictable and unfounded litigation can foster innovation. In 2006, after Dr. Anthony Fauci testified that fear of litigation had generated "considerable reluctance on the part of industry" to develop emergency vaccines and urged lawmakers to "reduce the liability risks that dissuade companies from producing pandemic countermeasures," Congress passed the Pandemic and All-Hazards Preparedness Act.[7] The Act addresses the overwhelming liability issues that might otherwise inhibit innovation by protecting manufacturers of medicines and other "covered countermeasure[s]," including vaccines, from the risk of damages in the event of a declared public health emergency. 42

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[6] *Biopharmaceuticals in Perspective*, *supra* note 3, at 26; PhRMA, *2019 PhRMA Annual Membership Survey* 4 tbls. 2–3 (2019), https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMA_2019_membership_survey_Final.pdf [hereinafter *Annual Membership Survey*].

[7] *Avian Flu: Addressing the Global Threat: Hearing Before the H. Comm. on Foreign Relations*, 109th Cong. 35, 44 (2005) (statement of Anthony Fauci, Dir., Nat'l Inst. of Allergy & Infectious Diseases); *see also* Rick Weiss, *Bush, Executives Consider Strategies to Ramp Up Vaccine Production*, Wash. Post, Oct. 8, 2005, at A3 (statement of Dr. Fauci that "liability issues must be addressed" in order to "have a robust vaccine production infrastructure in place" that would enable the country to "produce a pandemic vaccine on short notice").

U.S.C. § 247d-6d. Effective February 4, 2020, Secretary of Health and Human Services Alex Azar issued such a declaration with respect to COVID-19. 85 Fed. Reg. 15,198 (Mar. 10, 2020). Today, more than 1,350 clinical trials are ongoing, involving 442 unique therapies and 23 unique vaccines. *See COVID-19 Tracker*, *supra*.

By contrast, the anti-nausea drug Bendectin, used to treat severe morning sickness in pregnant women, illustrates the potential for unfettered liability to deprive patients of innovations that improve quality of life. In 1983, after Bendectin was named as the cause of birth defects in thousands of lawsuits in centralized multidistrict litigation ("MDL") proceedings, its manufacturer withdrew Bendectin from the market, only later to be vindicated by scientific studies showing that Bendectin posed no maternal fetal risk.[8] In 2013, after nearly thirty years off the market, Bendectin returned under a new name.[9] In the interim, hospital admissions for excessive vomiting during pregnancy had doubled, costing the U.S. economy an estimated $1.7 billion annually in time lost from work, caregiver time, and hospital expenses.[10]

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[8] *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).

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

[10] *See* Nina Nuangchamnong & Jennifer Niebyl, *Doxylamine Succinate–Pyridoxine Hydrochloride (Diclegis) for the Management*

The current scope of litigation against life sciences companies is immense and rapidly expanding. Last year, 38,872 pharmaceutical product liability lawsuits were filed in federal courts alone, nearly double the number filed just two years earlier and more than thirteen times the number filed in 2001.[11] Today, out of sixty-four pending product liability MDL proceedings, twenty-one involve pharmaceuticals.[12] By comparison, between 1960 and 1999, there were a total of five MDL product liability actions involving FDA-approved medicines.[13]

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of Nausea and Vomiting in Pregnancy: An Overview, 6 Int'l J. Women's Health 401, 401–02 (2014), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3990370/pdf/ijwh-6-401.pdf.

[11] *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, 2015 Through 2019*, https://www.uscourts.gov/sites/default/files/data_tables/jb_c2a_0930.2019.pdf; Lisa Girion, *State Vioxx Trial Is Set as Drug Suits Boom*, L.A. Times, June 27, 2006, at C1.

[12] *See* U.S. Jud. Panel on Multidistrict Litig., *MDL Statistics Report—Distribution of Pending MDL Dockets by District* (July 16, 2020), https://www.jpml.uscourts.gov/sites/jpml/files/Pending_MDL_Dockets_By_District-July-16-2020.pdf; *see also* Eric Lasker & Michael Junk, *Holding Pharma Plaintiffs to Their Pleading Burden: Implications of* Twombly *and* Iqbal, 11 Engage: J. Federalist Soc'y Prac. Grps. 113, 113 (2010) ("Nearly 40% of the product liability MDLs created by the Judicial Panel on Multidistrict Litigation since 2006 involved pharmaceutical products.").

[13] *See* Deborah Hensler, *Has the Fat Lady Sung? The Future of Mass Toxic Torts*, 26 Rev. Litig. 883, 897–902 tbl. 1 (2007); *see also Standards and Best Practices for Large and Mass Tort MDLs*, Duke L. Sch. Ctr. for Jud. Stud., at xi (2014), https://

This alarming growth of litigation does not suggest that medicines are somehow becoming less safe or that FDA has become deficient in its oversight. To the contrary, more than four out of every five federal product liability cases resolved on the merits between 2015 and 2019 were resolved in the defendant's favor, including because there is no reliable science to support the plaintiff's claim.[14] That statistic should come as no surprise. Lawsuits typically allege that a medicine is unreasonably dangerous or that its labeling fails to warn of the known risks. Yet FDA—the agency responsible for "protecting the public health by ensuring the safety" of medicines and "helping the public get the accurate, science-based information

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law.duke.edu/sites/default/files/centers/judicialstudies/standards_and_best_practices_for_large_and_mass-tort_mdls.pdf (MDL actions "are becoming more concentrated in . . . primarily products liability, and particularly pharmaceutical and health-care cases").

[14] *See* Ronald Porter, *Product Liability Litigation Report* 21, Lex Machina (2020), https://images.law.com/contrib/content/uploads/documents/292/68165/LexMachina_2020_Product_Liability_Litigation_Report.pdf; *see also, e.g.*, *In re Mirena IUS Levonorgestrel-Related Prod. Liab. Litig. (No. II)*, 387 F. Supp. 3d 323, 358 (S.D.N.Y. 2019) (granting summary judgment on all pending cases because there was no "basis on which a jury could reliably find the required element of general causation"); *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prod. Liab. Litig.*, 424 F. Supp. 3d 781, 799 (N.D. Cal. 2020) (excluding causation experts, where no study "has produced results that any person or organization other than plaintiffs' experts have believed support a conclusion of causation"); *In re Accutane Litig.*, 191 A.3d 560, 595 (N.J. 2018) (concluding after more than a decade of litigation that plaintiffs' claim "flies in the face of consistent findings of no causal association").

they need to use medical products"[15]—subjects a medicine's design and labeling to close scrutiny as part of the approval process. *See* 73 Fed. Reg. 49,603, 49,604 (Aug. 19, 2008) (FDA "makes approval decisions . . . based on a comprehensive scientific evaluation of the product's risks and benefits"); 73 Fed. Reg. 2848, 2851 (proposed Dec. 4, 2007) (before approval, "FDA undertakes a detailed review of the proposed labeling"). Indeed, FDA typically reviews and analyzes more than 100,000 pages of pre-clinical and clinical testing results,[16] with approval "expressly conditioned upon the applicant incorporating the specified labeling changes exactly as directed," 73 Fed. Reg. at 2851.

Nor does FDA's close scrutiny end with a medicine's approval. "[A]fter approval, FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate." 73 Fed. Reg. at 2851. By law, FDA must independently consider whether labeling remains adequate in light of its continuous monitoring of adverse event reports and other research, 21 U.S.C. § 355(o)(4),[17] and it must suspend or withdraw

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[15] *What We Do*, FDA, https://www.fda.gov/about-fda/what-we-do.

[16] *See* PhRMA, *Biopharmaceutical Research & Development: The Process Behind New Medicines* 14 (2015), https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/rd_brochure.pdf [hereinafter *Biopharmaceutical R&D*].

[17] Section 355(o)(4) was passed as part of the Food and Drug Administration Amendments Act of 2007. Even before 2007, FDA possessed considerable practical ability to generate labeling

approval if it believes the drug is unsafe, 21 C.F.R. § 314.150(a)(2). In short, FDA brings to bear its expertise at all times to ensure that medications are safe, effective, and accompanied by appropriate warnings.

Conflict preemption takes proper account of FDA's labeling supremacy and serves as an essential check against absolute tort liability. Where a life sciences company promptly brings a potential safety risk to FDA and the agency disagrees about the necessity of a warning, subsequent civil litigation challenging that decision serves only to undermine FDA's oversight. *See Levine,* 555 U.S. at 582 (Breyer, J., concurring) ("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."); *see also Riegel v. Medtronic, Inc.*, 552 U.S. 312, 325 (2008) (jurors "see[] only the cost" of a product and are unlikely to "apply cost-benefit analysis similar to that applied by the experts at the FDA"); 150 Cong. Rec. S8657-01 (daily ed. July 22, 2004) (statement of former FDA Chief Counsels) ("If every state judge and jury could fashion their own labeling requirements[,] . . . FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information would be seriously eroded.").

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changes through its powers to (1) withdraw approval of a medicine whose labeling is "false or misleading in any particular," and (2) bring an enforcement action for misbranding. 21 U.S.C. §§ 355(e), 352(a).

Accordingly, state-law failure-to-warn claims are preempted whenever a company cannot "unilaterally add[] a stronger warning" to its labeling, either because the CBE process is unavailable, or because there is "clear evidence that the FDA would not have approved [the] change." *Levine*, 555 U.S. at 571; *see also PLIVA, Inc. v. Mensing*, 564 U.S. 604, 618 (2011) (failure-to-warn claims against generic manufacturers preempted because CBE process is unavailable to them).[18]

To subject life sciences companies to liability under state law for failing to act in ways that federal law prohibits would not only be constitutionally infirm, but also dis-incentivize innovation and harm public health. Accordingly, though the "question of pre-emption is one for a judge to decide," *Albrecht*, 139 S. Ct. at 1672, in deciding the question of preemption, judges must not adopt "an approach . . . that renders conflict pre-emption all but meaningless," *Mensing*, 564 U.S. at 621.

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[18] Similarly, because preemption attaches "when a party cannot satisfy its state duties without [FDA's] special permission and assistance," *Mensing*, 564 U.S. at 623–24, and because companies are "prohibited from making any major changes to the 'qualitative or quantitative formulation'" of an approved medication without FDA's approval, state-law design-defect claims are impliedly preempted, *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 477 (2013).

II. Because Science Continually Evolves, the Third Circuit's Framework Makes No Logical Sense

"[K]nowledge of drugs is not binary but continues to evolve over time."[19] Real-world use of a medicine produces information about adverse drug reactions that may not have been observed in clinical trials, with "an excess of adverse events compared to what would be expected" indicating a potential safety risk.[20] Additionally, scientists inside and outside the company commonly undertake further study of the medicine after approval, producing greater understanding regarding safety and efficacy. *See* Part III. And FDA itself collects adverse event reports through a voluntary reporting system and uses electronic health care data to monitor medicine safety.[21]

FDA regulations account for this evolving knowledge by requiring companies to submit updated

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[19] H.G. Eichler et al., *Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval*, 91 Clinical Pharmacology & Therapeutics 426, 427 (2012); *see also* Geoffrey Hazard, Jr., *"Practice" in Law and Other Professions*, 39 Ariz. L. Rev. 387, 390 (1997) (in medicine, "evolving science continually inflicts obsolescence on established knowledge").

[20] FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005), 2005 WL 3628217, at *3.

[21] *See MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, FDA, https://www.fda.gov/Safety/MedWatch/default.htm; *FDA's Sentinel Initiative—Background*, FDA, https://www.fda.gov/safety/fdas-sentinel-initiative/fdas-sentinel-initiative-background.

evaluations of a medicine's benefits and risks at specified intervals. *See* 21 C.F.R. § 310(c)(2) (requiring quarterly reports for three years and annual reports thereafter). These reports must take into account "any new information that has arisen during the reporting interval," including from post-approval clinical trials and other completed studies, scientific literature, and adverse event reporting.[22]

The Third Circuit's decision exposes companies to potential retroactive liability whenever some later scientific development might support a warning in the future, notwithstanding that FDA's earlier actions confirmed that the science during the time period at issue did not support that warning. *See* Pet. App. 16 ("[B]y arguing that it did not have access to the FDA's requested data and information until after the FDA's issuance of the Letter, GSK undermines its own argument that the FDA was 'fully informed.'"). New scientific information is always emerging, and a preemption rule that allows retroactive liability whenever a new and previously unknown safety issue arises effectively renders prior FDA determinations on the science meaningless—a result that cannot be squared with *Levine* and *Albrecht*.

The facts of this case illustrate the error in the Third Circuit's decision. Respondents allege that from 2000 to 2006, Avandia's labeling should have contained additional warnings regarding its cardiovascular risks. *See* Br. of Pl.-Appellants at 62, *In re Avandia Mktg., Sales Practices & Prod. Liab. Litig.*,

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[22] FDA, *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER): Guidance for Industry* (2016), 2016 WL 4058992, at *12–29 [hereinafter *FDA PBRER Guidance*].

945 F.3d 749 (2019) (No. 18-1010), 2018 WL 3218448. In July 2007, FDA "reviewed the data" GSK submitted—*i.e.*, all material information in existence bearing on the potential safety risk—and concluded that this information was "inadequate" to justify additional cardiovascular warnings like those Respondents seek. Pet. App. 64; *see also* 21 C.F.R. § 201.57(c)(6)(i) (requiring "reasonable evidence of a causal association" for a warning).[23] If the state of the science was "inadequate" in 2007, it necessarily was "inadequate" before 2007, when even less support for Respondents' proposed warnings was available.[24] Under those circumstances, it was impossible for GSK "to comply

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[23] FDA formally rejected GSK's Prior Approval Supplement ("PAS") application via a "not approvable letter," the method set forth in the pre-2008 regulations for FDA to officially communicate, upon "complet[ion] of its substantive review," its conclusion "that the information contained in the application [was] unable to support" approval. 47 Fed. Reg. 46,622, 46,639 (proposed June 23, 1982); *see also* 21. C.F.R. § 314.120(a) (reserved Aug. 11, 2008).

[24] *See, e.g.*, *Rheinfrank v. Abbott Labs., Inc.*, 680 F. App'x 369, 386 (6th Cir. 2017) ("Given, then, that as of 2008 the FDA did not believe the state of the data supported a developmental delay warning, it stands to reason that as of 2003, with even less data to go on, the FDA would similarly have rejected a developmental delay warning . . . ."); *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1105 (10th Cir. 2017) (FDA's 2009 conclusion that warnings were "unjustified" provided clear evidence that FDA would not have approved a warning in 1992); *Drescher v. Bracco Diagnostics Inc.*, 2020 WL 699878, at *6 (D. Ariz. Jan. 31, 2020) ("FDA's conclusion that no known causal association existed in 2017 precludes finding that Defendants could have made a CBE label change years earlier."); *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1179 (S.D. Cal. 2016) ("In light of the FDA's February 2014 conclusion that evidence of a causal association was

with both its state-law duty to strengthen the warnings" and "its federal-law duty not to alter" them. *Bartlett*, 570 U.S. at 480.

Instead, the Third Circuit held that data from the RECORD trial that did not yet exist prevented FDA from being "'fully informed . . . of the justifications for the [proposed] warning,'" greenlighting Respondents' claim that GSK failed to warn of a risk that was scientifically unknown until years later. Pet. App. 17 (alterations in original) (quoting *Albrecht*, 139 S. Ct. at 1678).[25] That holding does not comport with common sense. Newly-emergent scientific knowledge can support a labeling change only once it emerges. *See Roberto v. Boehringer Ingelheim Pharm., Inc.*, 2019 WL 5068452, at *21 (Conn. Super. Ct. Sept. 11, 2019) (scientific knowledge that emerged after plaintiff's injury "obviously could not have provided the basis for a label change that might have prevented" that injury).[26] By permitting plaintiffs to present

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indeterminate, it is clear that the FDA would have rejected a labeling change any time prior.").

[25] There can be no doubt that the RECORD results were a prerequisite to FDA's approval of a warning. FDA's not approvable letter emphasized the need for "accruing information from ongoing clinical trials" (*i.e.*, RECORD), Pet. App. 65, and FDA later remarked that of the various clinical trials presented at the Advisory Committee meeting, "the interim results of the RECORD trial" were "[m]ost notabl[e]," CA3.JA.1643.

[26] *See also, e.g.*, *Goodell v. Bayer Healthcare Pharm. Inc.*, 2019 WL 4771136, at *4 (D. Mass. Sept. 30, 2019) (requiring information to "manifest[] . . . before Plaintiff's injury"); *Mahnke v. Bayer Corp.*, 2019 WL 8621437, at *4 (C.D. Cal. Dec. 10, 2019) (literature published after plaintiff's medicine use was "outside

these "back-to-the-future" claims to juries, the decision below deprives life sciences companies of their constitutional protections. That the Third Circuit is home to three-quarters of the world's largest pharmaceutical companies only amplifies the impact of that deprivation.[27]

Moreover, the Third Circuit arrived at its incorrect holding by distorting this Court's precedents. FDA regulations permit companies to utilize the CBE process only to "'reflect newly acquired information.'" *Albrecht*, 139 S. Ct. at 1679 (quoting 21 C.F.R. § 314.70(c)(6)(iii)). Even then, "'FDA retains authority to reject labeling changes made pursuant to the CBE regulation.'" *Id.* at 1677 (quoting *Levine*, 555 U.S. at 571). Accordingly, the preemption analysis proceeds in two steps: First, a plaintiff must identify "'a labeling deficiency that [the defendant] could have corrected using the CBE regulation'"—*i.e.*, a warning for which the company possessed "newly acquired information." *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019) (quoting *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 41 (1st Cir. 2015)). If a plaintiff can point to such evidence, the defendant can still show "'clear evidence that the FDA would not have approved [the] change.'" *Id.* (quoting *Levine*, 555 U.S. at 571).[28]

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of the relevant time frame"); *McGrath v. Bayer HealthCare Pharm. Inc.*, 393 F. Supp. 3d 161, 168 (E.D.N.Y. 2019) (similar).

[27] *See Pharmaceuticals*, State of N.J. Business Portal, https://www.nj.gov/njbusiness/industry/pharmaceutical.

[28] For other cases that have articulated this two-step analysis, see, e.g., *Ridings v. Maurice*, 2020 WL 1264178, at *4 (W.D. Mo.

Under this framework, which flows directly from *Albrecht*, *Levine*, and the governing regulations, science demonstrating a new or greater risk that emerges after FDA's rejection of a proposed warning is relevant to the first step. Such information can provide "newly acquired information" that could permit a *subsequent* CBE labeling change and allow a failure-to-warn claim for plaintiffs injured *after* the risk emerges. *See* Br. for United States as Amicus Curiae Supporting Pet'r at 27, *Albrecht*, 139 S. Ct. 1668 (2019) (No. 17-290), 2018 WL 4562163 [hereinafter Br. for United States] (information that "arose after FDA's decision" would permit an argument that "information that FDA did not consider constitutes 'newly acquired information'"). But the proper question under the second prong is whether FDA was "fully informed" of all material *existing* information at the time it "informed the drug manufacturer that [it] would not approve [the] change." *Albrecht*, 139 S. Ct. at 1672. Information that did not exist at the time FDA rejected a warning cannot keep FDA from being "fully informed" under *Albrecht*.

III. The Third Circuit's Decision Punishes Life Sciences Companies for Their Continual Study of Medicine Safety

Before studying a new medicine in humans, a life sciences company must conduct a broad range of laboratory and animal studies to test how the medicine works and assess its safety. *See* 21 C.F.R. § 312.23(a)(8). If the results are promising, the company can seek FDA approval to study the medicine in

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Mar. 16, 2020); *Mahnke*, 2019 WL 8621437, at *3; and *Roberto*, 2019 WL 5068452, at *11.

humans. *See* 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)–(b). Human clinical trials generally occur in three phases, which on average take six to seven years to complete.[29] If the results show that the medicine's benefits outweigh its risks, the company can seek FDA approval to market the medicine. *See* 70 Fed. Reg. 57,607, 57,608 (Sept. 26, 2005).

But research on new medicines does not end with FDA approval. Because medicines are used in real-world clinical settings by much broader populations of patients, post-approval study can uncover new safety information, particularly regarding rare adverse events or those that take years to develop.[30] These post-approval discoveries are not "a failure of

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[29] *See* 21 C.F.R. § 312.21; PhRMA, *Modernizing Drug Discovery, Development and Approval* 1 (2016), http://phrmadocs.phrma.org/sites/default/files/pdf/proactive-policy-drug-discovery.pdf.

[30] Scott Gottlieb, Comm'r, FDA, *Opening Pandora's Pillbox: Using Modern Information Tools to Improve Drug Safety*, 24 Health Affairs 938, 940 (2005), *available at* https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.24.4.938 (noting the difficulty of "recruit[ing] rigorous clinical trials sufficiently large" to detect "rare or uncertain problems"). Whereas most clinical trials involve 1,000 to 5,000 patients, a study would need to recruit more than 600,000 volunteers to have a 95 percent chance of detecting an adverse event that occurs once in every 5,000 patients. *See Biopharmaceutical R&D*, *supra* note 16, at 13; Louis Lasagna, *Discovering Adverse Drug Reactions*, 249 JAMA 2224, 2225 (1983).

the drug-development process," but rather are "the expected consequence of the biologic diversity of humans."[31]

Accordingly, life sciences companies conduct extensive post-approval research to monitor the safety and long-term effects of their medicines. This real-world evidence can take a variety of forms, including additional clinical trials, observational studies, electronic health record or payor administrative claims reviews, patient registries, and meta-analyses. In 2018, PhRMA's members invested more than $9.2 billion in post-approval research that advances clinicians' understanding of a medicine's risks, benefits, and potential uses, with more than 750 industry-funded post-approval clinical trials and observational studies currently underway.[32]

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[31] Alastair Wood et al., *Making Medicines Safer—The Need for an Independent Drug Safety Board*, 339 New Eng. J. Med. 1851, 1852 (1998).

[32] *Annual Membership Survey*, *supra* note 6, at 4 tbl. 3; U.S. Nat'l Library Med., ClinicalTrials.gov, https://www.clinicaltrials.gov (last visited July 24, 2020). Reflecting the value of post-approval research, Congress in 2007 granted FDA the authority to mandate post-approval clinical trials and studies. *See* 21 U.S.C. § 355(o)(3)(A). This research is subject to FDA oversight, including input on a study's design. *See* FDA, *Guidance for Industry: Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (2011), 2011 WL 2836589, at *9–10. Companies must make periodic reports to FDA regarding any study mandated by FDA or voluntarily undertaken "to investigate a safety issue." 21 U.S.C. § 355(o)(3)(E)(ii). And companies are required to include information about clinical trials and non-interventional studies they sponsor in their Periodic Benefit-Risk Evaluation Reports. *See FDA PBRER Guidance*, *supra* note 22, at *18–19.

A. Assessing Whether FDA Was Fully Informed by Reference to Later Science Penalizes Companies for Contributing to Scientific Discovery

By holding that data or other information generated after FDA's rejection of proposed labeling can prevent FDA from being "fully informed" at the time of rejection, the Third Circuit's decision penalizes life sciences companies for undertaking post-approval research.

This case is a perfect example. Pre-approval studies suggested that Avandia's cardiovascular safety profile was "benign." CA3.JA.914. Initial GSK-sponsored post-approval research produced mixed signals, with one meta-analysis showing "'no consistent pattern'" regarding the risk of myocardial ischemia, Cert. Pet. 7 (quoting CA3.SA.280), and another showing "an increased risk," Pet. App. 64. In June 2007, FDA rejected GSK's proposed warning to account for this mixed record, concluding that the existing data and analysis were "inadequate" to support it. Pet. App. 64. Had GSK performed no additional study or analysis, Respondents' claim that Avandia's pre-2007 label failed to warn about the cardiovascular risk would have been preempted under a straightforward application of *Albrecht*. Instead, GSK sponsored a more robust study, RECORD, which when added to the pre-existing data appeared at the time to support "a conclusion that Avandia increases cardiac ischemic risk." CA3.JA.1085. As FDA Division Director Robert Meyer stated at the Advisory Committee, "considering

the results in the interim [RECORD] analysis many, myself included, find the data quite informative."[33]

According to the Third Circuit, because the RECORD results came into existence *after* June 2007, "FDA was not 'fully informed' at the time" it rejected GSK's PAS in June 2007.[34] Pet. App. 17. The holding below thus penalizes life sciences companies who proactively conduct and fund vigorous post-approval safety research. This Court could not have intended such an upside-down result when it "elaborate[d] *Wyeth*'s requirements." *Albrecht*, 139 S. Ct. at 1676.

B. If Information Revealing No Different or Greater Risk Can Be Material, Companies that Zealously Participate in Scientific Research Will Be Least Able to Assert Preemption

The Third Circuit's materiality ruling further magnifies the litigation risk for companies that pursue post-approval research. As data becomes more robust, FDA can more readily fashion requests to reanalyze it in different ways. If, as the Third Circuit

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[33] Tr. of Joint Meeting of Endocrinologic & Metabolic Drugs Advisory Comm. & Drug Safety Management Advisory Comm. (pt. 3), at 243, FDA (July 30, 2007), *available at* https://web.archive.org/web/20080921073731/http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic [hereinafter Advisory Comm. Tr.].

[34] Remarkably, the Third Circuit did not reach far enough into the future to account for FDA's 2013 decision—upon review of the final RECORD data—directing removal of the black box warning it had previously added based on RECORD's interim results. *See* CA3.JA.1641.

suggested, any information requested by FDA is presumptively material regardless of whether it shows a different or greater risk, then companies that generate a large body of new information through an extensive study of a medicine's safety will be most prone to follow-on FDA requests and least able to avail themselves of a preemption defense.

Instead, any consideration of materiality must give due consideration to the information that FDA itself considers material: information that would permit a labeling change. *See* Pet. App. 16 ("[T]he FDA, and only the FDA, can determine what information is 'material' . . . ."). Because labeling at all times reflects FDA's "careful balancing of how the risks and benefits of the product should be communicated" based on the agency's "comprehensive scientific evaluation" and "thorough . . . review of the pertinent scientific evidence," 73 Fed. Reg. at 2849, 2851, CBE labeling changes require information that "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA," 21 C.F.R. §§ 314.3(b), 314.70(c)(6)(iii).[35] Data or information that is "cumulative of" or "consistent in type, severity, and frequency with information previously provided" offers no reason to upset FDA's "careful balancing" and therefore does not justify a labeling change. 73 Fed. Reg. at 2849–50. Put simply, information is material to FDA's evaluation of proposed labeling if it demonstrates a different or greater

[35] Although promulgated in August 2008, section 314.3(b) merely "codif[ied] the agency's longstanding view on when a change to the labeling . . . may be made in advance of the agency's review and approval." 73 Fed. Reg. at 2849. FDA did not consider section 314.3(b) "to be a substantive change." *Id.* at 2851.

risk, but not if it is merely cumulative of or consistent with previously-submitted information. *See* Br. for United States, *supra*, at 28 n.11 ("If for instance, FDA previously determined . . . that evidence of X was insufficient to warrant a warning about risk Y, the existence of additional but similar information about X would be insufficient to justify a warning.").[36] *Albrecht* itself recognizes this balance, requiring companies to "fully inform[] the FDA of the *justifications* for the warning," not of every available scrap of cumulative data. 139 S. Ct. at 1672 (emphasis added). The Third Circuit failed to assess the materiality of the information that FDA requested from GSK under this framework.[37]

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[36] *See also, e.g.*, *Ridings*, 2020 WL 1264178, at *16 (where "substantially similar 'reasonable evidence' was presented to the FDA and that agency determined not to give different or more expansive warnings," additional information was not newly acquired).

[37] Had the Third Circuit conducted such an analysis, it would have been compelled to conclude that the underlying data from the ADOPT, DREAM, and Nissen studies was immaterial, particularly when GSK had already provided FDA with the results of those studies. FDA ultimately concluded that ADOPT and DREAM were inconclusive about the risk of myocardial ischemia, and the Advisory Committee remarked about the close similarities between the Nissen meta-analysis that FDA requested and the ICT-42 meta-analysis that had been the basis for GSK's PAS application. *See* CA3.JA.743, 748–49 (ADOPT and DREAM "have not confirmed or excluded" an increased risk); Advisory Comm. Tr. (pt. 5), *supra* note 33, at 422 ("One thing that I was struck by when I reviewed the data was how similar the analyses were by the sponsor, by the FDA and by Nissen.").

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

Michael X. Imbroscio
Counsel of Record
Emily Ullman
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
mimbroscio@cov.com
(202) 662-6000

Paul W. Schmidt
Gregory L. Halperin
COVINGTON & BURLING LLP
The New York Times Building
620 Eighth Avenue
New York, NY 10018

Counsel for Amicus Curiae

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