No. 21-55342

IN THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

JEAN ADAMS, on behalf of herself and all other similarly situated plaintiffs,

Plaintiff/Appellant,

v.

MERCK SHARP & DOHME CORP., et al.,

Defendants/Appellees.

On Appeal from the United States District Court
for the Southern District of California
(No. 3:13-md-2452-AJB-MDD)

BRIEF OF WASHINGTON LEGAL FOUNDATION AS *AMICUS CURIAE* IN SUPPORT OF APPELLEES AND AFFIRMANCE

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INTEREST OF *AMICUS CURIAE*[*]

Washington Legal Foundation is a nonprofit, public-interest law firm and policy center with supporters nationwide. Founded in 1977, WLF promotes free enterprise, individual rights, limited government, and the rule of law. It often appears as *amicus curiae* in important preemption cases to urge federal courts to prevent contrary state law from undermining the predictability and uniformity of federal law. *See, e.g.*, *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019); *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803 (7th Cir. 2018). In finding the plaintiffs' claims to be preempted, the decision below faithfully applies the Supreme Court's preemption precedents, vindicates the Food, Drug, and Cosmetic Act's (FDCA's) carefully balanced labeling regime, and should be affirmed.

WLF also regularly appears in products liability cases to argue that Rule 702 requires courts to exclude any expert opinion that lacks sufficient reliability. *See, e.g.*, *In re: Lipitor (Atorvastatin Calcium) Mktg., Sales Practices and Prods. Liab. Litig.*, 892 F.3d 624 (4th Cir.

[*] No party's counsel authored any part of this brief. No one, apart from WLF and its counsel, contributed money intended to fund the brief's preparation or submission.

2018); *In re: Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787 (3d Cir. 2017). The district court here acted well within its discretion in rejecting the plaintiffs' unreliable expert opinions on causation.

INTRODUCTION & SUMMARY OF ARGUMENT

Federal law imposes comprehensive, mandatory duties on prescription drug makers. Congress has charged the Food and Drug Administration with deciding both the precise risk information that must appear on a drug's label and how best to word it. Because the FDA's work requires expert knowledge both of the human body and the long-term effects of prescription drugs, a manufacturer of prescription drugs ordinarily must use FDA-approved labeling. If no FDA-authorized exception allows a manufacturer to change a drug's FDA-approved label, the Supremacy Clause forbids the States from imposing liability on the manufacturer because of that label.

Novo Nordisk Inc. manufactures and markets Victoza (liraglutide) to treat type-2 diabetes. The plaintiffs complain that Victoza's FDA-approved labeling failed to warn of an increased risk of pancreatic cancer. The FDA's "changes-being-effected" (CBE) regulation, 21 C.F.R.

§ 314.70(c)(iii), makes it possible for a manufacturer to comply with state-law labeling duties without violating federal law. But the CBE process is not open-ended. Rather, it applies *only* when the manufacturer has "newly acquired information"—material information not previously presented to the FDA but that significantly alters the risk profile of a drug.

As the district court rightly found, no newly acquired information exists here. And when no such information exists, that is the end of the matter under the Supremacy Clause. Simply put, complying with both federal and state law is "impossible" for drug manufacturers when "it is impossible for a private party to comply with both state and federal requirements." *Albrecht*, 139 S. Ct. at 1672. This case is no exception to that rule; the plaintiffs' claims are preempted.

What's more, agreeing to the plaintiffs' demand for warnings about unproven and speculative risks would erode the efficacy of prescription drug labeling. Overwarning harms the public health in two ways. First, consumers and physicians can disregard lengthy labeling filled with speculative warnings, thereby overlooking important, scientifically founded information. Second, warnings that are not

grounded in science will discourage the beneficial use of medicines. Overstating adverse risks often interferes with a physician's ability to deploy the best therapies. In both cases, imposing a duty to warn of unproven and speculative risks would undermine patient care. At a time when fear of adverse effects has increased vaccine hesitancy for the COVID-19 vaccine, this Court should insist on more—not less—scientific rigor.

The decision below should also be affirmed because the plaintiffs offered no reliable evidence to establish general causation. In seeking an abuse-of-discretion reversal, the plaintiffs invite the Court to disregard Rule 702 by relaxing their burden to come forward with scientifically reliable expert testimony derived from accepted methodologies. Yet doing so would not only sweep aside Rule 702 and decades of Supreme Court precedent but—in light of the inconsistent and unreliable methodologies employed by the plaintiffs' experts here—also inject harmful uncertainty well beyond this case.

Allowing a flimsy, unscientific "association" to serve as the basis for imposing massive tort liability on drug manufacturers would discourage the development of many beneficial drugs. Without enforced

thresholds for the reliability of expert evidence on causation, drug manufacturers facing unwarranted liability would be forced either to raise prices significantly or to exit the market altogether—reducing access to important, even life-saving, therapies. Ultimately, patients and their physicians who rely on such therapies would suffer the most.

ARGUMENT

I. ABSENT ANY SHOWING OF NEWLY ACQUIRED INFORMATION, IMPOSSIBILITY PREEMPTION PRECLUDES LIABILITY.

Both the public health and the American economy suffer whenever state law, including state tort law, interferes or conflicts with federal regulatory regimes like the FDCA, 21 U.S.C. § 301, et seq. Conflicting state and federal labeling duties are not merely inefficient—they make it impossible for drug and device makers to comply with federal law without incurring massive liability under state law. The Supremacy Clause prevents the States from imposing that quandary on anyone.

Federal preemption occurs when "it is impossible for a private party to comply with both state and federal requirements." *Albrecht*, 139 S. Ct. at 1672. A tort plaintiff's failure-to-warn claim escapes federal preemption only if the defendant drug maker could

"independently do under federal law what state law requires of it." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 621 (2011). As the district court held, and the record here shows, federal law precluded Novo from adding the specific warning the plaintiffs demanded.

The FDA's CBE regulation, 21 C.F.R. § 314.70(c)(iii), allows a branded drug maker to change a drug's label without the FDA's prior approval (subject, of course, to the FDA's later approval). A manufacturer can use the CBE process, however, only when "newly acquired information" reveals a "clinically significant hazard." 21 C.F.R. §§ 201.57(c)(6)(i), 314.70(b)(2)(iii). As defined by FDA regulations, newly acquired information "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA." 21 C.F.R. § 314.3(b).

True, the ordinary pharmaceutical preemption case usually turns on whether the FDA would have approved a label change under the CBE process. *See, e.g.*, *Wyeth v. Levine*, 555 U.S. 555, 571 (2009) ("[A]bsent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements."); *Dolin*,

901 F.3d at 813 ("[N]o reasonable jury could find that the FDA would have approved an adult-suicidality warning for Paxil under the CBE regulation.").

But when, as here, no "newly acquired information" would have allowed the manufacturer to unilaterally change the drug's label under federal law, the preemption analysis is over, and a plaintiff's claims are preempted. *See, e.g.*, *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019) (finding plaintiffs' claims preempted absent "newly acquired information that could have justified Defendants' revising the Eliquis label through the CBE regulation"); *In re Celexa and Lexapro Marketing and Sales Practices Litig.*, 779 F.3d 34, 41-42 (1st Cir. 2015) ("The CBE procedure is only available to make changes that * * * are based on 'newly acquired information.'") (citing 21 C.F.R. § 314.70(c)(6)(iii)).

In *Knight v. Boehringer Ingelheim Pharms, Inc.*, 984 F.3d 329 (4th Cir. 2021), for example, the Fourth Circuit explained that a plaintiff, to escape preemption, must show that the defendant possessed information that not only "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA"

but also shows "evidence of a causal association" between the drug and the harm. 984 F.3d at 338 (citing 21 §§ C.F.R. 314.3(b), 314.70(c)(6)(iii)(A)). Because the manufacturer possessed no such "newly acquired information," the court explained that the defendant could not unilaterally change the drug's label under the CBE process. *Id.* at 341. The plaintiffs' claims were thus preempted. *Id.*

Plaintiffs lacking newly acquired information "often ignore this essential first prong and move straight to arguing" about "clear evidence" under *Wyeth*. Arameh O'Boyle, et al., *"Newly Acquired Information" and Federal Preemption Defenses in Pharmaceutical Products Liability Cases*, American Bar Association, Practice Points (June 28, 2018) <https://bit.ly/2W0dgeK>. Although "contested brute facts will sometimes prove relevant to a court's legal determination," preemption is a matter of law and not a question of fact for the jury. *Albrecht*, 139 S. Ct. at 1679.

The plaintiffs propose an array of newly acquired evidence. But the district court, with care and precision, rightly found that none of the plaintiffs' "evidence" would permit Novo to use the CBE process because the studies in question were neither designed to evaluate pancreatic

cancer nor resulted in a pancreatic cancer event. That is, none of the information identified by the plaintiffs reveals "risks of a different type or greater severity or frequency that previously" known by the FDA. 21 C.F.R. § 314.3(b). Nor does it qualify as "reasonable evidence of a causal association" between Victoza and pancreatic cancer. 21 C.F.R. § 201.57(c)(6)(i). The MDL court's grant of summary judgment should be affirmed on that basis alone.

II. IMPOSING A DUTY TO WARN OF UNPROVEN AND SPECULATIVE RISKS WOULD ERODE THE EFFICACY OF DRUG LABELING.

When used under a physician's care, prescription drugs dramatically improve health outcomes and can even save lives. The FDA's labeling regime thus shuns "exaggeration of risk, or inclusion of speculative or hypothetical risks," that could undermine the efficacy of drug labeling. *Albrecht*, 139 S. Ct. at 1673 (cleaned up). That is why a drug label's Warnings and Precautions section must identify "clinically significant adverse reactions" and certain other safety hazards *only if* "reasonable evidence of a causal association" exists between the drug and those hazards. 21 C.F.R. § 201.57(c)(6)(i).

In other words, the FDA reserves warnings for a "discrete set" of "clinically significant" hazards serious enough to affect prescribing

decisions. FDA, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* 3 (Oct. 2011) <https://bit.ly/3gqCquB>. The FDA adopted this causal standard in part to "prevent overwarning" of potential risks that could dilute other "more important warnings" or "deter appropriate use" of the drug. 73 Fed. Reg. 49,603, 49,605-06 (Aug. 22, 2008).

No surprise, then, that the FDA has long cautioned against the perils of overwarning. Since 1979, the agency has insisted that "it would be inappropriate to require statements in drug labeling that do not contribute to the safe and effective use of the drug, but instead are intended solely to influence civil litigation." 44 Fed. Reg. 37,434, 37,435 (June 26, 1979). "If every judge and jury could fashion their own labeling requirements for drugs and medical devices," five former FDA Chief Counsels told members of Congress, the "FDA's ability to advance the public health by allowing scarce space in product labeling to the most important information would be seriously eroded." 150 Cong. Rec. 17,045, 17,403 (2004) (joint statement of former FDA Chief Counsels).

Yet the plaintiffs' preferred labeling regime, by allowing state-law demands for scientifically unjustified risk disclosures to override the FDA's own expert judgment, would invite the very overwarning dangers the FDA has sought to avoid. Under such a regime, drug makers seeking to protect themselves from "the 20/20 hindsight of juries" may conclude that they have little choice but to "pile on warnings for every conceivable adverse reaction, no matter how remote the odds." Frank Scaglione, *Resolving Drug Manufacturer Liability for Generic Drug Warning Label Defects*, 47 St. Mary's L.J. 219, 238 (2015). That would be a calamity.

First, the "resulting information overload would make label warnings worthless." *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 869 (7th Cir. 2010). Warnings on drug labels are already extensive. A study of more than 5,600 pharmaceutical package inserts found that the average drug label lists 49 potential adverse events, with one out of every ten labels containing more than 500 warnings. Jon Duke, et al., *A Quantitative Analysis of Adverse Events and "Overwarning" in Drug Labeling*, 171 Archives of Internal Med. 944, 945 (2011).

If the threat of tort liability were to compel drug makers "to list, and perhaps contraindicate, every possible risk" on drug labeling, then prescribing doctors may well "begin to ignore or discount the warnings provided." *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 816 n.40 (5th Cir. 1992). A drug label filled with speculative warnings would crowd out other vital, scientifically founded safety information. *See, e.g.*, 73 Fed. Reg. 2,848, 2,851 (Jan. 16, 2008) (unfounded statements in FDA labeling "can cause meaningful risk information to lose its significance"); H.R. Rep. No. 86-1861, at 2837 (1960), as reprinted in 1960 U.S.C.C.A.N. 2833, 2833 (speculative warnings "invit[e] indifference to cautionary statements on packages of substances presenting a real hazard of substantial injury of illness").

Second, "overwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted." *Mason v. SmithKline Beechum Corp.*, 596 F.3d 387, 391-92 (7th Cir. 2010). All medicines have risks. A doctor deciding whether to prescribe a drug must balance those risks against the drug's likely benefits. Overstating the risks can undercut a doctor's ability to make the best prescribing decision for her

patients by "discourag[ing] appropriate use of a beneficial drug." 73 Fed. Reg. at 2,851.

This danger is no abstract concern. Consider the hesitancy surrounding the COVID-19 vaccine. "Misinformation about consequences of vaccination can range from half-truths and unfounded speculations to targeted disinformation." Winfried Rief, *Fear of Adverse Effects and COVID-19 Vaccine Hesitancy,* JAMA Health Forum (Apr. 16, 2021) <https://bit.ly/3AfFAIt>. Like most decisions, health-care decisions are made by weighing potential costs against expected benefits. While costs "can span a variety of factors," a recent survey of U.S. health-care workers reveals that nearly one out of five "did not plan on receiving a COVID-19 vaccine because of concerns over adverse effects." *Id.* And when the FDA paused emergency-use authorization for the Johnson & Johnson vaccine in April 2021, vaccine hesitancy spiked. *See* Julie Wernau, *J&J Vaccine Pause Stoked Hesitancy That Threatens COVID-19 Vaccination Drive*, Wall St. J. (May 9, 2021) <https://on.wsj.com/ 3oAq1c0>.

History provides cautionary tales. For example, after new suicide-risk warnings discouraged many physicians from prescribing SSRI

antidepressants to patients aged 18 or younger, researchers found a steep drop in SSRI antidepressant use in pediatric patients and a sudden spike in pediatric suicide rates: "If the intent of the pediatric black box warning was to save lives, the warning failed, and in fact it may have had the opposite effect; more children and adolescents have committed suicide since it was introduced." Robert D. Gibbons, et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 Am. J. Psychiatry 1356, 1361-62 (2007).

The same study predicted that extending the black box warning to adults would "result in 3,040 more suicides (a 10% increase)" in one year. *Id.* at 1362. In recent years, independent clinical researchers have echoed concerns about the validity of the warning. *See, e.g.*, Michelle Fornaro, et al., *The FDA "Black Box" Warning on Antidepressant Suicide Risk in Young Adults: More Harm than Benefits?*, 10 Front Psychiatry 294 (2019).

The negative health consequences of drug-label overwarning are real and well known. To ignore these consequences is to ignore the real world in which the FDA operates and in which patients receive—or *fail*

to receive—ideal medical care. Especially when, as here, the FDA has carefully weighed the competing public health benefits and required a balanced label that ensures the continued availability of the drug therapy in question, juries should not be allowed to impose a different, "more is better" requirement under state tort law.

III. RELAXING THE RELIABILITY THRESHOLD FOR EXPERT EVIDENCE OF CAUSATION WOULD SIGNIFICANTLY HARM PUBLIC HEALTH.

The decision below should also be affirmed because the plaintiffs failed to prove general causation. Rule 702 demands that district courts exclude expert testimony that is not based on "sufficient facts or data" or "reliable principles and methods," or if the proposed witness has not "reliably applied the principles and methods to the facts of the case." Fed. R. Evid. 702. Judge Battaglia rightly did so here. His decision "must be afforded wide latitude both in deciding whether to admit expert testimony and in deciding how to test reliability." *United States v. Alatorre*, 222 F.3d 1098, 1102-02 (9th Cir. 2000). As Novo has ably shown, the plaintiffs cannot overcome that deferential standard of review here.

Nor should this Court relax Rule 702's demanding standard. Physicians routinely rely on incretin-based therapies like Victoza to

help stimulate increased insulin secretion in patients with type-2 diabetes. Since the parties' initial expert discovery in 2014, myriad bench studies, clinical trials, animal experiments, observational studies, and meta-analyses have been conducted. As the record shows—and the district court painstakingly confirmed—the cumulative body of scientific evidence reveals no causal association between incretin-based therapies like Victoza and pancreatic cancer.

From a public-health vantage, then, vindicating the district court's broad discretion in exercising its gatekeeping duty to exclude plaintiffs' unreliable expert evidence is crucial. As Justice Breyer has recognized:

> [M]odern life, including good health as well as economic well-being, depends upon the use of artificial or manufactured substances, such as chemicals. And it may, therefore, prove particularly important to see that judges fulfill their [Rule 702] gatekeeping function, so that they help assure that the powerful engine of tort liability, which can generate strong financial incentives to reduce, or to eliminate, production, points toward the right substances and does not destroy the wrong ones.

Gen. Elec. Co. v. Joiner, 522 U.S. 136, 148-49 (1997) (Breyer, J. concurring); *see also Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 678 (6th Cir. 2010) (explaining that "allowing the law to get ahead of science" would "stifle innovation unnecessarily").

"[S]imply because a person takes drugs and then suffers an injury does not show causation." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1243 (11th Cir. 2005). Many assumptions about risks of harm from taking certain drugs have been exaggerated and are overwhelmingly wrong. And yet, there are countless product-liability suits pending throughout the country—in both state and federal courts—against the manufacturers of pharmaceutical products.

Lay juries are naturally sympathetic to plaintiffs who appear to have suffered harm while using prescription drugs, and the temptation is great to indulge the *post hoc ergo propter hoc* fallacy, especially if manufacturer liability can be imposed based on a "scientific" expert's say-so. Given the sheer pace and number of such cases, rigorous gatekeeping is essential to ensure that "the powerful engine of tort liability" does not do more harm than good. *Joiner*, 522 U.S. at 149 (Breyer, J. concurring).

Without consistently enforced thresholds for the reliability of expert evidence on causation, drug manufacturers will be left with little guidance about how to structure their conduct in advance to avoid debilitating liability. Permitting flimsy, unscientific "expert" opinions to

serve as the basis for vexatious litigation imposing massive tort liability on drug manufacturers would create a strong disincentive for the continued development of innovative drugs. *See, e.g.*, *Browning Ferris Indus. of Vt., Inc. v. Kelco Disposal, Inc.*, 492 U.S. 257, 282 (1989) (O'Connor, J., concurring in part and dissenting in part) (observing that "the threat of * * * enormous awards" has convinced prescription drug manufacturers "that it is better to avoid uncertain liability than to introduce a new pill"); *Carlin v. Superior Court*, 920 P.2d 1347, 1361 (Cal. 1996) ("[T]he imposition of excessive liability on prescription drug manufacturers may discourage the development and availability of life-sustaining and lifesaving drugs."); Margaret Gilhooley, *Innovative Drugs, Products Liability, Regulatory Compliance, and Patient Choice*, 24 Seton Hall L. Rev. 1481, 1483 (1994) ("[M]edical experts have expressed concern that uncertain liability standards, coupled with litigation costs, may discourage useful drug innovation.").

For many manufacturers, the easiest way to prevent unwarranted litigation may be to avoid market participation altogether. Indeed, leading scientific organizations—such as the National Academy of Sciences and the American Association for the Advancement of

Science—have warned that permitting experts to present novel causation theories to juries "can unwittingly inject bad science into broader decisions affecting society (for example, by encouraging meritless litigation against the producers of products that in fact are safe, or, even worse, by causing the abandonment of products that might prevent injuries)." Br. for the Am. Ass'n for the Advancement of Science and the Nat'l Academy of Sciences as *Amici Curiae* in Support of Respondent, *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579 (1993) (No. 92-102), *available at* 1993 WL 13006381, at *23.

Drug manufacturers who opt to remain in the marketplace may nonetheless be forced to pass ever-increasing operating costs along to consumers in the form of significantly higher prices. *See, e.g.*, *Brown v. Superior Court*, 751 P.2d 470, 478 (Cal. 1988) (warning that "the consuming public * * * will pay a higher price for the product to reflect the increased expense of insurance to the manufacturer resulting from its greater exposure to liability"); S. Rep. No. 105-32, at 3 (1997) ("Increased product liability costs are reflected in dramatic increases in liability insurance costs. Over the last forty years, general liability

insurance costs have increased at over four times the rate of growth of the national economy.").

If, as the plaintiffs urge here, liability could be imposed even where the data shows no reliably causal link between incretin-based therapies and pancreatic cancer, the resulting "product price may reflect external costs not associated with the risks of the medication [and] distort the cost-benefit calculus faced by each consumer." Note, *A Question of Competence: The Judicial Role in the Regulation of Pharmaceuticals*, 103 Harv. L. Rev. 773, 781 (1990). Not only would that be unfair to manufacturers, but it would prove disastrous for the millions of Americans who rely on incretin-based therapies like Victoza in their life-long battle with type-2 diabetes.

CONCLUSION

The district court's judgment should be affirmed.

October 25, 2021

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I certify:

(i) That this brief complies with the type-volume limits of Fed. R. App. P. 29(a)(5) because it contains 3,711 words, excluding the parts exempted by Fed. R. App. P. 32(f).

(ii) That this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6), because it has been prepared using Microsoft Office Word 16 and is set in 14-point Century Schoolbook font.

October 25, 2021

/s/ Cory L. Andrews