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March 12, 2024

The Honorable Chief Justice Patricia Guerrero and Associate Justices
Supreme Court of California
350 McAllister Street
San Francisco, CA 94102

Re: Amicus Curiae Letter in Support of Petition for Review of *Gilead Tenofovir Cases*
San Francisco Superior Court, Case No. CJC-19-005043
First Appellate District, Division Four, No. A165558
Supreme Court, Case No. S283862

To the Honorable Supreme Court of California,

We write on behalf of amici curiae the Pharmaceutical Research and Manufacturers of America ("PhRMA"), Advanced Medical Technology Association ("AdvaMed"), Biotechnology Innovation Organization ("BIO"), and the Medical Device Manufacturers Association ("MDMA") urging this Court to grant the petition for review filed by Gilead Sciences, Inc. ("Gilead") in the above-captioned matter. The decision by the Court of Appeal imposes unfair and unworkable liability upon the life sciences industry—liability that will stifle innovation and undermine the scientific judgments of FDA in ensuring access to life-saving medicines and technologies in the United States.

Permitting liability to attach for indisputably non-defective products where a manufacturer has invented "what it knows is a safer, and at least equally effective, alternative to a prescription drug," Op. at 11, is unworkable in the life sciences industry, where companies must decide whether to proceed with development when the full scientific picture remains unclear. Manufacturers operate in the moment on limited information and must balance numerous complicated factors. Even after approval, a manufacturer of a biopharmaceutical or medical technology may never "know" that one product is "safer" and "at least equally effective" to another absent a rigorous comparative study. No jury, even with the benefit of hindsight, could reasonably discern when a manufacturer "knew" its invention was "safer and at least equally effective," triggering a duty. Because of the importance of this issue to all innovative companies, the Court should grant Gilead's petition and hear the case on the merits.

Interests of the Amicus Curiae

PhRMA is a voluntary, nonprofit association comprised of the leading biopharmaceutical research and technology companies.[1] 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 a trillion dollars in R&D since 2010, and in 2022 alone invested nearly $101 billion in discovering and developing new medicines.[2] PhRMA advocates in support of public policies that encourage the discovery of life-saving and life-enhancing new medicines.

AdvaMed is the world's largest medical technology association representing device, diagnostics, and digital technology manufacturers that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. Its more than 400 member companies span every field of medical science and range from cutting-edge startups to multinational manufacturers. AdvaMed's member companies are dedicated to advancing clinician and patient access to safe, effective medical technologies in accordance with the highest ethical standards.

BIO is the principal trade organization representing the biotechnology industry domestically and abroad. BIO has more than 1,000 members, which span the for-profit and nonprofit sectors and range from small start-up companies and biotechnology centers to research universities and Fortune 500 companies. BIO's members devote billions of dollars annually to researching and developing biotechnological healthcare, agricultural, environmental, and industrial products that cure diseases, improve food security, create alternative energy sources, and deliver many other benefits.

MDMA is a national trade association that provides educational and advocacy assistance to approximately 300 innovative and entrepreneurial medical technology companies. MDMA's mission is to promote public health and improve patient care through the advocacy of innovative, research-driven medical device technology.

This case presents a question that is critical to members of PhRMA, AdvaMed, BIO, and MDMA: can a company be held liable in hindsight for its decision to develop a particular medicine in lieu of a different pharmaceutical compound? Amici's members must decide where to devote research resources and how best to pursue regulatory approval in the face of scientific uncertainty

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[1] Pursuant to Rule 8.200(c), PhRMA, AdvaMed, BIO, and MDMA certify that no party or party's counsel authored this brief in whole or in part. No party or party's counsel made a monetary contribution intended to fund the preparation or submission of this brief, and no person or entity other than amicus curiae, its members, or its counsel made such a monetary contribution. Although Gilead Sciences, Inc, is a member of PhRMA and BIO, it has not contributed financially to the preparation of this brief.

[2] PhRMA, *2023 PhRMA Annual Membership Survey* (2023) p.3, <https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Refresh/Report-PDFs/A-C/PhRMA_membership-survey_single-page_70523_es_digital.pdf>.

and commercial reality. Decisions regarding whether to continue research on a life sciences product in its early stages—or whether to start that research at all—will be greatly impacted if liability can be imposed if the company makes the wrong prediction. PhRMA, AdvaMed, BIO, and MDMA thus have a unique interest in ensuring that a company's decision to develop one, non-defective product over another is not unfairly questioned with the benefit of hindsight.

Argument

The liability theory created by the Court of Appeal warrants this Court's review. The Court of Appeal's decision imposes a duty at a point in the development process before a company has the scientific data sufficient to make any definitive conclusion as to any new product. The Court of Appeal's ruling fails to appreciate the uncertain nature of the drug development process and how companies need to make decisions with imperfect information. Manufacturers should not be punished if it turns out with hindsight that the company could have pursued a different development path. As recognized by a range of scholars,[3] adopting such a liability framework will create a perverse and chilling effect in the life sciences industry whereby companies may refrain from investing in a newer innovative product (whether more effective or with a better safety profile) if there is the legal risk that it will be held liable retroactively for not moving more quickly to innovate beyond its current, non-defective product already on the market.

The Court of Appeal's decision fails to recognize the realities of the drug development process.

Bringing a new medicine to market is a lengthy and expensive process. Before studying a new medicine in humans, a pharmaceutical company must conduct a series of laboratory and animal studies to test how the medicine works and preliminarily 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 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).) FDA carefully reviews the IND, under which the company conducts a phased series of clinical trials, each of which must be

[3] *See, e.g.*, Richard Epstein, *How Legal Adventurism Stifles Medical Innovation*, Orange Cnty. Register (Feb. 16, 2024), <https://www.ocregister.com/2024/02/16/how-legal-adventurism-stifles-medical-innovation/>; George Priest, *California's Negligence Tort Empowers Juries, Hurts Innovation*, Bloomberg Law (Feb. 14, 2024), <https://news.bloomberglaw.com/us-law-week/californias-negligence-tort-empowers-juries-hurts-innovation>; Gary Myers, *Gilead Ruling Signals That Innovating Can Lead To Liability*, Law360 (Feb. 6, 2024), <https://www.law360.com/articles/1793143/gilead-ruling-signals-that-innovating-can-lead-to-liability>.

completed successfully 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 to complete.[4]

New medicines generally must undergo three distinct phases of clinical trials, which are the most lengthy and costly portion of the research and development process.[5] In Phase I, trials are conducted with a relatively small number of healthy volunteers in order to determine safety, tolerability, pharmacokinetics (how the drug is absorbed and metabolizes in the body), and pharmacodynamics (the drug's impact on the body). In Phase II, the drug will be tested on up to 500 participants to preliminarily assess the efficacy and dose response. During this phase, common, short-term potential side effects can be identified, and the optimal dose strength is analyzed. In Phase III, trials may enroll up to 5,000 patients or more in numerous clinical trial sites across the world. This phase typically uses randomized, controlled trials and generates rigorous, scientifically-validated data subject to strict statistical analysis demonstrating efficacy and safety risk over a longer period of time. The data generated in this phase both determines whether the medicine meets its predefined endpoints for success generally required for FDA approval, and also provides the most important data for drafting labeling to ensure proper use of the drug, including dosing instructions and potential interactions with other medicines.

If, after completing of the clinical trial program, FDA determines that the medicine has a favorable benefit-risk profile, FDA will permit a manufacturer to market the drug by approving a New Drug Application ("NDA"). (21 U.S.C. § 355(b).) The NDA 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.* § 355(b)(1).) The processes for the development and approval of biologics and certain new medical devices are similarly rigorous. (See, e.g., 21 C.F.R. § 600 et seq.; *id.* § 814.)

On average, developing a new medicine and obtaining FDA approval takes ten to fifteen years and costs $2.6 billion.[6] Through this process, the candidate medicines are culled dramatically: just one out of every 5,000 to 10,000 compounds under development, and less than

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[4] PhRMA, *Modernizing Drug Discovery, Development and Approval* (2016) p. 1 <https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/proactive-policy-drug-discovery.pdf>.

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

[6] PhRMA, *Biopharmaceuticals in Perspective: Fall 2020* (2020) p. 27 <https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/A-C/ChartPack_Biopharmaceuticals_in_Perspective_Fall2020.pdf> (hereafter *Biopharmaceuticals in Perspective*); *see also* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20 (2016).

one out of every eight medicines entering clinical trials, ultimately obtains FDA approval.[7] For example, just three new brain cancer medications achieved FDA approval between 1998 and 2019, with 122 unsuccessful attempts to develop a treatment.[8] Similarly, 268 unsuccessful attempts to develop a lung cancer treatment led to only 32 approved new medicines.[9]

The life sciences landscape is replete with uncertainty throughout the development process. Some medicines, despite promising early results, ultimately fail to meet the rigorous efficacy standards in large Phase III randomized controlled clinical trials sufficient to demonstrate the safety and efficacy of a potential new medicine. Indeed, more than half of medicines that show promise in early clinical trials will fail in Phase III clinical trials, often due to an inability to rigorously demonstrate efficacy.[10] The heartbreaking failures encountered over the last two decades in researching and developing treatments for Alzheimer's Disease perhaps present the most striking illustration.[11] By contrast, sometimes medicines exceed expectations when the Phase III results come in. The revolutionary results of the new novel oral anticoagulants turned out to provide remarkable (and unexpected) improvements over warfarin, which had been the standard of care for treatment of atrial fibrillation and related blood clotting disorders for 50 years.[12] Of special relevance here, warfarin remains available on the market, widely-used by medical professionals, and non-defective—despite the universal medical consensus, based on rigorous head-to-head clinical trials against warfarin involving tens of thousands of patients, that the new oral anticoagulants present undisputed improvements on numerous safety and/or efficacy parameters as compared to warfarin.

Science is always advancing, particularly when a company—like Gilead here—continues to invest in new research despite already having brought a life-saving product to patients. Thus,

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[7] PhRMA, *Clinical Trials—So Necessary but More Complex than Ever* (Mar. 3, 2011) <https://catalyst.phrma.org/clinical-trials-so-necessary-but-more-complex-than-ever>; *Biopharmaceuticals in Perspective*, *supra* note 6, at p. 27.

[8] *Biopharmaceuticals in Perspective*, *supra* note 6, at p. 40.

[9] *Id.*

[10] *See* Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA Internal Med. 1826 (2016); *see also* FDA, *Step 3: Clinical Research*, <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research>.

[11] *See* C. Kwon Kim et al., *Alzheimer's Disease: Key Insights from Two Decades of Clinical Trial Failures*, J. Alzheimer's Disease 87 (2022) (since 2003, 98 unique Phase II and Phase III compounds failed, compared with just two reported Phase III successes).

[12] *See* Suman Biswas et al., *Present Knowledge on Direct Oral Anticoagulant and Novel Oral Anti Coagulants and Their Specific Antidotes: A Comprehensive Review Article*, 48 Current Problems in Cardiology 2 (2023) ("The development of these new agents represents a landmark and revolutionary development in the therapy for [venous thromboembolisms].").

even for a medicine that by Plaintiffs' own admission is not defective, interested advocates after the fact can always come up with *something* the company could have done differently—another study the company could have performed or another formulation the company could have explored—or on a faster timetable.[13] After all, given the risk of failure inherent in the development of new medicines, life sciences companies often develop multiple medications in parallel, and companies must make complicated strategic decisions about where to devote resources based on limited information about which medicines may have the most promise. A company does not know with any measure of clarity during early stages of the development process—and indeed may never know with certainty—that a medicine is "safer" and "at least equally effective," and thus cannot fairly be subject to liability for decisions made at that time.

The Court of Appeal's decision harms patients by disincentivizing pharmaceutical development and stifling innovation in the life sciences.

Because of the slim chances of success for any particular medicine, biomedical companies often develop multiple medicine options in parallel, and must make resource-allocation decisions based on imperfect information. When deciding whether to invest hundreds of millions of dollars in clinical trials, companies already face extraordinary risks that the development program will fail to meet FDA's rigorous requirements for approval. Adding the possibility that every one of those decisions throughout the development process will be second-guessed years later—perhaps based on something far less than the kind of rigorous scientific data necessary to draw such a conclusion—will invariably discourage companies from investigating alternative treatments in the first instance. The Court of Appeal's decision would dangerously disincentivize biomedical research at all stages of development.

History is filled with examples of innovations involving previously FDA-approved medicines that dramatically improved public health. For example, new formulations for a malaria medicine have decreased dosing from eight daily tablets to two; the combination of two medications into a single dosage form has eased the strict treatment regimen for type 2 diabetes; and research into oral contraceptives has resulted in lower-estrogen formulations with dramatically reduced side effects.[14] On average each year, approximately two-thirds of global launches of new molecular entities involve improvements to existing molecules.[15] Further, sixty-

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[13] *See, e.g.*, Brief for the United States as Amicus Curiae Supporting Petitioner p. 25, *Wyeth v. Levine* (2009) 555 U.S. 555 (No. 06-1249) <https://www.justice.gov/sites/default/files/osg/briefs/2007/01/01/ 2006-1249.mer.ami.pdf> [noting the "post hoc imagination of lawyers" in pursuing pharmaceutical lawsuits].

[14] Steven Globerman & Kristina M. Lybecher, *The Benefits of Incremental Innovation: Focus on the Pharmaceutical Industry* (2014) pp. 46–48 <https://www.fraserinstitute.org/sites/default/files/benefits-of-incremental-innovation.pdf>.

[15] Int'l Fed. of Pharm. Mfrs. & Ass'ns, *Incremental Innovation: Adapting to Patient Needs* (2016) p. 11 fig.3 <https://www.ifpma.org/publications/incremental-innovation-adapting-to-patient-needs/>.

three percent of medications on the World Health Organization's Essential Drug Lists are follow-on innovations.[16]

These later scientific breakthroughs do not discredit earlier scientific discoveries. Scientific knowledge is ever-evolving, and later scientific discoveries often build on prior advances. California's liability framework should encourage these discoveries, not penalize researchers for continuing to improve on existing treatments. (See *Brown v. Superior Court* (1988) 44 Cal.3d 1049, 1063 [California public policy "favors the development and marketing of beneficial new drugs," so "the broader public interest in the availability of drugs at an affordable price must be considered" in deciding liability frameworks].)

The liability framework that results from the Court of Appeal's decision creates an untenable research environment for innovators, who regularly must make difficult resource allocation decisions. ***As FDA recognizes, "it is not known whether [a] potential medical treatment offers benefit to patients until clinical research on that treatment is complete."***[17] Innovators necessarily make decisions about what medicines to prioritize for development with imperfect information about clinical results and with a frequently shifting commercial landscape. Setting aside whether a company can ever be held liable for making a commercial decision not to sell a product, innovators should not be subject to potential liability whenever a different treatment turned out to be more favorable than the one they chose initially to develop.

One need only think about how this framework would play out in two real world examples:

- Company A already developed a safe and effective medicine with a favorable benefit-risk profile. The benefit-risk profile of the medicine has been established in clinical trials, and the company has secured FDA approval for the medicine. But the company knows that the medicine, like all medicines, carries risks. The company could continue research efforts to try to develop alternative treatments perhaps with comparable benefits and fewer risks, or it could leave its FDA-approved product as is. There might be a benefit to patients to develop alternative treatments but doing so would risk opening up the company to liability from users of the initial formulation under the Court of Appeal's decision. That may lead the company to make the economically rational decision not to even begin researching ways to improve its existing, FDA-approved medicine, even if that decision ultimately means that future patients may have fewer treatment options.

- Company B markets an approved medicine to treat a particular disease. Company B then develops a new molecule that shows potentially better activity fighting the target disease in preliminary drug discovery experiments prior to Phase I clinical testing. Company C, however, is already pursuing development of a medicine shown in early clinical trials to

[16] Joshua Cohen & Kenneth Kaitin, *Follow-On Drugs and Indications: The Importance of Incremental Innovation to Medical Practice*, 15 Am. J. Therapeutics 89, 90 (2008).

[17] FDA, *Conducting Clinical Trials* <https://www.fda.gov/drugs/development-approval-process-drugs/conducting-clinical-trials>.

potentially have greater efficacy or fewer side effects than the profile anticipated for Company B's new molecule, so Company B decides to reduce or cut off its investment in its new molecule. Company C's medicine turns out to fail its Phase III trials and is not approved. Only at that point, once the external commercial environment shifted, does Company B decide to increase investment and ultimately obtain approval for its new molecule. Under the Court of Appeal's ruling, Company B could be subject to liability for delaying its development of the new compound for commercial reasons.

In both of these situations, the threat of liability discourages, rather than encourages, innovation, contrary to this Court's decision in *Brown*. Without sensible protections from such an irrational liability framework, innovation will be negatively impacted and patients in need of advancing treatments will suffer. A rational liability framework should not encourage companies to abandon development of what might otherwise have turned out to be beneficial medicines based on the risk that a jury down the road might conclude in hindsight that the company should have allocated more resources to the project, at some earlier point in time.

Conclusion

The Court of Appeal's decision will result in a chilling effect on the life sciences industry, which will harm public health. Accordingly, amici PhRMA, AdvaMed, BIO, and MDMA respectfully requests that the Court grant Gilead's petition for review and hear the case on the merits.

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