No. 13-180

In the Supreme Court of the United States

W. SCOTT HARKONEN,
Petitioner,

v.

UNITED STATES,
Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

BRIEF OF *AMICUS CURIAE* ABIGAIL ALLIANCE FOR BETTER ACCESS TO DEVELOPMENTAL DRUGS IN SUPPORT OF PETITIONER

DANIEL MERON
Counsel of Record
KATHERINE I. TWOMEY
LATHAM & WATKINS LLP
555 11th Street, NW
Suite 1000
Washington, DC 20004
(202) 637-2200
daniel.meron@lw.com

Counsel for Amicus Curiae

QUESTIONS PRESENTED

(1) Whether a conclusion about the meaning of scientific data, one on which scientists may reasonably disagree, satisfies the element of a "false or fraudulent" statement under the wire fraud statute, 18 U.S.C. § 1343.

(2) Whether applying 18 U.S.C. § 1343 to scientific conclusions drawn from accurate data violates the First Amendment's proscription against viewpoint discrimination, or renders the statute, as applied, unconstitutionally vague.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTE

OTHER AUTHORITIES

TABLE OF AUTHORITIES—Continuted

Page(s)

TABLE OF AUTHORITIES—Continuted

Page(s)

INTEREST OF *AMICUS CURIAE*[1]

The Abigail Alliance for Better Access to Developmental Drugs ("Abigail Alliance") is a nonprofit organization committed to increasing access to developmental drugs that combat cancer and other serious and life-threatening illnesses. Abigail Alliance was founded in 2001 by Frank Burroughs in memory of his daughter, Abigail, an honors student at the University of Virginia who died of cancer at age 21 on June 9, 2001. Abigail was denied access to new cancer drugs that her oncologist believed could save her life, but which were still in clinical trials. In response to this and the numerous other patients who have been denied access to experimental drugs, Abigail Alliance has advocated for expanded access and compassionate use programs before Congress, the U.S. Food and Drug Administration Drug ("FDA"), and in court, and for reform of the FDA drug approval process and clinical trial design.

Its members include patients that are suffering from terminal and other serious illnesses and people who have lost loved ones to such illnesses. For many of these patients, their best chance of survival is to obtain access to certain drugs with a record of clinical success

---

[1] Pursuant to Supreme Court Rule 37.2(a), *amicus* timely informed all parties of its intent to file a brief in support of Dr. Harkonen's petition for certiorari. All parties consent to the filing of this brief. Pursuant to Supreme Court Rule 37.6, *amicus* states that no counsel for a party authored this brief in whole or in part; and no such counsel or any party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than *amicus* and its counsel, made a monetary contribution intended to fund the preparation or submission of this brief.

in preliminary testing, but which have not yet been approved by the FDA.

Abigail Alliance has an interest in this case because the criminalization of speech about developmental drugs will halt development of drugs and create an additional barrier for patients seeking access to potentially life-saving drugs. This prosecution will discourage researchers from publicizing preliminary results or expressing judgments that are not widely held or differ from government scientists, which will seriously constrain the flow of information to patients and physicians about potentially effective treatments.

SUMMARY OF ARGUMENT

The Ninth Circuit's decision allows the government to *criminalize* a doctor's expression of a scientific view simply because the view departs from the government's own view. It will significantly limit the reporting and exchange of non-government sanctioned interpretations of the results of clinical trials, and it threatens to end meaningful scientific debate in medicine.

Dr. Harkonen's conviction was based on statements in a press release that the Actimmune trial "demonstrat[ed]" a survival benefit in idiopathic pulmonary fibrosis (IPF) patients and that it "[r]educes [m]ortality by 70% in [p]atients with [m]ild to [m]oderate [d]isease." App. 26a-27a. It is undisputed that the data presented in the press release were accurate. *See* Pet. 2. As the press release stated, in the overall population, 40% more patients who received Actimmune survived than did patients who received a

placebo, with a p-value of 0.084.[2] App. 27a. And of the 254 patients with mild to moderate disease, 70% more patients who received Actimmune survived than did patients who received a placebo, with a p-value of 0.004. *Id.*

The government's theory at trial, which the Ninth Circuit upheld on appeal, was that Dr. Harkonen's statements were false because the primary endpoint—survival—of the clinical trial was not statistically significant at a p-value of 0.05 and the subgroup analysis of patients with mild to moderate disease, while statistically significant, was not meaningful because it was a retrospective analysis. Relying on the dogmatic and extremely conservative views of four scientists, the government argued to the jury that those scientists' rejection of a particular form of statistical analysis established that the statements were false, *see, e.g.*, ER1601-02, and that their expression of that view to Dr. Harkonen established that he knew the statements were false, *see, e.g.*, ER1616, 1619.[3]

The Ninth Circuit upheld that theory on appeal, finding that the conviction was supported by sufficient evidence. App. 3a-4a. The court then rejected Dr. Harkonen's First Amendment challenge by

---

[2] As explained in Dr. Harkonen's petition, a p-value is a statistical calculation of the likelihood that the observed result would have occurred randomly (*i.e.*, if the drug caused no effect). *See* Pet. 5 n.2. Thus, a lower p-value gives a scientist greater confidence that the drug produced the effect.

[3] "ER" refers to the Excerpts of Record and "SER" refers to Supplemental Excerpts of Record from *United States v. Harkonen*, Nos. 11-10209, 11-10242 (9th Cir. filed Oct. 31, 2011, Mar. 30, 2012).

"defer[ring]" to the jury's findings, which it determined satisfied the constitutionally required "independent review" of the record. *Id.* at 4a-5a.

The Ninth Circuit's decision is astounding. It condones the criminal prosecution of a doctor's expression of a scientific view—the interpretation of clinical trial results—simply because the view departs from the government's own view. Scientific speech about matters of public concern is at the core of the First Amendment. *See, e.g.*, *Roth v. United States*, 354 U.S. 476, 484 (1957); *Keyishian v. Bd. of Regents*, 385 U.S. 589, 603 (1967); *Snyder v. Phelps*, 131 S. Ct. 1207, 1215 (2011). And the First Amendment absolutely forbids punishing speech because it expresses a particular view. *See, e.g.*, *West Va. State Bd. of Educ. v. Barnette*, 319 U.S. 624, 641-42 (1943); *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2664 (2011).

As Dr. Harkonen's petition for certiorari explains, this Court's review is warranted because the Ninth Circuit's decision is a dramatic departure from this Court's precedents and decisions of other circuits. *See* Pet. 15-21. Review is also warranted because Dr. Harkonen's conviction violates fundamental First Amendment and Due Process protections. *Id.* at 21-31.

Abigail Alliance submits this brief to further explain the exceptional importance of these issues to the public. The Ninth Circuit's decision will have dire consequences for doctors and patients by chilling the scientific debate that is necessary for the advancement of science. It will be especially detrimental to terminally-ill patients who suffer from diseases that have no cure. Often, the only hope for these patients is experimental treatments. The Ninth Circuit's decision threatens to cut off the flow of information about such

treatments by muzzling doctors who express views about the safety and effectiveness of medical treatments that do not fully line up with the rigid scientific methods put forth by some government scientists.

At no time has open and unfettered debate regarding how we obtain, evaluate and interpret clinical and medical data been more important than it is now. A rapidly expanding knowledge of the biology of disease coupled with equally rapid advances in the technology required to design targeted treatments, is transforming medical science. By its own admission, FDA is lagging behind the science it regulates and struggling to catch up. The conventions advanced by the prosecution as expert opinions intended to establish that Dr. Harkonen's interpretation fell outside the bounds of defensible science, are themselves being discredited. New underlying medical knowledge shows that failing to accept insights gained from subset analyses, whether pre-specified or not, is slowing and even preventing the arrival of new, better classes of medicines for serious and life-threatening diseases, and dramatically slowing the rate of medical progress.

ARGUMENT

THE QUESTIONS PRESENTED ARE EXCEPTIONALLY IMPORTANT

The Ninth Circuit's decision will have particularly harmful consequences for doctors and patients because it threatens to cut off scientific debate. If scientists cannot draw conclusions based on retrospective subgroup analyses or effects they observe that were not predefined endpoints, then doctors and scientists—

at least those employed or retained by the drug manufacturer, and thus usually the experts with the best information—will not even be able to *talk* about the potential for a drug to treat a certain strain or stage of an illness or to have a different effect than the study was designed to test.

These consequences are particularly damaging for terminally-ill patients seeking experimental treatments. The expert opinions presented by the prosecution, and supported by certain FDA reviewers, have caused a powerful, built-in bias for years-long delays in the delivery of new, safe and effective, life-extending medicines to patients who need them to remain alive. Instead, these patients die waiting for a particular, pre-specified p-value to be produced from one or more Phase III randomized controlled trials that do little more than ask and answer questions already asked and answered in earlier, less statistically-perfect, but medically and scientifically adequate Phase I and II clinical trials. The cost in human pain and suffering has been enormous, and will continue if *speech* about what constitutes sufficient evidence for drawing conclusions about the usefulness of new medicines must comply with the dogmatic position presented at trial.

Furthermore, if a doctor cannot opine that a drug has demonstrated a benefit for a patient or group of patients without meeting the supposedly "magical" number of a p-value of 0.05, then there will be no room for personalized medicine. And for rare diseases that are challenging to diagnose, it can be difficult to design a study that generates results at this level of significance. But that does not indicate that the drug is not helpful for certain patients with the disease (*e.g.*, who process the drug in a particular way), or who have

a particular form of the disease (*e.g.*, "rapidly progressing"). Even if the FDA were to always require a p-value of 0.05 for drug *approval*, the communication of results with a higher degree of uncertainty may still be valuable, especially for patients that face a terminal illness for which there is no known cure.

There are numerous examples of drugs that do not produce clinical trial results that are statistically significant at the 0.05 level based on pre-defined endpoints, but nonetheless are effective and life-saving treatments. Indeed, even the FDA itself sometimes retreats from the dogmatic view the government put forth at trial and has approved drugs without clinical trial data that meet those rigid standards.[4] Below, are only a few of many examples of such situations.

1. When the drug Provenge was tested as a treatment for advanced prostate cancer, survival was not an endpoint in the initial trial (but the positive results were statistically significant) and survival was only a secondary endpoint in the second trial (but the results were not statistically significant). ER2568. Based on these two studies, an FDA advisory panel voted to recommend approval of Provenge as providing "substantial evidence" of a survival advantage. Dr. Fleming—the government's expert in this case—wrote a letter to the director of FDA opposing FDA approval based on the same statistical

---

[4] The FDA Director of the Center for Drug Evaluation and Research, Janet Woodcock, has even publicly disavowed such inflexible positions. *See, e.g.*, David Pittman, *FDA Rethinking Personalized Drug Trials*, MedPage Today (May 22, 2013), http://www.medpagetoday.com/PublicHealthPolicy/ClinicalTrials/39330.

principles he advocated in this case, even drawing a specific parallel to the drug at issue here. ER2568-69. The FDA followed Fleming's advice and did not approve the drug until three years later when another trial demonstrated a statistically significant 21% survival advantage, which was comparable to the non-significant 22% survival advantage measured in the previous study. ER2569.

The result of Fleming's position—which a scientific panel of experts had disagreed with—was that *thousands of patients were deprived of this life-saving treatment for three years.* The history of Provenge illustrates the drastic potential consequences of going even further and criminalizing the release of information to doctors and patients based on rigid scientific views.

2. The approval history of the chemotherapy drug Eloxatin, a drug developed for the treatment of colorectal cancer, involved similar delay for similar reasons. Sanofi, the drug's sponsor, withdrew the drug application after the FDA took a negative position against approval in an Oncologic Drugs Advisory Committee (ODAC) in March 2000. *See* U.S. Department of Health & Human Services, FDA, Center For Evaluation And Research, FDA Medical Officer and Biometrics Review of a New Drug Application at 13, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-492_Eloxatin_medr_P1.pdf (last visited Sept. 6, 2013) ("FDA Medical Officer and Biometrics Review"). Sanofi submitted its application based primarily on the results of four randomized controlled clinical trials testing Eloxatin in combination with other drugs, and four non-randomized trials of the drug used alone. *See*

Sanofi-Sythelabo Research: Oncologic Drug Advisory Committee, *Briefing Document of the Effectiveness and Safety of Oxaliplatin in Combination with 5-FU-Based Chemotherapy in the Treatment of Advanced Colorectal Cancer* at 4, 27 (Feb. 14, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3592b1.htm ("ODAC Briefing Document"). Sanofi and its experts concluded that the drug was shown to be safe and effective as a first-line treatment (meaning the first treatment regimen a patient receives after diagnosis) in the pivotal randomized controlled trial, supported by corroborating evidence from other trials. *See id.* at 5, 14-44. Sanofi's conclusions were in part based on statistical analyses to take into account prognostic factors that were not pre-specified in prior communications with the FDA—sometimes referred to as post-hoc analyses.

At the time of the ODAC meeting, according to the American Cancer Society, about 56,000 people were dying from colorectal cancer each year in the US. *See* American Cancer Society, Inc., *Estimated New Cancer Cases and Deaths by Sex for All Sites, United States, 2000*, Cancer Facts & Figures at 4 (2000) ("Cancer Facts & Figures 2000"). Existing therapies were capable of extending the lives of some patients, on average, by only two to three months. Average survival for patients with advanced disease (termed Stage IV), based on treatment with FDA-approved therapies at the time, was about one year. Stage IV colorectal cancer was then, and remains today, incurable for nearly all persons diagnosed.

Despite an enormous unmet need for new therapies, the FDA picked apart Sanofi's application based on rigid statistical rules and policies—similar to those

advanced by the prosecution in this case. The FDA took the position that Sanofi's data did not demonstrate *survival* based on the FDA's preferred statistical analysis method (the log rank test). *See* U.S. Department of Health & Human Services, FDA, Oncologic Drugs Advisory Committee 65th Meeting Tr. at 120-26 (Mar. 16, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Oncologic%20Drugs%20Advisory%20Committee ("ODAC Tr."); *see also* FDA Medical Officer and Biometrics Review at 12. Instead, multiple clinical trials showed that Eloxatin controlled progression of the cancer for a longer period and shrank patients tumors by a greater degree than existing approved drugs. *See* ODAC Briefing Document at 43-44. Eloxatin in combination with two already approved drugs called 5FU and leucovorin was clearly active in the treatment of colorectal cancer, clearly superior in two of the three primary measures of efficacy for treatment of colorectal cancer (delayed progression and response rate), and likely superior in extending the lives of terminal colorectal cancer patients. *Id.*

Despite this evidence and direct questioning from FDA advisory committee members on whether the delayed progression could serve as the basis for approval, the FDA refused to approve the drug. *See* ODAC Tr. at 140-41, 157-59, 163-64. The FDA then sent a warning letter to Sanofi, claiming that it was illegal for Sanofi to share the results of its laboratory tests on colorectal cancer cell lines because the communication "clearly suggests that Eloxatin is effective for the treatment of colon cancer." *See* Letter from Regulatory Review Officer of FDA to Mark Moyer of Sanofi-Synthelabo at 2 (June 22, 2000),

available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/ucm164551.htm. As a result, the dissemination of scientific facts about Eloxatin was so muted that many practicing oncologists in the US assumed the drug did not work, and did not even recommend pursuing access in a clinical trial or the compassionate access program.

At the time of the FDA's disapproval of Eloxatin, the drug was approved as a first-line treatment for colorectal cancer in Europe. *See* ODAC Briefing Document at 4. Because FDA insisted on dogmatic inflexibility, it made a lethal mistake in rejecting a safe and effective drug capable of improving and extending the lives of people afflicted with the third leading cancer killer in the US.

Over two years later, and more than 120,000 deaths from colorectal cancer from the date of the ODAC meeting, the FDA approved Eloxatin. *See* Cancer Facts & Figures 2000 at 4; American Cancer Society, Inc., *Estimated New Cancer Cases and Deaths by Sex for All Sites, United States, 2001*, Cancer Facts & Figures at 5 (2001); American Cancer Society, Inc., *Estimated New Cancer Cases and Deaths by Sex for All Sites, United States, 2002*, Cancer Facts & Figures at 4 (2002). In the approval letter, the FDA stated that Eloxatin in combination with other drugs "was shown to shrink tumors in some patients and delay resumed tumor growth," but it acknowledged that there was "no data on the effects of the combination on survival." *See* Press Release, FDA, FDA Approves Eloxatin For Colorectal Cancer (Aug. 12, 2002) (on file with author). The FDA thus retreated from its rigid adherence to

dogmatic convention, similar to the statistical rules advocated by the prosecution in this case.

The FDA's delay in approving Eloxatin was a result of adherence to rigid statistical rules requiring statistical significance for a pre-defined primary endpoint of survival. That decision prevented US patient access to the most effective drug for the treatment of colorectal cancer in existence at the time for more than two years, and undeniably caused the premature deaths of tens of thousands of US patients denied access to the drug and its benefits. The prosecution in this case could be even more damaging because it *criminalizes* pure speech that conveys factually accurate information but does not conform to the government's rigid statistical rules. It is imperative for medical progress that experts be free to conduct analyses that may differ from those selected by the government and that open disagreement about the meaning of scientific data is allowed to occur.

3. Recently, the FDA approved Cetuximab for use as a first-line treatment for patients with certain mutations of colorectal cancer "based on retrospective analyses" of "patient subsets." *See* Press Release, FDA, Cetuximab in Combination with Folfiri/Therascreen, *available at* http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm310933.htm (last updated July 9, 2012). These analyses compared tumor marker data conducted on tissue samples after the initial trial was completed. They are comparisons of subgroups within the trial population that were not pre-specified. This approval again represents a retreat from the dogmatic statistical views that were the basis for Dr. Harkonen's conviction. It is a recognition by the government that

retrospective analyses of subgroups can provide meaningful information regarding the safety and effectiveness of a drug.

* * *

The Ninth Circuit's decision upholds a conviction that criminalizes pure speech. It will place an additional—and possibly insurmountable—barrier between terminally-ill patients and potentially lifesaving drugs. The FDA approval process and outdated clinical trial requirements already make it extremely difficult for patients to access drugs that their doctors believe would be beneficial. If scientists and doctors cannot freely discuss the benefits of new uses of approved drugs, then even that limited access will be eliminated. The communication of admittedly uncertain information is still critically valuable for patients—like IPF patients—that face a terminal illness for which there is no known cure and the standard treatment improves lung function in less than 30% of patients. Indeed, Actimmune is still used abroad to treat IPF and research continues to show that it is an effective treatment for some patients. *See* ER2631-32; SER4983. The First Amendment does not allow the government to *criminally* punish the dissemination of potentially lifesaving scientific information.

CONCLUSION

The petition should be granted.

Respectfully submitted,

DANIEL MERON
Counsel of Record
KATHERINE I. TWOMEY
LATHAM & WATKINS LLP
555 11th Street, NW
Suite 1000
Washington, DC 20004
(202) 637-2200
daniel.meron@lw.com

Counsel for Amicus Curiae *Abigail Alliance for Better Access to Developmental Drugs*

September 9, 2013