No. 13-

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

PETITION FOR A WRIT OF CERTIORARI

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QUESTIONS PRESENTED

The Ninth Circuit upheld a wire fraud conviction for the issuance of a press release about a pharmaceutical clinical study. The only statements charged as false expressed a conclusion, *i.e.*, that the data demonstrated that the drug benefitted patients. The government conceded that the data in the press release, which showed that far more patients survived on the drug than on placebo, were accurate. The government challenged as false only the inference that the drug (and not random chance) caused that beneficial outcome.

The questions presented are:

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.

PARTIES TO THE PROCEEDING

All parties to the proceeding are listed in the caption.

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PETITION FOR A WRIT OF CERTIORARI

Petitioner W. Scott Harkonen respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Ninth Circuit.

OPINIONS BELOW

The opinion of the court of appeals is unpublished, but is available at 510 F. App'x 633, and is reproduced at Pet. App. 1a-8a. The district court's decision denying the pre-trial motion to dismiss the indictment is unpublished and is reproduced at Pet. App. 55a-81a. That court's decision denying the post-trial motion to dismiss the indictment, for acquittal, or for a new trial is unpublished and is reproduced at Pet. App. 9a-54a.

JURISDICTION

The judgment of the court of appeals was entered on March 4, 2013. Pet. App. 1a. A timely petition for rehearing en banc was denied on May 7, 2013. Pet. App. 82a. This Court has jurisdiction pursuant to 28 U.S.C. § 1254(1).

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

This case involves the First Amendment, Due Process Clause, and 18 U.S.C. § 1343, reproduced at Pet. App. 83a.

STATEMENT OF THE CASE

This case has drawn national attention because the government has criminalized the expression of a reasonable scientific opinion. Harkonen, a physician, researcher, and former CEO of InterMune, Inc., was

convicted on one count of wire fraud. His conviction stemmed solely from the issuance of a single press release. The press release reported the preliminary results of a randomized, double-blind, placebo-controlled clinical trial, "the 'gold standard'" for clinical trials. Pet. App. 15a. The press release stated that study results demonstrated that a prescription medication, Actimmune, provided a survival benefit to patients with idiopathic pulmonary fibrosis ("IPF"). Pet. App. 84a (original press release reproduced at ER1906-09).

Harkonen's conviction is extraordinary because the "Government has always agreed that there was *no falsification of data here, so that fact is not in dispute*."[1] ER1670 (emphasis added); see ER1710-11. The government concedes that 40% more patients who received Actimmune survived than did patients who received a placebo and that, in a large subgroup of patients with mild-to-moderate IPF, 70% more survived. The results for the study's pre-specified primary endpoint, however, were not "statistically significant" (*i.e.*, the statistical calculation known as a "p-value" exceeded the pre-set target of 0.05). All this, and much more, is in the press release. The government contended, however, that because the study failed to meet its primary endpoint, the study itself was a failure, and the remarkable survival data "at best only '*suggested*'" a survival benefit, but did not *demonstrate* one. ER2497. It is this alleged *"falsification of the conclusions that could be drawn* from the data, that was what the trial was all about." ER1670 (emphasis added).

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[1] Excerpts of Record ("ER") and Supplemental Excerpts of Record ("SER") are from *United States* v. *Harkonen*, Nos. 11-10209 & 11-10242 (9th Cir. filed Oct. 31, 2011, Mar. 30, 2012), ECF Nos. 27, 63.

No federal fraud prosecution should ever be "all about" the conclusions drawn from concededly accurate data, at least where, as here, no law mandates adherence to the government's viewpoint, and no scientific consensus exists on the issue. The fraud laws do not apply to such scientific conclusions, and any prosecution of them violates the First Amendment and the Due Process Clause.

The constitutional violations here are particularly stark. After Harkonen's jury agreed with the prosecutors' "p-value theory" of scientific inference, the Solicitor General filed a brief urging this Court to *reject* that same theory, *i.e.,* that statistical significance determines scientific truth. Instead, the Solicitor General explained, "[s]tatistical significance is a limited and non-exclusive tool for inferring causation," and "a determination that certain data are not statistically significant . . . *does not refute* an inference of causation." Brief for the United States as *Amicus Curiae* at 13-14, *Matrixx Initiatives, Inc.* v. *Siracusano*, 131 S. Ct. 1309 (2010 (emphasis added).

A government witness and former federal medical researcher (SER1326-27) conceded this at Harkonen's trial. He testified that there can be "a lot of vigorous debate" about study data and "the conclusions that one ought to draw from those data," and admitted that the differing conclusions drawn from the data here reflected an "academic debate" for which "there wasn't an obvious right or wrong." ER1085-86.

In this country, "the conclusions that one ought to draw from . . . data" (*id.*) are for scientists to debate, not for the government to prosecute as wire fraud. This Court established that principle over a century ago in *American School of Magnetic Healing* v. *McAnnulty*, 187 U.S. 94 (1902). There, the Court limited the materially identical language of the civil

mail fraud statute to "cases of actual fraud in fact, in regard to which opinion formed no basis." *Id.* at 106. In subsequent criminal and civil cases alleging false or fraudulent scientific conclusions, most recently in *ONY, Inc.* v. *Cornerstone Therapeutics, Inc.*, No. 12-2414-cv, 2013 WL 3198153 (2d Cir. June 26, 2013), the courts of appeal and this Court have followed *McAnnulty*'s principle. By treating *McAnnulty* as a dead letter, the Ninth Circuit's decision sweepingly expands the scope of the federal fraud statutes, creates conflicts with other circuits concerning the constitutional limits on the imposition of liability for scientific interpretation, and validates blatant viewpoint discrimination without adequate notice of what is proscribed. The intended chilling effects of this extraordinary decision warrant review now.

1. The press release announced the preliminary results of a Phase III study, conducted at 58 medical centers world-wide. The study was by far the largest ever conducted for a treatment for IPF, a rare lung disease with a median survival time of only two to three years. The study followed a Phase II study on Actimmune, published in the *New England Journal of Medicine*, which was the first controlled study of any treatment to show "substantial improvements in the condition" of the IPF patients. ER2001.

The press release was issued on August 28, 2002, by InterMune, a public biotech company that sponsored the study. The headline stated: "InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF"; the subtitle stated: "Reduces Mortality by 70% in Patients with Mild to Moderate Disease." Pet. App. 84a. The opening paragraph stated that the "preliminary" data "demonstrate a significant survival benefit in patients with mild to moderate disease randomly

assigned to Actimmune versus control treatment (p=0.004)." *Id.*

Much other information, all accurate, followed the headlines. The opening paragraph stated, and a later sentence repeated, that the results on the study's primary endpoint, an approximately ten percent improvement in survival without progression in disease severity, were not statistically significant.[2] Pet. App. 84a-86a.

The press release also provided the results for survival alone. *Forty percent more* Actimmune patients survived the trial compared to patients given a placebo; the p-value for this result was 0.084. Pet. App. 86a. For a large subgroup (more than three-fourths of those studied) who began the study with mild-to-moderate IPF, the relative survival benefit was 70% and the associated p-value was 0.004. *Id.* These Phase III survival results were consistent with those of the long-term follow-up of the prior Phase II study, in which nearly all the Actimmune patients, but not the control group, survived: the "Kaplan Meier estimate of survival at five years was 77.8% and 16.7% in the Actimmune and control groups, respectively (p=0.009)." *Id.* at 86a-87a.

Dr. Ganesh Raghu, the lead investigator of both the Phase III study and the long-term follow-up on Phase II, was quoted saying that the "'mortality benefit'" was "'very compelling'" and Actimmune "'is the first

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[2] A p-value is a statistical calculation of the likelihood that the observed result (or one more extreme) would have occurred randomly if, in reality, the drug caused no effect. A result with a p-value of 0.05 means that, if the drug truly has no effect, then the probability that the study would have randomly generated the observed result (or one more extreme) is only 5%; the 5% figure is conventional, but arbitrary. ER2560, 2575.

treatment ever to show any meaningful clinical impact in this disease in rigorous clinical trials.'" Pet. App. 85a. Dr. James Pennington, InterMune's Executive Vice President of Clinical and Medical Affairs, said the two studies provide a "'compelling rationale for [the] consideration of Actimmune for the treatment of patients with this disease.'" *Id.* at 87a. Dr. Harkonen said:

> "We are extremely pleased with these results, which indicate Actimmune may extend the lives of patients suffering from this debilitating disease . . . . Actimmune is the only available treatment demonstrated to have clinical benefit in IPF, with improved survival data in two controlled clinical studies. We believe these results will support use of Actimmune and lead to peak sales in the range of $400-$500 million per year, enabling us to achieve profitability in 2004 as planned."

Id. at 85a.

The press release also stated that FDA had not approved any treatment for IPF, and nowhere claimed that FDA would approve Actimmune for IPF. Pet. App. 90a. It announced that InterMune would "discuss these results" on a conference call with analysts and investors that morning at 9:00 a.m. EDT. *Id.* at 85a, 88a. It also stated that "[t]hese data will be presented in more detail" at the annual European Respiratory Society ("ERS") conference in Stockholm on September 15, 2002, and at the annual American College of Chest Physicians conference in San Diego in November 2002. *Id.* at 88a.

The press release reported results on one other secondary endpoint (dyspnea) but not on seven others. It did not state that the "mild-to-moderate

subgroup" was not pre-specified in the study's statistical analysis plan. The survival p-values were not adjusted to account for the study's multiple endpoints (the study's statistical analysis plan, like most, did not require such adjustments). ER2281-94. Such facts and much other information were provided in the next days and month to investors and analysts, to investigators at the medical centers, at public presentations, at the ERS conference, and to FDA reviewers. *E.g.*, ER1917-18, 2345-2402, 2188-2204, 2623-29, 2653-55, 2763-82.

2. On March 18, 2008, the indictment charged Harkonen with wire fraud in violation of 18 U.S.C. § 1343, and misbranding of Actimmune in violation of 21 U.S.C. §§ 331(k), 333(a)(2) & 352(a). The jury acquitted Harkonen of misbranding.[3] With respect to wire fraud, the indictment alleged that Harkonen devised a scheme to "obtain money and property by means of materially false and fraudulent pretenses" to "induce doctors to prescribe, and patients to take, Actimmune for IPF." ER221. The indictment contained no allegation, however, that Harkonen personally and directly profited from the release (*e.g.*, through sales of stock).

Instead, it alleged that the Press Release "contained false and misleading information regarding Actimmune and falsely portrayed the results as establishing that Actimmune helped IPF patients live longer." *Id.* It cited the headline ("InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF") and the subheading ("Reduces Mortality by 70% in Patients with Mild to Moderate Disease") as the "false and misleading" statements. ER221-22.

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[3] The district court had jurisdiction under 18 U.S.C. § 3231.

The indictment also asserted that Harkonen knew the headlines were false because, in a phone call the day before the press release issued, two members of "FDA['s] medical review staff" told Harkonen and others that, in their personal view, the "data were inconclusive" and "would not be enough to get FDA approval for Actimmune to treat IPF, and that further study would be needed to determine whether Actimmune was effective for treating IPF." ER220; see ER509-10. This phone call allegedly put Harkonen on notice that the study "failed to show that Actimmune was effective in treating IPF." ER219.

3. Harkonen moved to dismiss the indictment because the charged statements are scientific opinions protected by the First Amendment. He submitted a biostatistician's declaration that the press release was "true and not misleading." ER2490-94 ¶3. He submitted reports published *one day* after the press release stating that medical experts found the survival data from the study "compelling and supportive of continued utilization of Actimmune" for IPF, and did so notwithstanding their awareness of the failure on the primary endpoint *and* the retrospective nature of the subgroup analysis. *E.g.*, Pet. App. 91a. One report noted that there was "reason to believe" FDA might approve Actimmune for IPF based on "the existing data set" because of "regulatory precedent," namely "FDA approval of Glaxo's Coreg" where mortality was not a pre-specified endpoint and there was "borderline" statistical significance on the primary endpoints.[4]

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[4] Ex. 15, at 4, Topel Decl., No. 3:08-cr-00164 (N.D. Cal. filed Mar. 23, 2009) (Dkt. 89).

The district court denied the motion, holding that a company press release is commercial speech and a jury should decide whether it is fraudulent. Pet. App. 65a-72a. The court rejected Harkonen's argument that "a finding of fraud is barred here because the press release contains statements of scientific opinions and perspectives about the meaning of the clinical data." *Id.* at 69a. The court held that if a jury credited the FDA reviewer's scientific viewpoint, Harkonen's statements would be false. *Id.* at 69a-70a.

4. At trial, the government pressed its theme that Harkonen knowingly defied "FDA's" scientific views. *E.g.*, ER1616-18. The government opened with the testimony of Dr. Marc Walton, an FDA medical reviewer who told InterMune the study results were inconclusive. The government next presented a biostatistics professor and "special FDA employee," Dr. Thomas Fleming, who chaired the study's Data Safety Monitoring Board, and who sent InterMune a letter strongly criticizing the press release as misleading. Other government witnesses included two former InterMune employees, Drs. Michael Crager and Steven Porter, a biostatistician and medical doctor respectively. Each expressed the view that if results on a study's primary endpoint are not statistically significant, then no conclusions about whether the drug caused an effect may be drawn, and "all other analyses arising out of that study, including analysis of secondary endpoints," are only "'exploratory.'" See Pet. App. 21a.

Citing this testimony, the government argued in closing that the study "failed." ER1601. The study's "only meaningful p-value" is for the primary endpoint, which "was 0.5," and that means "you can't draw any conclusions from this trial." ER1602. It

therefore was "just false," the prosecutor argued, to conclude "that Actimmune . . . has a survival benefit." ER1601.

5. Harkonen's counsel pointed to admissions that the personal views of an FDA reviewer on a phone call are not those of FDA, and that no rule or regulation establishes the prosecution's primary-endpoint/p-value theory of scientific inference. ER429-30, 514. No witness testified that the theory was universally accepted in the scientific community. Several government witnesses conceded that there can be "a lot of vigorous debate" about study data and "the conclusions that one ought to draw from those data." ER1085; see also ER834 (Raghu); ER507-08 (Walton).

Other government witnesses admitted that, in 2002, their view was that the study was "successful" and supported a finding of a "positive survival effect." *E.g.*, ER787, 2403 (Raghu); ER1928 (Crager). Long after Harkonen left InterMune, Porter approved InterMune's Final Clinical Study Report to FDA, which stated that a "stronger survival benefit was demonstrated" in the subgroup of patients with mild-to-moderate IPF. ER2303. At trial, Porter confirmed that this Report accurately concluded that the subgroup analysis "'showed a survival benefit'" (ER 1023-24, 2410, 2416); Porter viewed the likelihood that Actimmune *caused* that benefit as "65 percent" (ER1057-58).

6. Harkonen moved for acquittal under the First and Fifth Amendments and alternatively for a new trial. Citing and quoting *McAnnulty*, Harkonen argued that the evidence established that the challenged conclusions were at least subject to dispute by reasonable minds, and thus outside the wire fraud statute.

a. On July 27, 2010, the district court denied the post-trial motions. Pet. App. 54a.

The court acknowledged that "a number of witnesses who testified, including Crager . . . agreed . . . that the data demonstrated a survival benefit." Pet. App. 33a; see also *id.* at 33a n.3 (describing evidence). Ignoring *McAnnulty* altogether, however, the court stated that "simply because numerous individuals may have repeated a fraudulent characterization of the data from the [study] does not make that characterization less false or fraudulent." *Id.* at 33a.

The Court said it "need not expend much energy" on Harkonen's First Amendment arguments because it is "well settled that the First Amendment does not protect fraud." Pet. App. 40a (quotations omitted). The court explained that testimony supported the government's theory of falsity because it showed that "a p-value of 0.05 is somewhat of a magic number" above which "the results are generally considered unreliable and not statistically significant." *Id.* at 19a.

The court rejected Harkonen's due process challenge as "simply ludicrous" because all are on notice that it could be a crime to "lie[] in a press release about the success of a clinical trial for a drug that might have sales as high as $500 million per year." Pet. App. 42a. The court permitted the jury to infer that Harkonen knew the statements in the press release were false because FDA officials had told him the data were inconclusive (*id.* at 35a) and because he knew the subgroup highlighted in the press release was not pre-specified; the jury also could infer an intent to defraud from Harkonen's "financial motivation" as InterMune's CEO. *Id.* at 36a.

7. At sentencing, the government attributed all subsequent increases in Actimmune prescriptions to the press release, and argued for a 10-year prison term so it "will be noted in executive suites and boardrooms of drug companies across the United States"and because "[g]eneral deterrence is needed in this area." SER4950.

Harkonen presented evidence that pulmonologists prescribed Actimmune based on their evaluation of the study data, not on headlines in one press release. He submitted supporting declarations from a leading pulmonologist and assistant professor at Harvard Medical School who explained that in 2002, he and other pulmonologists independently concluded from the study data and other information that it was appropriate to prescribe Actimmune to patients with mild-to-moderate IPF, and that patients had benefitted from it. ER2622-60. He submitted declarations from two eminent biostatisticians who explained, *inter alia*, why Harkonen's conclusion was consistent with the subsequent article in the *New England Journal of Medicine*, why the scientific viewpoint supporting the prosecution and post-trial opinion "stunned" them, and why criminal punishment would gravely chill communication about scientific research. Pet. App 93a-104a; ER2556-66, 2572-82.

After two sentencing hearings, the district court could not determine "who is a victim in this case, and whether the victims were benefitted in some way." ER1857. The court acknowledged that "some people did apparently derive some benefit" from Actimmune (SER3568) and that "there may be other ways of handling violations of this nature besides through criminal charges." ER1854-55. Harkonen was sentenced to three years probation, with 200

hours of community service and six months of home confinement, which he currently is serving. ER1858.

8. Harkonen appealed the conviction, and the government cross-appealed the sentence. The Ninth Circuit affirmed.

a. The Ninth Circuit gave Harkonen's First Amendment challenge short shrift, because "the First Amendment does not protect fraudulent speech." Pet. App. 2a, 5a-6a. Even though the jury was instructed that it must find "'the defendant made a scheme to defraud by making false or fraudulent statements, with all of you agreeing on at least one false or fraudulent statement that was made'" (*id.* at 53a n.6), the court did not identify any false or fraudulent statement.

Instead, the court deemed the evidence of falsity sufficient because "nearly everybody actually involved in [the Phase III] clinical trial testified that the press release misrepresented [the] results." Pet. App. 3a. Such testimony "also strongly supports the finding that Harkonen had the specific intent to defraud," as did Harkonen's status as CEO. *Id.* at 4a.

b. The court rejected Harkonen's argument that the wire fraud statute does not cover what the government "might think to be false opinions" about science if "intelligent people may and indeed do differ among themselves as to the extent" of the medical benefit. *McAnnulty*, 187 U.S. at 104-06. Although "genuine debates of any sort are, by definition, not fraudulent" (Pet. App. 6a), the court found *McAnnulty* inapplicable because "intent to defraud" under the wire fraud statute criminalizes "*any* 'trick, deceit, chicane or overreaching.'" *Id.* (citing *Carpenter* v. *United States*, 484 U.S. 19, 27 (1987) (emphasis added)).

c. The Ninth Circuit summarily rejected Harkonen's due process challenge because an "ordinary person" would have understood "that if he made misleading statements in a press release with the specific intent to defraud he would be subject to the wire fraud statute." Pet. App. 6a.

REASONS FOR GRANTING THE PETITION

The petition should be granted because a wire fraud prosecution for drawing false conclusions from accurate clinical trial data conflicts with this Court's precedents and decisions of three other circuits, is inherently arbitrary, and is chilling valuable scientific speech and debate on matters of public concern. Harkonen's conviction "stunned" leading members of the scientific community (Pet. App. 97a) who vehemently disagree that p-values are "magic number[s]" (*id.* at 19a) that define when data are "reliable" and bar scientists from inferring causation from clinical trial results where p-values exceed 0.05. *Id.* at 98a-104a; ER2575.

This Court established long ago that the expression of a scientific conclusion about which reasonable minds can differ is not "false and fraudulent" within the meaning of the civil postal mail fraud statute. *McAnnulty*, 187 U.S. at 104-06. The Sixth and Eighth Circuits then faithfully applied *McAnnulty* to the criminal mail fraud statute that is, in all relevant respects, identical to today's wire fraud statute. *Infra* 15-17. The Second Circuit and other courts also have held that a press release expressing a scientific conclusion drawn from accurate data is not actionable under laws prohibiting false or fraudulent statements. *Infra* 17-19.

The Ninth Circuit's decision conflicts with these decisions and raises grave First Amendment and due

process concerns that *McAnnulty*'s limiting construction deliberately avoids. Review is warranted immediately, because pharmaceutical companies routinely do and must issue press releases announcing material clinical trial results. Chilling such speech—forcing it to conform to the opinions of FDA staff—was the avowed intent of this prosecution. Government officials are now empowered to say, in the investigations that pervade the pharmaceutical industry, that those who publicly disagree with the scientific views of government employees do so at their criminal peril. They may send the same message to the many scientists whose research depends on government grants or public funding. The chilling effect of this message is immediate and extraordinary, and fully warrants this Court's review.

I. THE NINTH CIRCUIT'S DECISION, WHICH EXPANDS THE WIRE FRAUD STATUTE TO COVER DEBATABLE SCIENTIFIC CONCLUSIONS, CONFLICTS WITH *MCANNULTY* AND DECISIONS FROM THREE OTHER CIRCUITS.

This Court held in *American School of Magnetic Healing* v. *McAnnulty* that the civil mail fraud statute does not apply to "mere matters of opinion upon subjects which are not capable of proof as to their falsity." 187 U.S. at 104. There, the Postmaster General banned the delivery of mail and postal money orders for a business that taught that "the mind of the human race is largely responsible for its ills, and is a perceptible factor in the treating, curing, benefiting and remedying thereof." *Id.* at 103 (quotations omitted).

The Court reversed because there was "no exact standard of absolute truth by which to prove the assertion false and a fraud." *Id.* at 104. The Court

recognized that the Postmaster's fraud order "raises some grave questions of constitutional law." *Id.* at 103. The Court found it "unnecessary to decide" those questions, *id.*, however, because it construed the statute not to encompass allegedly false statements that "cannot be the subject of proof as of an ordinary fact." *Id.* at 104. Where scientific knowledge is "still in an empirical stage," and the extent to which a claim is "borne out by actual experience" is a "matter of opinion" over which "intelligent people may and indeed do differ among themselves," then as a matter of law the claim is not "within these statutes relative to fraud." *Id.* at 104-05.

Several decades later, this Court again overturned a civil fraud order, reaffirming *McAnnulty* as a "wholesome limitation" on the government's ability to prosecute scientific opinion. *Reilly* v. *Pinkus*, 338 U.S. 269, 274, 275-76 (1949). Although a defendant cannot avoid a finding of fraud simply by producing a witness "who blindly adhere[s] to a curative technique thoroughly discredited by reliable scientific experiences," the expression of an opinion in a field "where knowledge has not yet been crystallized in the crucible of experience" is *not* "fraud." *Id.* at 274.

1. The Sixth and Eighth Circuits have applied *McAnnulty* to criminal mail fraud prosecutions. See *Stunz* v. *United States*, 27 F.2d 575, 578-79 (8th Cir. 1928) (*McAnnulty* and *Bruce* v. *United States*, *infra*, require reversal of a mail fraud conviction based on allegedly false claims about a medical treatment if "the case only presented a difference of opinion between two sets of experts"); *Bruce* v. *United States*, 202 F. 98, 105 (8th Cir. 1912) (citing *McAnnulty* and reversing mail fraud conviction where medical experts disputed a drug's efficacy where jury was not instructed that "'[n]o conviction of fraudulent purpose

can lawfully be based upon matters merely of opinion'"); *Harrison* v. *United States*, 200 F. 662, 665 (6th Cir. 1912) (*McAnnulty* provides "necessary limitations" on finding a scheme to defraud based on the "expression of honest opinion"). This application of *McAnnulty* is unsurprising because the criminal mail and wire fraud statutes, and the civil mail fraud statute in *McAnnulty*, all share the same relevant language.[5] Had Harkonen been prosecuted in the Sixth or Eighth Circuits, his conviction would have been overturned.

2. The Second Circuit also would have reversed his conviction. Tracking the reasoning of *McAnnulty,* although not citing it, the Second Circuit held that expressing debatable scientific conclusions based on accurate data does not fall within the Lanham Act's prohibition on false advertising. *ONY*, 2013 WL 3198153, at *6.

In *ONY*, two pharmaceutical companies disputed the conclusions that could fairly be drawn from a clinical study comparing their respective drugs. *Id.* at *2. The defendant funded the study "as part of its effort to promote and sell" its drug. *Id.* The defendant's conclusions, as presented at medical conferences, in a medical journal, and in a press release, were that plaintiff's drug was associated with a greater

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[5] *Compare* 18 U.S.C. § 1343 (outlawing "any scheme or artifice to defraud, or for obtaining money or property by means of false or fraudulent pretenses, representations, or promises" through use of the wire communication in interstate commerce), *with McAnnulty*, 187 U.S. 100, n.1 (interpreting Section 3929 of the Revised States, which authorized the Postmaster General to deny use of the mails to any person engaged in conducting a "scheme or device for obtaining money through the mails by means of false or fraudulent pretenses, representations, or promises").

likelihood of death than defendant's drug. *Id.* Plaintiff alleged that this conclusion was an "incorrect" statement of "fact." *Id.* Plaintiff alleged that the authors were self-interested, the journal's review process was corrupt, and the authors reached their conclusion only by intentionally omitting data to "mask the fact" that those treated with defendant's drug "had a greater ex ante chance of survival than did the group treated" with plaintiff's drug. *Id.* at *3.

The Second Circuit nevertheless held that, given First Amendment constraints, the defendant's expression was not actionable under the Lanham Act. *Id.* at *3. The court observed that "[g]enerally, statements of pure opinion—that is, statements incapable of being proven false—are protected under the First Amendment." *Id.* at *4 (citing *Milkovich* v. *Lorain Journal, Co.*, 497 U.S. 1, 19-20 (1990)).

The court observed that "[s]cientific academic discourse poses several problems for the fact-opinion paradigm of First Amendment jurisprudence." *ONY*, 2013 WL 3198153, at *5. It suggested that "[m]ost conclusions contained in a scientific journal article are, in principle, 'capable of verification or refutation by means of objective proof.'" *Id.* But it recognized, as this Court has in *McAnnulty,* that in a "sufficiently novel area of research," propositions of "empirical 'fact'" may be "highly controversial and subject to rigorous debate by qualified experts." *Id.* Where "a statement is made as part of an ongoing scientific discourse about which there is considerable disagreement," it is "understood by the relevant scientific communities" as "more closely akin" to an "opinion" than a "verifiable 'fact'." *Id.* at *6.

To avoid "intrud[ing] on First Amendment values," and because "courts are ill-equipped to undertake to referee such controversies" in science, *id.* at *4-5, the

Second Circuit held that "statements about contested and contestable scientific hypotheses" should be treated as statements of opinion for "purposes of the First Amendment and the laws relating to fair competition and defamation," *id.* at *6. Accordingly, if "a speaker or author draws conclusions from non-fraudulent data, based on accurate descriptions of the data and methodology underlying those conclusions, on subjects about which there is legitimate ongoing scientific disagreement, those statements are not grounds for a claim of false advertising under the Lanham Act." *Id.*

The Second Circuit restricted the application of the Lanham Act just as this Court restricted the application of the civil mail fraud statute. Neither statute may be used to punish the expression of a scientific conclusion about the meaning of accurate data that is the subject of "legitimate ongoing scientific disagreement," *id.*, on which "intelligent people may and indeed do differ among themselves," *McAnnulty*, 187 U.S. at 104.

3. The Ninth Circuit, in contrast, rejected as "unavailing" Harkonen's "*McAnnulty*-based argument," relying upon what it thought was intervening precedent from the circuit and this Court that rendered *McAnnulty* inapplicable. The prior circuit authority, however, was a *misbranding* prosecution under the Federal Food, Drug, and Cosmetic Act—the charge for which Harkonen was acquitted.

The Ninth Circuit also cited this Court's statement in *Carpenter* v. *United States*, 484 U.S. 19, 27 (1987), that "in the criminal mail fraud statutes, the term 'to defraud' has [a] commonplace definition" that "includes any sort of 'dishonest method[] or scheme[],' and any 'trick, deceit, chicane or overreaching.'" Pet. App. 6a (last two alterations in original). That broad

language, the Ninth Circuit thought, allows opinions about what accurate clinical trial data demonstrated to be actionable as a "false or fraudulent statement" under the mail or wire fraud statute. *Id.*

But *Carpenter* holds only that intangible property (there, inside information) can be "property" under the mail fraud statute. 484 U.S. at 28. Given the unrelated nature of its holding, *Carpenter* cannot fairly be read to supersede *McAnnulty* and *Reilly*. Indeed, *Carpenter* itself makes plain that there is no material difference in the statutory language of today's criminal mail and wire fraud statutes (18 U.S.C. §§ 1341 & 1343) and the civil mail fraud statute at issue in *McAnnulty*. Compare *Carpenter*, 484 U.S. at 27 (criminal fraud statutes "reach any scheme to deprive another of money or property *by means of false or fraudulent pretenses, representations, or promises*") (emphasis added), with *McAnnulty*, 187 U.S. at 103 (statute bars "obtain[ing] money and property through the mails *by means of false or fraudulent pretenses, representations or promises*") (emphasis added).

Only this Court can overrule its prior decisions. *Agostini* v. *Felton*, 521 U.S. 203, 237 (1997). This Court also has repeatedly cabined the government's efforts to expand the mail and wire fraud statutes beyond the limits Congress and the Constitution impose. See, *e.g., Skilling* v. *United States*, 130 S. Ct. 2896, 2925-35 (2010); *McNally* v. *United States*, 483 U.S. 350 (1987).

Had InterMune been located in New York, Cleveland, or St. Louis, Harkonen's conviction would have been overturned. The Sixth and Eighth Circuits already have applied *McAnnulty* to criminal mail fraud. And the Second Circuit surely would not accord less protection to scientific speech when

criminally prosecuted by the government than it did in a suit for money damages by a commercial competitor. Only this Court can resolve this conflict, confirm the continued vitality of *McAnnulty* and *Reilly*, and ensure that scientific speech receives the same protection regardless of where the speaker resides.

II. EXPANDING THE WIRE FRAUD STATUTE TO ENCOMPASS CONCLUSIONS DRAWN FROM ACCURATE DATA VIOLATES THE FIRST AMENDMENT AND THE DUE PROCESS CLAUSE.

The petition also should be granted because the Ninth Circuit's construction of the wire fraud statute squarely presents the "grave questions of constitutional law" that *McAnnulty*'s narrowing construction avoided. *McAnnulty*, 187 U.S. at 103.

1. The first such question implicates the First Amendment. Construing the criminal mail and wire fraud statutes to permit the government to prosecute scientific conclusions with which the government disagrees raises a question of exceptional importance about the role of independent judicial review to prevent the government from prosecuting as "fraud" scientific viewpoints that the First Amendment protects.

Viewpoint discrimination lies at the core of the First Amendment: the government may not proscribe speech "'because of disagreement with the message it conveys.'" *Sorrell* v. *IMS Health Inc.*, 131 S. Ct. 2653, 2664 (2011); *id.* at 2667 ("In the ordinary case it is all but dispositive to conclude that a law is content-based and, in practice, viewpoint-discriminatory") (citing *RAV* v. *St. Paul*, 505 U.S. 377, 382 (1992)). But here the government prosecuted Harkonen

because the press release expressed a conclusion about accurate data—that they demonstrated a survival benefit—with which two individuals at FDA—"FDA medical review staff"—disagreed. ER220, 224.

The freedom to disagree with other scientists, and especially with government staff, is fundamental to the First Amendment. The Second Circuit so held in *ONY*. The Ninth Circuit, however, fell back on the First Amendment's categorical exclusion of fraud as unprotected speech, and affirmed Harkonen's conviction without independently reviewing whether the challenged conclusions were, indeed, false or misleading. Pet. App. 2a, 5a-6a. First Amendment protections cannot rest solely on labels; they require fair scrutiny of the defendant's statement in the context of legitimate scientific disagreement.

The Ninth Circuit's decision thus raises an important question that this Court has resolved for other categories of unprotected speech, but not yet for fraud, about an appellate court's "constitutional duty to conduct an independent examination of the record as a whole" and to decide "whether a given course of conduct falls on the near or far side of the line of constitutional protection." *Hurley* v. *Irish-Am. Gay, Lesbian & Bisexual Grp. of Bos., Inc.*, 515 U.S. 557, 567 (1995).

There is, of course, no First Amendment right to commit fraud. *E.g.*, *United States* v. *Stevens*, 130 S. Ct. 1577, 1586 (2010). But "[s]imply labeling an action one for 'fraud,' of course, will not carry the day." *Ill. ex rel. Madigan* v. *Telemarketing Assocs. Inc.*, 538 U.S. 600, 617 (2003). A prosecution denominated as one for "fraud," when based on protected speech that a legislature cannot ban directly, requires a "swift dismissal" because a prosecutor "surely cannot gain case-by-case ground this Court

has declared off limits to legislators." *Id.* As Justice Scalia stated, it "is axiomatic that, although fraudulent misrepresentation of facts can be regulated," the "dissemination of ideas cannot be regulated to prevent it from being unfair or unreasonable." *Riley* v. *Nat'l Fed'n of the Blind*, 487 U.S. 781, 803 (1988) (Scalia, J., concurring).

This Court should now grant review to establish that courts have a constitutional duty independently to enforce that very line. When the government prosecutes, as false and misleading, speech the defendant maintains expresses a constitutionally protected viewpoint, the question of the protected nature of the speech cannot be left solely to the jury any more than in other cases, such as defamation, that involve a category of speech unprotected by the First Amendment.

Experience has shown that "[p]roviding triers of fact with a general description of the type of communication whose content is unworthy of protection has not, in and of itself, served . . . to eliminate the danger that decisions by triers of fact may inhibit the expression of protected ideas." *Bose Corp.* v. *Consumers Union of United States, Inc.*, 466 U.S. 485, 505 (1984). Therefore, this Court has requireed independent judicial review in cases involving speech that allegedly falls into many unprotected categories, including not only "fighting words," but also obscenity, child pornography, incitement to imminent lawless action, and libel. See *id.* at 504-10. Independent judicial review ensures that "the speech in question actually falls within the unprotected category" and "confine[s] the perimeters of any unprotected category within acceptably narrow limits" so "protected expression will not be inhibited." *Id.* at 505.

This Court recently exercised its duty to conduct an "'independent examination of the whole record'" and reversed a jury verdict because independent review established that the jury had punished speech on issues "'of public concern.'" *Snyder* v. *Phelps*, 131 S. Ct. 1207, 1216 (2011). The Court also independently reviewed the record and then reversed a state court's finding that an attorney's statement on his letterhead was "actually or inherently misleading" and thus outside the First Amendment's protection of commercial speech. *Peel* v. *Attorney Registration & Disciplinary Comm'n*, 496 U.S. 91, 108-10 (1990) (plurality opinion) (reversing sanction because there was no "empirical evidence" that the statement's "inherent character" was deceptive); *id.* at 111 (Marshall, J., concurring in the judgment). Just as independent review was necessary in *Snyder* and *Peel* to ensure that the factfinders did not punish protected speech, so it is necessary here, where prosecutors have attacked the expression of a protected scientific opinion that government officials condemned.

2. Independent review of the press release and record here would lead to reversal of Harkonen's conviction, just as independent review led to reversal of the bar censure in *Peel*, the defamation finding in *Bose*, and the jury verdict in *Snyder*.

The "magic number" p-value theory of when studies support inferences of causation is indefensible, which presumably is why the Ninth Circuit dodged the district court's analysis of the challenged statements. The Ninth Circuit's alternate tact—observing that "nearly all" government witnesses stated that the press release "misrepresented" the study results—is equally indefensible because those who so testified did so based on a single viewpoint about the proper

interpretation of data: that a clinical study lacking statistically significant p-values on pre-specified endpoints cannot "demonstrate" anything. ER304-05 & 502-03 (Walton); ER547-52 (Fleming); ER1037-39 & 1049 (Porter); ER1168 (Crager); ER1601-02 (closing argument). Yet the government made no attempt to establish the universality of its p-value restriction on truthful scientific inference. No such showing could be made.

Two weeks after the United States filed a brief in the district court asking for "a substantial sentence of 120 months in prison" (SER4951), the Solicitor General filed a brief in this Court that refutes the scientific "rules" prosecutors presented to Harkonen's jury. The Solicitor General's brief was premised on an extended section captioned "*Statistical significance is a limited and non-exclusive tool for inferring causation.*" *Matrixx* Brief at 13. Whereas prosecutors told Harkonen's jury that if the results on a study's primary endpoint are not statistically significant, then "*you cannot conclude* that the [drug] has a survival benefit" (ER1601-02), the Solicitor General told this Court the exact opposite: "a determination that certain data are not statistically significant . . . *does not refute* an inference of causation." *Matrixx* Brief at 14 (emphases added). The Solicitor General further explained that its core message—that "certain data are not statistically significant . . . does not refute an inference of causation"—applies equally "to studies suggesting that a particular drug is efficacious." *Id.* at 14, 15 n.2; see generally *id.* at 13-16, 19-20, 22 n.5.

This Court agreed with the Solicitor General, holding that a "lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link" between a drug and

an effect. *Matrixx Initiatives, Inc.* v. *Siracusano*, 131 S. Ct. 1309, 1319 (2011). It stated that courts "frequently permit expert testimony on causation based on evidence other than statistical significance," and medical professionals and researchers do not limit the data they consider to "'statistically significant evidence.'" *Id.* at 1319-20 (citing Brief for Medical Researchers as *Amicus Curiae* 31).

The First Amendment does not permit the government to prosecute a scientific viewpoint in one courtroom while championing that same viewpoint in another. By failing to conduct any independent analysis of whether the charged statements were false or misleading, the Ninth Circuit freed itself to ignore evidence that supports Harkonen's viewpoint and illustrates the legitimate scientific disagreement about the study results.

The separate elements of scienter and materiality do not moot the need for independent review of falsity. Every witness who testified on the issue *agreed* that Harkonen and Pennington consistently expressed their views that the data demonstrated a survival benefit and disagreed with those who suggested otherwise. *E.g.*, ER886, 949-50, 1061, 1118-21, 1434-36, 1514-16, 1569; Pet. App. 87a. The only practicing physician to testify at trial wrote in 2002 to his Department Chair, after receiving the study results and hearing Fleming's criticisms, that the study was "successful" and prescribed Actimmune to 60 of his IPF patients. ER787, 834.

Although independent review of scienter or materiality also would lead to reversal, and may indeed be warranted, independent review of falsity clearly is pivotal. If the charged statements are not false or misleading, then they are constitutionally protected. Publishing statements that cannot consti-

tutionally be deemed false or misleading, regardless of intent, cannot *deceive* people into parting with their money or property, which is the "legally cognizable harm associated with a false statement" that renders fraud unprotected by the First Amendment. *United States* v. *Alvarez*, 132 S. Ct. 2537, 2545 (2012) (plurality opinion); see also *id.* at 2553-54 (Breyer, J., concurring in judgment). Independent review of falsity is therefore essential to protect scientific speech.

Some of science's greatest leaps forward defied conventional thinking and were roundly and publicly condemned. Leaving juries to decide whether a scientific conclusion drawn from accurate facts is false or misleading, without the check of independent judicial review, is a recipe for viewpoint discrimination and chilling extraordinarily important speech. This Court should grant the petition to clarify that the First Amendment mandates independent judicial review of falsity where, as here, the government prosecutes speech about the meaning of scientific research results, to ensure that a fraud prosecution does not transgress "acceptably narrow limits" and impermissibly regulate protected scientific opinion.

3. The second "grave question[] of constitutional law" that *McAnnulty* avoided (187 U.S. at 103) implicates the Due Process Clause. Construing the wire fraud statute to encompass "conclusions drawn from" data violates due process because the public lacks fair notice of the standards that determine the truth or falsity of a scientific conclusion drawn from accurate facts. Were the standards invoked by prosecutors here universally applied, the jails would be flooded with scientists, including government employees.

It is a "fundamental principle in our legal system" that "laws which regulate persons or entities must give fair notice of the conduct that is forbidden or required." *FCC* v. *Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317 (2012). When "speech is involved, rigorous adherence" to this notice requirement "is necessary to ensure that ambiguity does not chill protected speech." *Id.* at 2317, 2320 (holding FCC violated due process by retroactively applying its revised "indecency" policy).

The Seventh Circuit overturned a wire fraud conviction on due process grounds where the defendant's conduct violated no rule or commonly accepted standard, and the government's case turned on the implication, from "the oral testimony of an agency [FDA] employee" that the conduct was improper. *United States* v. *Farinella*, 558 F.3d 695, 699 (7th Cir. 2009). As the court explained, the "'idea of secret laws is repugnant. People cannot comply with laws the existence of which is concealed.'" *Id.* Had Harkonen's conviction arisen in the Seventh Circuit, it would have been reversed on due process grounds.

The Ninth Circuit ignored both *Fox* and *Farinella*, though both cases were argued prominently. It summarily dismissed Harkonen's due process defense because an ordinary person would understand that it is a crime to make "misleading statements in a press release with the specific intent to defraud." Pet. App. 6a. That is a fair point *only* if the person has notice of the standards by which the law distinguishes a fair scientific inference from a misleading one. The Ninth Circuit never explains how a reasonable person would know that the criminal law bars inferring causation from accurate clinical study data in the absence of statistically significant p-values on pre-

specified endpoints. No reasonable explanation exists.

The due process violation here is even more extreme than in *Fox*, because no federal agency has ever issued a rule restricting scientists from drawing causal inferences from accurate data, let alone a "scientific conclusions" policy that Harkonen's statements would violate. The government's witnesses admitted there were no such rules. ER429-30, 514.

To the contrary, government scientists routinely publish press releases and reach conclusions that conflict with the prosecution's "rules" presented in this case. See *infra* at 33-34 & nn.8-9. Scientists regularly publish articles that do not comply with them. See, *e.g.*, See Rui Wang et al., *Statistics in Medicine—Reporting of Subgroup Analyses in Clinical Trials*, 357 New Eng. J. Med. 2189, 2192 (2007) (in 68% of articles reporting subgroup analyses it was unclear whether any subgroups were "prespecified or post hoc") (available at ER2745-50); ER2578-79 ("literature is replete with published examples of unadjusted p-values for secondary endpoints or subgroup analyses"). FDA itself has approved drugs based on data from clinical studies lacking statistically significant p-values on the primary endpoint (*see, e.g., supra* at 8; Pet. App. 99a-101a)—the very aspect of the Actimmune study data that the prosecutor said made it "just false" to conclude that the results demonstrated a "survival benefit." ER1601.

Case-law also gives no notice that a reasonable, even if government-disputed, interpretation of accurate clinical study data constitutes wire fraud. *McAnnulty* and *Reilly* protected the expression of scientific opinions about which reasonable minds could differ. *Supra*, at 15-16. The D.C. Circuit

mocked as "almost frivolous" FDA's argument that a disagreement between government and company scientists over the meaning of data could render a statement "inherently misleading" and justify a ban on the company's expression of its view. *Pearson* v. *Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999). Lower courts routinely dismiss civil claims that a scientifically debatable interpretation of data is false or fraudulent. *E.g.*, *United States ex. rel. Haight* v. *Catholic Healthcare W.*, No. cv-01-2253, 2007 WL 2330790, at *2 (D. Ariz. Aug. 14, 2007) (holding, in a False Claims Act case involving an NIH grant application, that "[e]xpressions of opinion, scientific judgment, or statements as to conclusions about which reasonable minds may differ cannot be false") (quotations omitted), *appeal dismissed*, 602 F.3d 949 (9th Cir. 2010); *Noble Asst Mgmt.* v. *Allos Therapeutics, Inc.*, No. CIVA-04CV-1030-RPM, 2005 WL 4161977, at *11 (D. Colo. Oct. 20, 2005) (dismissing securities fraud action where "interpretation of the data from the . . . clinical trials is a matter on which reasonable minds could differ"; that FDA's Oncology Drug Committee "ultimately did not recommend approval does not mean that the defendants' statements about the results" of the study were "false"); *DeMarco* v. *DepoTech Corp.*, 149 F. Supp. 2d 1212, 1225 (S.D. Cal. 2001) ("legitimate difference in opinion as to the proper statistical analysis" does not state "a securities fraud claim").

The final report to FDA on this study was over 950 pages, excluding appendices. ER2295-2303. The press release necessarily contained only a fraction of the data and analysis. No standards exist to determine which facts to include or exclude in announcing the preliminary results. For every omitted fact that allegedly rendered the press release

misleading (*e.g.*, that the cut-off for the mild-to-moderate subgroup was not pre-specified), there is at least another omitted fact that *supported* the reasonableness of the conclusion (*e.g.*, that the other subgroups of mild-to-moderate IPF patients also showed a high relative survival benefit with a p-value less than 0.05).

In the absence of standards as to what data must be included and what conclusions may be drawn, a reasonable scientist cannot know what omissions or conclusions could lead to a federal fraud conviction, a demand for incarceration, and collateral civil sanctions (also brought here by federal and state agencies) that seek to end a distinguished professional career. A jury's agreement with an FDA official's views can no more support Harkonen's conviction than it could Farinella's. The Court should grant the petition to reconcile that conflict and clarify that the due process principles of *Fox* apply equally to prosecutions of opinion under the mail and wire fraud statutes.

III. ALLOWING THE CONVICTION TO STAND WILL IMMEDIATELY, IRREPARABLY, AND INDEFINITELY CHILL SCIENTIFIC SPEECH ON MATTERS OF VITAL PUBLIC CONCERN.

The public interest in the free flow of information has particular relevance "in the fields of medicine and public health, where information can save lives." *Sorrell*, 131 S. Ct. at 2664. Press releases expressing opinions about the import of the latest clinical studies are integral to this communication.

Many such releases are issued every week. For pharmaceutical companies alone, we found 97 such press releases issued between January 2012 and

June 2013, often to comply with federal securities law. For example, SEC rules require public disclosure of information material to shareholders, and Regulation FD requires prompt public disclosure of material confidential information after disclosure to certain non-insiders. 17 C.F.R. § 243.100. A "press release distributed through a widely circulated news or wire service" is generally an "acceptable method[]" for satisfying these obligations. Selective Disclosure and Insider Trading, Securities Act Release, No. 7881, Fed. Sec. L. Rep. (CCH) ¶ 86,319 (Aug. 15, 2000). InterMune issued this press release to ensure prompt and uniform public disclosure within 24 hours after disclosure to the Steering Committee, which included leading outside physician-investigators. ER973-77, 1143-44, 1453, 2344. But pharmaceutical companies are not the only speakers.

Academic medical centers, nonprofit organizations, and government agencies such as the National Institutes of Health ("NIH") also regularly issue press releases trumpeting the results of clinical trials. During that same 2012-13 time period, for example, we found 25 such press releases from the American Cancer Society, eleven from the Susan G. Komen for the Cure Foundation, and 25 from the NIH. As for academic medical centers, a study in the *Annals of Internal Medicine* found that, in just one year, 20 such centers alone issued a combined total of almost 1000 press releases discussing their research.[6]

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[6] S. Woloshin et al, *Press Releases by Academic Medical Centers: Not So Academic?*, 150 Annals of Internal Med. 613, 616 & tbl.1 (2009) ("Press releases issued by 20 academic medical centers frequently promoted preliminary research . . . without providing basic details or cautions needed to judge the meaning, relevance, or validity of the science.").

Two criticisms have been and always can be levied against such press releases. One is that they omitted important information; that is unavoidable, because no release can contain the same details as could a full report to FDA, a journal article, or a conference presentation, and scientists will disagree on what is most important. The other is that the conclusions overstate the importance of the results; such disagreement again is inevitable, because drawing conclusions from data involves exercising judgment.

Inevitable disagreement over inferences from data is why FDA frequently convenes advisory committees, and why committee votes often are divided.[7] Even the press releases of academic medical centers are criticized for omissions and overstatement. Woloshin, *supra*, at 616. NIH itself "overstates" its results, at least according to the prosecutor's standards here. During Harkonen's trial, for example, NIH issued a press release that was roundly criticized for announcing that an expensive trial "demonstrates" that a combination of vaccines provided a benefit against HIV infection, while omitting data showing that, for those patients who actually followed the prescribed regimen, there was no statistically significant benefit; NIH officials responded that they had included the most important data and would discuss the rest at upcoming conferences.[8]

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[7] *See* U.S. Food & Drug Admin., *Advisory Committees: Critical to the FDA's Product Review Process*, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143538.htm (updated Aug. 12, 2011) (FDA convenes advisory committees to "comment on whether adequate data support approval, clearance, or licensing of a medical product for marketing" to address complex questions and hear "diverse perspectives"); ER2580-81.

[8] ER2680-82, 2710-11, 2715-26.

In May 2013, NIH issued a press release about a study that did not meet its primary endpoint; per Harkonen's prosecutors, this was a "failed" study, but NIH nonetheless claimed a "finding" that anti-oxidants provided two subgroups an important benefit.[9] The press release does not disclose that NIH retrospectively defined one of those subgroups.

Pharmaceutical companies sponsor important research. Their scientists should enjoy the same freedoms that government and academic scientists have to express conclusions about the meaning of data. See *Sorrell*, 131 S. Ct. at 2665 (invalidating law that "imposes a burden based on the content of speech and the identity of the speaker"). They certainly should be free to rely on criteria the Solicitor General identified in *Matrixx* for inferring causation.

By allowing fraud prosecutions to target scientific conclusions, the Ninth Circuit let the government cross a line into criminalizing scientific opinion that no court before let it cross. It authorized the government to send its message that speech contrary to the scientific views of government employees is subject to criminal prosecution. This decision chills speech on matters of profound public concern. Whether the government may convict scientists of fraud for the inferences they draw from accurate data is a question of exceptional importance to which this

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[9] *See* Press Release, Nat'l Insts. Of Health, *NIH Study Provides Clarity On Supplements For Protection Against Blinding Eye Disease* (May 5, 2013), http://www.nei.nih.gov/news/pressreleases/050513.asp; *Lutein+Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration, The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial*, 309 J. Am. Med. Ass'n 2005 (2013), http://jama.jamanetwork.com/article.aspx?articleid=1684847.

Court should promptly provide a uniform national answer.

CONCLUSION

For the foregoing reasons, the petition for a writ of certiorari should be granted.

Respectfully submitted,

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August 5, 2013

APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS,
NINTH CIRCUIT

Nos. 11-10209, 11-10242

UNITED STATES OF AMERICA,
Plaintiff-Appellee,

v.

W. SCOTT HARKONEN, M.D.,
Defendant-Appellant.

UNITED STATES OF AMERICA,
Plaintiff-Appellant,

v.

W. SCOTT HARKONEN, M.D.,
Defendant-Appellee.

Appeal from the United States District Court
for the Northern District of California

Marilyn Patel, Senior District Judge, Presiding,
D.C. No. 3:08-cr-00164-MHP-1

Argued and Submitted Dec. 6, 2012
Filed March 4, 2013

Before D.W. NELSON, TASHIMA, and MURGUIA, Circuit Judges.

MEMORANDUM*

A jury convicted Defendant W. Scott Harkonen of wire fraud for issuing a fraudulent press release. The district court sentenced Harkonen to three years probation and a $20,000 fine. Harkonen appeals his conviction, and the government cross-appeals Harkonen's sentence. We have jurisdiction pursuant to 28 U.S.C. § 1291 and affirm Harkonen's conviction and sentence.

First Amendment Challenge

We review First Amendment challenges to criminal convictions in two steps: (1) deferring to the jury's findings on historical facts, credibility determinations, and the elements of statutory liability, we ask whether sufficient evidence supports the verdict;[1] and (2) if it does, we determine whether the facts, as found by the jury, establish the core constitutional facts. *See United States v. Keyser*, 704 F.3d 631, 638 n. 1 (9th Cir.2012) (citing *Planned Parenthood of the Columbia/Willamette, Inc. v. Am. Coal. of Life Activists*, 290 F.3d 1058, 1070 (9th Cir.2002) (en banc)).

Constitutional facts determine "the core issue of whether the challenged speech is protected by the First Amendment." *United States v. Hanna*, 293 F.3d 1080, 1088 (9th Cir.2002). The First Amendment does not protect fraudulent speech, *United States v. Alvarez*, — U.S. —, 132 S.Ct. 2537, 2544, 183 L.Ed.2d 574 (2012), so the core constitutional issue in Harkonen's

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* This disposition is not appropriate for publication and is not precedent except as provided by 9th Cir. R. 36-3.

[1] Accordingly, our First Amendment analysis also addresses Harkonen's distinct argument on appeal that his wire fraud conviction was not supported by sufficient evidence.

case is whether the facts the jury found establish that the Press Release was fraudulent.

Step One: Whether Sufficient Evidence Supports the Verdict

Wire fraud comprises three elements: (1) knowing participation in a scheme to defraud; (2) use of the wires in furtherance of the scheme; and (3) a specific intent to deceive or defraud. *United States v. Green*, 592 F.3d 1057, 1064 (9th Cir.2010). The second element is uncontested on appeal and is irrelevant for First Amendment purposes.

Knowing Participation in a Scheme to Defraud

At trial, nearly everybody actually involved in the GIPF-001 clinical trial testified that the Press Release misrepresented GIPF-001's results. Testimony indicated that even Harkonen himself was "very apologetic" about the Press Release's misleading nature. Evidently, the jury credited all this testimony, and it supports the finding that the Press Release was fraudulent even if not "literally false." *See United States v. Woods*, 335 F.3d 993, 998 (9th Cir.2003).

In addition to his being "very apologetic" about the Press Release, further evidence supports the finding that Harkonen knew the Press Release was misleading. Harkonen prevented Intermune's clinical personnel from viewing the Press Release prior to its publication, even when they asked to see it, at one point becoming "visibly" upset and "castigat[ing]" the head of the communications firm that helped prepare the Press Release for permitting Intermune's Vice President of Regulatory Affairs to view a draft of the Press Release. Harkonen also did not want the FDA to know about all his post-hoc analyses—the analyses on which

the Press Release was based—because he "didn't want to make it look like we were doing repeated analyses looking for a better result."

Lastly, there is sufficient evidence that the Press Release was at least "capable" of influencing the decision of doctors to prescribe, or patients to seek, prescriptions of Actimmune, *United States v. Jenkins*, 633 F.3d 788, 802 n. 3 (9th Cir.2011), because the Press Release was purportedly a very effective marketing tool.

Specific Intent to Defraud

Our conclusion that the jury was justified in finding that the Press Release was misleading also strongly supports the finding that Harkonen had the specific intent to defraud. *See United States v. Sullivan*, 522 F.3d 967, 974 (9th Cir.2008). Further circumstantial evidence, *id*., supports the conclusion that Harkonen's GIPF-001 analyses were conducted with fraudulent intent: Harkonen stated he would "cut that data and slice it until [he] got the kind of results [he was] looking for," and requested the final post-hoc analysis "simply . . . to see what that did to the p-value." Given his clear financial incentive to find a positive result in the face of GIPF-001's failure to meet its predetermined goals, we conclude the evidence sufficiently supports the jury's determination that Harkonen had the specific intent to defraud.

Step 2: Whether the Facts as Found by the Jury Establish the Core Constitutional Facts

Because they are supported by sufficient evidence, we defer to the jury's findings that the Press Release was misleading, that Harkonen knew it was misleading, and that Harkonen had the specific intent to defraud. *Cf. Keyser*, 704 F.3d at 639 ("[W]e do not defer

to the jury's finding of intent, because, in this case, intent is not an element of statutory liability."). Thus, upon independent review of the record,[2] we affirm Harkonen's conviction. *See United States v. Stewart*, 420 F.3d 1007, 1019 (9th Cir.2005*); cf. United States v. Bagdasarian*, 652 F.3d 1113, 1123 (9th Cir.2011) (speech was protected "because the prosecution failed to present sufficient evidence" to convict).

McAnnulty Argument

Harkonen, relying on *American School of Magnetic Healing v. McAnnulty*, 187 U.S. 94, 23 S.Ct. 33, 47 L.Ed. 90 (1902), argues we should reverse his conviction because "genuine debates over whether a given treatment caused a particular effect are outside the scope of the mail and wire fraud statutes." We are unpersuaded.

First, *McAnnulty* does not categorically prohibit fraud prosecutions for statements about the efficacy of a particular drug; indeed, "[t]hat false and fraudulent representations may be made with respect to the curative effect of substances is obvious." *Seven Cases v. United States*, 239 U.S. 510, 517, 36 S.Ct. 190, 60 L.Ed. 411 (1916). Here, the government alleged the Press Release contained "false and misleading information" about Actimmune, and the government was permitted to go to trial on that theory.

Second, Harkonen's *McAnnulty*-based argument that his statements were fraudulent only if they were universally considered objectively false is unavailing.

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[2] Critically, Harkonen presented the evidence that most firmly supported his case for the first time at sentencing. Because we must defer to the jury's credibility determinations, *Keyser*, 704 F.3d at 639, we will not reverse the jury's verdict based on evidence it never considered.

As used in the criminal mail fraud statutes, the term "to defraud" has its commonplace definition and includes any sort of "dishonest method[ ] or scheme[ ]," and any "trick, deceit, chicane or overreaching." *Carpenter v. United States*, 484 U.S. 19, 27, 108 S.Ct. 316, 98 L.Ed.2d 275 (1987); *see also Woods*, 335 F.3d at 998 (stating a scheme's "fraudulent" nature is measured by a "non-technical" standard). Statements are fraudulent if "misleading or deceptive" and need not be "literally false." *Woods*, 335 F.3d at 998.

Third, Harkonen's request that we reverse his conviction because he was engaging in a genuine scientific debate is hardly different than arguing that he is innocent; genuine debates of any sort are, by definition, not fraudulent. Here, a jury found, beyond a reasonable doubt, that Harkonen issued the Press Release with the specific intent to defraud, and that finding is supported by the evidence presented at trial. We know of no case where, based on *McAnnulty*, a court disregarded a jury's factual findings to overturn a criminal conviction, and we will not do so here. *See Research Labs. v. United States*, 167 F.2d 410, 414-17 (9th Cir.1948) (limiting *McAnnulty* and stating it does not prohibit a jury from weighing conflicting scientific testimony to determine whether statements about a drug's efficacy were misleading).

Due Process

Harkonen's due process argument is essentially a re-dressing of his First Amendment and *McAnnulty* arguments, so it too must fail. An ordinary person would have understood, *see Skilling v. United States*, — U.S. —–, 130 S.Ct. 2896, 2927–28, 177 L.Ed.2d 619 (2010), that if he made misleading statements in a press release with the specific intent to defraud he would be subject to the wire fraud statute.

Jury Instructions

The district court did not abuse its discretion in formulating its jury instructions. *United States v. Hofus*, 598 F.3d 1171, 1174 (9th Cir.2010). When the district court provides adequate instructions on the specific intent element of wire fraud, no good faith instruction is required, *United States v. Frega*, 179 F.3d 793, 804 (9th Cir.1999), and because "puffing" "fall[s] under the umbrella of . . . good faith," *United States v. Gay*, 967 F.2d 322, 329 (9th Cir.1992), a specific intent instruction adequately covered Harkonen's puffing defense.

Brady Argument

Harkonen has failed to demonstrate a reasonable probability that the government's withholding of evidence caused prejudice, which occurs if the evidence withheld "undermines confidence in the outcome of the trial." *United States v. Kohring*, 637 F.3d 895, 901-02 (9th Cir.2010) (internal quotation marks omitted). The documents at issue here might demonstrate that the Press Release did not mislead some doctors, but there was other evidence that the Press Release was widely and successfully used as a marketing tool, indicating it was "capable" of misleading some addressees and was, therefore, "material."

Matrixx Motion

The district court did not abuse its discretion in denying Harkonen's "*Matrixx* motion" for a new trial, *see United States v. Del Toro-Barboza*, 673 F.3d 1136, 1153 (9th Cir.2012), because *Matrixx Initiatives, Inc. v. Siracusano*, — U.S. —, 131 S.Ct. 1309, 179 L.Ed.2d 398 (2011), does not undermine the thrust of the government's theory in Harkonen's case. Harkonen's scientific methods were not on trial; the issue was whether he misleadingly presented his analyses in the

Press Release. The distinction between these two issues was made clear at trial when, for instance, Intermune's former Senior Director of Biostatistics testified that post-hoc analyses are "good science" in the sense that they may generate hypotheses for future study, but that he "winced" when he saw the Press Release because "the conclusiveness of the results was overstated."

Harkonen's Sentence

The district court did not abuse its discretion in finding that the government failed to meet its burden on the U.S.S.G. § 2B1.1(b)(1) "intended loss" enhancement. *See United States v. Yepez*, 652 F.3d 1182, 1187 (9th Cir.2011). The district court never explicitly ruled on the government's § 2B1.1(b)(1) intended loss argument, but the record in its entirety indicates the district court was well aware of this argument. In that context, we read the district court's statement that, "when it comes to the loss . . . this case is really wanting in the kind of showing that would meet the preponderance standard," as a rejection of both the government's actual and intended loss arguments due to the government's failure to articulate a loss theory that made sense.

Nor did the district court erroneously require the government to prove an "actual" pecuniary loss (the U.S.S.G. § 2B1.1 definition of "victim") for a U.S.S.G. § 3A1.1 "vulnerable victim" enhancement; rather, the district court found that the government failed to meet its burden of identifying an actual victim. This is clear from the district court's conclusion that "we can't even figure out who is a victim in this case, and whether the victims were benefited in some way."

AFFIRMED.

APPENDIX B

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

[Filed 07/27/10]

No. C 08-00164 MHP

UNITED STATES OF AMERICA,

v.

W. SCOTT HARKONEN,

Defendant.

MEMORANDUM & ORDER

Re: Defendant's Post-Trial Motion to Dismiss the Indictment, for Acquittal or for a New Trial

On September 29, 2009, a federal jury found defendant W. Scott Harkonen ("Harkonen") guilty of one count of wire fraud, 18 U.S.C. § 1343, and not guilty of one count of felony misbranding, 21 U.S.C. §§ 331(k), 333(a)(2) & 352(a). Before the court is Harkonen's post-trial motion to dismiss the indictment, for acquittal under Federal Rule of Criminal Procedure 29, or for a new trial under Federal Rule of Criminal Procedure 33. Having considered the parties' arguments and submissions and for the reasons stated below, the court enters the following memorandum and order.

BACKGROUND

Because the evidence relevant to Harkonen's motion is discussed in greater detail below, the court provides

only a brief summary of the allegations and proceedings. The evidence at trial showed that from 1998 until at least June 3, 2003, Harkonen was the Chief Executive Officer of InterMune, Inc. ("InterMune"). InterMune, a California-based pharmaceutical company, developed, marketed and sold drugs for lung and liver diseases. One of the drugs that InterMune sold was called "interferon gamma-1b" and was marketed under the brand name of "Actimmune." By 2000, when InterMune fully purchased the rights to Actimmune from the company that had developed the drug, Actimmune had only been approved by the Food and Drug Administration ("FDA") for the treatment of two very rare conditions: chronic granulomatous disease and severe, malignant osteopetrosis.

In 1999, a small Austrian clinical trial showed that Actimmune might be a promising treatment for another rare and fatal disease, idiopathic pulmonary fibrosis ("IPF"). IPF is characterized by progressive scarring, or fibrosis, of the lungs which leads to the lung's deterioration and destruction. The cause of IPF is unknown, and once afflicted, IPF sufferers generally die within two to three years. There are approximately 200,000 individuals in the United States who suffer from the disease, and 50,000 new cases are diagnosed each year. In response to the Austrian study, InterMune launched its own, much more ambitious study of Actimmune's efficacy in treating IPF. The study, known as the GIPF-001 Phase III trial ("the GIPF-001"), was designed primarily to test whether patients being treated with Actimmune were more or less likely to experience "progression-free survival time"—delayed or prevented the worsening of patients' IPF. The GIPF-001 also collected data relevant to a number of other hypotheses regarding Actimmune's effect on IPF.

In mid-August 2002, InterMune was provided with the results from the GIPF-001. On August 28, 2002, InterMune issued a press release, claiming, among other things, that the data from the study "[d]emonstrat[ed a] survival benefit of Actimmune in IPF" and that Actimmune "Reduces Mortality by 70% in Patients with Mild to Moderate Disease". Gov't Exh. 1 (Press Release), attached to this order as appendix 1.

The press release, as well as other conduct engaged in by Harkonen and InterMune, formed the basis for the indictment in this case, which was filed on March 18, 2008. The ten-page, two count indictment charged Harkonen with wire fraud in violation of 18 U.S.C. section 1343 (Count One) and felony misbranding of a drug in violation of 21 U.S.C. sections 331(k), 333(a)(2) and 352(a) (Count Two). The wire fraud count alleged that the press release "contained materially false and misleading information regarding Actimmune and falsely portrayed the results of a GIPF-001 Phase III trial as establishing that Actimmune reduces mortality in patients with IPF." Docket No. 1 (Indictment) ¶ 26.

After significant pretrial motion practice, Harkonen's trial began on August 12, 2009. The case went to the jury on September 23, 2009. The jury deliberated for four days, finding Harkonen guilty of wire fraud and not-guilty of felony misbranding.

Harkonen filed his post-trial motion on December 4, 2009, and the court conducted a hearing on February 19, 2009.

LEGAL STANDARD

I. Rule 29

Upon a defendant's motion under Federal Rule of Criminal Procedure 29, a court "must enter a judgment of acquittal of any offense for which the evidence is insufficient to sustain a conviction." Fed. R. Crim. P. 29. "The evidence is sufficient to support a conviction if, 'viewing the evidence in the light most favorable to the prosecution, any rational trier of fact could have found the essential elements of the crime beyond a reasonable doubt.'" *United States v. Magallon-Jimenez*, 219 F.3d 1109, 1112 (9th Cir. 2000) (citing *Jackson v. Virginia*, 443 U.S. 307, 319 (1979)). "[A]ll reasonable inferences are to be drawn in favor of the government, and any conflicts in the evidence are to be resolved in favor of the jury's verdict." *United States v. Alvarez-Valenzuela*, 231 F.3d 1198, 1201-02 (9th Cir. 2000)

II. Rule 33

Federal Rule of Criminal Procedure 33 provides that "the court may vacate any judgment and grant a new trial if the interest of justice so requires." Fed. R. Crim. P. 33. In considering a Rule 33 motion, "'[t]he district court need not view the evidence in the light most favorable to the verdict; it may weigh the evidence and in so doing evaluate for itself the credibility of the witnesses.'" *United States v. A. Lanoy Alston, D.M.D., P.C.*, 974 F.2d 1206, 1211 (9th Cir. 1991) (quoting *United States v. Lincoln*, 630 F.2d 1313, 1319 (8th Cir. 1980)). "'If the court concludes that, despite the abstract sufficiency of the evidence to sustain the verdict, the evidence preponderates sufficiently heavily against the verdict that a serious miscarriage of justice may have occurred, it may set aside the verdict, grant a new trial, and submit the issues

for determination by another jury.'" *Id*. at 1212 (quoting *Lincoln*, 630 F.2d at 1319). Such a motion should be granted, however, only "in exceptional circumstances in which the evidence weighs heavily against the verdict." *United States v. Hsieh Hui Mei Chen*, 754 F.2d 817, 821 (9th Cir. 1985) (citing *United States v. Primentel*, 654 F.2d 538, 545 (9th Cir. 1981)).

DISCUSSION

Harkonen presents three arguments for why he is entitled to the dismissal of the indictment, a judgment of acquittal or, in the alternative, a new trial. First, Harkonen asserts that his Due Process rights under the Fifth Amendment were violated because the wire fraud statute did not provide him with sufficient notice that he could face criminal sanctions for the conduct at issue in this case, and thus, the court should dismiss the indictment. Second, Harkonen contends that he is entitled to a judgment of acquittal or a new trial under, Federal Rules of Criminal Procedure 29 and 33, because, at trial, the government failed to produce sufficient evidence that he violated the wire fraud statute. Finally, Harkonen argues that he is entitled to the dismissal of the indictment or a judgment of acquittal because the conviction violates the First Amendment. Because Harkonen's sufficiency of the evidence claim forms the core of his post-trial motion, the court assesses it first.

I. Sufficiency of the Evidence

Harkonen asserts that the government failed to present sufficient evidence such that the jury could find, beyond a reasonable doubt, that he knowingly made a false or fraudulent statement with the intent to defraud. The wire fraud statute provides that:

> Whoever, having devised or intending to devise any scheme or artifice to defraud . . . by means of false or fraudulent pretenses, representations, or promises, transmits or causes to be transmitted by means of a wire . . . communication in interstate or foreign commerce, any writings, signs, signals, pictures, or sounds for the purpose of executing such scheme or artifice . . . shall be guilty of an offense against the United States.

18 U.S.C. § 1343. The jury instructions required, in part, that the jury find beyond a reasonable doubt that Harkonen (1) made at least one "false or fraudulent statement"; (2) knew the statement(s) "were false or fraudulent at the time they were made"; and (3) "acted with an intent to defraud." Docket No. 256 (Gov't's Opp'n), Exh. A (Jury Instructions) at 16. Harkonen contends the evidence at trial was insufficient for the jury to find that each of these elements had been proven beyond a reasonable doubt. The court addresses each element in turn.

A. False or Fraudulent Statement

As discussed above, the indictment against Harkonen required that the government prove beyond a reasonable doubt that the August 28, 2002 press release contained "materially false and misleading information regarding Actimmune and falsely portrayed the results of the GIPF-001 Phase III trial as establishing that Actimmune reduced mortality in patients with IPF." Indictment ¶ 26. The jury instructions reflected that burden, requiring that the jury unanimously find beyond a reasonable doubt that "the defendant made up a scheme or plan to defraud by making false or fraudulent statements, with all of you agreeing on at least one false or fraudulent statement that was made." Jury Instructions at 16. The jury

instructions explained that "[f]alse or fraudulent statements may include deceitful statements, half-truths, or statements which omit material facts. A statement is false or fraudulent if known to be untrue or made with wanton or reckless disregard for its truth or falsity and made with the intent to deceive." *Id.*; *see United States v. Woods*, 335 F.3d 993, 998 (9th Cir. 2003); *Lustiger v. United States*, 386 F.2d 132, 138 (9th Cir. 1967). Harkonen asserts the evidence introduced at trial, even when viewed in the light most favorable to the government, is insufficient to establish that the statements in the press release were false or fraudulent.

To place this argument in context, it is necessary to provide significant detail about the GIPF-001 Phase III trial, the results of which the August 28, 2002 press release purported to summarize and interpret. The jury heard considerable testimony regarding how pharmaceutical trials are generally conducted and how the drug study at issue in this case was actually conducted. The GIPF-001, which sought to test Actimmune's efficacy as a treatment for IPF, was a randomized, double-blind, placebo-controlled trial. Randomized, double-blind, placebo-controlled studies represent the "gold standard" for determining the "relationship between a drug and a health outcome." *In re Neurontin Mktg., Sales Practices, and Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 125 (D. Mass. 2009) (citing Michael D. Green et al., *Reference Guide on Epidemiology*, in *Reference Manual on Scientific Evidence* 333, 335 (Fed. Judicial Ctr. 2d ed. 2000)).

> In such a trial, subjects are assigned randomly to one of two groups: one receives the drug and the other does not, often receiving a placebo instead. The study is also "double-blind," meaning that

> neither the participants nor those conducting the study knows which group is receiving the actual drug and which group is receiving the placebo.

Id.; *see also* Trial Transcript (TT) at 361-62 (Dr. Marc Walton ("Walton"), Associate Director at the FDA, testifying about randomized, double-blind, placebo-controlled trials). The GIPF-001 involved 330 patients at 58 separate locations throughout the United States. Gov't Exh. 288 (GIPF-001 Clinical Study Report) at 74. 162 patients were treated with Actimmune, while 168 received a placebo. *Id*.

The jury heard testimony that, before undertaking a Phase III trial, like the GIPF-001, researchers set forth detailed study protocol, which includes, among other things, the objectives of the study (i.e., what causal relationships the study is attempting to measure), the inclusion and exclusion criteria for determining who will be allowed to participate in the trial, the procedures for administering the treatment and recording results, and specifications for how the data from the study will be analyzed. TT at 359, 370-71 (Walton testimony); Gov't Exh. 281 (Final Protocol for GIPF-001). After a study begins, it is not uncommon for the protocol to be changed; however, a final protocol must be in place before the study's data is "unblinded" (i.e., made available) to the study's researchers. *Id*. at 360-61 (Walton testimony). The predetermination of the study's objectives (or "end-points" as they are typically called) as well as the criteria for how the data will be analyzed (known as a "statistical analysis plan") is crucial for maintaining the integrity of the study. By prespecifying what the study is intended to measure and how it will be measured, researchers preclude themselves from manipu-

lating the data after it is "unblinded" in order to identify a favorable result. *Id*. at 371 (Walton testifying that "[i]t's well-understood if one can look at the data and then pick out which parts of the data we would like to analyze and in which way, we can always find something in the data that will look positive"); *Id*. at 2187 (Michael Crager ("Crager"), former InterMune Senior Director of Biostatistics, testifying that a statistical analysis plan is crucial to "show that the methods were not determined by the data. That is, you set the methods in advance, didn't analyze several different ways and pick the one that looks best"); *Id*. at 673 (Thomas Fleming ("Fleming"), a professor of Biostatistics at the University of Washington and a supervisor of the GIPF-001, testifying that a statistical analysis plan "recognizes that there are a large number of ways you can analyze the data. And you need to structure what is the principal analysis and what the secondary and follow-up analyses are to understand these statistical analyses").

InterMune created a protocol for the GIPF-001 in 2000, prior to the start of the trial, and made several amendments to the protocol prior to the unblinding of the data on June 26, 2002. *See* Gov't Exhs. 274-81. Throughout the various iterations of the protocol, the GIPF-001 had one primary endpoint, progression-free survival time; progression of IPF was defined as either a specific, measurable decrease in Forced Vital Capacity ("FVC"), a measure of lung function, an increase in the A-a gradient of 5 mmHg, another measure of lung function, or the death of the patient. Gov't Exh. 274 (Original Protocol) at 10; Gov't Exh. 281 (Final Protocol) at CDER003-1147. In its final form, the protocol also identified ten secondary endpoints, listed in order of clinical relevance, along with eight exploratory endpoints. Final Protocol at CDER003-1147-48. The

seventh secondary endpoint, which (as will be seen below) ultimately became crucial to the August 28, 2002 press release, was "survival time." *Id*. at CDER003-1147. In addition, the investigators created a detailed statistical analysis plan. Gov't Exh. 282.

To establish the falsity of statements made in the August 28, 2002 press release, the government called Thomas Fleming ("Fleming"), a Professor of Biostatistics at the University of Washington, and Michael Crager ("Crager"), the former Senior Director of Biostatistics at InterMune who was the principal biostatistician working on the GIPF-001. Both witnesses had substantial and impressive experience in biostatistics. Fleming testified to his distinguished thirty-year record as a biostatistician, overseeing more than 200 clinical trials, publishing more than 200 articles and several books about biostatistics, and working as a special government employee, advising the FDA regarding the effectiveness of drugs in clinical trials. TT at 644-50; *see* Gov't Exh. 256 (Fleming's Curriculum Vitae). Relevant to the instant case, Fleming served as one of three members of the Data Monitoring Committee (DMC) for the GIPF-001, which was a group of outside, independent scientists responsible for protecting the safety of the patients involved in the study. Crager received a Ph.D. in biostatistics from Stanford University, and worked in industry as a biostatistician for twenty-seven years. TT at 2175-77. He testified that, during his employment with InterMune and elsewhere, he had worked on approximately 80 to 100 clinical trials in his career. *Id*. at 2178.

The jury heard substantial testimony from Crager and Fleming regarding how investigators analyze and interpret the data from clinical trials. The significance of a trial's results is primarily expressed through what

is known as a "p-value," which is a number between 1 and 0. *Id*. at 2185-86 (Crager testimony); *id*. at 674 (Fleming testimony). The p-value is a "measure of how likely the result you saw would have been to occur by chance alone . . . ." *Id*. at 2186 (Crager testimony); *see also id*. at 674 (Fleming testifying that "[a] p-value is an analytical tool that we use to present how unlikely the events would be by chance alone"). The lower a p-value is, the greater probability that the result perceived in the data is not due to chance. Both Crager and Fleming testified that in the world of biostatistics, a p-value of 0.05 is somewhat of a magic number. *Id*. at 2186 (Crager testifying that 0.05 is a "standard cutoff"); *id*. at 674 (Fleming testifying that "by tradition, [statisticians] define 'success' to be a two-sided p-value of .05"). A p-value of 0.05 indicates that the data obtained in the trial would occur by chance less than 5 percent of the time. *Id*. As a general matter, if the p-value is less than 0.05, a study's results are considered statistically significant; if greater, than 0.05, the results are generally considered unreliable and not statistically significant. *Id*.

Crager and Fleming provided other testimony, however, that emphasized that in order to properly interpret a p-value, it is necessary to know the context in which that p-value was generated. *Id*. at 703 (Fleming testifying that "I always say that you can only interpret [p-values] when you understand the sampling context in which they were derived"); *id*. at 676 (Fleming testifying that the significance of a p-value "all depends on your sampling context"). A p-value of 0.05 or lower for a primary endpoint, a study's primary objective, generally indicates statistically significant relationship. However, for a variety of reasons, researchers must apply different statistical methodology when analyzing secondary endpoints

or any data not prespecified in the protocol and statistical analysis plan.

First, Fleming and Crager testified that even in a study where there is a statistically significant finding with respect to the primary endpoint, researchers must adjust their analysis of the p-values of secondary endpoints in order to account for the "multiplicity" effect. *Id*. at 676-78, 685 (Fleming testimony*); see also id*. at 2326 (Crager testifying that "if you were trying to do a rigorous test of a secondary endpoint, then, yes, you have to put a procedure in place that accounts for multiple testing"). Fleming described this multiplicity effect using an analogy:

> [I]f you give yourself one chance to win, if you're looking at the prespecified primary analysis of the prespecified primary endpoint, then it is true, [that if you have a p-value of 0.05] you have only a five percent chance of a false positive, only a five percent chance of declaring that you're effective when you're not. But that's not at all true if you give yourself many analyses, many chances to win.
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> . . . .
>
> It's a multiplicity issue. . . . Suppose you were looking at somebody who is . . . a good marksman. . . . If you set up a target that any one of us if we took a shot would have one in twenty chance to hit, then you took a single shot, it would be impressive if you hit it. Only one in twenty people could . . . . But if you gave that person twenty, forty, sixty, eighty shots, and they hit it once, most of us could do that. So when you're understanding a p-value it's really important to know how many different analyses were done.

Id. at 677. Accordingly, Fleming testified that if you have more than one analysis, the measure of success no longer is 0.05, but a lower threshold. Fleming suggested that industry practice was to divide 0.05 by the number of endpoints "to ensure that you are accounting for having multiple chances to win." *Id*. at 678.

Second, Fleming and Crager testified that if a study misses its primary endpoint—that is, if the p-value for the primary endpoint is greater than 0.05—that all other analyses arising out of that study, including analysis of secondary endpoints, "from there on [are] exploratory." *Id*. at 2188. (Crager testimony); *see id*. (Crager testifying that if the primary endpoint misses, "[y]ou cannot make any definitive conclusions about any [secondary endpoints], and you're just trying to look at the data to generate new hypotheses to test hopefully in the future"); TT at 678 (Fleming testifying that "in a rigorous sense, one has to be incredibly cautious about that, because the p-values that we're giving can no longer really be interpreted the way that we've been discussing. . . . [Y]ou clearly cannot interpret the p-values on those secondary measures the way you would interpret the p-value on the primary endpoint"). According to Fleming, this caution is necessary for the following reason: In designing a study, investigators hypothesize that a drug will act through certain "mechanisms" to effect the targeted biological condition. The primary endpoint is selected as the best available measure of that mechanism of effect. Secondary endpoints typically are selected as less precise measures of the same mechanism. When the primary endpoint fails, it throws the entire hypothesis regarding the mechanism of effect of the drug into doubt. It therefore casts even greater doubt upon secondary endpoints, which were predicated upon the

same mechanism, but were even less precise measures of that mechanism. Therefore, once the primary endpoint fails, investigators must be very cautious about drawing any conclusions from secondary endpoints. *See id*. at 278-79 (Fleming testimony); *see id*. at 2326 (Crager testimony).

Third, the jury heard testimony from Crager and Fleming regarding the pitfalls of drawing conclusions from exploratory subgroup analyses of the data, especially when such analyses were not prespecified in the statistical analysis plan. A subgroup analysis examines the effect of the drug on a subset of trial participants who share certain characteristics, for example only men or only older individuals. *Id*. at 682 (Fleming testimony). Fleming explained that the data from subgroup analyses is of use for exploring future hypotheses to test as a primary or secondary endpoint, but has limited if any conclusive power. As Fleming stated, subgroup analyses "are widely-recognized to be, at best, what are called 'hypothesis generating'," meaning "if you see evidence that treatment effect may differ across subgroups, that in most instances it's really critical" that they be "independently confirmed by a future trial." *Id*. at 683; *see also* Gov't Exh. 3 (September 5, 2002, letter from Fleming to InterMune) at INR544-9768 ("It is recognized that conducting exploratory subgroup analyses can be a useful exercise, but the results are notoriously unreliable. . . . [W]hen one allows multiplicity of testing by multiple analyses over time, by multiple study endpoints, and particularly by multiple trial subgroups, [a p-value lower than 0.05] would be obtained in almost any trial even when treatment truly has no effect on outcomes."); TT at 2240 (Crager explaining that even a very low p-value on a subgroup analysis is "very hard to interpret"). Fleming and Crager testified that when

such analyses are conducted on a post-hoc basis—that is, any analysis that was not prespecified in the statistical analysis plan—researchers must exercise even greater caution. *Id*. at 682-83 (Fleming explaining that post-hoc analyses "are typically very unreliable"); *id*. at 2240 (Fleming stating that post-hoc p-values "are very hard to interpret" and that, at best, a low p-value in a post-hoc analysis "means that there's a suggestion that there may be something here").

With these biostatistics principles in mind, the jury also heard substantial testimony and received evidence regarding how Harkonen and InterMune analyzed, interpreted and ultimately publicized the data from the GIPF-001 trial. Pursuant to the study's protocol, the data was kept confidential until August 16, 2002, when three of the four members of InterMune's Sponsor Management Committee ("SMC"), including Harkonen, Dr. Jim Pennington ("Pennington"), InterMune's Executive Vice President of Medical and Scientific Affairs, and Crager were unblinded. *Id*. at 2195-98; *see* Gov't Exh. 283 (Plan for Sponsor Management Committee Assessment of Study GIPF-001).[1]

On August 16, 2002, Crager was the first to examine the results of the trial. TT at 2198 (Crager testimony). He received the analysis, which had been outsourced to a company named Pharmanet, by email. *Id*. To Crager, it was immediately apparent that the study had missed its primary endpoint as well as all ten of the secondary endpoints. The p-value for the primary

[1] Marianne Armstrong, InterMune's Vice-President of Regulatory Affairs, the fourth member of the SMC, was not unblinded at the time; pursuant to the protocol, she would only be unblinded on an ad-hoc basis. *See* Plan for Sponsor Management Committee Assessment of Study GIPF-001.

endpoint, progression-free survival time, was 0.52, far too high to demonstrate any statistically significant correlation. Def. Exh. 524 (GIPF-001 Study Results) at 3UW 021625; TT at 2201 (Crager testifying that he interpreted the data as showing "[n]o apparent effect at all on the primary efficacy endpoint. The indices didn't show any difference whatsoever, and the p-values were very high showing no evidence whatsoever"). Crager did notice a "trend" toward a survival benefit, one of the secondary endpoints, which had a p-value of 0.084, slightly above the traditional 0.05 threshold of statistical significance. GIPF-001 Study Results at 3UW 021700; TT at 2201-02 (Crager testimony). 16 of the 162 patients (9.9%) being treated with Actimmune died during the duration of the study, compared to 28 of 168 patients (16.7%), representing a more than 40% decrease in mortality. GIPF-001 Study Results at 3UW 021700. After his initial review of the results, Crager reported this information to Harkonen and Pennington. TT at 2202 (Crager testimony). He told them "we had no evidence of an effect on the primary efficacy endpoint, but that there was a trend in the survival data, and that we might want to follow-up and do another trial . . . . to make survival the primary endpoint." *Id*. at 2204 (Crager testimony).

The next day, August 17, 2002, of his own accord, Crager contacted Pharmanet and requested that it run a statistical analysis of survival time for subgroups of trial participants with FVCs greater and less than 60%. *Id*. at 2205-07 (Crager testimony). As is mentioned above, FVC is a measure of lung function, in which the higher the percentage, the better the function. Crager received the subgroup results on the afternoon of August 21, 2002. *Id*. at 2210 (Crager testimony). The data indicated that only 3 of 90 patients treated with Actimmune who had a FVC greater than

60% died during the study, while 12 of 92 with a FVC lower than 60% died, yielding a p-value of 0.024. GIPF-001 Study Results at 3UW 021702. Upon receiving the results, Crager shared them with Harkonen and Pennington. *Id*. at 2210 (Crager testimony). Harkonen then directed Crager to request that Pharmanet run a different subgroup analysis, dividing the patients into severe, moderate and mild IPF sufferers on the basis of their FVC. *Id*. at 2210 (Crager testimony). Harkonen suggested looking at three subgroups: those with severe IPF (FVC 0-55%), moderate IPF (FVC 56-70%) and mild IPF (FVC 71-100%), but asked Crager to verify that those FVC parameters represented appropriate definitions for severe, moderate and mild IPF. *Id*. at 2210-11 (Crager testimony). Crager conferred with pulmonologists inside and outside of InterMune, but was unable to confirm whether the categories suggested by Harkonen were well-established. *Id*. at 2211 (Crager testimony). Crager ultimately requested that Pharmanet conduct the subgroup analysis using the parameters selected by Harkonen. *Id*. at 2211-12.

Crager received the results from this second subgroup analysis the next day, on August 22, 2002. *Id*. at 2212 (Crager testimony). He delivered them to Harkonen, who then asked Crager to run the data for two subgroups, those with FVC greater than and less than 55%, essentially combining the moderate and mild IPF sufferers into one group. *Id*. at 2212-13. Crager did so, and he shared the somewhat optimistic results with Harkonen. Only 6 of the 126 (4.8%) participants treated with Actimmune in the mild to moderate group died during the study, while 21 of 128 (16.4%) in the corresponding placebo group died,

representing a greater than 70% reduction in mortality. GIPF-001 Study Results at 3UW 021707. This data yielded a p-value of 0.004. *Id*.

The 55% FVC subgroup analysis represented the last new piece of information regarding the GIPF-001 trial received by InterMune and Harkonen prior to the issuance of the August 28, 2002 press release. Thus, in sum, the jury heard competent evidence that (1) the GIPF-001 study showed no efficacy with respect to its primary endpoint, progression-free survival time (p=0.52); (2) none of the secondary endpoints produced a p-value below 0.05; (3) the closest secondary endpoint, survival time, yielded a p-value of 0.084 as a result of 40% decrease in mortality among those treated with Actimmune; (4) a post-hoc subgroup analysis of study participants with an FVC greater than 60% yielded a p-value of 0.02; and (5) a post-hoc, subgroup analysis of study participants with an FVC greater than 55% yielded a p-value of 0.004 as a result of a 70% decrease in mortality among those treated with Actimmune.

On August 28, 2002, InterMune issued a press release purporting to publicize the results of the GIPF-001 trial. *See* Press Release. As will be discussed in more detail below, Harkonen was the controlling force behind the content of the press release. At trial, the government contended that a number of the statements in the press release, as well as the press release as a whole, could be found to be false or fraudulent, including:

> —The headline: "InterMune announces Phase III data demonstrating survival benefit of Actimmune in IPF"

—The subheadline: "Reduces Mortality by 70% in Patients with Mild to Moderate Disease"

—"InterMune, Inc. (Nasdaq:ITMN) announced today that preliminary data from its phase III clinical trial of Actimmune (Interferon gamma-1b) injection for treatment of idiopathic pulmonary fibrosis (IPF) . . . demonstrates a significant survival benefit in patients with mild to moderate disease randomly assigned to Actimmune versus control treatment (p = 0.004)."

—"'We are extremely pleased with these results, which indicate Actimmune may extend the lives of patients suffering from this debilitating disease,' said W. Scott Harkonen, M.D., President and CEO of InterMune."

—"Importantly, Actimmune also demonstrated a strong positive trend in increased survival in the overall patient population, and a statistically significant survival benefit in patients with mild to moderate IPF. In the overall population, there were 16/162 deaths in the Actimmune-treated group (9.9%) compared to 28/168 deaths in the placebo group (16.7%), representing a 40% decrease in mortality in favor of Actimmune vs. placebo (p = 0.084)). Further, of the 254 patients with mild to moderate disease ([Forced Vital Capacity] (FVC) >= 55 percent), there were 6/126 deaths in the Actimmune-treated group (4.8%) and 21/128 deaths in the placebo group (16.4%), representing a 70% decrease in mortality in favor of Actimmune versus placebo (p = 0.004)."

Press Release.

Given the above-discussed evidence and testimony introduced at trial, there was sufficient evidence for

the jury to conclude beyond a reasonable doubt that multiple statements contained in the press release were false or fraudulent. First, the jury could have found that the headline of the press release was objectively untrue. The jury heard uncontroverted testimony from Crager and Fleming that any p-value greater than 0.05 indicates that the results of a study are not statistically significant. Throughout the trial, the jury also heard testimony and received evidence that the data for the secondary endpoint of survival time yielded a p-value of 0.084. Accordingly, the jury could have concluded beyond a reasonable doubt that the GIPF-001 study failed to "demonstrat[e]" a survival benefit and thus, that the statement—"Phase III data demonstrat[es] survival benefit of Actimmune in IPF"—was false or fraudulent.

Second, the jury could have found that Harkonen's choice of words in the press release implied causation between Actimmune and the survival of IPF patients, when the data from the study objectively did not establish any such certain and/or verifiable relationship. The jury heard credible testimony that in clinical trials with multiple endpoints, where the primary endpoint is missed, and where researchers conduct post-hoc, subgroup analyses, p-values are unreliable. Thus, depending on the context, sub-0.05 p-values do not "demonstrate", prove, establish or indicate anything. Under such circumstances, secondary endpoint and post-hoc, subgroup analyses can only be used in an exploratory manner, providing researchers with some indication about additional relationships between a drug and a condition that might warrant further investigation. The press release, however, equates a p-value of less than 0.05 with statistical significance, causation and efficacy without any adjustment for context, including for secondary endpoints and post-

hoc analyses. *See* Press Release ("Phase III data *demonstrat[es]* survival benefit of Actimmune in IPF"); *id*. (Actimmune "*Reduces* Mortality by 70% in Patients with Mild to Moderate Disease"); *see also id*. ("'Actimmune is the only available treatment *demonstrated* to have clinical benefit in IPF.'").

Magnifying this component of the press release's falsity is the complete omission of any mention that the only results with a p-value less than 0.05—the subgroup analysis of patients with mild to moderate IPF—were observed only after InterMune engaged in retrospective analysis. As the testimony of Crager and Fleming made clear, the import of such a finding cannot possibly be understood unless readers are provided with sampling context. Yet the press release never explains the context in which InterMune arrived at the 0.004 p-value for the mild to moderate IPF subgroup. Further, the press release does not explain that the study protocol set out ten secondary endpoints—of which survival time was ranked as only the seventh most clinically relevant—and that all ten failed to produce statistically meaningful results. These omissions of critical information—especially given that at the time of the press release there was no publically available data for the GIPF-001 such that interested individuals could verify the results—could have formed the basis for the jury's finding of falsity. The court instructed the jury that a statement is false or fraudulent if it "include[s] deceitful statements, half-truths, *or statements which omit material facts*." Jury Instructions at 16 (emphasis added). In light of Crager and Fleming's testimony, the jury could have found beyond a reasonable doubt that the sampling context—the use of multiple endpoints and post-hoc, subgroup analysis—was a material fact that

was omitted from the press release, and thus, that the press release was false or fraudulent.

Finally, the jury could have concluded that the press release, as a whole, was false or fraudulent. The overwhelming, undisputed evidence at trial was that the GIPF-001 study was a failure. It missed its primary endpoint as well as all ten secondary endpoints. The press release, however, describes the study as a success—demonstrating a survival benefit and reducing mortality for those who were treated with Actimmune. To be certain, pharmaceutical companies are permitted to put a positive spin on the results of a clinical trial. They must do so, however, with candor and disclosure. In the instant case, the jury could have found that the press release was so optimistic, in the face of the trial's objective failure, that it constituted fraud.

Harkonen's primary argument against these interpretations of the evidence is that none of the witnesses were properly qualified as experts to testify regarding the truth or falsity of the press release. At the June 24, 2009, hearing on the parties *in limine* motions, the court granted Harkonen's motion to limit the testimony of certain percipient witnesses—namely Dr. Marc Walton ("Walton"), an Associate Director at the FDA who communicated extensively with InterMune about the GIPF- 001 and the related press release, and Marianne Armstrong ("Armstrong"), InterMune's Vice President of Regulatory Affairs—who lacked professional and educational backgrounds in pulmonology or biostatistics. Under the Federal Rules of Evidence 701 and 702, the court held that such witnesses would not be permitted to opine regarding the truth or falsity of the statements in the press release, but would be

allowed to testify about their conversations or interactions with Harkonen, as such testimony went not to the truth of the matter asserted, but to Harkonen's notice of the alleged infirmities in the press release. Because these witnesses were limited to providing testimony that went to Harkonen's notice, Harkonen asserts that the jury possessed insufficient evidence to conclude that the press release did, in fact, contain at least one false or fraudulent statement.

In so arguing, Harkonen entirely overlooks that the testimony from Crager and Fleming regarding how to interpret statistical results was properly before the jury. Harkonen's motion *in limine* did not seek to exclude opinion testimony from Fleming, despite the fact that Harkonen was on notice that the government might proffer Fleming as an expert witness. *See* Docket No. 127 (Def.'s Mot. *In Limine*) (no mention of Fleming); Docket No. 116 (Gov't's Notice of Expert Testimony) at 5-6 (identifying Fleming as a potential expert witness and laying out his qualifications). Although Harkonen did move to exclude testimony from Crager regarding the truth or falsity of the press release, *see* Def.'s Mot. *In Limine* at 17-18, the above-discussed portions of his testimony regarding the proper method for interpreting clinical data did not speak directly to the press release's truth or falsity. Rather, he discussed general biostatistics methodology and conventions, about which he was qualified to testify. This testimony was therefore properly admitted.

Further, although the government did not officially proffer either Crager or Fleming as an expert, in its expert witness disclosure, the government did list Crager and Fleming as potential expert witnesses. *See* Gov't's Notice of Expert Testimony; Docket No. 132

(Gov't's Am. Notice of Expert Testimony). At trial, the government entered Fleming's curriculum vitae into evidence, and questioned both Fleming and Crager extensively about their "knowledge, skill, experience, training, or education." Fed. R. Evid. 702. On cross-examination, Harkonen had the opportunity to ask questions that might undermine the jury's confidence in the witnesses' expertise or knowledge of biostatistics methods. To the contrary, however, Harkonen asked both Crager and Fleming numerous questions about statistical methodology. Perhaps most damningly, at no point during the trial did Harkonen ever object to any of Crager or Fleming's testimony about general principles of biostatistics; specifically, no objection was raised to their testimony regarding the inherent problems of interpreting secondary endpoint and post-hoc, subgroup analyses.[2] Such testimony was properly before the jury; and the jury could have relied upon it to conclude that the statements in the press release were false or fraudulent.

Harkonen also suggests that his motion should be granted because that [sic] there was sufficient evidence introduced at trial from which the jury could have concluded that the statements in the press

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[2] Although it does not factor in the court's analysis, the court has little doubt that if the government had formally proffered Fleming or Crager as expert witnesses, the court would have so qualified them. Harkonen conceded as much, at least with respect to Crager, during the *in limine* motion hearing. Harkonen's counsel explained that Crager is "a biostatistician. He can say whatever he wants, you know. What I'm saying: he can say whatever is appropriate as an expert if he's duly qualified. *It's hard for us to argue that he's not qualified as a biostatistician, since he's working for the company. And I think it's fair to say that he will be qualified*." Docket No. 152 (*In Limine* Hearing Transcript) at 38 (emphasis added).

release were true. For this argument, Harkonen relies on the testimony of other individuals involved in conducting GIPF-001 and publicizing its results, and upon exhibits admitted at trial. In particular, Harkonen points to statements made by Crager in a patent application filed by InterMune regarding Actimmune.[3] To be certain, a number of witnesses who testified, including Crager, Armstrong and Stephen Rosenfield ("Rosenfield"), InterMune's general counsel, agreed, either contemporaneous with the issuance of the press release or at trial, with some of the statements in the press release, including the statement that the data demonstrated a survival benefit. Such information may be probative of whether Harkonen possessed an intent to deceive when issuing the press release. However, simply because numerous individuals may have repeated a fraudulent characterization of the data from the GIPF-001 does not make that characterization less false or fraudulent.

Accordingly, the court holds that there was sufficient evidence for the jury to conclude beyond a reasonable doubt that statements in the press release

[3] The patent application, on which Crager was identified as a co-inventor, included the statements that "[a] statistically significant improvement in probability or survival was apparent in certain subpopulations of the treatment and placebo groups" and that "[t]here is strong statistical evidence the [Actimmune] has a positive survival effect in [patients with mild to moderate FVC]." Def. Exh. 718 (Patent Application) at ITM_CBNY19106, ITM_CBNY19107. The statements sworn to by Crager in the patent application are irrelevant, however. Whether Crager believed that the statements in the press release were false or fraudulent speaks not at all to whether the statements were objectively false or fraudulent.

and/or the press release as a whole were false or fraudulent.

B. Knowledge of Falsity

At Harkonen's trial, there was also sufficient evidence for the jury to find that Harkonen knew that the statements in the press release were false—the second element of wire fraud. The government did not introduce any evidence at trial regarding Harkonen's own understanding of biostatistics such that the jury could have inferred that Harkonen knew that the press release's characterization of the data for the survival secondary endpoint and the post-hoc, subgroup analysis were false or fraudulent. Accordingly, the government was required to introduce other evidence that Harkonen was somehow on notice that the manner in which the press release interpreted the data was false or fraudulent.

The evidence showed that Harkonen received the requisite notice on a number of occasions prior to August 28, 2002, the date that the press release was issued. To begin with, the evidence overwhelmingly established that prior to August 28, 2002, Harkonen had been told by multiple sources that the GIPF-001 missed its primary endpoint, progression-free survival time, as well as all ten secondary endpoints, including survival time. *See, e.g.*, TT at 2204 (Crager testifying about informing Harkonen on August 16, 2002, that the study had missed the primary and all secondary endpoints); *id*. at 684-86 (Fleming informing Harkonen at an August 19, 2002, meeting of the Steering Committee that the study had missed the primary and all secondary endpoints and that "the trial had not provided evidence that Actimmune provides a clinically-meaningful effect."); Gov't Exh. 61 (Draft Minutes of August 27, 2002, conference call with FDA,

on which Harkonen was copied in which Dr. Marc Walton reemphasized that the study missed its primary and all secondary endpoints).

More importantly, at least two individuals informed Dr. Harkonen that the survival "trend" in the secondary survival endpoint and the 0.004 p-value for the post-hoc, subgroup analysis of the mild to moderate IPF sufferers were interesting findings, but unreliable and inconclusive. On August 26, 2002, at a meeting at InterMune's headquarters, Dr. Steven Porter, InterMune's Senior VP of Clinical Affairs and Chief Medical Officer, informed Harkonen that "[i]t was impossible to know if these findings [the secondary endpoint of survival and the subgroup analysis] were real or not." TT at 1366; *see id*. at 1364 (Porter indicating to Harkonen "that around the observations on survival that it was impossible to tell whether they were chance or real"). On August 27, 2002, InterMune, including Harkonen, Crager, Pennington, Porter and others, initiated a conference call with Drs. Jim Kaiser, Dwayne Rieves, and Marc Walton from the FDA. Armstrong recorded minutes of the meeting which were then circulated among the InterMune employees who were on the call so that they could make any edits they deemed appropriate. The final version of the minutes indicates that Walton stated that "because the physiologic measurements did not show any apparent treatment effect, the decrease in mortality in his opinion could be considered 'almost an anomalous finding in the face of no effect on pulmonary function and so warrants extra caution.' Furthermore, he stated '[t]here was no way to give it [the survival data] a meaningful p-value in the face of the failed primary endpoint.'" Def. Exh. 671 (Minutes from August 27, 2002, conference call with FDA).

Accordingly, the government introduced sufficient evidence from which the jury could conclude that Harkonen was on notice (1) that the study failed to meet its primary endpoint and any of its secondary endpoints, and (2) that no conclusions could be drawn from the data regarding a survival benefit (both regarding the secondary endpoint and the post-hoc subgroup). From these inferences, the jury could have found beyond a reasonable doubt that Harkonen knew the statements in the press release trumpeting the success of the study were false.

C. Intent to Defraud

The jury also could infer from evidence introduced at trial that Harkonen issued the document with an intent to defraud. The press release itself indicates Harkonen's financial motivation; the release states in its third paragraph InterMune expected that the results of the GIPF-001 study would "lead to peak sales in the range of $400 - $500 million per year, enabling [InterMune] to achieve profitability in 2004 as planned." Press Release. Stephen Rosenfield, InterMune's general counsel at the time, testified that the press release was the most important in the company's history. TT at 2560, 3285-86, 3366. Further, given the testimony about Harkonen's role in the company as the CEO, the jury could have concluded that he and the company stood to benefit substantially if Actimmune sales increased.

Finally, the efforts engaged in by Harkonen to prevent certain individuals, both outside and inside InterMune, from reviewing the press release serves as powerful circumstantial evidence of his intent to defraud, as well as his knowledge of falsity. To draft the release, Harkonen worked with James Weiss ("Weiss"), the head of Weiscomm, a communications firm that

helps companies in drafting press releases. Weiss and Harkonen began trading drafts on August 25, 2002, and continued to refine the press release until it was finalized on August 27, 2002. Gov't Exhs. 13-14 (Email with attachment from Weiss to Harkonen dated August 25, 2002). Prior to the August 27, 2002 offsite meeting of the steering committee for the GIPF-001 study, no one other than Harkonen or Weiss viewed any of the drafts of the press release. TT at 2562-81 (Weiss testimony). During that meeting, Armstrong, Porter and Crager were able to briefly view a draft of the release by looking over Weiss' shoulder, but were not provided with an opportunity to comment on its contents. TT at 2584 (Weiss testimony). None of them was provided with a full version of the press release at that time or any time before its issuance. *Id*. Toward the end of the meeting, Armstrong, Porter and Crager had gathered around Weiss to attempt to examine the press release; Harkonen ordered Weiss out of the conference room and sent him back to InterMune's headquarters so that he would not be bothered. *Id*. at 2588 (Weiss testimony). Although some InterMune employees, including James Donovan from InterMune's investor relations and Rosenfield did review the entire press release before it was issued the following morning, no one with a medical or statistical background or who had reviewed the data from the GIPF-001, ever reviewed the press release prior to its issuance. *Id*. at 2577 (Weiss testimony). This lack of review occurred despite testimony from Weiss that on other occasions when he worked with InterMune on pharmaceutical related press releases, he had access to the raw data as well as InterMune's medical staff. *Id*. at 2581 (Weiss testimony). Although this testimony about Harkonen's departure from normal press

release procedures and his desire to prevent his technical staff from reviewing the press release, standing alone, would likely have been insufficient to satisfy the intent to defraud element of wire fraud, in conjunction with the other evidence in the record and discussed above, it could have bolstered the jury's finding with respect to intent.

Accordingly, the court holds that the government introduced sufficient evidence for the jury to find beyond a reasonable doubt that Harkonen acted with the intent to defraud.

* * * *

Having found that the government introduced sufficient evidence to satisfy each of the elements of wire fraud beyond a reasonable doubt, defendant Harkonen's motion for a judgment of acquittal under Federal Rule of Criminal Procedure 29 is DENIED.

II. Rule 33 Motion

The court further finds that the evidence in this case did not "preponderate sufficiently heavily against the verdict that a miscarriage of justice may have occurred." *A. Lanoy Alston, D.M.D., P.C.*, 974 F.2d at 1212. The court incorporates, by reference, the preceding discussion of the evidence introduced at trial, both in favor of and against conviction. Although Harkonen cites to some additional evidence that militated in favor of an acquittal—that none of the statistics cited in the press release were false; that on August 23, 2002, Crager characterized the results of the trial as showing a trend of a survival benefit, TT at 2342-43; that Walton testified that debate about the meaning of p-values can be "vigorous," *id*. at 632-33; that Crager testified that the 55% FVC cutoff for mild to moderate IPF was an appropriate cutoff according

to the scientific understanding of IPF, *id*. at 2309; that Armstrong testified to telling the FDA in 2003 that three clinical trials of Actimmune, of which the GIPF-001 was one, "demonstrated a survival benefit," *id*. at 2023-24; that Rosenfield testified that Crager was "euphoric" about the subgroup analysis, *id*. at 3094-95, and that Crager and Pennington had used the word "demonstrating" with respect to survival benefit prior to the issuance of the press release, *id*. at 3136-37; that personnel at InterMune later stood by the press release's characterization of the data, *id*. at 2023-25 (Armstrong testimony); *id*. at 3393-94 (Rosenfield testimony); *id*. at 1617-18 (Dr. Wayne Hockmeyer, member of the InterMune board of directors at the time of the press release's dissemination, testifying that Pennington stood by the characterization of the data at the September 2002 InterMune board meeting); that Crager admitted to never complaining to anyone at InterMune about the accuracy of the press release prior to his leaving the company, *id*. at 2301-02; and that InterMune personnel characterized the data in a positive light in documents created both before and after the issuance of the press release, Gov't Exh. 12 at 4 (Slide created by Crager summarizing the key results of the GIPF-001); Def. Exh. 718 at 36 (Patent application); Gov't Exh 288 at 84 (InterMune's Final Clinical Study Report for the GIPF-001, which was submitted to the FDA)—no miscarriage of justice occurred in his trial. The government met its burden of proof, and did so convincingly. Furthermore, none of the other grounds for acquittal or a new trial argued for by Harkonen and discussed fully below, alter the court's appraisal of the proceedings. Accordingly, Harkonen's motion for a new trial pursuant to Rule 33 is DENIED.

III. Motion to Dismiss or Acquit Under First Amendment

Having found that the government introduced sufficient evidence to support Harkonen's conviction for wire fraud and that the "interests of justice" do not compel a new trial, the court need not expend much energy discussing Harkonen's arguments for dismissal on First Amendment grounds. On June 4, 2009, before Harkonen's trial, the court denied a motion to dismiss the indictment on First Amendment grounds. *United States v. Harkonen*, No. C 08-00164 MHP, 2009 WL 1578712 (N.D. Cal. June 4, 2009). The court held that because, at least according to the indictment, the speech at issue was not "First Amendment-protected as pure scientific speech or ideas, the court must allow the case to advance to a jury for determination of whether the government can prove the fraud charges based on speech that may be entitled to lesser protection under the First Amendment." *Id*. at *8.

The jury concluded that Harkonen committed wire fraud by knowingly issuing false or fraudulent statements in the August 28, 2002 press release with an intent to defraud. As a result, the First Amendment provides Harkonen with no defense from his conviction, as "it is well settled that the First Amendment does not protect fraud." *United States v. Philip Morris USA Inc*., 566 F.3d 1095, 1123 (D.C. Cir. 2009) (citing *McIntyre v. Ohio Elections Comm'n*, 514 U.S. 334, 357 (1995)); *see, e.g., United States v. Lyons*, 472 F.3d 1055, 1066 (9th Cir. 2007) (holding, with respect to mail fraud conviction, that the First Amendment does not "insulate[] defendants from criminal prosecution for fraudulent misrepresentations"). Accordingly, Harkonen's motion to dismiss the indictment or for a new

trial grounded in the First Amendment is therefore DENIED.

IV. Motion to Dismiss or Acquit Under Fifth Amendment

Harkonen's assertion that he is entitled to the dismissal of the indictment or a judgment of acquittal under the Fifth Amendment because he was not provided with fair notice that the conduct he engaged in was criminal requires only slightly more discussion. Harkonen is certainly correct that in order to protect individuals' Fifth Amendment rights, criminal statutes must provide explicit guidance regarding what is illegal and what is not. *See, e.g., Vill. of Hoffman Estates v. The Flipside*, 455 U.S. 489, 498 (1982) ("[W]e insist that laws give the person of ordinary intelligence a reasonable opportunity to know what is prohibited, so that he may act accordingly. Vague laws may trap the innocent by not providing fair warning."). In certain circumstances, vagueness concerns might imperil a conviction for wire fraud. *See, e.g., United States v. Bruchhausen*, 977 F.2d 464 (9th Cir. 1992) (dismissing indictment and reversing conviction for wire fraud because the word "property" in the wire fraud statute could not be read to include either (1) manufacturers interest in controlling who possessed goods that were fully paid for or (2) the United States' "ethereal" forfeiture interest in the goods that were sold).

The instant case does not, however, implicate any vagueness concerns. As the above-discussion details, the jury had before it sufficient evidence to conclude that Harkonen misrepresented the GIPF-001 results by stating that the data demonstrated a survival benefit when it, in fact, did not demonstrate anything. Further, Harkonen's omission of the material fact that

the data regarding the mild to moderate subgroup was derived from post-hoc analysis also subjected him to criminal liability. In other words, the jury could have concluded that the statements in the press release were objectively false, and not open to any reasonable interpretation. To contend that Harkonen was not on notice that if he lied in a press release about the success of clinical trial for a drug that might have sales as high as $500 million per year is simply ludicrous. The cases relied upon by Harkonen do not require the court to reach a different conclusion.[4]

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[4] Each of the cases cited by Harkonen is readily distinguishable.

In *United States ex rel. Haight v. Catholic Healthcare West*, 2007 WL 2330790, at *2 (D. Ariz. Aug. 14, 2007), the court granted summary judgment for the defendant in a False Claims Act action because the alleged misstatements of scientific fact in an NIH grant application that formed the basis for the action were colorably true. In the instant case, as discussed above, Harkonen's statement that the GIPF-001 demonstrated a survival benefit was objectively false.

In *In re Medimmune, Inc. Securities Litigation*, 873 F. Supp. 953 (D. Md. 1995), the court granted the defendants' motion to dismiss a shareholder lawsuit. Harkonen seizes on a quotation from the case—that "[m]edical researchers may well differ over the adequacy of given testing procedures and the interpretation of test results." *Id*. at 966. Harkonen ignores, however, that the court dismissed the case not because the statements made by representatives of the company were not false or fraudulent, as a matter of law, since they touched upon issues of scientific debate, but rather because plaintiffs failed to adequately plead facts to support the requisite scienter—that defendant acted in "bad faith or . . . with an intent or recklessly to deceive, manipulate, or defraud." *Id*. In the case at bar, the court has already discussed the evidence introduced at trial regarding Harkonen's intent to defraud.

In re Biogen Securities Litigation, 179 F.R.D. 25 (D. Mass. 1997), cited by Harkonen for the proposition that failure to disclose that a study failed to meet its primary endpoint and

secondary endpoints could not form the basis for a securities class action, actually supports the government in Harkonen's case. In *Biogen*, the court found that some, but not all, of the alleged misrepresentations made by the defendants could support a shareholder action. To begin with, the court held that the following statements—"that the results of the 'pivotal TIMI-7 trial' encouraged Biogen, that 'what we've seen to date looks good' and that 'we believe that given positive clinical results we have a very large potential market for the drug,'" *id*. at 36—were sufficiently definite to serve as the foundation of a fraud claim. The claim by Harkonen that the GIPF-001 demonstrated a survival benefit, along with the generally positive tone of the press release, are similar in nature. More importantly, the misstatements of fact rejected by the court differed in material ways from the statements made by Harkonen in the press release. In *Biogen*, the plaintiffs sought to predicate the defendants' liability on defendants' failure to disclose that the positive results of the study were achieved solely through post-hoc, retrospective analysis and to explain that the study had missed all twenty-four of its secondary endpoints. As in *Medimmune*, the court rejected such claims because of the plaintiffs' failure to support the scienter element of fraud, and not because the omissions could not satisfy the first element—a false or fraudulent statement—of a fraud claim.

In *DeMarco v. Depotech Corp*., 149 F. Supp. 2d 1212, 1224-25, 1230-31 (S.D. Cal. 2001), a court dismissed a securities class action because, in Harkonen's words, the "plaintiffs only established a *legitimate* difference of opinion as to the proper statistical analysis." Docket No. 247 (Def.'s Mot.) at 16 (emphasis added). Here, however, as is discussed at length above, the press release's characterization of the GIPF-001's results were illegitimate and objectively false.

Finally, in *Noble Asset Management v. Allos Therapeutics*, 2005 WL 4161977, at *6-8 (D. Colo. Oct. 20, 2005), the defendant disclosed in a press release that certain results from its study were the product of post-hoc subgroup analysis. The court dismissed plaintiffs claims because plaintiffs merely complained that the defendant did not explicitly state that, according to the FDA, post-hoc subgroup analyses, are exploratory. Because the FDA had made public its position regarding such analyses, the

Harkonen also argues that since no law or regulation other than the wire fraud statute placed him on notice that his conduct was criminal, his Fifth Amendment rights were violated. In so arguing, Harkonen mischaracterizes the nature of his criminal violation. Admittedly, there is no law that precludes a company from reporting results of a post-hoc, subgroup analysis in a press release touting the results of a clinical trial. In fact, there was substantial testimony from Crager and Fleming that such analyses are good science and part of the investigatory process. There is, however, a law—the wire fraud statute—that prohibits individuals from making objective misrepresentations about clinical trial results and from omitting material facts about the nature of the analysis of those results with an intent to defraud. The wire fraud statute provided Harkonen with more than sufficient notice about what was legal and what was illegal.

Accordingly, Harkonen's motion to dismiss the indictment and for acquittal on Fifth Amendment grounds is DENIED.[5]

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defendant's omission of the information could not form the basis for a fraud claim. Quite obviously, Harkonen's case differs because the press release that he drafted fails entirely to disclose that the reduction in mortality for those with mild to moderate IPF was observed only through post-hoc, subgroup analysis.

[5] On July 7, 2010, Harkonen filed a motion for leave to file a supplemental brief regarding the impact of a recent Supreme Court case, *Skilling v. United States*, 130 S. Ct. 2896 (2010), on his Fifth Amendment notice claims. Docket No. 264 (Mot. for Leave to File Supp. Br.). *Skilling* involved a defendant's challenge to the "honest services" provision of the wire fraud statute, which provides that one type of a "scheme or artifice to defraud" punishable as wire fraud is "a scheme or artifice to deprive another of the intangible right of honest services." 18 U.S.C. § 1346. In *Skilling*, the Supreme Court narrowed the reach of the

V. Motion for New Trial because of Erroneous Evidentiary Rulings

Harkonen asserts that the court issued three erroneous evidentiary rulings that entitle him to, at a minimum, a new trial. The court addresses each independently.

Firstly, Harkonen contends that the court erred in excluding evidence, proffered by Harkonen, that the FDA took no formal action to condemn the issuance of the press release. *See* Docket No. 152 (Hearing Transcript, 6/24/09) at 60-61. The court ruled that such evidence was irrelevant because "there are a whole variety of reasons" why an agency may or may not take action. *Id*. at 60. The court stands by its initial ruling, as evidence of FDA action or inaction would have had no bearing on either the falsity of the press release or Harkonen's state of mind.

Secondly, Harkonen argues that the court impermissibly excluded a set of analyst reports interpreting the press release and the results of the Phase III trial. *See* TT at 1200-01. The court excluded the reports

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"honest services" provision to "encompass only bribery and kickback schemes" in order to avoid construing the statute in a manner that would give rise to fair notice and vagueness challenges. *Skilling*, 130 S. Ct. at 30.

While *Skilling* addresses the issue of fair notice in a general manner, the decision has absolutely no bearing on Harkonen's case. Harkonen was charged with and convicted of violating 18 U.S.C. section 1343, the wire fraud statute. As discussed above, Harkonen was on notice that if he sent a misrepresentation using the wires as part of a scheme to defraud, he could be prosecuted under section 1343. The "honest services" provision, narrowed by the Supreme Court in *Skilling*, played no role in this prosecution. Therefore, Harkonen's motion for supplemental briefing is DENIED.

as inadmissible hearsay, and rejected Harkonen's contention that they could be admitted through the business records exception to the hearsay rule. Harkonen now argues that the reports were admissible as non-hearsay to demonstrate that Harkonen could reasonably believe in the accuracy and appropriateness of the press release. Harkonen preserved this argument in his opposition to the government's motion to exclude the analyst reports. *See* Docket No. 180 (Response to Govt's Objections to Hearsay and Reliance Evidence) at 5-6. Harkonen's argument remains unpersuasive. The jury instructions clearly explained that Harkonen could only be found guilty of wire fraud if the contents of the press release were false or fraudulent. Analyst reports interpreting the press release after its issuance cannot possibly reflect on Harkonen's state of mind as he was issuing the press release over the wires. Those analyses are thus irrelevant to the wire fraud count.

Finally, Harkonen complains that the court improperly permitted Fleming, Crager and Armstrong to testify, over objection, regarding the truth or falsity of the press release. In each instance, however, the testimony was properly admissible to explain the witnesses' state of mind and why they engaged in certain conduct. Accordingly, none of the purported evidentiary errors that occurred during Harkonen's trial would justify dismissal or a new trial.

VI. Motion for New Trial Because of Prosecutorial Misstatements

Harkonen also contends that the prosecutor made three misstatements during closing arguments that necessitate a new trial: (1) that InterMune "never sought a label for Actimmune for IPF" (even though Harkonen asserts it spent millions of dollars seeking

FDA approval), TT at 3708; (2) that an August 27, 2002, phone call, between Drs. Kaiser and Walton, both FDA employees, and various InterMune employees, was an official "FDA call" (even though both parties acknowledge it was an unofficial conversation), *id*. at 3584-85; and (3) that numerous witnesses, including Drs. Fleming, Crager, Porter, Schwieterman and Armstrong, testified as to the falsity of the August 28, 2002 press release (when, in fact, they were only permitted to testify as to Harkonen's notice regarding the contents of the press release), *id*. at 3698-99.

Prosecutorial misconduct justifies granting a new trial, when, "considered in the context of the entire trial, that conduct appears likely to have affected the jury's discharge of its duty to judge the evidence fairly." *United States v. Simtob*, 901 F.2d 799, 806 (9th Cir. 1990) (citing *United States v. Young*, 470 U.S. 1, 11 (1985)). Because Harkonen did not make contemporaneous objections to any of the purported misstatements, his prosecutorial conduct claims face an uphill battle; a district court's denial of a motion for a new trial predicated on accusations of prosecutorial misconduct or misstatements to which the defendant did not object at trial is reviewed only for plain error, *see United States v. Sanchez*, 176 F.3d 1214, 1218 (9th Cir. 1999).

To begin, even assuming the first two alleged misstatements were in fact misstatements, they do not require a new trial. Both statements, especially the first, were of relatively minor import and neither were central to the jury's primary considerations for the wire fraud count: the falsity of the August 28, 2002 press release and Harkonen's intent in drafting and issuing the press release. The statement regarding whether InterMune sought a label, i.e., FDA approval,

for Actimmune was primarily related to the misbranding count, and was nearly irrelevant to the wire fraud count. As for the use of the phrase "FDA call" and its potential to confuse the jury as to the unofficial nature of that call, it is clear, when viewed in the context of the prosecutor's argument, that the phrase was simply used as a shorthand. Further, the prosecutor emphasized in the same stage of her argument that the "the call was unofficial. FDA made that clear up front . . . ." TT at 3585.

The prosecutor's statements regarding various doctors' views of the reliability of the data from the GIPF-001 study presents a slightly closer issue. Harkonen is correct that the government was limited to presenting those individuals' views for the notice they provided to Harkonen about the potential inaccuracies in the press release, and not as proof of the press release's actual falsity. At points, the prosecutor's argument came close to asserting that the witnesses testified regarding the falsity of the press release. Because the truth or falsity of the press release was absolutely central to the trial, the prosecutor ought to have more carefully cabined her comments. Still, when viewed in the context of the relevant portion of her rebuttal argument, the statements ultimately do go to notice as opposed to falsity. As a run-up to the challenged statements, the prosecutor said that Harkonen was "told time and again that the trial did not demonstrate a survival benefit." *Id*. at 3697. The prosecutor then proceeded to list a number of instances in which Harkonen was put on notice of the problems with the press release and his interpretation of the study's results. The prosecutor concluded this section of her argument with the following passage, to which Harkonen primarily objects:

> Every single witness: Professor Fleming, Michael Crager, Steven Porter, Marianne Armstrong, although for her it really was for notice to the defendant, Dr. Schwieterman, . . . every single one of them said either before or after the press release, and some of them before and after the press release, that you couldn't rely on this data.

Id. at 3698-99. Harkonen contends that by specifying that Armstrong's testimony "really was for notice to the defendant," the prosecutor insinuated that the other witnesses were testifying regarding something else, namely the falsity of the press release. However, by referring to what the witnesses testified to regarding what they "said either before or after the press release," the prosecutor made clear that she was discussing Harkonen's notice of their views, not the views themselves. Viewed in that manner, the prosecutor's statement goes to notice, not falsity. Accordingly, because the prosecutor's statement was proper, Harkonen is not entitled to a new trial.

VII. Motion for New Trial Because of Improper Jury Instructions

Finally, Harkonen asserts that two errors in the jury instructions necessitate a new trial. First, Harkonen objects to the court's refusal to grant his request to deliver a "good faith" instruction. Second, Harkonen contends that the court erred in including an instruction that permitted the jury to convict Harkonen of the wire fraud count based on half-truths or omissions.

Neither of Harkonen's complaints entitles him to a new trial. To begin, it is well established in the Ninth Circuit that "a criminal defendant has no right to any

good faith instruction when the jury has been adequately instructed with regard to the intent required to be found guilty of the crime charged . . . ." *United States v. Shipsey*, 363 F.3d 962, 967 (9th Cir. 2004) (internal citation and quotation marks omitted). Harkonen concedes that the court delivered an instruction indicating that Harkonen could only be convicted if the jury found that he had the specific "intent to defraud"; Harkonen asserts, however, that the "intent to defraud" instruction was confusing and thus insufficient to adequately instruct the jurors. Specifically, Harkonen contends that Instruction No. 22, which defines both "intent to defraud" and "intent to mislead" failed to adequately distinguish between the elements of wire fraud and felony misbranding.

Written Instruction 16 provided that to convict Harkonen, the jurors must find beyond a reasonable doubt that "the defendant acted with the intent to defraud." Jury Instructions at 16. The instruction contained a cross reference, instructing the jurors to "[s]ee Instruction No. 22 for definition of intent to defraud." *Id*. The first paragraph of Instruction No. 22 explains that:

> [t]o act with 'intent to defraud' means to act knowingly with the specific intent to deceive or cheat, ordinarily for the purpose of either causing some financial loss to another or bringing about some financial gain to one's self. It is not necessary, however, to prove that anyone was, in fact, defrauded as long as it is established beyond a reasonable doubt that the defendant acted with intent to defraud.

Id. at 23. The second paragraph of Instruction No. 22 provides a definition of "intent to mislead." The third

paragraph explains that intent can be proved indirectly through circumstantial evidence. The fourth and final paragraph provides that "[t]he element 'intent to defraud or mislead' is written in the disjunctive. Thus you can find either that the defendant's actions were done with the intent to defraud or the intent to mislead, as long as all of you agree which intent and which object." Harkonen believes that by placing the "intent to defraud" and "intent to mislead" instruction on the same page, Instruction No. 22 impermissibly combined the elements of wire fraud and felony misbranding. As a result, Harkonen argues, "jurors reasonably but erroneously could have applied 'intent to mislead' to the wire fraud count." Docket No. 247 (Def.'s Mot.) at 44.

Such an instruction might have been confusing if the jurors were relying solely upon the written instructions. During the oral delivery of the instructions, however, the court clarified that "intent to mislead" applied only to the misbranding count. First, in delivering the "intent to defraud" portion of Instruction 16, the court stated "I'm going to explain that a little bit later, because that term is used in both; for both counts. And I'll explain what 'intent to defraud' means. And I will write in here and tell you to see instruction number 22 for that definition—that will come a bit later." TT at 3554. Later, in explaining Instruction No. 22, the court repeatedly pointed out to the jury the distinction between the elements of the two counts. After defining "intent to defraud," the court stated "so keep in mind: that applies to both counts." *Id*. at 3558. Before defining "intent to mislead," the court clarified that "this definition—to act with 'intent to mislead'—applies only to the misbranding." *Id*. The court continued, explaining that "in the first count—the wire fraud—the word 'mislead'

is not used in the element. It's just '[sic] with 'intent to defraud.'" *Id*. The court then separately defined "intent to mislead." Finally, when the court explained the phrase "intent to defraud or mislead" is written in the disjunctive, the court again clarified that the an "intent to mislead" applied only to the misbranding count. *Id*. at 3559. These oral clarifications by the court were more than sufficient to accurately instruct the jury that, in order to convict Harkonen of the wire fraud count, it must find beyond a reasonable doubt that he possessed a specific intent to defraud. Because the instructions adequately informed the jury that wire fraud is a specific intent crime, the court properly denied Harkonen's request for a good faith instruction.

Harkonen next argues that the instructions, by permitting the jury to convict him "on the basis of half-truths or omissions," constituted an unconstitutional material variance from the indictment, requiring a new trial. The court resolved a lengthy pretrial dispute between the parties over the scope of the wire fraud charge in the indictment by ruling that the government could only prove wire fraud on the basis of "false or misleading" statements, as opposed to scheme liability. *See* Docket No. 178 (Transcript, 8/6/09) at 4-14. The instruction, in fact, limited Harkonen's potential criminal liability in exactly that manner. Before the jury could convict Harkonen of wire fraud, the instructions required the government to prove beyond a reasonable doubt that the August 28, 2002 press release contained at least one "false or fraudulent statement." *See* Jury Instructions at 16 ("Second, the defendant knew that the statements made in the August 28, 2002 press release were false or fraudulent

at the time they were made.").[6] Instruction No. 16 defined a false or fraudulent statement as "deceitful statements, half-truths, or statements which omit

[6] In full, Instruction No. 16 provides:

> The defendant is charged in Count One of the indictment with wire fraud in violation of Section 1343 of Title 18 of the United States Code. In order for the defendant to be found guilty of that charge, the government must prove each of the following elements beyond a reasonable doubt:
>
> First, the defendant made a scheme or plan to defraud by making false or fraudulent statements, with all of you agreeing on at least one false or fraudulent statement that was made. False or fraudulent statements may include deceitful statements, half-truths, or statements which omit material facts. A statement is false or fraudulent if known to be untrue or made with wanton or reckless disregard for its truth or falsity and made with the intent to deceive.
>
> Second, the defendant knew that the statements made in the August 28, 2002 press release were false or fraudulent at the time they were made.
>
> Third, the statements were material; that is, they had a natural tendency to influence, or were capable of influencing, a person to part with money or property. It is not necessary for the government to prove that the scheme was successful, that the defendant actually realized any gain from the scheme, or that an intended victim actually suffered any loss.
>
> Fourth, the defendant acted with the intent to defraud. [*See* Instruction No. 22 for definition of intent to defraud]
>
> Fifth, the defendant used, or caused to be used, the interstate wires to carry out or attempt to carry out the scheme.
>
> A wire communication is caused when one knows that the wires will be used in the ordinary course of business or when one can reasonably foresee such use. It does not matter whether the thing sent by the wire was itself false or deceptive so long as the wires were used as part of the scheme.

material facts." Jury Instructions at 16. Such a definition is well accepted within the Ninth Circuit. *See Woods*, 335 F.3d at 998; *Lustiger*, 386 F.2d at 138 ("[D]eceitful statements of half truths or the concealment of material facts is actual fraud violative of the [wire] fraud statute. . . . [T]he deception need not be premised upon verbalized words alone. The arrangement of the words, or the circumstances in which they are used may convey the false and deceptive appearance."). Because the instruction was proper and did not materially vary from the indictment, it does not provide grounds for a new trial.

CONCLUSION

For the aforementioned reasons, defendant Harkonen's post-trial motion is DENIED in its entirety.

IT IS SO ORDERED.

Dated: July 27, 2010

/s/ Marilyn Hall Patel
MARILYN HALL PATEL
United States District Court Judge
Northern District of California

APPENDIX C

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

[Filed 06/04/2009]

No. C 08-00164 MHP

UNITED STATES OF AMERICA,
Plaintiff,

v.

W. SCOTT HARKONEN,
Defendant.

MEMORANDUM & ORDER

Re: Defendant's Motions in Limine re: "Labeling" and to Exclude Protected First Amendment Speech or, In The Alternative, to Dismiss the Indictment

A grand jury indicted defendant W. Scott Harkonen ("Harkonen") for fraudulently promoting the drug Actimmune® (interferon gamma-1b) by putting out false and misleading information about the drug's effectiveness in treating idiopathic pulmonary fibrosis ("IPF"). The indictment charges one count of wire fraud and one count of misbranding under the Food, Drug, and Cosmetic Act. Now before the court are two motions in limine re: "labeling" and to exclude protected First Amendment speech, or alternatively, to dismiss the indictment. Having considered the parties' arguments and for the reasons set forth below, the court enters the following memorandum and order.

BACKGROUND[1]

Harkonen is a resident of California who served as the Chief Executive Officer ("CEO") of InterMune, Inc. ("InterMune"), a pharmaceutical company based in the Bay Area, from February 1998 through June 2003. Harkonen was also a member of InterMune's Board of Directors from February 1998 through September 2003.

In 2004, the Department of Justice ("DOJ") began an investigation into allegations that InterMune marketed and promoted the sale of its drug Actimmune® for the treatment of IPF, an indication for which the drug had not been approved by the Food and Drug Administration ("FDA"). Actimmune® was approved by the FDA to treat chronic granulomatous disease in or about 1990, and was also approved to treat severe, malignant osteopetrosis in or about 2000. Both of these diseases are rare disorders that primarily affect children. By contrast, IPF is a fatal lung disease that affects mainly middle-aged people.

When the FDA approves a drug, it does so for a particular use or "indication." That indication will be included on the drug's label or package insert and the drug may be marketed only for the indications that appear on the label. *See* 21 U.S.C. § 355(b)-(d). The Food, Drug, and Cosmetic Act ("FDCA") makes it illegal to market, advertise or otherwise promote an

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[1] Unless otherwise noted, all facts are taken from the indictment against Harkonen, unless otherwise noted, and are not disputed for purposes of the instant motions. *See U.S. v. Boren*, 278 F.3d 911, 914 (9th Cir. 2002) ("In ruling on a pre-trial motion to dismiss an indictment for failure to state an offense, the district court is bound by the four corners of the indictment. . . .[and] the court must accept the truth of the allegations in the indictment in analyzing whether a cognizable offense has been charged.")

indication for which the FDA has not approved the drug and that is not on the drug's FDA-approved label, i.e., an "off-label" use. *See* 21 U.S.C. §§ 301-99. Promoting an off-label use of a drug renders it misbranded. 21 U.S.C. § 352 (f). A drug is misbranded if its labeling or advertising is "false or misleading in any particular." 21 U.S.C. §§ 352(a), 321(n).

In March 2008, Harkonen was indicted for disseminating and causing to be disseminated information regarding Actimmune® for the treatment of IPF with the intent to defraud and mislead, thereby causing Actimmune® to be misbranded. The first count of the two-count indictment charges Harkonen with violating the federal wire fraud statute, which makes it unlawful to "devise any scheme or artifice to defraud, or for obtaining money or property by means of false or fraudulent pretenses, representations, or promises" and use "wire, radio, or television communication in interstate or foreign commerce" in furtherance of that scheme. 18 U.S.C. section 1343. The second count charges Harkonen with making false and misleading statements and doing acts, with "intent to defraud or mislead," resulting in drugs being misbranded while held for sale following shipment in interstate commerce under the FDCA. 21 U.S.C. §§ 331(k), 333(a)(2) and 352(a).

According to the indictment, in October 1999, the *New England Journal of Medicine* published the results of Austrian study of eighteen participants that concluded interferon gamma-1b had anti-fibrotic properties and the lung function of the nine patients who received interferon gamma-1b improved. The study also stated that a larger, more scientifically controlled study was needed to test whether the results were valid.

In October 2000, InterMune began a Phase III clinical trial (named the GIPF-001 trial) to determine whether treating IPF patients (patients with fibrotic scar tissue in their lungs) with Actimmune® was effective. In August 2002, data from that clinical trial failed to show that Actimmune® was effective in treating IPF. Harkonen discussed the results of the trial with his staff at InterMune and instructed them to conduct additional analyses in an effort to ascertain whether Actimmune® might be efficacious for certain subgroups of the patient population. This after-the-fact subgroup analysis suggested a survival trend for patients whose IPF was described as "mild to moderate."

In late August 2002, Harkonen and some InterMune employees discussed the results of the GIPF-001 Phase III trial and additional subgroup analyses of patient deaths with the FDA. The FDA's medical reviewers advised Harkonen that the trial data were not sufficient to gain FDA approval for Actimmune® to treat IPF and that further clinical testing would be required to determine whether Actimmune® could reduce or delay death for IPF patients. Thereafter, Harkonen began discussions with the FDA regarding the design of another trial targeted at patients with mild to moderate IPF. In December 2003, InterMune began enrolling a subgroup of such patients in a Phase II clinical trial and in 2007 InterMune announced it was discontinuing the study because it did not benefit the patients.

According to the indictment, beginning in or about October 2000, Harkonen and others at InterMune began to promote the use of Actimmune® to treat IPF by misrepresenting the import of the earlier data. On August 28, 2002, InterMune issued a nationwide

press release publicly announcing the results of the GIPF-001 Phase III clinical trial. Harkonen wrote the headline and byline and controlled the content of the entire press release. The headline stated that: "InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF," with the subheading "Reduces Mortality by 70% in Patients With Mild to Moderate Disease." The press release was distributed by e-mail from an InterMune executive to the company's sales representatives, along with a document instructing the sales representatives how to discuss the press release with doctors.

InterMune, with the knowledge and approval of Harkonen, hired a marketing firm to determine whether the press release would affect pulmonologists' (doctors who treat lung cancer) willingness to prescribe Actimmune® to treat IPF. The firm reported survey results indicating that the press release would have a positive impact on the likelihood of such prescriptions. Harkonen and others at InterMune established sales goals for Actimmune® and sent sales representatives to visit pulmonologists and provided incentive and bonus plans for sales representatives based upon the number of Actimmune® prescriptions written by those doctors. At the direction of Harkonen, T-shirts were distributed to InterMune sales staff and other employees at a party to celebrate the announcement of the trial results. The front of the T-shirt stated: "ACTIMMUNE GIPF-001 IPF" and the back stated: "FEEL BETTER LIVE LONGER."

Harkonen and others also assisted and caused the dissemination by a specialty pharmacy in Florida of information to patients and doctors about the claimed efficacy of Actimmune® for treating IPF. That phar-

macy sent a "fax blast" with the press release to more than 2,000 pulmonologists. That same pharmacy also distributed to patients who took Actimmune®, along with their medications, a letter containing information from the press release stating that "preliminary data" had shown:

> . . . a statistically significant reduction in mortality by 70% in patients with mild to moderate IPF. Interferon-gamma-1b is the first treatment ever to show any meaningful impact in this disease in clinical trials. These results indicate that Actimmune® should be used early in the course of treatment of this disease in order to realize the most favorable long-term survival benefit.

Overall, these marketing efforts were successful. Between 2000 and 2003, Actimmune® sales increased significantly, from $11 million in 2000 to $141 million in 2003. The majority of these sales were attributable to prescriptions for the off-label treatment of IPF.

Harkonen now moves to dismiss the indictment, or in the alternative, in limine to establish the parameters of the trial in this action with regard to two issues: "labeling" and First-Amendment-protected speech. Specifically, Harkonen argues that the press release, related communications and other iterations charged as disseminations should be excluded from evidence because (1) they cannot constitute impermissible "labeling" within the meaning of the FDCA and (2) they are speech protected under the First Amendment. Alternatively, Harkonen requests that the court dismiss the indictment in its entirety because the government cannot prove the charges without inadmissible evidence and that

which relies on constitutionally-protected speech the FDA cannot lawfully prohibit.

The government argues that both motions should be denied because the charged counts require the government to prove that Harkonen disseminated false and misleading information with an intent to defraud or mislead. Because the information and materials cited in the indictment clearly constitute "labeling" under the FDCA and the First Amendment does not protect fraud, the government contends that it sustains the right to present the case to a jury for decision on the merits.

LEGAL STANDARD

The Federal Rules of Criminal Procedure permit a defendant to "raise by pretrial motion any defenses, objection, or request that the court can determine without a trial of the general issue." Fed. R. Crim. P. 12(b); *United States v. Shortt Accountancy Corp*., 785 F.2d 1448, 1452 (9th Cir. 1986). In considering a motion to dismiss, the court is limited to the face of the indictment and must presume the truth of the allegations in the charging instrument. *United States v. Caicedo*, 47 F.3d 370, 371 (9th Cir. 1995); *United States v. Buckley*, 689 F.2d 893, 897 (9th Cir. 1982). In addition, "[a] defendant may not properly challenge an indictment, sufficient on its face, on the ground that the allegations are not supported by adequate evidence." *United States. v. Jensen*, 93 F.3d 667, 669 (9th Cir. 1996) (citation omitted). "A motion to dismiss the indictment cannot be used as a device for a summary trial of the evidence . . . . The Court should not consider evidence not appearing on the face of the indictment." *Id*. A court must decide such a motion before trial "unless it finds good cause

to defer a ruling." Fed. R. Crim. P. 12(d); *Shortt Accountancy*, 785 F.2d at 1452 (if the motion "is substantially founded upon and intertwined with evidence concerning the alleged offense, the motion falls within the province of the ultimate finder of fact and must be deferred.")

DISCUSSION

I. The First Amendment

Harkonen argues that the press release and all related communications alleged in the indictment, including statements and disseminations of information from or about the press release, constitute scientific opinions that are entitled to protection under the First Amendment. Harkonen alleges the speech at issue is either pure scientific speech, or it is inextricably intertwined as mixed scientific and commercial speech, or even if it is commercial speech it is still protected by the First Amendment under any of the applicable standards. Harkonen alleges that because the disseminations form the actual criminal acts charged in the indictment, there can be no stated offense without the protected speech and the indictment should be dismissed or, in the alternative, the disseminations should be excluded as evidence of Harkonen's culpability at trial.

The government asserts that Harkonen's argument that his statements are constitutionally protected because they are not fraudulent goes directly to the merits of the factual allegations of the case. The indictment charges Harkonen with violating the FDCA by causing Actimmune® to be misbranded with "intent to defraud or mislead" and a drug is misbranded if its labeling is "false or misleading in any particular." 21 U.S.C. §§ 331(k), 333(a)(2), 352(a).

The indictment also charges Harkonen with wire fraud, under 18 U.S.C. section 1343. In the Ninth Circuit, "[w]ire fraud has three elements: a scheme to defraud, use of the wires in furtherance of the scheme, and the specific intent to defraud." *United States v. McNeil*, 320 F.3d 1034, 1040 (9th Cir. 2003). Because the allegations allege fraud, and the First Amendment does not protect fraud, the government contends it is for the jury to decide whether those allegations have been proven beyond a reasonable doubt.

The court recognizes that "the First Amendment does not shield fraud." *Illinois, ex rel. Madigan v. Telemarketing Associates, Inc*., 538 U.S. 600, 612 (2003); *Central Hudson Gas & Electric Corp. v. Public Service Comm'n*, 447 U.S. 557, 593 (1980) (holding that "false and misleading" speech is unprotected by the First Amendment). Contrary to the government's allegation, however, this does not mean that a prosecution for fraudulent misbranding "cannot present First Amendment concerns." The court must do more than accept the government's legal conclusions and must test the indictment by its sufficiency to charge an offense. *U.S. v. Boren*, 278 F.3d 911, 914 (9th Cir. 2002).

On its face, the indictment charges Harkonen with violating the federal wire fraud statute and the FDCA by devising a scheme to defraud and by making fraudulent statements and disseminating false and misleading information about the efficacy of Actimmune® to treat IPF. The court interprets Harkonen's motion as contending that the indictment cannot state an offense because it relies on an interpretation of statutes that is overbroad as applied to Harkonen's conduct and infringes on his First

Amendment right to make statements of a scientific position and promote scientific discourse. On oral argument, Harkonen summarized his position by stating "the First Amendment does not allow criminalization of opinions." Harkonen urged the court to act as a gatekeeper and determine whether the speech in question is protected under *Reilly v. Pinkus*, 338 U.S. 269, 273-74 (1949), as scientific speech about "medical practices in fields where knowledge has not yet been crystallized in the crucible of experience" and where there exists "no exact standard of absolute truth by which to prove the assertions false and a fraud." The government's position is that this entire First Amendment motion is nothing more than a red herring, because neither the government nor the FDCA seeks to make criminal good-faith scientific debate.

Plainly, Harkonen is seeking to protect more than just good-faith scientific debate. Harkonen is requesting that the court deem protected a series of communications, namely, the content of a press release and its related disseminations.[2] Accordingly, this First

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[2] The court finds no meaningful distinction between speech (or the *content* thereof) and *conduct* (or dissemination) as argued by Harkonen. Repeated references to the government's assertion in *United States. v. Caronia*, 576 F. Supp. 2d 385, 395 (E.D.N.Y. 2008), that its use of speech as a proxy for conduct is exempt from First Amendment scrutiny, are unavailing here. The government is not trying to get protected speech in through back-door means by asserting the statements at issue are merely "evidence" of a crime Harkonen committed. Rather, the government contends the fraud charges turn on a series of communications, stemming from the press release and continuing with deceptive disseminations to doctors and to patients, all of which together constituted a scheme to defraud. These allegations involve both the content of speech (the press release and copies and excerpts thereof in writings) and conduct

Amendment protection issue raises an appropriate, albeit limited, question for the court to consider. While the court must accept as true the government's factual allegations of fraud, the court need not accept the fraud charges outright and without review of whether the alleged speech or conduct supporting the fraud charges in the indictment is entitled to complete protection under the First Amendment so as to require dismissal. Harkonen asserts the court need not invalidate any statute regulation or rule in making such a determination. This is true, because case law has already established the outer bounds of, or "safe harbor" carve-out from, liability under the FDCA for First Amendment protected speech. Accordingly, the court must assess whether the alleged speech at issue is wholly protected as a matter of law.

A. The Speech At Issue

The law provides a boundary for what drug product-related speech the government may prohibit. While the FDCA prohibits speech that promotes off-label uses for approved drug products (which thereby "misbrands" the drug), the government cannot wholesale proscribe the open dissemination of scientific opinions and ideas concerning all beneficial uses for approved drug products. Such a prohibition has been deemed to violate the First Amendment rights of the speakers to communicate scientific information and engage in scientific discourse about such products.

(dissemination of those items). Thus, Harkonen is wrong when he claims that "no conduct extrinsic to the speech is being prosecuted" because the government stated a conviction could be based upon both the press release and its disseminations. The court refers to both "speech" and "conduct" where appropriate in this Order.

See Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 74 (D.D.C. 1998) (holding certain FDA restrictions on the promotion of off-label uses an unconstitutional restriction on commercial speech that communicates and promotes scientific conclusions to a physician audience), *order vacated as moot sub nom. Wash. Legal Found. v. Henney*, 202 F.3d 331, 334 (D.C. Cir. 2000) (noting the prior judgment rendered moot in part by superceding legislation).

In a tortured series of litigations over the bounds of the government to infringe upon a drug manufacturer's freedom to communicate information about its products, the government asserted it had "established a procedure for manufacturers who distribute certain materials regarding off-label uses in such a way that they will not be used as evidence against them in a prosecution under the misbranding provisions." *Henney*, 202 F.3d at 336. The government recognized that a "safe harbor" existed for industry-supported scientific and educational speech and associated conduct concerning drug products, *id*. at 335, while the D.C. Circuit recognized in *dicta* that a drug manufacturer "may still argue that the FDA's use of a manufacturer's promotion of off-label uses as evidence in a particular enforcement action violates the First Amendment." *Id*. at 336.

With the case law still in an unsettled state, *see, e.g., United States v. Caputo*, 517 F.3d 935, 939 (7th Cir. 2008); *Caronia*, 576 F. Supp. 2d at 394, this would present a thorny issue for the court were it not for the fact that the allegations of the indictment do not trench anywhere near the outer bounds of speech deemed controversial. As best can be gleaned from the case law and from the government's position in prior cases and in this case, speech is protected by

the First Amendment if it is a *bona fide* scientific and educational speech that appears in independent and peer-reviewed sources, such as a journal article reprint or a medical textbook. While questions remain about when such "pure" speech gets converted to a "less pure" form of commercial speech when a drug company is involved, e.g., by funding the studies or by disseminating the speech through various promotional activities, they are of no moment here because nowhere does the indictment invoke any "pure" scientific speech.

The mere fact that Harkonen is an M.D., that the press release he prepared presented actual data and statistical analyses, and that the dissemination of the press release may have generated vigorous debate in the pulmonological and pharmaceutical analyst community, do not disturb this conclusion. That the speech is a press release and not a peer-reviewed publication, that it refers to a specific commercial product on the market (Actimmune®), and that it was unquestionably disseminated for commercial benefit (e.g., the first line notes InterMune's Nasdaq stock symbol), are allegations that take the speech at issue outside the realm of pure science speech and move it towards the realm of commercial speech. *See, e.g.*, *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66-68 (1983) (noting that factors such as whether the form of speech is an advertisement; whether it refers to a specific product; and whether there is a clear economic motivation behind the speaker's activities, provide strong support that the speech is commercial in nature). While commercial speech is entitled to "qualified but nonetheless substantial protection" under the First Amendment, *see id.*, it is nevertheless not entitled to complete exemption from FDCA liability *per se*. *See also, Thompson v. Western States Med.*

Ctr., 535 U.S. 357, 367 (2002). ("Although commercial speech is protected by the First Amendment, not all regulation of such speech is unconstitutional.")

On oral argument, Harkonen asserted that the press release's reference to data is the "heart of the cut-out for protected speech." The court disagrees. What the indictment alleges, and what the law does not protect as a First Amendment carve-out to liability under the FDCA, is that the press release and associated speech incorporates, reformats and post hoc reinterprets scientific results in a false and misleading manner and is then disseminated at Harkonen's direction to physicians and patients. As the government affirms, "the [d]efendant is under indictment not because he promoted Actimmune[®] for an unapproved use . . . but because he made knowingly false and misleading statements in doing so." Pl.'s Opp., Docket No. 104, at 13, n.3. The government is not barred from proceeding with its case because the facts alleged do not entitle the speech at issue to complete First Amendment protection.

B. The "Fraudulent" Nature of the Speech

Harkonen contended on oral argument that the speech at issue can never be fraudulent because, under *Reilly*, it is "no more than 'opinion' in a field where imperfect knowledge made proof 'as of an ordinary fact' impossible." 338 U.S. at 273. Harkonen argued that *Reilly* is the controlling case for this inquiry and the court should reach a decision pre-trial rather than post-trial because of the potentially "chilling effect" on speech. And yet, as the Supreme Court noted in the very case upon which Harkonen relies to argue for dismissal at this stage, the issues in fraud cases "*make cross-examination peculiarly appropriate*." *Reilly*, 338 U.S. at 276. "An intent to

deceive might be inferred from the universality of scientific belief that advertising representations are wholly unsupportable; conversely, the likelihood of such an inference might be lessened should cross-examination cause a witness to admit that the scientific belief was less universal than he had first testified." *Id*. In so reasoning, the Court explicitly rejected the argument that a finding of fraud is barred "whenever there is the least conflict of opinion as to curative effects of a remedy." *Id*. at 273-274.

Following this reasoning, Harkonen's argument that a finding of fraud is barred here because the press release contains statements of scientific opinions and perspectives about the meaning of the clinical data is unavailing, because it is belied by the allegations in the indictment. Harkonen's argument that the press release merely represents inferences drawn from the subgroup analysis of the data that the government believes should not have been so drawn is premature at this stage of the proceedings. Harkonen cannot successfully argue that "imperfect knowledge" in the field somehow sanitized the press release's communication that the clinical trial data, albeit missing its primary endpoint, suggested a mortality benefit in a subgroup of IPF patients. At this stage, Harkonen cannot dispute that the FDA affirmatively disagreed that the subgroup analysis showed a benefit sufficient to gain FDA approval for Actimmune® to treat IPF and refused to accept that Actimmune® could reduce or delay death for IPF patients without further testing. It is not enough to carry the day here for Harkonen to cite case law that the government cannot criminalize the dissemination of allegedly false scientific ideas or opinions. *See, e.g., Riley v. Nat'l Fed'n of the Blind of N.C., Inc*., 487 U.S. 781, 803 (1988) (Scalia, J., concurring) ("[i]t is axio-

matic that, although fraudulent misrepresentation of facts can be regulated, . . . the dissemination of ideas cannot be regulated to prevent it from being unfair or unreasonable").

Because Harkonen must accept the factual allegations as true for the purposes of this motion, he is hamstrung in his ability to go behind the allegations and challenge the merits of the facts alleged. Harkonen cannot argue that the statements are merely a scientific interpretation of data that would be accepted by the relevant health care community because the allegation in the indictment that the FDA's medical reviewers disagreed with this interpretation is in direct conflict with such an argument. This was not a mere statement by an FDA employee that did not represent the views of the FDA but rather, as alleged, it constituted the underlying basis for the FDA's refusal to approve Actimmune® to treat IPF. Harkonen's argument that the FDA may not establish scientific truth *vel non* is misplaced. The allegation goes to the non-approved status of Actimmune® in treating IPF and the fraudulent representations made in the press release and its disseminations in spite of this non-approved status.

The inclusion of a declaration with Harkonen's moving papers by Dr. Patrick Hannon, an expert statistician and physician who testifies to the merits of the press release's interpretation of the data, i.e., that the speech was *truthful*, admits its own impropriety at this stage. The court must accept the indictment's allegations that medical staff at the FDA advised Harkonen that the trial data were not sufficient to gain FDA approval for Actimmune® to treat IPF or to show that Actimmune® could reduce or delay death for IPF patients. Whether the press

release and its iterations constituted puffery by Harkonen on behalf of InterMune or intentional misrepresentations of the data is an issue for trial that goes to the merits of the case.

Likewise, the court cannot accord weight to Harkonen's contention that the press release did no more than "merely describe the results of a clinical trial" and in no way presents any manufacturer-driven false and misleading statements. This interpretation urged by Harkonen is controverted by the allegations in the indictment that the press release falsely claims that the GIPF-001 trial results "demonstrated a survival benefit" of Actimmune® in IPF and that Harkonen distorted the results in an intentional effort to deceive doctors and patients. The indictment charges Harkonen with felony violations of 21 U.S.C. section 331(k) done "with the intent to defraud or mislead" under 21 U.S.C. section 333(a)(2). Because the government explicitly alleges fraudulent intent, the court must at this stage accept the government's contention that it is neither seeking to restrict truthful, non-misleading promotion of the off-label uses of Actimmune®, nor attempting to regulate Harkonen or InterMune's ability to engage in a discourse on whether Actimmune® might someday prove beneficial as a treatment for IPF.

It is undisputed that the government has the right to regulate false and misleading statements made to doctors and patients about drug products in interstate commerce. Accepting the indictment's allegations as true for the purposes of this motion, it is clear to the court that the speech at issue is not outside the bounds of the FDCA's regulatory reach as being wholly protected by the First Amendment as a matter of law. Accordingly, the conduct associated

with this speech, i.e., disseminating the press release and related communications, is also not outside the bounds of the FDCA. The court DENIES defendant's motion to dismiss the indictment and also DENIES defendant's alternative motion in limine to exclude the speech at issue. The allegations in the indictment will not be excluded on the basis that they seek to regulate the mere dissemination of ideas, because the conduct alleged is fraudulent in nature.

Having found that the alleged speech at issue is not First Amendment-protected as pure scientific speech or ideas, the court must allow the case to advance to a jury for determination of whether the government can prove the fraud charges based on speech that may be entitled to lesser protection under the First Amendment. The Supreme Court has made clear that in a First Amendment analysis of commercial speech under the *Central Hudson* test, the threshold matter is whether the speech "concerns unlawful activity or is misleading." *Caronia*, 576 F. Supp. 2d at 396-397, *citing Western States*, 535 U.S. at 367. It is not the case here that the factual allegations of the indictment concerning the press release and other communications are so clear that reasonable minds could not differ as to whether Harkonen committed fraud. Thus, the matter must be decided by a jury. *See Facade v. Price Co*., 70 F.3d 1078, 1081 (9th Cir. 1995) (whether a public statement is misleading, or whether adverse facts were adequately disclosed is a mixed question to be decided by the trier of fact unless it is "so obvious that reasonable minds [could] not differ").

II. "Labeling"

Harkonen is charged with misbranding under the FDCA, which states that a drug "shall be deemed to be misbranded . . . if its labeling is false or misleading." 21 U.S.C. § 352(a). Harkonen contends that the press release and related communications alleged in the indictment—which include copies of the press release sent to InterMune sales force and disseminated by a third-party pharmacy, the results from the marketing firm assessing the impact of the press release, and T-shirts that were distributed to InterMune employees—do not constitute "labeling" as defined by the FDCA. Thus, Harkonen alleges the count of misbranding must be dismissed because it fails to state a statutory violation under the FDCA.

Harkonen argues all of these "communications" do not constitute labeling for two main reasons. First of all, because the communications did not "supplement or explain" the drug product itself, the communications do not provide the required guidance or assistance in the use of Actimmune®. As explained in *Cartel v. United States*, 335 U.S. 345, 350 (1948), which remains the leading Supreme Court authority on the scope of the labeling provision, labeling includes any literature or communication that accompanies an article (i.e. a drug product), and one thing is deemed to be "accompanied" by another when it "supplements or explains" it. Harkonen contends that the communications alleged in the indictment therefore do not constitute part of the labeling because they do not "perform the same function as [they] would if [they] were on the article or on the containers or wrappers." *Id*. at 351. Thus, in Harkonen's view, because the communications did not serve to guide or assist the purchaser in how to use Actim-

mune® or provide "substantial information about the use or benefit of the article," *United States v. Hanafy*, 302 F.3d 485, 490 (5th Cir. 2002), they did not constitute an essential supplement designed to be used with the product such that it can be classified as labeling under the FDCA. *See United States v. Urbuteit*, 336 U.S. 804, 806 (1949) (*per curiam*) (clarifying on appeal from remand that advertising material constituted labeling where the "controlling factors were whether the leaflets were designed for use with the [product] and whether they were so used.")

Harkonen also argues the press release and communications in question are not "labeling" because they do not form part of an "integrated distribution program," as *Kordel* requires materials to be if they do not physically accompany the product. 335 U.S. at 350. Harkonen argues (a) the press release was not integrated as such because it was not presented in immediate connection with the prescription and/or actual purchase of the drug; (b) the T-shirts and e-mail distributed to InterMune's sales force were not integrated because they were internal only and any consequent oral statements made by the sales force to physicians were not in writing; (c) the marketing research results about the impact of the press release were not an integrated distribution program because they had nothing to do with actually distributing the product; and (d) the copies of the press release and letters distributed by the third-party pharmacy were not integrated because they were not controlled by Harkonen and were also not part of a program because they were only distributed for a short time.

Finally, Harkonen concludes that because the government failed to provide to Harkonen the consti-

tutionally mandated fair notice that the aforementioned communications could be considered "labeling" within the meaning of the FDCA to trigger criminal liability, Harkonen is entitled to a dismissal of the indictment. Harkonen points to an FDA regulation on drug promotion that allegedly provides a "safe harbor of protection" for press releases, by stating "this provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings." 21 C.F.R. § 312.7. Harkonen argues that the rule of lenity should be applied to any ambiguity that remains concerning the scope of what the FDCA and its accompanying regulations intended to encompass. *See, e.g.*, *Liparota v. United States*, 471 U.S. 419, 427 (1985) (criminal statutes should be resolved in favor of lenity); *United States v. Santos*, 128 S.Ct 2020, 2028 (2008) ("the rule of lenity requires ambiguous criminal laws to be interpreted in favor of the defendants subjected to them.")

In response, the government first asserts that dismissal of the indictment is inappropriate because the wire fraud charge has not been challenged. Second, the government contends the materials or "communications" alleged in the indictment plainly constitute labeling within the meaning of the FDCA. The government argues it is undisputed that Harkonen shipped or caused to be shipped in interstate commerce both Actimmune® and the information or "communications" alleged in the indictment. Because that information explains how the drug is to be used and shares a common origin (InterMune) and a common destination (prospective and actual patients and doctors) with the drug that formed part of an integrated distribution program, it qualifies as

labeling within the FDCA. *See Kordel*, 335 U.S. at 348, 350.

A. The Scope of "Labeling" Under the FDCA

Upon reviewing the case law, the court finds this issue a relatively straightforward one. The FDCA broadly defines labeling as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. §§ 321(k), (m). The courts have long held that information need not be included with the actual drug product for it to be considered labeling. *See*, *e.g.*, *Kordel*, 335 U.S. at 347-48. There, the manufacturer was found guilty of misbranding, where the product and the literature involved were shipped separately and at different times, but "had a common origin and a common destination," so the literature was held to accompany the drugs in interstate commerce within the meaning of the FDCA (21 U.S.C. section 321(m)) and to comprise a part of the "labeling." The Supreme Court concluded: "[t]he fact that [the brochures] went in a different mail was *wholly irrelevant*." *Id*. at 350 (emphasis added).

Harkonen takes far too narrow a view of what types of information or communications can be designed for use with the drug. Information about what indications the drug may be effectively used to treat clearly falls within this provision; the communications need not transmit all details about dosages and methods of administration so as to usurp the role of the "directions for use" component of the drug label itself. The test is whether the drug product and the information or communications are "interdependent." *Kordel*, 335 U.S. at 346, 348. Here, the communications as alleged promote the use of a product (Actimmune®) for a specific, unapproved indication

(patients with mild to moderate IPF) with supplemental or explanatory guidance for its usefulness (to be used early in the course of treatment). The results of the marketing firm research served to "supplement or explain" that guidance and thus effectively also "accompanied" it and the product. *See id*. at 350. Accordingly, the communications as alleged indisputably satisfy the test and bear a textual relationship to the product itself. *See id*.; *see also Urbuteit*, 336 U.S. at 805.

It is not surprising that Harkonen cites no case to support the proposition he argues, that the communications must substitute for the drug product label itself to function as labeling under the FDCA, because that is not the law. Contrary to Harkonen's assertion that the government is relying on "an outmoded notion of statutory construction," both the FDA regulations and the case law make clear that labeling under the FDCA is construed expansively, such that it may encompass nearly every form of promotional activity, including package inserts, pamphlets, mailing pieces, fax bulletins, reprints of press releases, and all other literature that supplements, explains, or is otherwise textually related to the product. For a review of this body of law, *see* Katherine A. Helm, *Protecting Public Health From Outside the Physician's Office: A Century of FDA Regulation From Drug Safety Labeling to Off-Label Drug Promotion*, 18 Fordham Intell. Prop. Media & Ent. L.J. 117, 147-157 (2007).

B. Due Process Requirement for Fair Notice

As to Harkonen's fair notice argument, the court addresses both the FDA regulation on drug promotion and the rule of lenity. In the FDCA context, fair

notice means that "criminal law is not to be read expansively to include what is not plainly embraced within the language of the statute, since the purpose fairly to apprise men of the boundaries of the prohibited action would then be defeated." *Kordel*, 335 U.S. at 349 (citations omitted).

Here, Harkonen's argument that 21 C.F.R. section 312.7 protects, rather than proscribes, the dissemination of scientific findings in press releases to the media is of no moment. Not only does the cited regulation provide no mention of the term "press release," but it also fails to provide a "safe harbor" that could exempt the press release at issue from being included as labeling under the FDCA. Taken in its full context, the regulation makes abundantly clear that promotion of an off-label or pre-approved indication of a drug is prohibited and the press release at issue is not exempted from liability by this regulation:

> A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

21 C.F.R. § 312.7(a).

As noted elsewhere in this Order, the indictment does not charge Harkonen with disseminating or exchanging scientific information in and of itself, but rather with disseminating information regarding Actimmune® for the treatment of IPF with the intent to defraud and mislead. Nothing in the FDCA or its corresponding regulations provide a "safe harbor" from these disseminating actions as alleged.

The rule of lenity does nothing to alter this conclusion. Due process principles only require that ambiguities be resolved against the government. *See*, *e.g.*, *United States v. Geborde*, 278 F.3d 926, 932 (9th Cir. 2002). Here, there is no ambiguity that the issuance of the press release could form the basis for a mislabeling charge, based on the expansive construction of "labeling" under *Kordel* and the aforementioned cases in its orbit. Harkonen's arguments that the government will not be able to prove at trial the intent to defraud, do not support dismissal of the indictment based on the rule of lenity. The Ninth Circuit has expressly rejected the idea that courts may make pretrial determinations of the sufficiency of the evidence in criminal cases in the face of an otherwise valid indictment. *See, e.g.*, *Costello v. United States*, 350 U.S. 359, 363 (1956); *see also*, *United States v. DeLaurentis*, 230 F.3d 659, 661 (3d Cir. 2000) (holding that dismissal under Rule 12 "may not be predicated upon the insufficiency of the evidence to prove the indictment's charges").

Accordingly, the court DENIES Harkonen's motion to dismiss the indictment on the basis that Harkonen has not moved to dismiss the first count, and the second count properly alleges misbranding, to the extent that it contains allegations of false and misleading promotional advertising of Actimmune®

for an off-label use by Harkonen and others at InterMune.

Viewing the motion as a request to exclude evidence, however, the court GRANTS in limited part Harkonen's motion in limine and excludes the evidence relating to the T-shirt distribution to prove labeling. The T-shirts do not constitute labeling even under its broad construction of matter which "accompanies" the product in any form. 21 U.S.C. §§ 321(k), (m). The T-shirt distribution was internal to InterMune employees only and was not designed for use in the distribution and sale of the drug, nor did it otherwise serve the "purposes of labeling" so as to "supplement or explain" Actimmune®'s intended use. *See Kordel*, 335 U.S. at 350; *United States v. Urbuteit*, 335 U.S. 355, 357 (1948) (original ruling). There was no integration between the shipment of the Actimmune® product and the distribution of the T-shirts, nor was there a common destination for the matter (sales staff v. prospective and actual patients and doctors). Accordingly, the court excludes the evidence that Harkonen distributed T-shirts to InterMune sales staff and other employees at a party to celebrate the announcement of the GIPF-001 Phase III trial results as not constituting labeling under the FDCA. Notably, this ruling does not prevent the government from offering the evidence for other purposes, e.g., to prove part of the marketing plan overall.

CONCLUSION

For the foregoing reasons, the court DENIES defendant's motion to dismiss the indictment or alternatively to exclude First Amendment-protected speech. The court also DENIES defendant's motion to dismiss the indictment re "labeling," but GRANTS in

limited part defendant's motion in limine to exclude certain evidence, as set forth above.

IT IS SO ORDERED.

MARILYN HALL PATEL
United States District Court Judge
Northern District of California

Dated: June 3, 2009

APPENDIX D

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

[Filed May 07 2013]

Nos. 11-10209
11-10242

UNITED STATES OF AMERICA,
Plaintiff - Appellee,

v.

W. SCOTT HARKONEN, M.D.,
Defendant - Appellant.

D.C. No. 3:08-cr-00164-MHP-1
Northern District of California,
San Francisco

ORDER

Before: D.W. NELSON, TASHIMA, and MURGUIA, Circuit Judges.

Judge Murguia votes to deny the petition for rehearing en banc and Judges Nelson and Tashima so recommend.

The full court has been advised of the petition for rehearing en banc and no judge has requested a vote on whether to rehear the matter en banc. Fed. R. App. P. 35.

The petition for rehearing en banc is denied.

APPENDIX E

CONSITITUTIONAL PROVISIONS

U.S. Const. Amend. I

> Congress shall make no law . . . abridging the freedom of speech . . . .

U.S. Const. Amend. V

> No person shall . . . be deprived of life, liberty, or property, without due process of law . . . .

FEDERAL STATUTE

18 U.S.C. § 1343. Fraud by wire, radio, or television

Whoever, having devised or intending to devise any scheme or artifice to defraud, or for obtaining money or property by means of false or fraudulent pretenses, representations, or promises, transmits or causes to be transmitted by means of wire, radio, or television communication in interstate or foreign commerce, any writings, signs, signals, pictures, or sounds for the purpose of executing such scheme or artifice, shall be fined under this title or imprisoned not more than 20 years, or both. If the violation occurs in relation to, or involving any benefit authorized, transported, transmitted, transferred, disbursed, or paid in connection with, a presidentially declared major disaster or emergency (as those terms are defined in section 102 of the Robert T. Stafford Disaster Relief and Emergency Assistance Act (42 U.S.C. 5122)), or affects a financial institution, such person shall be fined not more than $1,000,000 or imprisoned not more than 30 years, or both.

APPENDIX F

INTERMUNE®

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INTERMUNE ANNOUNCES PHASE III DATA DEMONSTRATING SURVIVAL BENEFIT OF ACTIMMUNE IN IPF

– Reduces Mortality by 70% in Patients with Mild to Moderate Disease –

BRISBANE, Calif., August 28, 2002 — InterMune, Inc. (Nasdaq: ITMN) announced today that preliminary data from its Phase III clinical trial of Actimmune® (Interferon gamma-1b) injection for the treatment of idiopathic pulmonary fibrosis (IPF), a debilitating and usually fatal disease for which there are no effective treatment options, demonstrate a significant survival benefit in patients with mild to moderate disease randomly assigned to Actimmune versus control treatment ($p = 0.004$). These data confirm the survival benefit seen in the Phase II trial presented earlier this year at the 98th Annual Conference of the American Thoracic Society. There was also approximately a 10% relative reduction in the rate of progression-free survival associated with Actimmune versus placebo, the trial's primary endpoint, but this was not a statistically significant difference.

The company will hold a conference call at 9:00 a.m. EDT today to discuss these results (details below).

"We are extremely pleased with these results, which indicate Actimmune may extend the lives of patients suffering from this debilitating disease," said W. Scott Harkonen, M.D., President and CEO of InterMune. "Actimmune is the only available treatment demonstrated to have clinical benefit in IPF, with improved survival data in two controlled clinical trials. We believe these results will support use of Actimmune and lead to peak sales in the range of $400-$500 million per year, enabling us to achieve profitability in 2004 as planned."

"The mortality benefit is very compelling and represents a major breakthrough in this difficult disease," said Ganesh Raghu, M.D., Professor of Medicine, University of Washington in Seattle, and the Phase III study's lead principal investigator. "Interferon gamma-1b is the first treatment ever to show any meaningful clinical impact in this disease in rigorous clinical trials, and these results would indicate that Actimmune should be used early in the course of this disease in order to realize the most favorable long-term survival benefit."

Study Details and Results

A total of 330 patients were randomized into this double-blind, placebo-controlled trial conducted at 58 centers around the United States and Europe. Patients received either placebo or 200 micrograms of Actimmune injected subcutaneously three times per week. All patients remained in the trial until the last patient received 48 weeks of therapy. Median treatment duration was 60 weeks. The primary endpoint was progression free survival time defined

as either one of the following: (i) a decrease in forced vital capacity (FVC) of >10 percent, (ii) an increase in A-a gradient of 5 mmHg, or (iii) death. While this endpoint did not reach statistical significance, there was a trend in favor of Actimmune-treated patients, representing an approximately 10% relative reduction in the rate of progression-free survival versus placebo.

Importantly, Actimmune also demonstrated a strong positive trend in increased survival in the overall patient population, and a statistically significant survival benefit in patients with mild to moderate IPF. In the overall population, there were 16/162 deaths in the Actimmune-treated group (9.9%) compared to 28/168 deaths in the placebo group (16.7%), representing a 40% decrease in mortality in favor of Actimmune vs. placebo (p=0.084). Further, of the 254 patients with mild to moderate disease (FVC> = 55 percent), there were 6/126 deaths in the Actimmune-treated group (4.8%) and 21/128 deaths in the placebo group (16.4%), representing a 70% decrease in mortality in favor of Actimmune versus placebo (p = 0.004).

There were also trends later in the course of the study in favor of Actimmune in terms of improved breathing (i.e., dyspnea) and reduced need for supplemental oxygen. Actimmune treatment was also very well tolerated with the most common side effects reported being flu-like symptoms.

These data appear to confirm long-term follow-up data, reported earlier this year at the ATS meeting, which involved 18 patients from a randomized, controlled, open-label trial of Actimmune, in which 16 patients received one or more doses of Actimmune following study completion. The Kaplan Meier estimate of survival at five years was 77.8% and 16.7% in

the Actimmune and control groups, respectively (p=0.009).

Tracking Longer Term Outcomes

InterMune plans to transition all remaining Phase III trial patients in the active and placebo groups into an open-label clinical trial in which all patients receive Actimmune to track longer-term outcomes with Actimmune for a minimum of one year.

"We felt we had an ethical obligation to get this important news out about the survival benefit of Actimmune so physicians can evaluate it when making treatment decisions for their patients," said James E. Pennington, M.D., InterMune's Executive Vice President of Clinical and Medical Affairs. "We now have two well-controlled trials in IPF patients supporting a survival benefit, providing what we believe is compelling rationale for consideration of Actimmune for the treatment of patients with this disease."

About Actimmune

Interferon gamma-lb is a naturally occurring protein that stimulates the immune system. InterMune markets Actimmune for the treatment of life-threatening congenital diseases chronic granulomatous disease and severe, malignant osteopetrosis. InterMune is also conducting a Phase III study of Actimmune in ovarian cancer and a Phase II study of Actimmune for the treatment of severe liver fibrosis, or cirrhosis, caused by hepatitis C virus (HCV).

About Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia. Once

symptoms appear, there is a relentless deterioration of pulmonary function and death three to five years after diagnosis. The most common treatment is steroids; however, previously published studies suggest that fewer than 20 percent of patients with IPF respond to steroids. In patients having failed treatment with steroids, cytotoxic drugs such as azathioprine or cyclophosphamide are sometimes added to the steroid treatment. However, a large number of studies have shown little or no benefit from treatments involving steroids and other cytotoxic drugs. There are currently no drugs approved by the FDA for the treatment of IPF.

Conference Call Details

To access the live teleconference, dial 888-799-0528 (U.S.) or 706-634-0154 (international). A replay of the webcast and teleconference will be available approximately three hours after the call for two business days. To access the replay, please call 1-800-642-1687 (U.S.) or 706-645-9291 (international), and enter the conference ID# 5479918. To access the webcast, please log on to the company's website at www.intermune.com at least 15 minutes prior to the start of the call to ensure adequate time for any software downloads that may be required.

These data will be presented in more detail at the European Respiratory Society meeting in Stockholm at a symposium on Sept. 15, 2002, and later this year at the American College of Chest Physicians meeting in November in San Diego, Calif.

About InterMune

InterMune is a commercially driven biopharmaceutical company focused on the marketing, development

and applied research of life-saving therapies for pulmonary disease, infectious disease and cancer. For additional information about InterMune, please visit www.intermune.com.

Except for the historical information contained herein, this press release contains certain forward-looking statements that involve risks and uncertainties, including without limitation the statements indicating that the company believes that these results will: (i) support use of Actimmune for the treatment of IPF, (ii) lead to $400-$500 million in peak Actimmune sales, (iii) enable the company to achieve profitability in 2004, and (iv) provide compelling rationale for consideration of Actimmune for the treatment of patients with IPF. All forward-looking statements and other information included in this press release are based on information available to InterMune as of the date hereof, and InterMune assumes no obligation to update any such forward-looking statements or information. InterMune's actual results could differ materially from those described in InterMune's forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to those discussed under the heading "Risk Factors" and the risks and factors discussed in InterMune's 10-K report filed with the SEC on March 21, 2002, and other periodic reports (i.e., 10-Q and 8-K) filed with the SEC. The risks and other factors that follow, concerning the forward-looking statements in this press release, should be considered only in connection with the fully discussed risks and other factors discussed in detail in the 10-K report and InterMune's other periodic reports filed with the SEC.

The forward-looking statements that the company believes that these results will: (i) support use of Actimmune for the treatment of IPF, (ii) lead to $400-$500 million in peak Actimmune sales, (iii) enable the company to achieve profitability in 2004, and (iv) provide compelling rationale for consideration of Actimmune for the treatment of patients with IPF, are subject to the uncertainties and risks of a continuing increase in sales of Actimmune for IPF, an indication for which Actimmune has not been approved by the FDA; reimbursement risks associated with third-party payors; and regulation by the FDA with respect to InterMune's communications with physicians concerning Actimmune for the treatment of IPF.

# # #

PHYSICIAN CONFERENCE SERIES

LEERINK SWANN & COMPANY | MEDACORP PERFORMING INTELLIGENCE

Update on the Prospects for Actimmune in the Treatment of Idiopathic Pulmonary Fibrosis (IPF)

August 29, 2002
Review of August 28, 2002 Conference Call

Daniel B. Dubin, M.D. **(617) 918-4879**
Rene Mora, M.D., Ph.D. **(617) 918-4802**

On August 28, we conducted a conference call with nine MEDACorp consultants who were Actimmune (Intermune **[ITMN, $23.49, Not Rated]**) investigators to discuss their reactions to the published results of the Phase III trial for the treatment of idiopathic pulmonary fibrosis (IPF).

While the study did not achieve its primary composite endpoint of progression-free survival, there was a non-statistically significant 40% mortality reduction in favor of Actimmune among the entire 330 patient group, and a statistically significant 70% mortality reduction identified in the subgroup of 254 patients with a forced vital capacity (FVC) of ≥55% on trial entry. This report summarizes the perceived impact of the trial on our consultants' prospective utilization of Actimmune.

CONFERENCE HIGHLIGHTS

- In aggregate, these nine consultants have initiated off-label treatment in approximately 144 patients and have enrolled an estimated 78 patients in the Phase III trial.
- Although the consultants view the post-hoc analysis of mortality benefit on a subgroup of these patients skeptically, they believe that the enrollment cut-off of FVC>50% is somewhat arbitrary in the first place, and that using a cut-off of 55% for the subgroup analysis for mortality is reasonable.
- Uniformly, these consultants found the mortality signal to be compelling and supportive of continued utilization of Actimmune for the treatment of IPF going forward. Several consultants suggested that their overall utilization could increase based on both greater utilization among existing patients and their expectations that referral rates to their practices may increase in light of the mortality signal.
- From a medical perspective, in light of the mortality benefit signal, our consultants did not believe that the data would jeopardize reimbursement for the drug.

Please see last page for important disclosure.

All prices are intraday on 8/29/02.

Important Disclosure:
This information (including, but not limited to, prices, quotes and statistics) has been obtained from sources that we believe reliable, but we do not represent that it is accurate or complete and it should not be relied upon as such. All information is subject to change without notice. This is provided for information purposes only and should not be regarded as an offer to sell or as a solicitation of an offer to buy any product to which this information relates. Leerink Swann & Company or its affiliates ("the Firm") or persons associated with affiliates or other clients of the Firm may maintain a long or short position in the securities referred to herein or in other securities of issuers named herein. The past performance of securities does not guarantee or predict future performance. Transaction strategies described herein may not be suitable for all investors. Additional information is available upon request.

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Leerink Swann & Company makes a market in ITMN.

Explanation of ratings:

***Outperform**: We expect this stock to outperform its benchmark by more than 10 percentage points over the next 12 months.*
***Market Perform**: We expect this stock to perform within a range of plus or minus 10 percentage points of its benchmark over the next 12 months.*
***Underperform**: We expect this stock to underperform its benchmark by more than 10 percentage points over the next 12 months.*

For the purposes of these definitions the relevant benchmark will be the Russell 2000® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Index for issuers with a market capitalization over $2 billion.

MEDACorp • One Federal Street • 37th Floor • Boston, Massachusetts • 02110

APPENDIX H

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

[Filed 10/28/10]

Case No. CR 08-0164 MHP

UNITED STATES OF AMERICA,
Plaintiff,

v.

W. SCOTT HARKONEN,
Defendant.

DECLARATION OF
STEVEN N. GOODMAN, M.D., M.H.S., Ph.D.,
IN SUPPORT OF DEFENDANT
W. SCOTT HARKONEN'S SENTENCING
MEMORANDUM

Date: November 15, 2010
Time: 10:00 AM
Place: Courtroom 15, 18th Floor
Judge: Hon. Marilyn Hall Patel

I, STEVEN N. GOODMAN, M.D., M.H.S., Ph.D., declare:

1. I have written this declaration for the court's consideration in connection with the judgment and sentencing of Dr. Scott Harkonen.

2. The two principal opinions I will present in this declaration are as follows.

A. The testimony before the court regarding the statistical rules of inference that Dr. Harkonen was convicted of violating was one-sided at best, profoundly misleading at worst, and reflected neither the very considerable controversy over such principles, nor prominent examples from the FDA and in the published literature where it was necessary to violate such rules for demonstrably correct inferences to be made.

B. The criminal punishment of Dr. Harkonen without consideration of the full range of respected scientific and statistical opinion on this matter could have a chilling effect on legitimate scientific discourse.

3. I am highly experienced in the field of scientific and statistical inference, and have been recognized nationally and internationally for that expertise. The details of my background are as follows.

4. I am a Professor in the Department of Oncology at the Johns Hopkins School of Medicine, with joint appointments in Epidemiology, Biostatistics, and Pediatrics. I received an AB in Biochemistry from Harvard College (1976), an M.D. from New York University School of Medicine (1981), and completed a three year residency in Pediatrics at St. Louis Children's Hospital, Washington University (1984) and was board-certified in Pediatrics in 1986. I received a M.H.S. in Biostatistics and a Ph.D. in Epidemiology at the Johns Hopkins School of Public Health in 1989. After completing my Ph.D., I joined the faculty of Johns Hopkins School of Medicine in the cancer

center's Division of Biostatistics, where I remain today.

5. I am the author of well over 100 scientific papers, scholarly reviews, and book chapters covering a broad range of topics, including basic scientific research, evidence synthesis, epidemiology, and inferential, methodological, and ethical issues in epidemiology and clinical research.

6. Virtually all of my professional career has been devoted to the evaluation and interpretation of clinical trial and epidemiologic evidence, and this expertise has been widely recognized by respected national bodies, as:

6.1 Editor of the journal *Clinical Trials: Journal of the Society for Clinical Trials*, since 2004. This is an academic, professional society devoted to fostering and disseminating proper methods in clinical research.

6.2 Senior Statistical Editor since 1987 for *Annals of Internal Medicine*, one of the world's premier medical journals.

6.3 First author of the "Causal Criteria" chapter in the 2004 US Surgeon General's report on "Smoking and Health," setting forth the principles of causal reasoning and evidential standards to be used in that assessment.

6.4 Scientific advisor of the Medical Advisory Panel member for the national Blue Cross-Blue Shield Technology Assessment Program, which evaluates evidence on emerging medical therapies.

6.5 Member of the Medicare Coverage Advisory Commission (2001-2004).

6.6 One of two expert witnesses retained by the federal government to support its position in the recent Omnibus Vaccine case evaluating the theories that vaccines cause autism. The opposing expert was an internationally renowned epidemiologist and statistician. All three independent opinions from the Special Masters overseeing the case strongly supported details of my testimony as well as the government position.

6.7 Member of numerous committees and panels of the Institute of Medicine, US National Academy of Sciences, including:

- Veterans and Agent Orange (1998)
- Immunization Safety Review (2001-2004)
- Committee on Alternatives to Daubert Standards (2006)
- Treatment of Post-traumatic Stress Disorder in Veterans (2007)
- Committee on Scientific and Ethical Issues in the Evaluation of the Safety of Approved Drugs (2010, Co-Chair). This committee was requested by the FDA to provide guidance in the post-approval assessment of drug benefit and safety.

7. A large number of my publications concern the foundational principles underlying the proper scientific inference from statistical data derived from clinical experiments. I wrote the chapter on "The P-value" for the Encyclopedia of Biostatistics, a definitive reference on the topic, in addition to many other articles in major medical and methodologic journals.

8. In addition to the above, I write and teach extensively at the Johns Hopkins Bloomberg School of Public Health on clinical and epidemiologic research methods, and inferential principles.

9. I have served as an investigator on many grants and contracts from a wide variety of research agencies and foundations, including the National Cancer Institute, the Agency for Health Research and Quality (AHRQ), Centers for Disease Control and Prevention, the National Library of Medicine, and others.

10. I have never been retained to represent the pharmaceutical industry in any litigation, nor have I received industry funding for pharmaceutical research.

11. I have not met Dr. Harkonen, and have no personal relationship with him.

12. In preparation for this declaration, I have reviewed the press release of August 28, 2002, and the decision of the District Court on the post-trial motions. I have also reviewed the publications in the New England Journal of Medicine reporting the results of the trial that was the subject of the press release, as well as the trial testimony of Professor Fleming and Dr. Crager.

13. I will speak plainly here; I was stunned. I have spent a professional lifetime teaching how the statistical rules described in the testimony and adopted by the court serve merely as conventions of conduct, not rules of science, which must often be bent or even violated to derive proper scientific conclusions. Their rigid interpretation or application is vigorously opposed by many leading statisticians and clinical researchers, who recognize that they are merely

useful guidelines and not inviolable laws of science or logic. In science, the interpretation of the results from a clinical trial is not black or white; it involves many shades of gray, and can be subject to vigorous dispute by reasonable people on all sides.

14. In particular, P-values below 0.05 are not determinate of truth and P-values over 0.05 are not determinate of falsity; innumerable examples of studies with results on both sides of that divide can be cited for relationships that turned out to be different than the statistical significance would indicate. I recently published in the peer-reviewed medical literature an article that outlined 12 highly prevalent interpretations of P-values that are categorically wrong. Goodman, Steven, "A Dirty Dozen: Twelve P-Value Misconceptions," Seminars in Hematology 45: 135-140, (2008). I list below those that are most directly relevant to the court's opinion:

> Four (of twelve) P-value Misconceptions
>
> 1.) If P =.05, the null hypothesis has only a 5% chance of being true.
>
> 2.) A nonsignificant difference (e.g., P >.05) means there is no difference between groups.
>
> 3.) A statistically significant finding is clinically important.
>
> ---
>
> 12.) A scientific conclusion or treatment policy should be based on whether or not the P value is significant.

15. This is not fringe material; it is standard statistical teaching. Leading biostatisticians have long tried to dispel misconceptions like these, but such

beliefs have proven remarkably persistent among doctors and non-scientists looking for formal, "bright line" rules to guide their interpretations of statistical evidence.

16. Another particularly contentious and difficult area involves the interpretation of secondary endpoints in clinical trials, as well as subgroup analyses. In this area, the jury heard just one point of view, a particularly conservative one. One would find wide variance both in practice and in theory about how to approach such problems. The representations made about the rules to be applied in such circumstances did not serve the court well. The scientific literature is filled with inferences from data that do not comport with the principles that Dr. Fleming and Dr. Crager applied to the press release, and many of those inferences have not only turned out to be correct, but the basis of FDA drug approval.

17. A prime example of this was the case of the drug carvedilol, whose clinical trial results posed very similar issues to those that arose in this case. In short, carvedilol was a drug designed to improve cardiac function among patients with heart failure, and thereby improve survival. The company sponsoring the pivotal trials for carvedilol designed most of them to measure exercise tolerance as a primary endpoint, not because survival was less important, but because they did not think they would observe enough deaths to achieve a statistically significant result. That was the same logic used in the design of the trial in this case. The results surprised the investigators and confounded the FDA advisory committee considering the carvedilol application: the drug showed no effect on the primary endpoint of exercise tolerance, yet appeared to improve survival.

18. Like this court, the FDA advisory committee struggled with how to consider a clinical trial that was negative on the primary endpoint, but provided evidence supporting the much more important survival benefit. These struggles were reported in articles published in 1999, copies of which have been submitted to the court. Lloyd D. Fisher and Lemuel A. Moye, "Carvedilol and the Food and Drug Administration Approval Process: An Introduction" Controlled Clinical Trials 20:1-15 (1999); Lloyd D. Fisher, Carvedilol and the Food and Drug Administration (FDA) Approval Process: The FDA Paradigm and Reflections on Hypothesis Testing," Controlled Clinical Trials 20:16-39 (1999). The committee debated vigorously, and those deliberations showed the many competing principles and inferential approaches brought to bear on this situation.

19. The committee initially disapproved the drug, mainly on the basis of the principle that a drug cannot be approved on the basis of secondary endpoints when a primary endpoint was not reached. The FDA was very troubled by this reasoning, and made the following statement to the committee. "The Advisory Committee's initial decision was based in part on the position that one cannot reach definitive conclusions about secondary end points from a study that fails to demonstrate effectiveness using its primary end point. This position requires careful consideration, as it is consistent neither with past Agency actions nor past Advisory Committee recommendations." Fisher and Moye, "Carvedilol and the Food and Drug Administration Approval Process: An Introduction" Controlled Clinical Trials 20:1-15 (1999). A second committee that was convened to reconsider the evidence rejected the first committee's reasoning, and the drug was approved. The principle

that studies negative on their primary endpoints cannot be further analyzed, and that such analyses cannot be considered reliable is contrary to both FDA policy, practice and scientific principles. This is very difficult territory, one has to wade into it very carefully, and there are no bright line rules. But by the testimony cited by the court in Dr. Harkonen's case, a press release touting the survival benefit of carvedilol could have been declared "objectively false" and thereby fraudulent when made, even with the FDA and its advisory committees later supporting the claim.

20. We actually have a similar situation here, with a scientific follow-up that completely vindicated the reasonableness of the inference suggested by the press release. In the New England Journal report of the trial described in the press release (whose authors did not include Dr. Harkonen), the report's final conclusion, stated in the abstract, is that "a clinically significant survival advantage could not be ruled out." Ganesh Raghu et al., "A Placebo-Controlled Trial of Interferon Gamma-lb in Patents [sic] with Idiopathic Pulmonary Fibrosis," N. Engl. J. Med. 350:125-33 (2004). It is hard to overstate the importance of that statement with respect to the findings of the court. The New England Journal editors are extremely scrupulous (some would say overly so) about the accuracy of such conclusory language. This is particularly true for language appearing in the abstract, which is the most-read section of the article, and whose statements cannot be attended by qualifications and elaborations. The authors (and editors) were bending over backwards here to make sure that the non-significance (i.e. P=0.08) of the survival endpoint not be interpreted as dispositive of no survival benefit. They had only room for a two-sentence

conclusion, and that was one of them. This is a very direct statement from both the scientists who conducted the trial and the New England Journal editors that a claim for a survival advantage of this drug would not be inconsistent with the results of this trial. To sharpen the point, their conclusion was that the only "objectively false" statement one could make about this trial was that it had proven that the drug had no survival benefit. Their conclusion thus leaves ample room for others to draw inferences about the likelihood of a survival advantage, and validates as reasonable and within the range of acceptable scientific communication the statements and inferences in the press release.

21. Finally, I would like to draw the court's attention to what, in my opinion, is a critical confusion that I found in the testimony and adopted by the court. The one rule that must be followed for proper inference, and perhaps the only one upon which the descriptor "objective falsity" can legitimately be applied, is that data and analyses be accurately reported. In the press release at issue, the data, including which endpoints were primary and which were secondary, were accurately reported, as was the subgroup analysis. This is all that is necessary for proper inferences to be made. What is not true is that there is only one proper inference from data. Many reasonable judgments can be made, and in medical research, claiming that an observed survival advantage with a P=0.08 is real is certainly one of them, as indicated above. Such inferences are made every day in the published medical literature. It is certainly not surprising to see such an inference here, where there was a large clinical effect (40%) on an endpoint (mortality) that is of such profound importance in addressing an inevitably fatal disease.

22. I want to make it clear that I regard Dr. Fleming as a respected authority in the field of clinical trial statistics, whose opinions on these matters are always to be taken seriously, and one whose sometimes lonely stands are often vindicated. His position was an eminently defensible one, but opposing ones are as well, just as top legal scholars will espouse and defend different positions on complex legal matters. Where in my opinion his testimony led the court astray was in not making apparent that his was just one of many positions on such issues, that even the FDA, the most rule-driven of agencies, occasionally bends or breaks the rules he laid down, and that such rules do not represent inviolable laws of science, statistics or logic.

23. Should it become widely known that a physician was criminally punished for making defensible scientific inferences from accurately reported data, the kind made on the pages of medical journals every day, and in this case, specifically supported as reasonable in the most visible and respected of medical research forums — the New England Journal of Medicine — I believe the consequences will not be good for scientists, medical research, or for the normal procedures of scientific inquiry.

24. In my opinion, to imprison an individual who did not misreport the trial data or the endpoints themselves, and who drew a causal inference that was deemed permissible by mainstream scholarship, would have a profoundly negative effect on the efforts of many scholars to clarify persistent confusion about the misuse of p-values and about the permissible bases for drawing causal inferences. Imprisonment will send scientists a message that their inferences from data must follow the rules testified to at this

trial, rules that should be considered in, but do not define the limits of, proper scientific procedure; imposing criminal punishment here thus could confuse or disrupt legitimate scientific claims and communications. I respectfully ask the court, as it considers the question of punishment for Dr. Harkonen, to take into account the broader impact its sentence may have on the scientific community and scientific communication.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this declaration was executed on October 25th, 2010, at Baltimore, Maryland.

/s/ Steven N. Goodman
Steven N. Goodman, M.D., M.H.S., Ph.D