

No. 09-1156

In The
Supreme Court of the United States

MATRIX INITIATIVES INC., ET AL., PETITIONERS,

v.

JAMES SIRACUSANO, ET AL.

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

**BRIEF OF BAYBIO AS AMICUS CURIAE
SUPPORTING PETITIONERS**

STEPHEN B. THAU
ERIK J. OLSON
ANDREW T. HALL
MORRISON & FOERSTER LLP
755 Page Mill Rd.
Palo Alto, CA 94304

JORDAN ETH
MORRISON & FOERSTER LLP
425 Market St.
San Francisco, CA 94105

DEANNE E. MAYNARD
Counsel of Record
BRIAN R. MATSUI
MARC A. HEARRON
MORRISON & FOERSTER LLP
2000 Pennsylvania Ave., N.W.
Washington, DC 20006
dmaynard@mof.com
(202) 887-8740

Counsel for BayBio

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BRIEF OF BAYBIO AS AMICUS CURIAE SUPPORTING PETITIONERS

BayBio respectfully submits this brief as amicus curiae in support of petitioners.¹

INTEREST OF AMICUS CURIAE

Amicus curiae BayBio is an independent, non-profit trade association serving the life science industry in Northern California. Northern California is the birthplace of the biotechnology industry and contains the largest cluster of life sciences companies in the United States. Amicus's membership consists of more than 400 organizations engaged in or supportive of research, development, and commercialization of life science products. Amicus supports the Northern California bioscience community through advocacy, enterprise support, and the enhancement of research collaboration. Amicus represents the point of view of the life science industry on issues at every level of government, regularly working with legislators, officials, and policymakers.

¹ Pursuant to Rule 37.3(a), letters from the parties consenting to the filing of this brief have been filed with the Clerk of the Court. No counsel for a party authored this brief in whole or in part, and no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of the brief. No person other than amicus curiae, its members, or its counsel made a monetary contribution to the preparation or submission of this brief.

Amicus is concerned that the decision below will expose its membership to potential liability for securities fraud for failing to disclose isolated reports of adverse events, even when those reports do not constitute medically or statistically significant evidence that the adverse events were caused by use of a drug.

SUMMARY OF ARGUMENT

The Nation's leading biotechnology companies produce and develop important as well as life-saving drugs. They are constantly inundated with adverse event reports and other data about the efficacy and safety of their products in clinical trials and on the market. These companies—many of which are members of amicus BayBio—thoroughly investigate these reports and, when required by law, transmit the reports to government regulators for further analysis.

They do not, however, routinely disclose the existence of adverse event reports when making statements about their financial results or the safety and efficacy of their products. That is so because adverse event reports, without more, say nothing about whether the drug caused the adverse event—let alone whether the drug is safe or effective. Accordingly, at least when a company is not making a statement expressly about adverse event reports, the non-disclosure of these reports cannot state a claim under Section 10(b) and Rule 10b-5.

A.

1. Biotechnology companies regularly receive reports of adverse events from users of their products or from those participating in clinical trials. While such anecdotal evidence may prompt further inquiry into a drug's safety, it does not, standing alone, constitute scientific evidence that the drug causes a dangerous or undesirable reaction. Indeed, history has demonstrated that anecdotal evidence of correlation

is often misleading, and reliance on it can result in erroneous conclusions. Such speculative, uninformed conclusions are particularly pernicious when they cause consumers to stop using safe, beneficial pharmaceutical drugs or when they discourage people from participating in clinical trials.

In contrast with anecdotal evidence, more reliable data can be derived from controlled experiments (i.e., clinical trials) and observational studies. In such studies, only a statistically significant deviation between the incidence of a result in the treatment group as compared to the control group is evidence of correlation, and possibly causation, between the two. Scientists rely not on anecdotal evidence but on these scientific investigations to determine whether detrimental side effects are associated with a drug or are the result of chance or some other factor.

2. Pre-market approval for drugs is a rigorous process. The Food and Drug Administration (FDA) carefully considers sophisticated studies conducted by the drug manufacturer; it does not rely on anecdotal evidence of efficacy or safety. And once a drug has been approved, the FDA continues actively to monitor drug safety by collecting adverse event reports. Indeed, drug manufacturers are required by statute to report adverse events to the FDA. Recognizing that these reports are not necessarily an indication of a safety concern associated with use of a particular drug, the FDA investigates whether the adverse reports signal the possibility of a safety problem or are just statistical “noise.” Many times, the FDA

determines that such reports are associated not with the drug's use but with other factors, such as underlying disease. The measured, scientific approach taken by the FDA is in sharp contrast with that of the Ninth Circuit's decision, which would lead to public disclosure of anecdotal reports of adverse events that are not statistically significant.

3. Improper or premature disclosure of adverse event reports to the public may create false alarms that discourage participation in clinical trials or cause individuals to reduce their use of beneficial medications, thereby creating a different hazard. Only if a statistically significant connection between use of the drug and the adverse event is established is there any meaning from the incidence of the adverse event.

B.

1. Unless adverse event reports are statistically significant, a plaintiff bringing a securities fraud suit cannot establish that their non-disclosure rendered the defendant's general statements about its products and business materially misleading. For an omitted fact to be material, there must be a substantial likelihood that a reasonable investor would have viewed the fact as significantly altering the total mix of information available. But, just as the FDA and biotechnology companies do not view anecdotal reports of adverse events as establishing causation, or even correlation, there is no substantial likelihood that a reasonable investor would view such reports as

having any bearing on the safety of a drug, unless those events occur to a statistically significant degree.

2. There also can be no “strong inference” of scienter, which is the pleading standard for securities fraud actions. A defendant acts with scienter when he or she makes a statement knowing that it is materially misleading. Biotechnology executives who make statements about a company’s products or business, but do not address adverse events (one way or the other), are not trying to mislead investors. To the contrary, they avoid making statements about adverse events because doing so would not inform investors of meaningful information and threatens to mislead or confuse. Moreover, in determining whether allegations create a strong, (i.e., cogent or compelling) inference of scienter, courts must examine opposing, nonculpable explanations for the defendant’s conduct. Because no plausible inference can be drawn from statistically insignificant adverse event reports, an allegation that the defendant was aware of, but did not disclose, such reports cannot create a strong inference of intentional deceit.

ARGUMENT**THE NON-DISCLOSURE OF STATISTICALLY
INSIGNIFICANT ADVERSE EVENT REPORTS
DOES NOT MAKE A COMPANY'S STATEMENTS
ABOUT ITS PRODUCTS OR EARNINGS FRAUD-
ULENT UNDER THE SECURITIES LAWS**

Biotechnology companies constantly make statements to investors about their company, their existing products, and new products that are being developed or are in clinical trials. These statements are made not only in filings with the Securities and Exchange Commission, but also in press releases, conference calls, and other similar situations. The Ninth Circuit's ruling will subject companies to potential liability for securities fraud, and attendant litigation costs, any time that they make such routine statements without disclosing reports of adverse events. That decision is erroneous.

As this Court has explained, “[s]ilence, absent a duty to disclose, is not misleading under Rule 10b-5.” *Basic Inc. v. Levinson*, 485 U.S. 224, 239 n.17 (1988). Such a duty to disclose may arise where the omitted fact is “necessary in order to make statements made, in the light of the circumstances under which they were made, not misleading.” 17 C.F.R. § 240.10b-5(b). Thus, in determining whether any particular omission is fraudulent, the statements being made must be carefully examined.

As discussed below, statements about a company's product, its earnings, or even about effects caused by its product are not made materially misleading by the non-disclosure of adverse event reports, unless the adverse event reports are statistically significant. Nor can a company have acted with scienter in not disclosing such unreliable, statistically insignificant data. That is so because adverse events that do not occur at a statistically significant rate do not alone say anything—positive or negative—about whether a drug causes any particular side effect.

If left standing, the Ninth Circuit's rule will require companies to make boilerplate disclosures of adverse event reports virtually every time that they make a statement, along with a disclaimer that the company does not believe that such reports have any bearing on their statements. Such an information dump will add nothing to the mix of information already available to reasonable investors. At the same time, such disclosures will needlessly cause consumers to avoid using safe, beneficial drugs.

A. Biotechnology Companies Are Constantly Inundated With Anecdotal Evidence That Does Not Indicate Any Safety Risk

There is good reason for not disclosing anecdotal adverse event reports every time a company makes a statement about its products. Often these events,

upon further investigation, are found not to be caused by use of the drug. As explained below, unless the occurrence of adverse events is, at a minimum, statistically significant, there is no basis to say that use of the product led to the adverse event. This principle is universally recognized in the scientific community, by the Food and Drug Administration, and by drug developers and manufacturers. And before the decision below, it had widespread acceptance in the courts.

1. Anecdotal evidence about the efficacy or dangerousness of a product does not establish causation

Anecdotal evidence—such as the adverse events at issue in this case—is frequently subject to misinterpretation. Such evidence is often “obtained haphazardly or selectively, and the logic of ‘post hoc, ergo propter hoc’ does not suffice to demonstrate that the first event causes the second.” David H. Kaye & David A. Freedman, *Reference Guide on Statistics*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 83, 91 (Federal Judicial Center, 2d ed. 2000). While anecdotal evidence can be informative, it is “more useful as a stimulus for further inquiry than as a basis for establishing association.” *Ibid.*

Indeed, history has demonstrated that overreliance on anecdotal evidence can lead to erroneous conclusions that mask the actual underlying cause of

a problem. Anecdotal evidence that people living by roads developed lung cancer once led to the misconception that lung cancer was caused by the fumes from the tarring of roads. *Tarred Roads & Lung Cancer*, 1 BRIT. MED. J. 178 (1940). But while people exposed to tar fumes did develop lung cancer, so too did people at a similar rate who were never exposed to such fumes. The anecdotal evidence hid the fact that the real difference between the person who developed lung cancer and the person who did not was exposure to cigarette smoke. Richard Doll & A.

Bradford Hill, *A Study of the Aetiology of Carcinoma of the Lung*, 2 BRIT. MED. J. 1271 (1952).²

In contrast to anecdotal evidence, more reliable data are derived from controlled experiments and, at times, observational studies. In determining the efficacy or potential dangerousness of a drug, amicus's members often view controlled experiments as

² Courts have long recognized that anecdotal evidence does not establish causation. See *Hendrix v. Evenflo Co.*, 609 F.3d 1183, 1197 (11th Cir. 2010) (“Case studies and clinical experience, used alone and not merely to bolster other evidence, are also insufficient to show general causation.”); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1211 (10th Cir.) (case reports “contain only limited information” and are “unreliable evidence of causation”), cert. denied, 537 U.S. 1088 (2002); *Turner v. Iowa Fire Equip. Co.*, 229 F.3d 1202, 1209 n.5 (8th Cir. 2000) (“Case reports are generally not considered reliable evidence of causation.”); *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1316 (11th Cir. 1999) (“case reports and case studies are universally regarded as an insufficient scientific basis for a conclusion regarding causation because case reports lack controls” (quoting *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1411 (D. Or. 1996)); *Muzzey v. Kerr-McGee Chem. Corp.*, 921 F. Supp. 511, 519 (N.D. Ill. 1996) (“Anecdotal reports * * * are not reliable bases to form a scientific opinion about a causal link.”); *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995) (“case reports are not reliable scientific evidence of causation, because they simply describe reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group”); *Merrell Dow Pharms., Inc. v. Havner*, 953 S.W.2d 706, 720-721 (Tex. 1997) (“[A]necdotal * * * evidence accomplishes no more than a false appearance of direct and actual knowledge of a causal relationship.” (citing David Rosenberg, *The Causal Connection in Mass Exposure Cases: A “Public Law” Vision of the Tort System*, 97 HARV. L. REV. 851, 870 (1984))), cert. denied, 523 U.S. 1119 (1998).

the “gold standard” for evidenced-based medicine. Donald W. Miller, Jr. & Clifford G. Miller, *On Evidence, Medical & Legal*, 10 J. AM. PHYSICIANS & SURGEONS 70, 71 (2005); *see also* Jerry Avorn, *In Defense of Pharmacoepidemiology*, 357 NEW ENG. J. MED. 2219, 2219 (2007).

A controlled experiment “compare[s] outcomes for subjects who are exposed to some factor—the treatment group—and other subjects who are not so exposed—the control group.” Kaye & Freedman, *supra*, at 92; *see also* Paul R. Rosenbaum, *Observational Study*, in 3 ENCYCLOPEDIA OF STATISTICS IN BEHAVIORAL SCIENCE 1451, 1451 (2005) (“In the ideal, the effects caused by treatments are investigated in experiments that randomly assign subjects to treatment or control, thereby ensuring that comparable groups are compared under competing treatments.”). By using a treatment and a control group, particularly when the two groups are randomized, the results can demonstrate a high degree of confidence in the existence or absence of causation. In other words, when there is a certain minimum deviation between the results among the treatment group versus the control group, there is statistically significant evidence of causation. Thus, while doctors think that taking aspirin reduces the risk of heart attack based on their observations, a controlled experiment to support that hypothesis must not only compare the heart attack rates for the treatment group (those who took aspirin) and the control group (those who did not), but it also must account for potential biases

between the two groups. If the control group is healthier than the treatment group, the result of the study will be biased against the drug. Kaye & Freedman, *supra*, at 93.

To be sure, not every experiment or study can control for variables.³ Thus, amicus's members often must rely on statistical analyses that are derived from observational studies rather than controlled experiments. Like a controlled experiment, observational studies compare two groups—a treatment group and a control group—but who is in the control versus the treatment group is not dictated by the investigator.

³ Particularly in the field of medicine, ethical standards sometimes preclude the use of controlled experiments:

Experiments with human subjects are often ethical and feasible when (a) all of the competing treatments under study are either harmless or intended and expected to benefit the recipients, (b) the best treatment is not known, and in light of this, subjects consent to be randomized, and (c) the investigator can control the assignment and delivery of treatments. Experiments cannot ethically be used to study treatments that are harmful or unwanted, and experiments are not practical when subjects refuse to cede control of treatment assignment to the experimenter. When experiments are not ethical or not feasible, the effects of treatments are examined in an observational study.

Rosenbaum, *supra*, at 1451; see also Nick Black, *Why We Need Observational Studies to Evaluate the Effectiveness of Health Care*, 312 BRIT. MED. J. 1215 (1996).

An observational study into the efficacy of aspirin preventing heart attacks, for instance, will also observe whether there is a decreased rate of heart attacks for those who take aspirin (treatment) versus those who do not (control). If the treatment group rate is a certain degree higher or lower than the control group, it is statistically significant, and there generally is an *association* between aspirin and heart attacks. But that does not necessarily show *causation*—i.e., that aspirin reduces or increases the likelihood of a heart attack—because the observational study’s methodology might not account for the possibility that some other factor in one group versus the other led to the result. Rosenbaum, *supra*, at 1451 (“When subjects are not assigned to treatment or control at random, when subjects select their own treatment or their environments inflict treatments upon them, differing outcomes may reflect these initial differences rather than effects of the treatments.”).⁴

⁴ Observational studies can remove or account for biases in group selection. Rosenbaum, *supra* at 1451. For example, biases might be removed if an association “is seen in studies of different types among different groups. This reduces the chance that the observed association is due to a defect in one type of study or a peculiarity in one group of subjects.” Kaye & Freedman, *supra*, at 95; *see also* Rosenbaum, *supra*, at 1455-1456.

2. Regulators and biotechnology companies carefully scrutinize adverse event reports

Review of adverse event reports by biotechnology companies and government regulators is one part of a drug's "rigorous" preapproval process. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 317 (2008). Adverse events that occur during a drug's preapproval clinical trials are reported to the FDA and investigated. And after a product has received approval from the FDA and has been released to the market, observations about the drug's safety continue. Amicus's members regularly receive or uncover anecdotal reports of adverse events that may or may not be associated with a drug's safety.⁵

But, as discussed above, an adverse event report is anecdotal evidence, and thus does not, by itself, establish a safety concern. For one thing, a report of an adverse event that is received by a biotechnology company does not even necessarily mean that an adverse event has, in fact, occurred. Pet. Br. 20 (citing S. Rep. No. 109-324, at 6 (2006)); *Saari v.*

⁵ In this case, respondents allege that petitioners failed to disclose adverse event reports that were received after a drug went on the market, but such anecdotal reports also arise in clinical trials and testing during the preapproval phase. Under the ruling below, non-disclosure of preapproval adverse event reports may also prompt allegations of securities fraud, because stock prices of biotechnology companies are influenced not only by the success of products already on the market but also by the potential viability of products being tested before approval.

Merck & Co., 961 F. Supp. 387, 394 (N.D.N.Y. 1997) (adverse event report is “simply a report of what plaintiff told [her doctor] about what she believed was her reaction to the [drug]”). And absent investigation, there is often no way to discern which reports signal a safety concern and which are merely background “noise.”

That is especially so where the adverse event is the type that has a high incidence among the general population, such as heart disease. Institute of Med. of the Nat’l Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* 54 (Alina Baciu et al. eds. 2007) (“IOM Report”).⁶ For example, if a patient has a heart attack and dies, the manufacturers of drugs being taken by the patient to treat the heart disease at the time of the heart attack may be notified that an adverse event has occurred while someone was taking one of their drugs. Since heart attack and death may occur due to heart disease, it is difficult to determine whether drugs taken to treat heart disease played a role in the death or whether the underlying disease or diseases caused the death. If the patient was taking multiple drugs at the time of the event and/or has other diseases that may have a negative impact on the heart, it is

⁶ The IOM Report was commissioned by the FDA to study and make recommendations regarding the effectiveness of its postmarketing safety evaluations. The report was the basis of Congressional expansion of the FDA’s postmarketing authority in the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823.

even more difficult to determine whether a particular drug or combination of drugs caused the adverse event. Furthermore, events such as heart attacks are often multifactorial and not necessarily attributable solely to one factor. Drug companies and the FDA are thus left to analyze a large number of reports collected over a period of time and to look for patterns (or safety signals) in a number of these reports that would suggest a particular drug or combination of drugs may cause or contribute to particular adverse events. Often, therefore, controlled experiments or sophisticated observational studies are needed to assess whether common adverse events (such as heart attacks in older adults) can be attributed to a drug's use. *Id.* at 106. And because adverse events occur with more frequency among segments of the population that already are more susceptible to complications or disease than the general population, determining whether an adverse event is caused by the drug or by another factor—or even is occurring at random—is rarely straightforward.

Rigorous assessment of adverse events is therefore critical to evaluate a drug's safety. The FDA recognizes that adverse events will occur in clinical trials during the preapproval process and imposes certain reporting requirements. *See, e.g.*, 21 C.F.R. § 312.32(c)(1)(i). But the FDA does not require that all adverse events be reported to the institutional review board that has been designated to review the study or trial. Rather, the FDA recognizes that some adverse events are statistically insignificant, while others require further investigation or immediate action.

To that end, an adverse event “observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the [institutional review board], **only** if it were unexpected, serious, and would have implications for the conduct of the study.” FDA, U.S. Dep’t of Health & Human Servs., *Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection* at 3 (Jan. 2009), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079753.pdf>. An individual occurrence of an adverse event ordinarily does not satisfy these criteria. *Ibid.* Nor do adverse events that “are commonly associated with the underlying disease process that the study intervention is intended to treat (e.g., deaths in a cancer trial) or that are otherwise common in the study population independent of drug exposure (e.g., cardiovascular events in an elderly population).” *Ibid.*

Nor does inquiry into the safety of a drug end after FDA approval. Due to the limited sample size and duration of use by trial participants during the preapproval process, clinical trials do not always identify every adverse event. Margaret Gilhooley, *Addressing Potential Drug Risks: The Limits of Testing, Risk Signals, Preemption, and the Drug Reform Legislation*, 59 S.C. L. REV. 347, 360-361 (2008). Adverse events that are rare may go undetected, or their incidence may be at a rate so low that it is not possible to distinguish between an event

caused by the drug and one expected by chance. IOM Report, *supra*, at 106. Thus, although safety concerns are uncovered during the preapproval stage, adverse events are not unexpected. And Congress expects that biotechnology companies will continue to monitor and study their drugs to determine whether there are adverse side effects resulting from their use, or known events with an increased incidence.

Congress thus has charged the FDA not only with making the initial drug-approval determination—which is based on whether the drug’s benefits outweigh its risks—but also with monitoring drug safety after approval. *See* 21 U.S.C. § 355(k)(3), (4). The FDA requires drug manufacturers to report to the FDA serious, unexpected adverse events within 15 days of their initial receipt. 21 C.F.R. § 314.80(c)(1).⁷ For all other adverse events, the manufacturer must submit to the FDA reports summarizing such events quarterly for the first three years and annually thereafter. *Id.* § 314.80(c)(2); *see also* 21 U.S.C. § 355(k)(1) (requiring manufacturers to make such reports to the FDA in accordance with FDA regulations). The FDA also has a voluntary reporting system, MedWatch, which enables healthcare providers and consumers to

⁷ A serious adverse event is one that results in, or that requires medical or surgical intervention to prevent, death or the immediate risk of death, inpatient hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. 21 C.F.R. § 314.80(a). An unexpected adverse event is one that is not listed in the current labeling for the product. *Ibid.*

report adverse events directly to the FDA. See FDA, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, <http://www.fda.gov/Safety/MedWatch/default.htm> (last updated Aug. 25, 2010). Last year, the FDA received more than 580,000 adverse event reports. FDA, *Reports Received and Entered into AERS by Year* (Mar. 31, 2010), <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm>.

The FDA recognizes that the receipt of adverse event reports is not necessarily an indication of a safety concern associated with use of a drug. FDA, *Annual Adverse Drug Experience Report: 1996* at 2 (1997), <http://druganddevicelaw.net/Annual%20Adverse%20Drug%20Experience%20Report%201996.pdf> (“For any given [adverse event report], there is no certainty that the suspected drug caused the [event]. * * * The adverse event may have been related to an underlying disease for which the drug was given, to other concomitant drugs, or may have occurred by chance at the same time the suspect drug was administered.”). Otherwise, of course, the FDA would take action on receipt of *any* such report, which it does not do. That it takes no action is not surprising because, without any control group against which to measure the adverse event report, these reports demonstrate nothing about causation. Cf. Kaye & Freedman, *supra*, at 95 (“Was there a control group? If not, the study has little to say about causation.”). Rather, once the FDA receives sufficient numbers of adverse reports, it decides whether the reports are a real

signal indicating the possibility of a safety problem, or “just ‘noise’ in the system.” IOM Report, *supra*, at 110.⁸

And even when adverse event reports are identified as a safety “signal,” such “[s]ignals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event” or that “it represents a potential safety risk.” FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* at 4 (Mar. 2005) (“FDA Guidance for Industry”), [http://www.fda.gov/downloads/Regulatory Information/Guidances/UCM126834.pdf](http://www.fda.gov/downloads/Regulatory%20Information/Guidances/UCM126834.pdf). To that end, the FDA can require drug manufacturers to conduct postmarketing studies or clinical trials to assess drug safety when, “on the basis of scientific data deemed appropriate by the [FDA],” there are signals or the potential of serious risk related to use of the drug. 21 U.S.C. § 355(o)(3)(a).

⁸ Indeed, as data collection has become more sophisticated, the number of adverse event reports has become overwhelming, and new systems are needed to analyze the reports. But such systems can “generate errant signals that turn out to be false alarms.” Jerry Avorn & Sebastian Schneeweiss, *Managing Drug-Risk Information—What to Do with All Those New Numbers*, 361 NEW ENG. J. MED. 647, 648 (2009). In particular, with the use of “automated algorithms” to “search for associations between medication use and adverse events in large observational data sets, rigorous analytic techniques will be necessary to ensure that confounding does not produce spurious associations that could generate safety signals warning of nonexistent hazards.” *Ibid.*

3. *The public is not served when anecdotal information, rather than statistically significant information, is disclosed*

The scientific community, biotechnology companies, and the FDA all recognize that reliance on anecdotal evidence is not a sound way to demonstrate that a drug is effective or unsafe. But that does not mean such information is ignored. As discussed above, amicus's members rigorously examine the degree to which adverse event reports require further scientific study or other action, and they dutifully report, as required by law, adverse events to the FDA. The FDA, in turn, studies the reports, and takes any action when necessary—either through ordering studies, modifications to labeling or, in some instances, a withdrawal of the drug from the market.

This deliberative examination recognizes that the FDA is charged with determining, during the drug approval process, that the drug's societal benefits sufficiently outweigh its safety concerns. And it provides biotechnology companies and regulators adequate time to vet scientific data to ensure that individuals do not prematurely quit (or decline to participate in) clinical trials, or that patients do not prematurely discontinue use of beneficial drugs, due to public misperceptions of dangerousness. It also helps ensure that such drugs are not prematurely pulled from the market. Indeed, even when the FDA investigates an adverse event report, it often finds

insufficient evidence to link the drug to the adverse event or concludes that the events were caused, not by the drug, but the underlying disease, patient's age, or other treatment. See FDA Guidance for Industry, *supra*, at 9; FDA, *Postmarketing Drug Safety Evaluations*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm> (last updated June 22, 2010) (FDA investigation determined that adverse events reported for Bystolic, Doribax, and Pristiq were not caused by use of the drugs).

But the ruling below has the potential to undermine that goal. Under the Ninth Circuit's standard, even where a biotechnology company discloses scientifically established risks associated with its drugs, its statements about its financial results or products may still be materially misleading if the company does not also disclose all anecdotal reports of adverse events—notwithstanding the lack of any indication of a linkage between the adverse event and the drug. Such forced disclosure of unreliable data harms the public by potentially discouraging consumers from using therapeutic drugs. And it discourages people—who already are informed in detail about the risks associated with clinical trials—from participating in such trials due to anecdotal reports that may have no bearing on the safety of the drug being studied.⁹ Both

⁹ Amicus's members already have difficulty finding volunteers for clinical trials. Without these trials, the approval process for potentially life-saving drugs can be delayed.

these results, in turn, will harm investors of the companies that manufacture the drug.

These concerns are anything but inchoate. When doctors and consumers learn of reports of adverse events (particularly from the company itself), they understandably become reluctant to prescribe and use those drugs, even when there is no evidence from scientific studies to support any association between the drug and the adverse event. Judyth Pendell, AEI-Brookings Joint Center for Regulatory Studies, *The Adverse Side Effects of Pharmaceutical Litigation* at 7 (Sept. 2003) (in a poll of health care professionals and patients, “[a] sizable number of physicians (43%) have avoided prescribing a particular drug that was appropriate for a patient because they were aware that it might be involved in product liability litigation”). And companies, rather than face potentially staggering liability under United States securities laws, now have an incentive to prematurely disclose such reports, even if it is not scientifically responsible to do so.

For example, rather than wait for a study to be carefully vetted, pharmaceutical companies Merck & Co. and Schering-Plough Corp. announced that preliminary results of a clinical study showed an increased risk of cancer in patients taking Vytorin. Shirley S. Wang & Ron Winslow, *More Vytorin Bad News Hits Merck, Schering*, WALL ST. J., July 22, 2008, at B1. This announcement caused significant same-day declines in the prices of the two companies’ shares. *Ibid.* A few months later, however, the

researchers published the study's full results, and the FDA concluded it was "unlikely" that Vytorin increases the risk of cancer. Jared A. Fovole, *FDA: Vytorin, Zetia 'Unlikely' To Raise Cancer Risk*, Dow Jones Newswires, Dec. 22, 2008. Vytorin remains on the market today.

In making the early disclosure, the companies wanted to inform regulators and investors immediately. But the companies' decision to disclose the results of the study before it had been carefully vetted by outside experts was widely criticized. Sarah Rubenstein, *Were Vytorin Cancer Data Made Public Too Soon?*, WALL ST. J. HEALTH BLOG (Sept. 3, 2008, 9:02 AM), <http://blogs.wsj.com/health/2008/09/03/were-vytorin-cancer-data-made-public-too-soon/> (noting that a Merck spokesman explained that the criticism "makes us feel like we're damned if we do and we're damned if we don't"); Matthew Herper, *Vytorin Study's Ethical Morass*, FORBES, Sept. 3, 2008, http://www.forbes.com/2008/09/02/vytorin-cholesterol-schering-biz-healthcare-cx_mh_0903vytorin.html. There was a significant concern that patients or doctors would make health decisions based on inconclusive or erroneous information. *Ibid.* As a pathology professor explained: "Now you've got a fear out there that I don't think is justified that I think patients and physicians will be reticent to use a drug that I think is very useful clinically." *Ibid.*; see also Michael Shermer, *How Anecdotal Evidence Can Undermine Scientific Results*, SCIENTIFIC AMERICAN, Aug. 2008, <http://www.scientificamerican.com/article.cfm>

?id=how-anecdotal-evidence-can-undermine-scientific-results (noting that, despite the absence of any scientific causal link between vaccines and autism in children, anecdotal evidence often appears so “powerful that they cause people to ignore contrary evidence”).

B. Where The Company’s Statement Is Not Expressly About Adverse Events, A Securities Fraud Plaintiff Cannot Demonstrate A Materially Misleading Statement Or Scierer From The Non-Disclosure Of Adverse Event Reports That Are Not Statistically Significant

In addition to undermining the deliberative process by which adverse events are examined, the decision below cannot be reconciled with this Court’s holdings regarding materiality and scienter. As noted, the Ninth Circuit held that drug manufacturers’ statements about their products may be materially and intentionally misleading, and therefore fraudulent under the federal securities laws, unless manufacturers also disclose the occurrence of adverse events, even when those events lack any statistically significant relationship to the use of the drug. But unless the incidence of adverse events among users of a drug is at a rate that is, to a statistically significant degree, higher than among non-users, there is no evidence that the drug is the cause of the adverse events. Thus, reports of adverse events occurring at a statistically insignificant rate need not be disclosed because their non-disclosure does not make the company’s statements materially misleading. And a

manufacturer cannot have acted with scienter in not disclosing information that is not evidence of a causal relationship between the drug and the adverse events.

1. *The non-disclosure of statistically insignificant data does not render a company's statements materially misleading*

a. To prevail on a securities fraud claim under Section 10(b) and Rule 10b-5, the plaintiff must prove that the defendant made a statement that was misleading as to a material fact. *Basic*, 485 U.S. at 238; 17 C.F.R. § 240.10b-5. “It is not enough that a statement is false or incomplete, if the misrepresented fact is otherwise insignificant.” *Basic*, 485 U.S. at 238.

“Silence, absent a duty to disclose, is not misleading * * * ”. *Id.* at 239 n.17. For an omission to be materially misleading, “there must be a substantial likelihood that the disclosure of the omitted fact would have been viewed by the reasonable investor as having significantly altered the ‘total mix’ of information made available.” *Id.* at 231-232 (quoting *TSC Indus., Inc. v. Northway, Inc.*, 426 U.S. 438, 449 (1976)). “[A]n omitted fact is material if there is a substantial likelihood that a reasonable shareholder would consider it important” in making an investment decision. *Id.* at 231 (quoting *TSC Indus.*, 426 U.S. at 449).

Biotechnology companies, including amicus's members, routinely make statements about their products in various contexts. At least when the statements are not expressly about adverse event reports, the non-disclosure of anecdotal reports of adverse events occurring among users of a drug does not render those statements materially misleading. There is no evidence of a causal relationship between use of the drug and the incidence of the adverse events. As discussed above, anecdotal reports of isolated adverse events are inherently unreliable. Without more, they are not scientifically conclusive evidence, because "[s]ome adverse events may be expected to occur randomly, especially with a drug designed to treat people that are already ill." *In re Carter-Wallace, Inc. Sec. Litig.*, 220 F.3d 36, 41 (2d Cir. 2000). The hypothetical reasonable investor already knows that adverse event reports are to be expected, both during a drug's preapproval clinical trials and after it is placed on the market, and that such anecdotal evidence, without more, does not signify a safety issue. A reasonable investor would rely on scientifically grounded evidence about a drug's safety in making investment decisions, not on speculative, conjectural information such as isolated adverse event reports. *See In re Rockefeller Center Props., Inc. Sec. Litig.*, 184 F.3d 280, 290 (3d Cir. 1999) ("In determining the effect of an omission, we examine whether the information omitted is speculative or unreliable * * * or if it is contingent." (internal citation omitted)).

Accordingly, when making statements about a biotechnology company's products, there is no duty to also disclose statistically insignificant instances of adverse events. There is no substantial likelihood that a reasonable investor would view reports of such adverse events—which do not scientifically establish any concern about the safety of a drug—as having any bearing on the drug's commercial viability or on the drug company's earnings. Thus, “[d]rug companies need not disclose isolated reports of illnesses suffered by users of their drugs until those reports provide statistically significant evidence that the ill effects may be caused by—rather than randomly associated with—use of the drugs and are sufficiently serious and frequent to affect future earnings.” *In re Carter-Wallace, Inc. Sec. Litig.*, 150 F.3d 153, 157 (2d Cir. 1998); *see also Oran v. Stafford*, 226 F.3d 275, 284 (3d Cir. 2000) (Alito, J.) (“Had [defendant] simultaneously disclosed * * * the adverse reaction reports [that lacked statistical significance], the aggregate of available information would nevertheless have led a reasonable investor to the same conclusion—that the relationship between the two drugs and heart valve disorders was still inconclusive.”).

This is true even though disclosure of statistically insignificant adverse reports could prompt individual users of the drug to prematurely discontinue its use. *See pp. 24-26, supra.* Anecdotal reports of adverse events, although not a scientific basis for concern, could prompt especially risk-averse

consumers to avoid use or find alternative treatments. But that reaction among users is of no moment to the question whether non-disclosure of information renders prior statements materially misleading. The securities laws require disclosure based on whether a hypothetical, objectively reasonable investor would consider the information significant. *TSC Indus.*, 426 U.S. at 445. Companies have never been subject to a judgment for fraud based on the non-disclosure of objectively meaningless information, even if there are some persons who might (irrationally) act based on that information. For example, except in limited circumstances, companies are not required to comment on speculative information, *see, e.g., Nathenson v. Zonagen Inc.*, 267 F.3d 400, 422 (5th Cir. 2001); *General Elec. Co. v. Cathcart*, 980 F.2d 927, 935-936 (3d Cir. 1992), or to republish rumors, *see, e.g., SEC v. Monarch Fund*, 608 F.2d 938, 942-943 (2d Cir. 1979). Thus, a plaintiff cannot allege and pursue a claim for fraud when a company fails to disclose meaningless, transitory information about products, such as the delay of shipments due to a tropical storm, even if rumors of the delays might cause a temporary decline in the stock's price. And for good reason: the disclosures are supposed to inform the market, not to mislead it. Yet the Ninth Circuit's rule would subject companies to after-the-fact liability for fraud due to non-disclosure of information that is, by definition, random.

b. Moreover, in addition to discouraging doctors and patients from prescribing and using the drugs,

see pp. 24-26, *supra*, the decision below will require disclosure of reports that may inject confusion into the marketplace. “The role of the materiality requirement is * * * to filter out essentially useless information that a reasonable investor would not consider significant * * * .” *Basic*, 485 U.S. at 234. The securities laws do not require excessive disclosure, which would deluge the market with needless, irrelevant, possibly misleading data that might drown out important information that would otherwise enhance investment decisionmaking. *See id.* at 231 (“a minimal [materiality] standard might bring an overabundance of information within its reach, and lead management ‘simply to bury the shareholders in an avalanche of trivial information—a result that is hardly conducive to informed decisionmaking’” (quoting *TSC Indus.*, 426 U.S. at 448-449)). Reports of adverse events that lack any statistical significance are exactly the type of speculative data that the materiality requirement should filter from the marketplace.

Indeed, subjecting biotechnology companies to liability for failing to disclose anecdotal reports of adverse events could require amicus’s members to disclose every new incidence of a possible adverse event any time that they make statements about their products. Biotechnology companies are constantly asked, and constantly make statements, about products that are in development, being tested, or on the market—not only in public filings, but also in press releases, television appearances, investor

calls, and the like. This is especially true for companies, like petitioner, with few (or even just a single) widely-used products. Since adverse event reports are ubiquitous, these companies would be making constant disclosures of possible adverse events. This barrage of immaterial information on the investing public is not the type of disclosure that federal securities laws require.

2. *There can be no “strong inference” of scienter if the defendant failed only to disclose statistically insignificant data*

The Ninth Circuit’s decision also subjects amicus’s members to potential liability for securities fraud without evidence or allegations of intent to deceive or defraud.

a. To establish liability under Section 10(b) and Rule 10b-5, a plaintiff must prove not only that the alleged misstatement or omission was material but that the defendant made the misstatement or omission with scienter, i.e., intent to deceive, manipulate, or defraud. *Ernst & Ernst v. Hochfelder*, 425 U.S. 185, 193 (1976). Thus, in a Section 10(b) lawsuit, the plaintiff must show that, at the time of the alleged non-disclosure of adverse events, the drug manufacturer intended to deceive investors into believing that the adverse events were not caused by the drug.

But such a defendant cannot have acted with the requisite scienter unless the incidence of adverse events was statistically significant. “A statement

cannot be intentionally misleading if the defendant did not have sufficient information at the relevant time to form an evaluation that there was a need to disclose certain information and to form an intent not to disclose it.” *New Jersey Carpenters Pension & Annuity Funds v. Biogen Idec Inc.*, 537 F.3d 35, 45 (1st Cir. 2008). Thus, a drug manufacturer cannot have committed fraud if it did not know that not disclosing them would be misleading. *Id.* at 48. And a drug manufacturer cannot have had sufficient evidence to subjectively understand that not disclosing adverse events would be misleading in the context of statements about its products or earnings unless the incidence was statistically significant and a causal relationship could be inferred from it.

b. Moreover, unless the complaint alleges that the defendant was aware of not just isolated adverse events but statistically significant events, the complaint cannot satisfy the pleading requirements of the Private Securities Litigation Reform Act of 1995 (“PSLRA”). The PSLRA requires securities fraud plaintiffs to plead “with particularity facts giving rise to a strong inference that the defendant acted with” scienter. 15 U.S.C. § 78u-4(b)(2). A complaint that alleges facts that create merely a possibility of scienter, as opposed to a “strong inference” of scienter, must be dismissed.

This Court has held that “in determining whether the pleaded facts give rise to a ‘strong’ inference of scienter, the court must take into account plausible opposing inferences.” *Tellabs, Inc. v. Makor Issues &*

Rights, Ltd., 551 U.S. 308, 323 (2007). That is, “plausible[,] nonculpable explanations for the defendant’s conduct” must be considered, in addition to inferences favoring the plaintiff. *Id.* at 324. “[T]he inference of scienter must be more than merely ‘reasonable’ or ‘permissible’—it must be cogent and compelling, thus strong in light of other explanations.” *Ibid.* A complaint will survive a motion to dismiss “only if a reasonable person would deem the inference of scienter cogent and at least as compelling as any opposing inference one could draw from the facts alleged.” *Ibid.*

Where the complaint’s only allegations of scienter are that the defendant was aware of isolated reports of adverse effects, but that those reports do not amount to statistically significant occurrences, that does not give rise to the requisite “strong inference” of scienter. Indeed, “no plausible inference” may be drawn from reports that are not statistically significant because they establish no causal relationship between the adverse events and use of the drug. *New Jersey Carpenters Pension*, 537 F.3d at 50. For the same reason that reports of isolated adverse events are not required to avoid making statements materially misleading to a reasonable investor, a biotechnology defendant would likewise not find such reports to be significant to its drug’s safety or commercial viability. Moreover, because it is reasonable for a company, given its experience and prevailing wisdom, to conclude that such adverse event reports are not material, it would not be plausible to conclude that it

had an intent to defraud the market, rather than that it simply did not disclose information that it thought was not scientifically relevant. *See City of Philadelphia v. Fleming Cos.*, 264 F.3d 1245, 1261 (10th Cir. 2001) (to establish scienter in securities fraud action, plaintiff must prove not only that defendant knew of allegedly omitted fact but also that “failure to reveal the potentially material fact would likely mislead investors”). Thus, the pleading of such isolated reports, without more, does nothing to advance an inference of scienter, much less a strong inference.

To hold otherwise would effectively gut the gatekeeping function of the PSLRA as it relates to public companies whose drugs become the subject of safety concerns. If a plaintiff can state a claim simply by alleging that a drug manufacturer failed to disclose statistically insignificant events, plaintiffs will almost always be able to state a claim, because reports of such adverse events will always precede statistically meaningful information or even the ability of drug safety professionals to detect a meaningful safety signal. But the converse is not true: adverse events are not always followed by statistically significant information or detectable safety signals. Companies therefore should not be subject to liability for securities fraud for making statements about their products or earnings without disclosing such statistically insignificant events. If the Ninth Circuit’s decision is left standing, a securities plaintiff will be able to survive the pleadings stage, and potentially get to the jury, on claims based on drug safety simply

by alleging the failure to disclose a meaningless adverse event—an allegation a plaintiff almost certainly will be able to make.

CONCLUSION

For the reasons set forth above and in petitioners' brief, the judgment should be reversed.

Respectfully submitted,

STEPHEN B. THAU
ERIK J. OLSON
ANDREW T. HALL
MORRISON & FOERSTER LLP
755 Page Mill Rd.
Palo Alto, CA 94304

JORDAN ETH
MORRISON & FOERSTER LLP
425 Market St.
San Francisco, CA 94105

DEANNE E. MAYNARD
Counsel of Record
BRIAN R. MATSUI
MARC A. HEARRON
MORRISON & FOERSTER LLP
2000 Pennsylvania Ave., N.W.
Washington, DC 20006
dmaynard@mofa.com
(202) 887-8740

Counsel for BayBio

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