No. 09-1156

IN THE
Supreme Court of the United States

MATRIXX INITIATIVES, INC., ET AL.,
Petitioners,

v.

JAMES SIRACUSANO AND NECA-IBEW PENSION FUND,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Ninth Circuit

BRIEF FOR PETITIONERS

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QUESTION PRESENTED

Respondents filed suit under § 10(b) of the Securities Exchange Act of 1934 and Securities and Exchange Commission ("SEC") Rule 10b-5, alleging that petitioners committed securities fraud by failing to disclose "adverse event" reports—i.e., reports by users of a drug that they experienced an adverse event after using the drug. The First, Second, and Third Circuits have held that drug companies have no duty to disclose adverse event reports until the reports provide statistically significant evidence that the adverse events may be caused by, and are not simply randomly associated with, a drug's use. Expressly disagreeing with those decisions, the Ninth Circuit below rejected a statistical significance standard and allowed the case to proceed despite the lack of any allegation that the undisclosed adverse event reports were statistically significant. The question presented is:

Whether a plaintiff can state a claim under § 10(b) of the Securities Exchange Act and SEC Rule 10b-5 based on a pharmaceutical company's nondisclosure of adverse event reports even though the reports are not alleged to be statistically significant.

PARTIES TO THE PROCEEDING

Petitioners are Matrixx Initiatives, Inc., Carl Johnson, William Hemelt, and Timothy Clarot, defendants-appellees below.

Respondents are James Siracusano, named plaintiff and appellant below, and the NECA-IBEW Pension Fund, lead plaintiff and appellant below, on behalf of themselves and all others similarly situated who purchased Matrixx securities between October 22, 2003, and February 6, 2004.

RULE 29.6 DISCLOSURE

Matrixx Initiatives, Inc. has no parent corporation and no person or publicly traded corporation owns more than 10% of Matrixx's stock.

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BRIEF FOR PETITIONERS

OPINIONS BELOW

The decision of the court of appeals is reported at 585 F.3d 1167 and is reprinted in the Appendix to the Petition ("Pet. App.") at 1a-34a. The district court's opinion is available at 2005 WL 3970117 and is reprinted at Pet. App. 35a-54a.

JURISDICTION

The court of appeals issued its decision on October 28, 2009, and denied a petition for rehearing and rehearing *en banc* on December 23, 2009. Pet. App. 55a-56a. The petition was filed on March 23, 2010, and granted on June 14, 2010. The Court's jurisdiction rests on 28 U.S.C. § 1254(1).

STATUTES AND REGULATION INVOLVED

The relevant provisions of the Securities Exchange Act of 1934, 15 U.S.C. § 78j(b), and the Private Securities Litigation Reform Act of 1995 ("PSLRA"), 15 U.S.C. § 78u-4(b)(2), and Securities and Exchange Commission ("SEC") Rule 10b-5 are reproduced at Pet. App. 57a-58a.

STATEMENT OF THE CASE

A. Statutory Background

To state a claim of fraud under § 10(b) of the Securities Exchange Act and SEC Rule 10b-5, a plaintiff must allege (1) the misrepresentation or omission of a material fact; (2) made with scienter; (3) in connection with the purchase or sale of a security; (4) on which the plaintiff relied; and (5) that was causally connected to (6) the plaintiff's loss. *See Stoneridge Inv. Partners, LLC v. Scientific-Atlanta, Inc.*, 552 U.S. 148, 157 (2008). This case implicates two of those elements: materiality and scienter.

1. *Materiality*

A statement can be "false or incomplete" and yet not actionable under § 10(b) "if the misrepresented fact is otherwise insignificant." *Basic Inc. v. Levinson*, 485 U.S. 224, 238 (1988). "The plain language of Rule 10b-5 . . . requires any successful securities-fraud suit to allege a fact that is both untrue *and* material." *Greenhouse v. MCG Capital Corp.*, 392 F.3d 650, 656 (4th Cir. 2004). A fact is material when there is "'a substantial likelihood'" that a reasonable investor would view it as "'significantly alter[ing] the "total mix" of information made avail-

able.'" *Basic*, 485 U.S. at 232 (quoting *TSC Indus., Inc. v. Northway, Inc.*, 426 U.S. 438, 449 (1976)).

The materiality requirement serves to "filter out essentially useless information that a reasonable investor would not consider significant." *Id.* at 234. Indeed, "[s]ome information is of such dubious significance that insistence on its disclosure may accomplish more harm than good." *TSC Indus.*, 426 U.S. at 448. The materiality filter helps ensure that corporations do not "bury the shareholders in an avalanche of trivial information—a result that is hardly conducive to informed decisionmaking." *Id.* at 448-49; *see also Basic*, 485 U.S. at 231. When a complaint alleges that a statement is misleading because a material fact was omitted, the complaint must "specify the reason or reasons why" the omission makes the statement misleading. 15 U.S.C. § 78u-4(b)(1)(B).

2. Scienter

A private plaintiff asserting a § 10(b) action must also establish that the defendant acted with "scienter," which "refers to a mental state embracing intent to deceive, manipulate, or defraud." *Ernst & Ernst v. Hochfelder*, 425 U.S. 185, 193 n.12 (1976). The scienter element requires a plaintiff to show that the defendant engaged in "intentional or willful conduct designed to deceive or defraud investors by controlling or artificially affecting the price of securities." *Id.* at 199.

To satisfy this element at the pleading stage, a complaint must satisfy demanding requirements. The Private Securities Litigation Reform Act of 1995 ("PSLRA"), Pub. L. No. 106-47, 109 Stat. 737 (codi-

fied at 15 U.S.C. §§ 77z-1 and 78u-4), was enacted to curb "abusive litigation by private parties," and one of its key "control measures" is a heightened pleading requirement for scienter. *Tellabs, Inc. v. Makor Issues & Rights, Ltd.*, 551 U.S. 308, 313 (2007). To survive a motion to dismiss, a complaint not only must "state with particularity" the facts establishing scienter, but those facts must "giv[e] rise to a strong inference" that the defendant intended to deceive investors. 15 U.S.C. § 78u-4(b)(2). A "strong inference" of scienter means an inference "at least as compelling as any opposing inference one could draw from the facts alleged." *Tellabs*, 551 U.S. at 324. The reviewing court thus must consider—on the basis of the complaint as a whole, including all documents incorporated by reference, *id.* at 322-23, as well as the court's own "judicial experience and common sense," *Ashcroft v. Iqbal*, 129 S. Ct. 1937, 1950 (2009)—whether there are "nonculpable explanations for the defendant's conduct" that are more likely than the plaintiff's explanation, *Tellabs*, 551 U.S. at 324. If so, the suit cannot proceed, because the inference of scienter is not "*at least as likely* as any plausible opposing inference." *Id.* at 328.

B. Factual Background

1. Petitioner Matrixx Initiatives, Inc. ("Matrixx") is a pharmaceutical company that sells cold remedy products through its wholly owned subsidiary, Zicam, LLC. Pet. App. 2a. One of Matrixx's main products is Zicam Cold Remedy ("Zicam"), a homeopathic remedy that has been clinically proven to reduce the duration and severity of the common cold. J.A. 212a.

Zicam comes in a variety of forms. The nasal spray and gel swab forms at issue here were marketed during the Class Period. *Id.*; *see also* Pet. App. 4a. The active ingredient in Zicam is zinc gluconate. *See* Pet. App. 4a. Prior to the events at issue here, Matrixx conducted two published double-blind, placebo-controlled, randomized clinical studies of intranasal application of zinc gluconate. J.A. 193a-94a. In both studies, "[t]he overall incidence of adverse events associated with zinc gluconate treatment was extremely low, with no statistically significant difference between the adverse event rates for the treated and placebo subsets." *Id.* at 194a.

2. Respondents allege that, starting in December 1999, petitioners began to receive isolated reports that some consumers were experiencing anosmia, or loss of smell, following use of Zicam. According to respondents:

- Matrixx was first advised by Dr. Alan Hirsch in December 1999 that he was aware of "at least one" user who complained of anosmia after using the product. J.A. 67a-68a (Compl. ¶ 25).
- In September 2002, petitioner Timothy Clarot, Matrixx's Vice President and Director of Research and Development, corresponded with Dr. Miriam Linschoten, a doctor at the University of Colorado Health Sciences Center, after one of Linschoten's patients contacted Matrixx to complain of anosmia. J.A. 68a (Compl. ¶ 26).
- In September 2003, Dr. Bruce Jafek, also at the University of Colorado, prepared a poster

presentation with Dr. Linschoten and another colleague, claiming ten reports of anosmia after using Zicam to treat a cold. J.A. 69a-70a (Compl. ¶ 28).

- By February 6, 2004, four lawsuits, with a total of nine plaintiffs, had been filed claiming anosmia caused by Zicam use. J.A. 87a-92a (Compl. ¶ 49); Pet. App. 25a-26a.

Because the complaint does not identify any user by name, it is possible, even likely, that some of these reports are "double counted." For instance, some or all of the nine plaintiffs were likely among the ten unnamed patients described in Jafek's poster presentation, especially given that Jafek was an expert for plaintiffs in some of the cases. *See, e.g.*, *Sutherland v. Matrixx Initiatives, Inc.*, 2006 U.S. Dist. LEXIS 96652 (N.D. Ala. Nov. 7, 2006). The total number of specific reports identified in the complaint as made during the class period is thus either 12 if the personal-injury plaintiffs are not treated separately—and they should not be, given the requirements for pleading with specificity—or 21 if they are.[1]

3. Matrixx attempted to obtain more information about the user complaints reported by Linschoten and Jafek. In the course of her conversation with Clarot, Linschoten allegedly referred to polio studies from the 1930s concerning the intranasal application of zinc sulfate—a compound different from the zinc gluconate used in Zicam. J.A. 68a-69a

[1] Respondents count the reports slightly differently and produce a figure of 23. Opp. to Pet. for Cert. 20. The exact figure is irrelevant for the reasons explained in this brief.

(Compl. ¶¶ 26-27).[2] Clarot advised Linschoten that Matrixx had already hired a consultant to examine the issue. Clarot also inquired whether she would be willing to participate in animal studies examining the effects of zinc gluconate. J.A. 69a (Compl. ¶ 27). Linschoten declined. *Id.*

Matrixx also attempted to obtain more information from Jafek about the incident reports he was claiming. On September 12, 2003, after becoming aware of Jafek's forthcoming poster presentation, Matrixx wrote him a letter explaining that it took very seriously any questions about Zicam's safety and was "very much interested in learning more about the adverse reports included in [the] presentation." J.A. 117a-18a; *see also id.* at 118a ("Prior to your presentation next week, we would very much appreciate the opportunity to learn more about the reports you will be describing and the basis for linking them with the use of zinc nasal products."). Matrixx's letter also advised Jafek that he lacked permission to use the trademark "Zicam" in his presen-

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[2] In subsequent products liability lawsuits, the opinions of plaintiffs' experts (including Jafek) on the effects of Zicam relied heavily on the old polio studies, and courts repeatedly rejected those opinions as unreliable. *See*, *e.g.*, *Benkwith v. Matrixx Initiatives, Inc.*, 467 F. Supp. 2d 1316, 1327 (M.D. Ala. 2006); *Evans v. Matrixx Initiatives, Inc.*, 2009 WL 2914252, at *10 (M.D. Fla. Feb. 18, 2009); *Lusch v. Matrixx Initiatives, Inc.*, 2007 U.S. Dist. LEXIS 72068, at *11-12 (D. Or. Sept. 25, 2007); *O'Hanlon v. Matrixx Initiatives, Inc.*, 2007 U.S. Dist. LEXIS 65655, at *7 & n.5 (C.D. Cal. Jan. 3, 2007); *Rose v. Matrixx Initiatives, Inc.*, 2009 WL 902311, at *8-9 (W.D. Tenn. Mar. 31, 2009); *Sutherland*, 2006 U.S. Dist. LEXIS 96652, at *26-27; *Wyatt v. Matrixx Initiatives, Inc.*, 2007 U.S. Dist. LEXIS 67986, at *9-10 (N.D. Ala. Mar. 30, 2007).

tation. J.A. 118a. The complaint includes no indication that Jafek ever provided Matrixx any additional information about the reports he was claiming. *Id.* 58a-111a.

Jafek presented the poster later in September 2003, but did not refer to Zicam by name. J.A. 70a (Compl. ¶ 29).

4. On January 30, 2004, the *Dow Jones Newswire* reported that three lawsuits had been filed against Matrixx. The report caused a dip in price of Matrixx shares. J.A. 62a, 79a-80a (Compl. ¶¶ 6, 40-41); *id.* at 188a-92a (Longo Decl. Ex. 7).

In response to the *Dow Jones* report, Matrixx issued a press release on February 2, 2004, stating its belief that "statements alleging that intranasal Zicam products cause anosmia (loss of smell) are completely unfounded and misleading." J.A. 77a-78a (Compl. ¶ 38); *id.* at 193a-95a (Longo Decl. Ex. 8). The press release explained that Matrixx had not received any reports of anosmia during the premarket clinical trials. *Id.* at 193a-94a. Matrixx further explained that because anosmia is frequently caused by the common cold—the very condition Zicam is used to treat—"the population most likely to use the cold remedy products is already at [an] increased risk of developing anosmia," which could lead users to report an erroneous association between use of Zicam and anosmia. *Id.* at 78a (Compl. ¶ 38).[3] The stock price normalized after Matrixx is-

[3] This phenomenon is known as "confounding by indication," where a known cause of the reported event is the very condition for which the drug is indicated, which makes establishing causation very difficult. "When a drug is claimed to

sued the press release. *Id.* at 80a (Compl. ¶ 41).

On February 6, 2004, however, Jafek appeared in a *Good Morning America* segment and affirmatively declared that Zicam causes anosmia. J.A. 80a-81a (Compl. ¶¶ 42-43); *id.* at 196a-200a (Longo Decl. Ex. 9). The *Good Morning America* feature also mentioned the products liability suits that had been filed against Matrixx. *Id.* at 199a-200a. The day the program aired, Matrixx's stock price dropped from its previous day close of $13.04 to $9.94 at the close of trading on February 6, despite Matrixx's issuance of another press release that day reiterating the facts asserted in its previous release. *Id.* 81a-82a (Compl. ¶¶ 43-44). That day—February 6, 2004—marked the end of the class period.[4]

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cause the very symptoms for which it is a designated treatment, determining the direction of causation is difficult at best." *Robinson v. McNeil Consumer Healthcare*, 2010 WL 3156548, at *5 (7th Cir. Aug. 11, 2010); *see* FDA, Center for Drug Evaluation and Research, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment ("Good Pharmacovigilance") 7, 13 (Mar. 2005) ("Confounding by indication is one example of an important concern in performing a pharmacoepidemiologic study."), *available at* http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl 0002.pdf.; *see generally* Michael D. Green et al., Reference Guide on Epidemiology, in Federal Judicial Center, Reference Manual on Scientific Evidence ("Reference Guide on Epidemiology") 369-70 (2d ed. 2000) (discussing problem of confounding).

[4] The complaint also cites a Matrixx 8-K issued on February 19, 2004—*after* the close of the Class Period—which stated that Matrixx "had convened a two-day meeting of physicians and scientists to review current information on smell disorders," and that "the opinion of the panel" was that "there is insufficient evidence at this time to determine if zinc gluconate, when used as recommended, affects a person's ability to smell."

C. Proceedings Below

1. Respondents filed suit on May 19, 2004, alleging that petitioners' omission of the aforementioned adverse event reports ("AERs") caused company statements about business growth and Zicam safety to be false and misleading. Respondents claimed that failure to disclose the AERs led to investment losses suffered on February 6, 2004, after Jafek announced on *Good Morning America* that Zicam causes anosmia.

Respondents allege that between October 23, 2003, and February 6, 2004 (the "Class Period"), petitioners "touted the growth of business" based primarily on "the increased success of [the] Zicam cold remedies" (J.A. 61a (Compl. ¶ 5)) and made several statements concerning the safety of Zicam in response to media reports and statements by Jafek (*id.* 62a-64a (Compl. ¶¶ 7, 9); *see id.* at 71a-79a (Compl. ¶¶ 32, 33, 35, 37, 39)). These Zicam-related business-growth and safety statements were false and misleading, respondents say, because petitioners failed to disclose that "large numbers [sic] of Zicam users had lost their sense of smell." Opp. to Pet. for Cert. 12; *see* J.A. 64a (Compl. ¶ 9).[5]

J.A. 82a (Compl. ¶¶ 45-46); *id.* at 205a-07a (Longo Decl. Ex. 11). The statement has no bearing on Matrixx's statements or scienter during the Class Period.

[5] Respondents also alleged that a statement made in November 2003 that Matrixx could "incur significant costs resulting from product liability lawsuits," was misleading because one lawsuit had already been filed. J.A. 75a (Compl. ¶ 35). That allegation is not directly pertinent to the question before this Court, *see infra* note 25, except insofar as the lawsuit was the effective equivalent of an isolated incident report petition-

Respondents further allege that petitioners acted with scienter because they "were aware since at least September 2003, that numerous users of their Zicam product had experienced a rare condition known as anosmia or loss of smell." J.A. 101a (Compl. ¶ 64). Respondents also assert that petitioners' statement to Jafek that he lacked permission to use the trademarks Matrixx and Zicam, while wholly accurate, nevertheless demonstrated a willful intent to deceive. *Id.*

2. Matrixx moved to dismiss the complaint for failure to state a claim for securities fraud under § 10(b) and Rule 10b-5. The district court granted the motion, concluding that respondents had failed to sufficiently plead the elements of materiality and scienter. *See* Pet. App. B.

As to materiality, the district court invoked the statistical significance requirement enunciated in *In re Carter-Wallace, Inc. Securities Litigation (Carter-Wallace II)*, 220 F.3d 36 (2d Cir. 2000), to hold that respondents had failed to allege "the reliability and accuracy of the user complaints," and that "[e]ven if there were data as to the reliability" of the complaints, "12 user complaints is not statistically significant." Pet. App. 50a. Accordingly, the district court concluded that nondisclosure of the reports was not a "material omission." *Id.*

The court further held that respondents had failed to plead scienter adequately because they did not plead facts establishing that petitioners "*knew*

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ers were obliged to disclose under respondents' materiality theory.

there was a definitive and statistically significant link between Zicam and anosmia *during the Class Period* that was sufficiently serious and frequent to affect future earnings." *Id.* at 54a (internal quotation marks omitted).

The court granted respondents leave to cure these defects and plead additional facts concerning the materiality of the omitted AERs or concerning petitioners' willful intent to deceive. Respondents chose instead to appeal.

3. The court of appeals reversed. *See* Pet. App. A. The court rejected the *Carter-Wallace* statistical-significance requirement, *see* Pet. App. 34a, and held that respondents had sufficiently pled materiality by alleging the nondisclosure of the anosmia-related AERs, *id.* at 26a, 34a. It further held that respondents had adequately pled scienter, concluding that the allegations of nondisclosure, combined with the statement that Jafek lacked permission to use Matrixx's trademarks, gave rise to an inference that petitioners acted "intentionally or with deliberate recklessness" that was "at least as compelling as any plausible nonculpable explanation." *Id.* at 34a.[6]

This Court granted certiorari.

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[6] At no point during the class period did the FDA issue a warning letter or otherwise publicly question Zicam's safety. On June 16, 2009, while the appeal was pending in the Ninth Circuit, and more than five years after the close of the Class Period, the FDA issued a warning letter stating that Zicam "may pose a serious risk to consumers." J.A. 268a. Matrixx disputes the claims in the letter, but, in any event, it has no bearing on the events that occurred more than five years earlier.

SUMMARY OF THE ARGUMENT

I. Respondents' complaint does not plead facts establishing that the omitted AERs identified by respondents were material under § 10(b) or Rule 10b-5.

A. The reports of anosmia allegedly received during the Class Period—between 12 and 23 reports out of millions of Zicam units sold by Matrixx—are not material information.

The FDA and the courts have recognized that AERs are not evidence that product use caused the reported event, because they are unreliable and do not consider the background rate in a relevant population of the reported event. They are, however, ubiquitous in the pharmaceutical industry, because the FDA requires companies to file them so the agency can identify potential safety signals justifying further inquiry. The Ninth Circuit's rule would effectively compel pharmaceutical companies to disclose all AERs (to avoid potential securities fraud liability), flooding the market with trivial or meaningless information that would only obscure genuinely important information and thereby undermine sound investment decisionmaking.

B. To plead the element of materiality under § 10(b), a plaintiff alleging that a company failed to disclose AERs should be required to allege facts establishing that the AERs represented statistically significant evidence that the company's product was a cause of the reported event. Statistical significance is a concept very familiar to the law, especially in cases involving alleged product harms, where statistical significance is generally considered essential to proving causation through statistical data. A rea-

sonable investor would rely only on AERs where they provide statistically significant evidence of causation, because only then do AERs provide information that could objectively affect the product's sales. Accordingly, requiring securities-fraud plaintiffs to plead facts establishing that AERs represent statistically significant evidence of causation is entirely consistent with *Basic*'s interpretation of § 10(b)'s materiality requirement. It also ensures that the requirement serves its essential function of filtering out information that is trivial, unreliable, or meaningless.

C. Respondents' complaint fails to plead facts establishing materiality under the foregoing principles. The complaint's own allegations correctly indicate that a leading cause of anosmia is upper respiratory infections associated with the common cold—the very condition for which people take Zicam. Accordingly, to suggest a causal link between Zicam use and anosmia, the reports would have to indicate that the rate of anosmia among Zicam users exceeds, by a statistically significant degree, the rate of anosmia among people with the common cold who do not use Zicam (the "background rate"). The 12 to 23 AERs alleged in the complaint cannot themselves indicate any causal link between Zicam use and anosmia, and the complaint thus fails to allege facts establishing that respondents' omission of the AERs was material.

II. The complaint also does not plead with specificity facts establishing a strong inference of scienter, i.e., that petitioners omitted the AERs with the specific intent to deceive investors. Given that AERs themselves do not establish causation, and

given that the number of reports alleged comes nowhere close to indicating a potentially causal link between Zicam use and anosmia—especially in light of the known association between anosmia and upper respiratory infections—the much more compelling inference is that petitioners did not disclose the AERs because they considered the reports nonmaterial and potentially affirmatively misleading.

ARGUMENT

Respondents' class-action complaint fails to plead facts sufficient to establish the elements of materiality and scienter under § 10(b) of the Securities Exchange Act, 15 U.S.C. § 78j(b), and Rule 10b-5, 17 C.F.R. § 240.10b-5.

As noted above, the complaint alleges that petitioners failed to disclose the fact that some 12 to 23 Zicam users had reported experiencing anosmia—loss of smell—some time after using the product. J.A. 61a-62a, 68a-69a, 71a-75a, 78a-79a (Compl. ¶¶ 3, 26, 32, 33, 34, 39). That omitted fact allegedly rendered false or misleading statements touting the Zicam-related growth of Matrixx's business and disputing the basis for affirmative declarations that Zicam causes anosmia. *Id.* at 71a-80a (Compl. ¶¶ 32-41); Pet. App. 45a.

The omitted fact—that Matrixx had received 12 to 23 isolated hearsay reports of adverse events following Zicam use, compared to *millions of products sold*—is not material, especially given that the reported adverse event is *already closely associated with the common cold*. Because anecdotal incident reports, under such circumstances, do not provide any scientifically reliable basis for inferring a causal

link between product use and the event, inundating the market with such reports would only confuse and mislead investors by obscuring genuinely material product information. The existence of AERs can provide information material to an investment decision only when the reports reflect statistically significant evidence that product use may cause the reported event. The reports identified in the complaint here fail to show that the rate of anosmia incidents among Zicam users exceeded, by a statistically significant degree, the rate of anosmia among people with the common cold who do not use Zicam. Accordingly, the complaint fails to plead materiality and must be dismissed.

Respondents also do not plead facts establishing a strong inference that petitioners acted with scienter. Because the reports fell so far short of indicating that Zicam use actually causes anosmia, the inference that petitioners intentionally concealed the reports in order to deceive investors is nowhere near as compelling as the obvious alternative explanation: petitioners omitted the reports because they did not believe the reports reflected meaningful evidence of a causal relationship between Zicam use and anosmia, and thus could serve to mislead investors, as well as the product market.

I. ADVERSE EVENT REPORTS THAT DO NOT REVEAL A STATISTICALLY SIGNIFICANT INCREASED RISK OF ADVERSE EVENTS FROM PRODUCT USE ARE NOT MATERIAL INFORMATION

A. A Reasonable Investor Would Not Make Investment Decisions On The Basis Of Isolated Adverse Event Reports

1. *Regulators And Courts Consistently Recognize That Adverse Event Reports Are Not Reliable Indicators Of A Causal Link Between Product Use And The Reported Event*

Various forms of "adverse event reports" ("AERs") are a common feature of the pharmaceutical industry, used to track drug performance by manufacturers, doctors, researchers, and regulators. While AERs are useful for the limited purposes they serve, AERs do *not* reliably indicate even whether an adverse event occurred, much less whether there is a causal link between use of a drug or medical device and a subsequent adverse event.

a. At the most basic level, an AER is any anecdotal report that the user of a drug experienced an adverse event at some point during or following the use of that drug. AERs appear in many forms, including direct complaints by users to manufacturers, reports by doctors about reported or observed patient reactions, more detailed case reports published by doctors in medical journals, or larger scale published clinical studies. *See* FDA, Good Pharmacovigilance, at 4.

AERs are ubiquitous in the pharmaceutical industry, particularly because the FDA has created a

specific system—known as MedWatch—for consumers and healthcare practitioners to report adverse events that follow use of a drug. *See* FDA, Center for Drug Evaluation and Research, Annual Adverse Drug Experience Report: 1996 ("1996 Annual Report") 2 (Oct. 30, 1997).[7] Consumers and healthcare practitioners also may send AERs directly to the manufacturer of a drug, in which case the manufacturer has an obligation to report the adverse event to the FDA. *See* Federal Food, Drug, and Cosmetic Act ("FDCA") § 760, 21 U.S.C. § 379aa; 21 C.F.R. § 314.80.

Reporting of adverse events may be required both for prescription and non-prescription ("over the counter" or "OTC") drugs. Under the current law governing OTC drugs (enacted in 2006, after the close of the Class Period in this case, *see infra* note 9), the details of the reporting obligation depend on whether the drug is marketed based upon an FDA-approved new drug application. *Compare* FDCA § 760, 21 U.S.C. § 379aa (reporting obligations for OTC drugs that do not have new drug application) *with* 21 C.F.R. § 314.80 (reporting obligations for approved new drugs).[8] During the class period there was no requirement that the manufacturer of an

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[7] *Available at* http://druganddevicelaw.net/Annual%20Adverse%20Drug%20Experience%20Report%201996.pdf.

[8] *See* FDCA § 201(p), 21 U.S.C. § 321(p) ("new drug" means "[a]ny drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof").

OTC drug, including a homeopathic OTC drug such as Zicam, report adverse events. Current law requires manufacturers of OTC drugs (including homeopathic products) to report any "serious adverse event" within 15 business days, and to keep records of non-serious events for six years (although the latter need not be reported). *See* FDCA §§ 760(c)(1), (e), 21 U.S.C. §§ 379aa(c)(1), (e).[9] Products marketed under a new drug application are subject to more stringent reporting requirements, including filing periodic reports regarding any adverse drug event. *See* 21 C.F.R. § 314.80(c)(2).

b. An AER does not itself show causation—when a consumer takes a drug and thereafter reports an adverse event, the sequence may be mere coincidence. *See* FDA, 1996 Annual Report, at 2. FDA regulations define an "adverse event" as any "adverse event associated with the use of a drug in humans, whether or not considered drug related." 21 C.F.R. § 314.80(a). The FDA's reporting system is designed to be overinclusive, and thus "[c]ausality is not a prerequisite for MEDWATCH reporting." FDA, The Clinical Impact of Adverse Event Reporting ("Adverse Event Reporting") 2 (Oct. 1996).[10] The

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[9] The reporting requirements for OTC drugs in FDCA § 760, 21 U.S.C. § 379aa, were enacted in 2006. *See* Dietary Supplement and Nonprescription Drug Consumer Protection Act ("Act"), Pub. L. No. 109-462, § 2, 120 Stat. 3469, 3469-72 (Dec. 22, 2006); *see also* S. Rep. No. 109-324, at 3 (2006) (Committee report to Dietary Supplement and Nonprescription Drug Consumer Protection Act, Pub. L. No. 109-462) ("Although . . . OTC drugs are not currently required to file adverse event reports, many companies file AERs on a voluntary basis.").

[10] *Available at* http://www.fda.gov/downloads/Safety/MedWatch/UCM168505.pdf.

only requirement is that a person reporting an adverse event must have a "suspicion that a medical product may be related to a serious event." *Id.*

Because the FDA's reporting system is overinclusive, pharmaceutical companies are flooded with hundreds of thousands of adverse event reports every year, regardless whether there is any evidence of a causal link between any of the reported events and their drugs. For example, in 2009, the FDA received more than half a million adverse event reports for drugs and therapeutic biologic products. *See* FDA, Adverse Event Reporting System (AERS), Reports Received and Reports Entered into AERS by Year (Mar. 31, 2010) ("FDA AERS Reports Received").[11] In the first quarter of 2010 alone, the FDA received more than 150,000 AERs. *Id.*

c. It is widely recognized that these ubiquitous AERs are inherently unreliable and do not by themselves establish *even that an adverse event actually occurred*, much less that there was a causal link between a reported event and a drug. *See, e.g.*, S. Rep. No. 109-324, at 6 ("The fact of a report of an adverse event is not determinative that the event occurred or that the event was caused by a consumer's use of the product."); 21 C.F.R. § 314.80(k) (reporting of adverse event by manufacturer is not admission of causality).

i. To start, the FDA emphasizes that MedWatch AERs may be unreliable and do not themselves prove that a drug causes an adverse event. AERs

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[11] *Available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformaion/Surveillance/AdverseDrugEffects/ucm070434.htm.

"are subject to a variety of reporting biases," the FDA has explained, in that "some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other comorbidities or unrecorded confounders, may cause the events to be reported." FDA, Good Pharmacovigilance, at 9. The agency division that monitors AERs further explains that "any given" AER is of limited utility, because "there is no certainty that the suspected drug caused" the reported event. FDA, 1996 Annual Report, at 2.

The probative value of an AER is especially weak when the "adverse event may have been related to an underlying disease for which the drug was given." *Id*. In that situation—which involves what statisticians call a "confounding indicator"—the lay consumer will often associate the adverse event with use of the drug, rather than with the underlying condition that actually caused it. *See* FDA, Good Pharmacovigilance, at 7, 9; FDA, 1996 Annual Report, at 2. There is also the ever-present random chance: although the consumer may associate the event with the drug, in fact the event "may have occurred by chance at the same time as the suspect drug was administered." FDA, 1996 Annual Report, at 2.

Because the FDA recognizes that AERs are "quite subjective and imprecise," the agency explains that they cannot be used by themselves to calculate the "incidence rate" of an adverse event—i.e., how often the event actually occurs following use of a product. *See* FDA, Adverse Event Reporting, at 5. AERs thus may not indicate any association greater than the "background" incidence rate—i.e., how of-

ten the event occurs in the general population or in a relevant sub-population: "[I]t is well known that placebos and even no treatment can be associated with adverse events." *Id.* (footnotes omitted). This is true, the FDA explains, even in the case of accumulated AERs. *See* FDA, 1996 Annual Report, at 2; *see also* Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Prods., 71 Fed. Reg. 3922, 3950 (Jan. 24, 2006) ("[f]or postmarketing reporting, the impetus for reporting, the frequency with which a suspected adverse reaction is reported, and the number of exposures to the drug compared to the number of suspected reactions reported are unknown"); FDA, Guidance for Industry: ICH E2E Pharmacovigilance Planning 11 (Apr. 2005) (warning that data accompanying adverse event reports is often incomplete).[12] At most, AERs can be used to calculate "crude adverse event reporting rates as a valuable step" in investigating adverse events and forming hypothesis, but such rates "can by no means be considered incidence rates, for either absolute or comparative purposes." FDA, Good Pharmacovigilance, at 11.

The "great utility" of AERs thus is not that they establish an association between a drug and an adverse event, but rather that they may "generate signals of potential problems that warrant further investigation." Adverse Event Reporting at 6; *see also* S. Rep. No. 109-324, at 7 (AER reporting systems "are designed to generate signals which require further evaluation"); FDA, Good Pharmacovigilance, at

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[12] *Available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129423.pdf.

4. When the FDA identifies such "signals," it follows up with further research, including commissioning studies to determine whether there may, in fact, be an association between a drug and a reported adverse event. *See* FDA, Adverse Event Reporting, at 6-7; *see also Stephens' Detection of New Adverse Drug Reactions* 354-59 (John Talbot & Patrick Walker eds., 5th ed. 2004). The FDA does not apply any particular metric for determining when a sufficient "signal" exists to justify further inquiry; instead, whether the FDA will exercise its discretion turns upon its subjective and fact-specific estimation of the signal strength established by AERs in any particular case. *See* Adverse Event Reporting at 7; *id.* at 5 (because "recognition of [adverse events] . . . is quite subjective and imprecise," agency must engage in "careful, thoughtful review of adverse event reports").[13]

ii. Courts, too, have recognized that because AERs in any of their various forms are, at bottom, nothing more than uncontrolled and anecdotal hearsay information, they are far too unreliable to establish causation. Courts thus generally exclude expert testimony on medical causation when that testimony is premised solely upon AERs. A representative

[13] Although the agency assumes that due to underreporting AERs "generally represent only a small portion of the number" of adverse events in a population, *see* FDA, Adverse Event Reporting, at 5, it recognizes that calculating reporting rates based upon AERs is usually a precursor to determining whether a safety signal indicates a potential safety risk, *see* FDA, Good Pharmacovigilance, at 17. Only in rare cases, such as when "coincidental drug-event associations are [highly] unlikely," will a handful of AERs themselves justify further study. *See* FDA, Adverse Event Reporting, at 7.

sample of 50 federal and state opinions holding that (1) AERs and similar reports or (2) expert testimony premised upon them are unreliable and inadmissible is available at Appendix A. As these opinions discuss, AERs suffer from two particular infirmities that make them particularly unreliable indicators of causation.

First, consumer complaints and AERs are hearsay, and, in cases involving multiple layers of reporting, may be double or treble hearsay. Such "second-or-third hand reports . . . have inherent biases" that make them "unreliable for determining causation." *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1050, 1057 (D.N.J. 1992), *aff'd* 6 F.3d 778 (3d Cir. 1993); *accord Richardson v. Richardson-Merrell, Inc.*, 649 F. Supp. 799, 801 n.5 (D.D.C. 1986) (AERs are not "exceptions to the hearsay rule"), *aff'd on other grounds* 857 F.2d 823 (D.C. Cir. 1988); *Wolf v. Proctor & Gamble Co.*, 555 F. Supp. 613, 620 (D.N.J. 1982) (consumer complaint to company is hearsay); *Smith v. Pfizer Inc.*, 2010 WL 1754443, at *5 (M.D. Tenn. Apr. 30, 2010) (isolated AERs are "second- or third-hand reports" and not admissible to show causation or notice); *Peters v. Johnson & Johnson Prods., Inc.*, 783 S.W.2d 442, 444-45 (Mo. Ct. App. 1990) (consumer complaints do not fall under business exception to hearsay rule). An AER is not produced by a government agency and thus has no entitlement to the presumption of trustworthiness accorded to public records under an exception to the hearsay rule. *See* Fed. R. Evid. 803(8); *see also Appleby v. Glaxo Wellcome, Inc.*, 2005 WL 3440440, at *3 (D.N.J. Dec. 13, 2005).

Second, even assuming they are trustworthy reports of the basic incident, AERs do not reliably indicate 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*." *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995) (emphases added). AERs also "do not isolate and exclude potentially alternative causes; and do not investigate or explain the mechanism of causation." *Id.*; *see also Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1359-63 (N.D. Ga. 2001) (collecting cases on use of AERs and holding that "even if relevant case reports existed, they cannot establish general causation"). Instead, AERs may reflect nothing more than a chance sequence of events, i.e., a person takes a drug and thereafter experiences an adverse event. *See, e.g.*, *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1481 (D.V.I. 1994) (drug experience reports and product liability lawsuits "represent anecdotal information of chance associations"); *Saari v. Merck & Co.*, 961 F. Supp. 387, 394 (N.D.N.Y. 1997) (AER is "simply a report of what plaintiff told [her doctor] about what she believed was her reaction to the [drug]"). But as the familiar Latin logical fallacy *post hoc ergo propter hoc* admonishes, mere temporal association between two events does not suffice to show a causal relationship between the two. *See McLain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1243 (11th Cir. 2005).

2. *Anecdotal Hearsay AERs Themselves Are Not Material And Requiring Their Disclosure Would Affirmatively Harm The Markets*

In light of their well-recognized limitations, the mere existence of AERs is not information a reasonable investor would consider material to her investment decision. Indeed, treating them as material would effectively compel companies to disclose all such reports, inundating the market with useless, trivial, and even affirmatively misleading information, which will only undermine reasoned investment decisionmaking.

a. As noted above, a fact is not material unless there is "a substantial likelihood" that a reasonable investor would view it as "significantly alter[ing] the total mix of information made available." *Basic*, 485 U.S. at 232 (internal quotation marks omitted). Information that does not shed significant light on the value of an issuer's product cannot be "significant to the reasonable investor's trading decision." *Id.* at 235.

Information that reliably indicates a drug may cause an adverse health effect can be potentially material, because a manufacturer of a drug that harms consumers may lose market share, face regulatory action, or be subject to costly litigation. But absent a reliable indication of a causal link to an adverse health effect, any of those potential consequences for the manufacturer's business would be wholly speculative, and a reasonable investor would not base an investment decision on unreliable speculation. *See In re Rockefeller Ctr. 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)); *see also Epstein v. Wash. Energy Co.*, 83 F.3d 1136, 1141 (9th Cir. 1996); *Craftmatic Sec. Litig. v. Kraftsow*, 890 F.2d 628, 645-46 (3d Cir. 1989); *In re Par Pharm., Inc. Sec. Litig.*, 733 F. Supp. 668, 678 (S.D.N.Y. 1990). AERs do not provide the reliable basis for inferring a causal association on which a reasonable investor would rely.

AERs are also immaterial because they merely indicate what a reasonable investor *already knows*: from time to time consumers experience adverse events after using a company's drug. *See In re Carter-Wallace, Inc. Sec. Litig.*, 220 F.3d at 41 ("Some adverse events may be expected to occur randomly, especially with a drug designed to treat people that are already ill."); *cf. Jackvony v. RIHT Fin. Corp.*, 873 F.2d 411, 415 (1st Cir. 1989) (Breyer, J.) (internal merger discussions categorically nonmaterial because "[a]ny reasonably sophisticated investor in securities buying shares in a large corporation would expect that, from time to time, other corporations might express an interest in buying, or that the large corporation's directors might discuss what it should do if it obtains such offers"). Given the presumed efficiency of securities markets, *see Basic*, 485 U.S. at 247, the reasonable investor will be fully aware that the FDA receives hundreds of thousands of AERs every year, *see supra* at 19-20, and that neither the FDA nor courts treat those AERs as reliable indicators of a causal association between use of the drug and the reported adverse event, *see supra* at 20-25.

b. Disclosure of AERs not only would be unnecessary for a hypothetical reasonable investor, it would be affirmatively harmful to actual investors and the market generally.

Under the rule adopted by the Ninth Circuit, companies will be driven to disclose essentially *all* AERs in order to inoculate themselves against the securities-fraud suits that would otherwise inevitably follow any regulatory warning letter or voluntary recall. Such actions are hardly an unusual feature of the pharmaceutical business (or indeed any product manufacturing business generally). *See* FDA, The Enforcement Story 10-9, 10-15 (2009) (FDA's Center for Drug Evaluation and Research, which regulates OTC and prescription drugs, issued 379 product recalls and 87 warning letters in the fiscal year 2008).[14] When warning letters are issued—or, similarly, when a product is voluntarily recalled—the price of the company's stock often drops, which in turn prompts securities class-action lawyers to file § 10(b) actions asserting that if the company had disclosed whatever safety or performance indicators it had before the regulatory action or recall, investors would have sold their shares and avoided the stock-price loss. *See N.J. Carpenters Pension & Annuity Funds v. Biogen IDEC Inc.*, 537 F.3d 35, 47 (1st Cir. 2008) (situation is "paradigmatic of securities fraud cases against drug development companies"). And of course the strike value of such class action suits can "impose substantial costs" even "on companies and individuals whose conduct conforms

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[14] *Available at* http://www.fda.gov/downloads/ICECI/EnforcementActions/EnforcementStory/UCM129824.pdf.

to the law." *Tellabs*, 551 U.S. at 313; *see Merrill Lynch, Pierce, Fenner & Smith Inc. v. Dabit*, 547 U.S. 71, 80 (2006) ("Even weak cases brought under [Rule 10b-5] may have substantial settlement value . . . because '[t]he very pendency of the lawsuit may frustrate or delay normal business activity.'" (quoting *Blue Chip Stamps v. Manor Drug Stores*, 421 U.S. 723, 740 (1975)).

Accordingly, if the law subjects companies to the costs of securities-fraud lawsuits for failing to disclose AERs as unreliable as those at issue here, companies would have a strong incentive simply to disclose all the AERs they receive. But to avoid confusion about the actual value of the information being disclosed, companies might also include with the disclosure the additional statements that AERs are uncontrolled, unconfirmed multi-layer hearsay, which do not themselves demonstrate any incidence beyond known background incidence, and which the FDA and courts reject as the basis for establishing a causal inference. Such disclaimer language would be an entirely accurate characterization of AERs, but it would of course also make disclosure of the AERs utterly unhelpful to investors—which simply demonstrates why *AERs themselves*, when accurately described and understood, do not provide investors with material information.

Whether or not companies provide investors additional information necessary to understand the function and value of AERs, they will certainly have an incentive to disclose the AERs themselves, as noted. This will undermine reasoned investment decisionmaking in at least two ways. First, actual investors would have no meaningful basis for under-

standing whether and when product safety concerns are "real," as opposed to merely the predictable and common noise of untested AERs. Investors generally are not scientists or epidemiologists and cannot be expected to sift significant from insignificant scientific data with ease. And they presumably expect companies in general to disclose only meaningful adverse information, and so seeing the disclosure of AERs could lead some or many investors to believe, erroneously, that the AERs actually reflect a serious product concern. In other words, disclosure of AERs can mislead investors into undervaluing or prematurely selling a security, which is as just as economically harmful to investors and the markets as overvaluing a security or holding it too long.

Second, in addition to misleading investors by drawing their attention to unreliable information, a materiality rule that leads companies to disclose AERs as a matter of course to avoid securities-fraud liability will also obscure information that is genuinely material. As discussed above, this Court has long recognized that the "role of the materiality requirement" is to "filter out" information such as AERs because, although a reasonable investor "would not consider [such information] significant," *Basic*, 485 U.S. at 234, disclosure of the information would bury investors in an "avalanche of trivial information," *TSC Indus.*, 426 U.S. at 448.

Excessive disclosure makes "informed decision-making" more difficult, *id.* at 448-49, and thereby harms markets just as assuredly as does insufficient disclosure. "Studies have shown that as a decision maker is given more information, decision quality initially increases; once the information level

reaches a certain point, however, the decision maker's decision quality decreases if she is given additional information." Troy A. Paredes, *Blinded By The Light: Information Overload and its Consequences for Securities Regulation*, 81 Wash. U. L.Q. 417, 441 (2003). In fact, the effect of *over*disclosure is essentially the same as *non*disclosure, because genuinely material information becomes hidden in plain sight. "[T]he more information there is the more each bit of it is diluted. The immediate and salient crowds out the less attention-grabbing." Donald C. Langevoort, *Toward More Effective Risk Disclosure for Technology-Enhanced Investing*, 75 Wash. U. L.Q. 753, 759 (1997) (footnote omitted). As a result of this "information overload," a "large amount of information" can become "equivalent to no information at all." Cass R. Sunstein, *Informing America: Risk, Disclosure, and the First Amendment*, 20 Fla. St. U. L. Rev. 653, 668 (1993).

The problem of overdisclosure is well recognized in the law and literature concerning product manufacturers' duty to warn consumers about product risks. *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 2010 WL 3156548, at *7 (7th Cir. Aug. 11, 2010) ("information overload would make label warnings worthless to consumers"); *Cotton v. Buckeye Gas Prods. Co.*, 840 F.2d 935, 937-38 (D.C. Cir. 1998) ("The inclusion of each extra [warning] item dilutes the punch of every other item. Given short attention spans, items crowd each other out; they get lost in fine print."); W. Kip Viscusi, *Individual Rationality, Hazard Warnings, and the Foundations of Tort Law*, 48 Rutgers L. Rev. 625, 633 (1996) ("consumers may be inundated with so many pieces of in-

formation that they cannot process all the warning messages they receive"). The FDA, in particular, has opined that "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to 'lose its significance.'" 71 Fed. Reg. at 3935. "Overwarning, just like underwarning, can similarly have a negative effect on patient safety and public health." *Id.* The same problem exists for overdisclosure in securities filing, as this Court has recognized. *See TSC Indus.*, 426 U.S. at 448-49.

The "filtering" effect of § 10(b)'s materiality requirement, in short, is just as important as the underlying disclosure principle it constrains. Section 10(b) should not be construed and applied in a way that will cause companies to overload investors with trivial, unreliable product information. AERs can be material only when they reflect a scientifically reliable basis for inferring a potential causal link between product use and the adverse event, as the next section shows.

B. Statistical Significance Should Be Required As A Threshold Element Of Materiality In § 10(b) Cases Based On Undisclosed AERs

Statistical significance is a concept very familiar to the law. In legal contexts where it is necessary to distinguish random chance from a causal relationship, courts regularly use statistical significance to draw that distinction. And causation is ultimately what matters here: the existence of facts indicating a causal link between use of a significant company product and an adverse health event could be impor-

tant to a reasonable investor, whereas routine, unreliable reporting "noise" would not be, as shown above. Accordingly, before disclosure of AERs is required under the securities laws, they at least must "provide statistically significant evidence that the ill effects may be caused by—rather than randomly associated with—use of the drug[]." *Oran v. Stafford*, 226 F.3d 275, 284 (3d Cir. 2000) (Alito, J.) (internal quotation marks omitted); *see Masters v. GlaxoSmithKline*, 271 F. App'x 46, 50 (2d Cir. 2008); *In re Carter-Wallace, Inc. Sec. Litig. (Carter-Wallace I)*, 150 F.3d 153, 157 (2d Cir. 1998).[15] This means that § 10(b) plaintiffs must at least plead facts establishing that the rate of reported adverse incidents among product users exceeded the relevant background rate by a statistically significant degree.

[15] Even then, AERs are not *necessarily* material—the underlying data may be flawed, the indicated association may not be causal, and even with a causal link, the link may be too weak or the effect too minor (or both) to have consequences for product sales and company finances. *See*, *e.g.*, *Masters*, 271 F. App'x at 50 ("reports of harmful drug effects are immaterial—and thus need not be disclosed—unless those reports (1) show statistically significant evidence of an adverse effect; (2) establish that the adverse effect threatens the 'commercial viability' of the drug; and (3) show that the effect poses a significant risk to the company's future earnings" (quotation omitted)). The issue here is whether statistical significance is a *necessary*—though perhaps not always sufficient—threshold requirement for pleading and proving materiality.

1. *Statistical Significance Is A Commonly Recognized And Understood Means For Distinguishing Between Chance And Association*

Statistical significance is a device for analyzing the relationship between two events—a device almost as familiar to courts as it is to scientists.

a. Scientists commonly measure whether data indicates an association between use of a product and an event by determining whether the data is statistically significant. Green et al., Reference Guide on Epidemiology, at 354-58. An "association" between two variables—for example, a drug and a health event—exists when the variables "occur together more frequently than one would expect by chance." *Id.* at 348.

Textbooks, treatises, and articles have been written on statistical analysis and the concept of statistical significance. What follows is necessarily a capsule summary, for purposes of explaining the importance of statistical significance in this context.

A researcher examining the potential association between two events begins with a "null hypothesis," i.e., there is *no* association in fact, and any association observed in a sample will be "due to the luck of the draw." David H. Kaye & David A. Freeman, Reference Guide on Statistics, *in* Federal Judicial Center, Reference Manual on Scientific Evidence ("Reference Guide on Statistics") 122 (2d ed. 2000). The researcher then determines whether to reject the null hypothesis based upon the observed data. The researcher calculates a "p-value," which is the probability that, if there was no actual association between the variables, an association in any given

sample would be observed simply as a result of random error. The researcher then compares that value against a "significance level" selected during research design. If the p-value is lower than the significance level, then the researcher can be confident that random error is *not* responsible for the observed association, and the null hypothesis is rejected. *Id.* at 124.[16]

Generally statisticians and epidemiologists use a .05 significance level, meaning there is only a 5% probability of observing an association when there is actually no association. Green et al., Reference Guide on Epidemiology, at 358. This Court has recognized and employed this standard, explaining in both the jury discrimination and employment law contexts that the null hypothesis may be rejected after taking a "large sample[]" and observing an association more than "two or three standard deviations" from the "expected value" indicated by the null hypothesis.[17] *Castaneda v. Partida*, 430 U.S. 482, 496 n.17 (1977); *see Hazelwood Sch. Dist. v. United States*, 433 U.S. 299, 311 n.17 (1977). Although statisticians and courts debate the "finer points," including whether there are situations in which a lower or

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[16] Statistical significance does not reveal whether there is a "practically important" link between the two variables observed. Kaye & Freeman, Reference Guide on Statistics, at 124. In other words, the association may be very weak—for example, in the product realm, indicating only a slight increase in risk from use of the product.

[17] Two or three standard deviations from the expected value indicated by the null hypothesis corresponds to .05 and .01 significance levels. Kaye & Freeman, Reference Guide on Statistics, at 124 n.138.

higher significance level than .05 is appropriate, significance testing at some meaningful level is a generally accepted means of determining whether an observed association may be the basis for further reasoning regarding causation. *See Mister v. Ill. Cent. Gulf R.R. Co.*, 832 F.2d 1427, 1430-31 (7th Cir. 1987); Daniel L. Rubinfeld, *Econometrics in the Courtroom*, 85 Colum. L. Rev. 1048, 1054 (1985) ("The importance of determining meaningful statistical significance levels is a concern which permeates nearly every context in which statistical methods are introduced in litigation.").[18]

b. Courts employ statistical significance devices in a wide variety of legal contexts to distinguish between random occurrence and associations that

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[18] Various analytical methods can be used to determine whether data reflect a statistically significant result. One such method, calculating confidence intervals, is especially useful for epidemiological analysis of drug safety, because it allows the researcher to estimate the *relative risk* associated with taking a drug by comparing the incidence rate of an adverse event among a sample of persons who took a drug with the background incidence rate among those who did not. Dividing the former figure by the latter produces a relative risk figure (e.g., a relative risk of 2.0 indicates a 50% greater risk among the exposed population). The researcher then calculates the confidence interval surrounding the observed risk, based on the preset confidence level, to reflect the degree of certainty that the "true" risk falls within the calculated interval. If the lower end of the interval dips below 1.0—the point at which the observed risk of an adverse event matches the background incidence rate—then the result is not statistically significant, because it is equally probable that the actual rate of adverse events following product use is identical to (or even less than) the background incidence rate. Green et al., Reference Guide on Epidemiology, at 360-61. For further discussion, *see id.* at 348-61.

could be causal. Such contexts include product liability, toxic torts, employment discrimination, equal protection jury discrimination claims, and vote dilution claims.

Product liability is the context most pertinent to this case, which involves statements and omissions affecting the commercial viability of a pharmaceutical product based on potential safety concerns. The issue in product liability cases based on epidemiological evidence of potential harm is very similar to the question facing reasonable investors who learn of an isolated AER, *viz.*, whether the available information indicates a causal link between the product and an adverse health event. Nearly identical causation-related issues are raised in toxic tort litigation as well. And it is well-settled in the product liability and toxic tort contexts that the simple numerical reporting of anecdotal observations or raw numbers of adverse events will *not* suffice to establish causation, or even to support an admissible expert opinion on causation.

This Court has upheld the exclusion of expert testimony on causation[19] premised upon epidemiol-

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[19] Product liability suits require proof of both general and specific causation. *See generally* Restatement (Second) of Torts § 430 (1965) (causation necessary for tort liability); Green et al., Reference Guide on Epidemiology, at 392, 396 (distinguish general from specific causation). *General* causation refers to whether a given drug is generally capable of causing a particular adverse event. *See*, *e.g.*, *McLain*, 401 F.3d at 1239. *Specific* causation is whether the drug caused that adverse event in plaintiff's specific case. *See*, *e.g.*, *Baker v. Chevron USA, Inc.*, 680 F. Supp. 2d 865, 874 (S.D. Ohio 2010). Statistical significance is mainly relevant to proof of general causation.

ogical data that is not statistically significant. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 145 (1997). Statistical significance, the Court recognized, is a means by which an expert's opinion evidence is "connected to existing data," as opposed to being a mere "*ipse dixit*" opinion. *Id.* at 146. And lower courts consistently reject as unreliable expert opinion regarding causation when it relies upon epidemiological or other numerical data regarding incidence rates that is not statistically significant. *See*, *e.g.*, *Hendrix v. Evenflo Co.*, 609 F.3d 1183, 1196-97 (11th Cir. 2010); *Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 380 (5th Cir. 2010); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1215-16 (10th Cir. 2002); *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001); *Brock v. Merrell Dow Pharms., Inc.*, 884 F.2d 166, 167 (5th Cir. 1989); *Baker v. Chevron USA, Inc.*, 680 F. Supp. 2d 865, 881-82 & nn.11-12 (S.D. Ohio 2010); *Milward v. Acuity Speciality Prods. Grp., Inc.*, 664 F. Supp. 2d 137, 149 (D. Mass. 2009); *Cano v. Everest Minerals Corp.*, 362 F. Supp. 2d 814, 821 (W.D. Tex. 2005); *Newman v. Motorola, Inc.*, 218 F. Supp. 2d 769, 775-79 (D. Md. 2002), *aff'd* 78 F. App'x 292 (4th Cir. 2003); *In re Norplant Contraceptive Prods. Liab. Litig.*, 215 F. Supp. 2d 795, 831 (E.D. Tex. 2002); *Chambers v. Exxon Corp.*, 81 F. Supp. 2d 661, 665 (M.D. La. 2000); *Marder v. G.D. Searle & Co.*, 630 F. Supp. 1087, 1092 (D. Md. 1986), *aff'd sub nom.*, *Wheelahan v. G.D. Searle & Co.*, 814 F.2d 655 (4th Cir. 1987); *Merrell Dow Pharms., Inc. v. Havner*, 953 S.W.2d 706, 723-24 (Tex. 1997).

In excluding this evidence, courts recognize that without statistical significance, "'there is simply

too great an analytical gap between the data and the opinion proffered.'" *Baker*, 680 F. Supp. 2d at 881-82 (quoting *Joiner*, 522 U.S. at 146)). By "scrutinizing the basis, reasoning, and statistical significance of studies presented" by the parties, courts ensure that lay jurors are not misled by raw numbers that may seem compelling in the abstract, but do not, in fact, reliably indicate the possibility of a causal link between the drug and an adverse event. *Brock*, 884 F.2d at 167.[20]

Courts also use statistical significance to distinguish between chance and association in employment discrimination cases. This Court invoked statistical significance in *Hazelwood* to explain how an employer could rebut a prima facie case of pattern-or-practice discrimination, *see* 433 U.S. at 311 & n.17, and again in *Bazemore v. Friday*, 478 U.S. 385 (1986), in noting that regression analyses offered to prove discrimination did indicate "statistically significant[] racial effect[s]," *id.* at 399-401 & n.9. Lower courts have similarly emphasized that numerical data on employment actions (hiring, promotion, firing, etc.) "will not permit an inference of discrimination" in a pattern-or-practice case unless the data reveal a "statistical[ly] significan[t]" correlation between the employment action and the prohibited classification. *Segar v. Smith*, 738 F.2d 1249, 1283

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[20] Even data that is statistically significant may not be reliable, if the data source itself is not sufficiently reliable. In *Wells*, for example, the Fifth Circuit explained that a poster presentation that was never peer-reviewed or published would not be sufficiently reliable to serve as a basis for an expert opinion on causation, even though the presentation described statistically significant findings. 601 F.3d at 380.

(D.C. Cir. 1984); *see Kohlbek v. City of Omaha*, 447 F.3d 552, 557 (8th Cir. 2006); *Schwartz v. Veneman*, 252 F.3d 436, 2001 WL 361113, at *1 (5th Cir. 2001); *Anderson v. Zubieta*, 180 F.3d 329, 339-40 (D.C. Cir. 1999); *Anderson v. Douglas & Lomason Co.*, 26 F.3d 1277, 1291 n.26 (5th Cir. 1994); *Ottaviani v. State Univ. of N.Y.*, 875 F.2d 365, 371 (2d Cir. 1989); *Palmer v. Shultz*, 815 F.2d 84, 96 (D.C. Cir. 1987); *Mister*, 832 F.2d at 1431; *Lilly v. Harris-Teeter Supermarket*, 720 F.2d 326, 337-38 (4th Cir. 1983); *Taylor v. Teletype Corp.*, 648 F.2d 1129, 1133 (8th Cir. 1981). The same is generally true for disparate impact cases: given the "dangers of relying on . . . raw, undifferentiated data," *Soria v. Ozinga Bros., Inc.*, 704 F.2d 990, 996 (7th Cir. 1983), a plaintiff seeking to establish a prima facie case based on numerical data must show a "statistically significant adverse effect of a rule that is neutral in its terms," *Wis. Cmty. Servs., Inc. v. City of Milwaukee*, 465 F.3d 737, 756 (7th Cir. 2006) (Easterbrook, J., concurring); *see McClain v. Lufkin Indus.*, 519 F.3d 264, 280 (5th Cir. 2008); *Paige v. California*, 233 F. App'x 646, 648 (9th Cir. 2007) (collecting cases); *Cooper v. S. Co.*, 390 F.3d 695, 716 (11th Cir. 2004); *Malave v. Potter*, 320 F.3d 321, 327 (2d Cir. 2003); *Anderson*, 180 F.3d at 340; *Hameed v. Int'l Ass'n of Bridge, Structural & Ornamental Iron Workers*, 637 F.2d 506, 512-14 (8th Cir. 1980).[21]

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[21] Some courts have followed the Equal Employment Opportunity Commission's ("EEOC") "four-fifths rule," under which a prima facie case of disparate impact may be established by a showing that the minority pass rate under an employment test is less than four-fifths (80%) of the majority pass rate. *See Smith v. Xerox Corp.*, 196 F.3d 358 (2d Cir. 1999).

Courts also use statistical significance testing to assess whether chance or discrimination explains racial disparities in the selection of juries in violation of the Equal Protection Clause. In *Castaneda*, the Court explained the "general rule" that for "large samples, if the difference between the expected value and the observed number is greater than two or three standard deviations, then the hypothesis that the jury drawing was random" rather than racially motivated "would be suspect to a social scientist." 430 U.S. at 496 n.17. Lower courts have likewise recognized that "comparing straight racial percentages is of little value," *Jefferson v. Morgan*, 962 F.2d 1185, 1189 (6th Cir. 1992), and thus have modeled standard deviations and calculated statistical significance to "determine if chance alone could account for a meager representation of minorities" on jury arrays, *Alston v. Manson,* 791 F.2d 255, 258 (2d Cir. 1986); *see Moultrie v. Martin*, 690 F.2d 1078, 1082 (4th Cir. 1982).

Statistical significance analysis is also relevant in establishing claims under § 2 of the Voting Rights Act. In *Thornburg v. Gingles*, 478 U.S. 30 (1986), this Court approved the district court's threshold "three-part inquiry" into the voting data: "[D]id the data reveal any correlation between the race of the voter and the selection of certain candidates; was the revealed correlation statistically significant; and was

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But even the EEOC acknowledges that the four-fifths rule should be supplemented with a statistical significance test in some cases, *see* 29 C.F.R. § 1607.4(D), and, in any event, the four-fifths rule "has . . . been used with caution" and "has been criticized as unreliable and overly simplistic," *Frazier v. Consol. Rail Corp.*, 851 F.2d 1447, 1451 (D.C. Cir. 1988).

the difference in black and white voting patterns 'substantively significant'?" *Id.* at 53, 58, 61. Courts subsequently have examined whether vote dilution plaintiffs relying upon statistical data have made a statistically significant threshold showing of political cohesiveness and racial bloc voting, and have rejected expert opinions that fail to include such analysis. *See Monroe v. City of Woodville*, 881 F.2d 1327, 1330-32 (5th Cir. 1989); *Overton v. City of Austin*, 871 F.2d 529, 544-45 (5th Cir. 1989) (Jones, J., concurring); *cf. Sanchez v. Colorado*, 97 F.3d 1303, 1317 (10th Cir. 1996) (discussing proof of "statistically significant polarization"). Statistical significance testing can also "cast considerable doubt on the existence of a causal link" in other types of claims of discriminatory effect in violation of § 2. *See Irby v. Va. State Bd. of Elections*, 889 F.2d 1352, 1358-59 (4th Cir. 1989) (affirming dismissal of claim that appointment system for local school boards has discriminatory effect and "recogniz[ing] the dangers of drawing conclusions from statistics involving boards with relatively few members").

2. *A § 10(b) Case Based On Nondisclosure Of AERs Must Plead Facts Showing A Statistically Significant Correlation Between Product Use And The Reported Event*

Drawing upon the many other legal contexts where statistically significant evidence is required, § 10(b) cases based on a company's failure to disclose AERs involving a company product should fail at the threshold when the complaint does not plead facts establishing that the AERs reflect a statistically significant correlation between use of the product and the reported adverse event. When the complaint

merely cites AERs without a statistically meaningful comparison to relevant background incident rates, it does nothing to show that the AERs reflect a potentially causal relationship between product use and the reported event and thus could affect a reasonable investor's decisionmaking. *See Oran*, 226 F.3d at 284; *Masters*, 271 F. App'x at 50; *Carter-Wallace I*, 150 F.3d at 157.

Requiring that AERs be statistically significant in order to sufficiently allege materiality fully accords with, and indeed implements, this Court's ruling in *Basic*. As explained above, the Court in *Basic* held that a fact is material for purposes of securities fraud where there is "'a substantial likelihood'" that its disclosure "'would have been viewed by the reasonable investor as having significantly altered the "total mix" of information made available.'" 485 U.S. at 231-32 (quoting *TSC Indus.*, 426 U.S. at 449). The Court applied that principle to reject a proposed bright-line rule that would exempt disclosure of all pre-merger negotiations "not yet at the agreement-in-principle stage." *Id.* at 233-36. As the Court explained, the proposed rule would "artificially exclud[e] from the definition of materiality information . . . which would otherwise be considered significant to the trading decision of a reasonable investor." *Id.* at 236. Here, in contrast, far from "artificially excluding" otherwise relevant information, the statistical significance standard *defines* the information a reasonable investor would consider relevant, i.e., information that may indicate that the company product can cause an adverse event, thereby potentially exposing the company to financial losses. And it works to "filter out essentially useless information,"

namely, AERs reporting events that cannot be distinguished from background incident rates of that event. *Id.* at 234. Filtering out this type of information is precisely "[t]he role of the materiality requirement." *Id.*

Statistical significance also gives both companies *and* investors guidance they need to understand corporate disclosure obligations. As discussed above, absent any intelligible basis for determining when AERs become material, companies will have strong incentives to disclose *all* AERs, which will deprive investors of any sound basis for understanding which AER disclosures actually matter. This Court's admonition bears repeating: a materiality rule that causes a company "simply to bury the shareholder in an avalanche of trivial information," is hardly a rule that would be "conducive to informed decisionmaking." *TSC, Indus.*, 426 U.S. at 448-49; *see supra* at 30-32. Statistical significance is a perfectly intelligible basis for distinguishing material from immaterial AERs, thereby avoiding an avalanche of overdisclosure, while still permitting plaintiffs to proceed when a company fails to disclose AERs that actually could matter to a reasonable investor, i.e., AERs that reveal a potentially causal link between a significant company product and harm to product users.[22]

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[22] In some drug product liability cases—especially those involving rare or "novel" events—courts permit an inference of causation on the basis of scientifically reliable evidence other than statistically significant epidemiological data. *See*, *e.g.*, *Ealy v. Richardson-Merrell, Inc.*, 897 F.2d 1159, 1162-64 (D.C. Cir. 1990) (discussing cases); *In re Neurontin Mktg., Sales Practices & Prods. Liability Litig.*, 612 F. Supp. 2d 116, 141 (D. Mass. 2009). In such cases experts rely on a lengthy list of fac-

C. Respondents' Complaint Does Not Allege Facts Establishing That The AERs At Issue Revealed An Incidence Rate That Differed From The Relevant Background Rate By Any Statistically Significant Degree

According to respondents, the complaint satisfies any statistical significance "benchmark" for materiality because it "tabulates at least 23 specifically linked Zicam-anosmia complaints." Opp. to Pet. for Cert. 20. Respondents' submission only illustrates

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tors to draw reliable inferences, including, for example, (1) the "strength" of the association, including "whether it is statistically significant"; (2) temporal relationship between exposure and the adverse event; (3) consistency across multiple studies; (4) "biological plausibility"; (5) "consideration of alternative explanations" (i.e., confounding); (6) "specificity" (i.e., whether the *specific* chemical is associated with the *specific* disease at issue); and (7) dose-response relationship (i.e., whether an increase in exposure yields an increase in risk). *Magistrini v. One Hour Martinzing Dry Cleaning*, 180 F. Supp. 2d 584, 592-93 (D.N.J. 2002).

This case does not present the question whether a securities fraud case can be premised on nondisclosure of information establishing a causal inference on the basis of such criteria. Respondents instead focus on the mere nondisclosure of AERs involving Zicam use and anosmia. In their words, "a correct analysis of materiality on the facts alleged here asks whether a reasonable shareholder would consider it important that large numbers [sic] of Zicam users had lost their sense of smell." Opp. to Pet. for Cert. 12 (internal quotation marks omitted); *see id.* at 16 (identifying "specific information" that petitioners "failed to disclose" as injuries reported by "a number of Zicam users immediately after they used the product"); *id.* at 17 (noting "pointed complaints about Zicam-induced anosmia that petitioners received"); *id.* at 19 (emphasizing "the requisite *materiality* of the undisclosed Zicam injuries known to petitioners").

the importance of the principles discussed above. Even accepting that 23 is the correct figure and indulging the assumption that double and treble hearsay complaints represent satisfactory data, the mere fact of 23 AERs is nowhere close to statistically significant evidence that Zicam use causes anosmia.[23]

The 23 AERs cited by respondents were received over the course of four years—from 1999 to early 2004—when Matrixx sold literally *millions* of units of Zicam. *See generally* Matrixx Initiatives, Inc., Form 10-K Annual Report (Mar. 28, 2003) (Zicam Cold Remedy accounted for more than 70% of 2002 net sales of $23.5 million). What is more, the complaint fails to compare that trivially minuscule reported incident rate to the known incident rate of anosmia in the population—and in particular, in the population of people *who have colds*, and thus take remedies like Zicam. That omission is critical because an AER may simply reflect an adverse event that was *caused by the underlying condition*, not the drug used to treat that condition. *See* FDA, Good Pharmacovigilance, at 9 ("other factors, including the disease being treated . . . may cause the events to be reported"); *see also supra* note 3 (describing "confounding by indication"). The common problem of confounding by indication is a key reason *post hoc ergo propter hoc* assumptions by lay consumers are not accepted by researchers, regulators, or courts.

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[23] In fact, respondents themselves did not even contend otherwise below—their complaint does not in terms purport to plead statistically significant facts, and they did not amend their complaint to plead such facts when allowed to do so by the district court. Instead they appealed and argued that statistical significance simply is not required.

Indeed, one of the important functions of statistical analysis—when done properly—is to control for these effects, and thus to determine whether the adverse event is potentially caused by use of the product, and not something else also associated with product use. *See* Green et al., Reference Guide on Epidemiology, at 370.

This case exemplifies the point. Respondents' complaint notes the statement that the common cold is a leading factor affecting sense of smell, and that "the population most likely to use cold remedy products is already at an increased risk of developing anosmia." J.A. 78a (Compl. ¶ 38). While criticizing other statements, the complaint alleges no facts denying or contradicting the observation that Zicam users are members of the population *already* most likely to experience anosmia, as a result of the very condition for which they are taking Zicam. Nor could it—the causal link between anosmia and upper respiratory infections associated with the common cold is well-recognized.[24] The complaint's allegations thus amount to a textbook example of when and how a cofounding indicator can dramatically undermine any basis for inferring that an adverse event was caused by use of a product. *See Robinson*, 2010 WL 3156548, at *5; *supra* note 3. There is simply no conceivable basis on which to conclude that 23 inci-

[24] *See* Mayo Clinic, *Loss of Smell (Anosmia)* (Feb. 2, 2009), *available at* http://www.mayoclinic.com/health/loss-of-smell/MY00408/DSECTION=causes; Anil Lalwani, Olfactory Dysfunction, *in* Current Diagnosis & Treatment in Otolaryngology—Head & Neck Surgery 240 (2d ed. 2007); Norman M. Mann, *Management of Smell and Taste Problems*, 39 Cleveland Clinic J. Med. 329, 330 (2002).

dents reported out of millions of uses were *caused by* Zicam, and *not* the condition for which Zicam was used.

To plead a complaint alleging a plausible basis for concluding that anosmia-related AERs were material, plaintiffs would at least need to allege facts establishing that the rate of reported incidents exceeded, by a statistically significant degree, the known rate of anosmia among people with the common cold. Plaintiffs do not and cannot allege such facts.[25]

Absent that kind of allegation, it is difficult to understand the nature of the disclosure obligation envisioned by plaintiffs. Suppose petitioners had received 20 reports rather than 23 or 21—would the nondisclosure be material? What if it were only 18? Do respondents believe the 12 reports counted by pe-

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[25] In their opposition to the petition for a writ of certiorari, respondents suggested that a statement made in November 2003 that Matrixx could "incur significant costs resulting from product liability claims," J.A. 177a, "shows that the truth behind petitioners' omissions and misleading denials would have been highly material to Matrixx investors." Opp. to Pet. for Cert. 21. Respondents make no effort to explain how a statement of the blindingly obvious—product-liability lawsuits can be costly—shows why a reasonable investor would want to know about 21 scientifically unreliable AERs, out of millions of units sold. Those reports themselves do nothing to show that Matrixx would actually be facing litigation *with a material impact on the company's finances*, which is the only potentially relevant point. And litigation impacts in any event are already governed by a separate disclosure duty, *see* Regulation S-K, 17 C.F.R. § 229.103, which is not implicated here. Neither the district court nor the court of appeals considered Matrixx's generic lawsuit-related statement a relevant aspect of the materiality analysis in this case. *See* Pet. App. 21a-26a, 44a-50a.

titioners would qualify as material? What about 11, or seven, or four? Or just one? Respondents cannot answer these questions. Apart from statistical significance, there is no intelligible basis on which petitioners—or a reasonable investor—could understand when and why anosmia-related AERs indicate that it is Zicam, and not the common cold for which people are taking Zicam, that is causing the rarely reported anosmia reactions.

II. FAILURE TO DISCLOSE UNRELIABLE ANECDOTAL INCIDENT REPORTS DOES NOT GIVE RISE TO A "STRONG INFERENCE" OF SCIENTER

Respondents also fail to plead with particularity specific facts that give rise to an inference that petitioners intended to deceive that is "cogent and at least as compelling as any opposing inference one could draw from the facts alleged." *Tellabs*, 551 U.S. at 324.

Given the unreliability of mere AERs, and the fact that 12 or 21 or any number remotely close to that range does not show any statistically significant difference between Zicam users reporting anosmia and common cold sufferers experiencing anosmia, there is no basis for considering the inference of intentional deception to be at least as compelling as alternative inferences. Rather, the most obvious inference is that petitioners did not disclose the AERs simply because petitioners believed they were far too few, and too caught up with the confounding cold indicator, to indicate anything meaningful about adverse reactions to use of Zicam. *See Carter-Wallace II*, 220 F.3d at 40-42 (explaining that defendant's

awareness of statistically insignificant adverse event reports did not satisfy pleading requirement under Federal Rule 9(b)). Respondents plead nothing that would call that inference into doubt.

Especially given the "[e]xacting" requirements for pleading scienter imposed by the PSLRA, *Tellabs*, 551 U.S. at 313, an inference of scienter based upon scientifically unreliable AERs would be particularly inappropriate. Because the reports revealed no statistically significant association between Zicam use and anosmia, petitioners were faced simply with a handful of double and triple hearsay AERs from users already disproportionately susceptible to anosmia. Petitioners' "awareness of [AERs] that could have been random cannot lead to the conclusion" that petitioners acted with scienter, *Carter-Wallace II*, 220 F.3d at 42, in projecting further growth or in asserting that the allegations of a causal link between Zicam and anosmia were unfounded. These statements were entirely consistent with the FDA's and courts' assessment of the limited probative value of AERs. As the FDA explains, "[f]or any given [AER], there is no certainty that the suspected drug caused the [alleged adverse event]." FDA, 1996 Annual Report, at 2. That is why "[c]ase studies" reporting anecdotal evidence are by themselves generally "insufficient to show general causation." *Hendrix*, 609 F.3d at 1197. Respondents have not alleged facts sufficient to establish that the handful of AERs involved in this case demonstrate a causal link between Zicam and anosmia, much less specific facts that would support a strong inference that petitioners acted with scienter in not disclosing the AERs. *See* Adverse Event Reporting at 7. In-

deed, recognizing that unreliable AERs might be confused by many investors for meaningful evidence of causation—a common enough mistake among laypersons—petitioners may well have believed that disclosing the reports would have been *contrary* to their duty to avoid making misleading statements.

Respondents, in short, allege no facts establishing that the inference of scienter was at least as compelling as the obvious alternative: petitioners believed the handful of reports did not reveal any causal link that needed to be disclosed, and that disclosure would be more likely to mislead investors and consumers than to inform them.

CONCLUSION

For the foregoing reasons, the court of appeals' judgment should be reversed.

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APPENDIX

Case Law Finding AERs And Case Reports To Be Unreliable Evidence Of Causation

Examples from Federal Case Law

1) *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1316 (11th Cir. 1999) ("[C]ase reports and case studies are universally regarded as an insufficient scientific basis for a conclusion regarding causation because case reports lack controls.")

2) *Appleby v. Glaxo Wellcome, Inc.*, 2005 WL 3440440, at *3, *7 (D.N.J. Dec. 13, 2005) (AERs "may not be sufficiently reliable or relevant to be admissible on the issue of causation")

3) *Baker v. Chevron USA, Inc.*, 680 F. Supp. 2d 865, 886 (S.D. Ohio 2010) ("case studies must be viewed with caution")

4) *Benkwith v. Matrixx Initiatives, Inc.*, 467 F. Supp. 2d 1316, 1327, 1329 (M.D. Ala. 2006) (AERs are "are even less persuasive than case reports" because they are "[u]ncontrolled anecdotal information")

5) *Brumbaugh v. Sandoz Pharms. Corp.*, 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999) (AERs "do not demonstrate a causal link but instead represent coincidence")

6) *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995) ("case reports are not reliable scientific evidence of causation")

7) *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp. 2d 1046, 1050 (S.D. Ill. 2001) ("scant number of case reports indicating that [drug] is temporally associated" with adverse event cast doubt on reliability)

8) *Cloud ex rel. Cloud v. Pfizer, Inc.*, 198 F. Supp. 2d 1118, 1133, 1138 (D. Ariz. 2001) (AERs and "retrospective case reports" are "merely compilations of occurrences, and have been rejected as reliable scientific evidence supporting an expert opinion")

9) *Dellinger v. Pfizer Inc.*, 2006 WL 2057654, at *9 (W.D.N.C. July 19, 2006) ("[M]any courts have recognized that adverse drug reaction case reports and other regulatory reports fail to test a causal hypothesis and therefore cannot support a causation opinion.")

10) *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1050-51, 1057 (D.N.J. 1992) ("methodology" of relying upon AERs "produces inaccurate and unreliable results because such data are unreliable for determining causation")

11) *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 682 (M.D.N.C. 2003) ("Case reports are not scientific proof of causation")

12) *Ervin v. Johnson & Johnson, Inc.*, 2006 WL 1529582, at *6-*7 (S.D. Ind. May 30, 2006) ("Courts should treat with caution those expert opinions based on case reports.")

13) *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001) ("case reports" suffer from numerous flaws and are "not scientifically valid proof of causation")

14) *Gibson v. Sanofi-Aventis U.S., LLC*, 2009 WL 3490454, at *7-*8 (W.D. Ky. Oct. 27, 2009) ("scant review of a number of case reports" insufficient to establish reliable causation opinion)

15) *Hagaman v. Merrell Dow Pharms.*, 1987 WL 342949, at *8 (D. Kan. June 26, 1987) ("inherent unreliability of the [AERs] requires this court to prohibit their use as a basis for causation")

16) *Haggerty v. Upjohn Co.*, 950 F. Supp. 1160, 1165 (S.D. Fla. 1996) (AERs have "inherent bias" and "cannot be relied upon to form causation opinions")

17) *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.")

18) *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1211 (10th Cir. 2002) (case reports "contain only limited information" and are "unreliable evidence of causation")

19) *In re Accutane Prods. Liab. Litig.*, 2007 WL 1288354, at *3-*4 (M.D. Fla. May 2, 2007) (excluding AERs and causality assessments from evidence because they "reflect[] nothing more than an assessment of a possible relationship, not an actual relationship")

20) *In re Diet Drugs Prods. Liab. Litig.*, 2001 WL 454586, at *15 (E.D. Pa. Feb. 1, 2010) (AERs "are universally recognized as insufficient and unreliable evidence of causation")

21) *Leathers v. Pfizer, Inc.*, 233 F.R.D. 687, 694 (N.D. Ga. 2006) (AERs "generally do not, standing alone, render an expert's opinion reliable under *Daubert*")

22) *Lopez v. Wyeth-Ayerst Labs.*, 1996 WL 784566, at *4 (N.D. Cal. Dec. 13, 1996) ("Generally, courts have excluded expert causation testimony that is based upon . . . anecdotal or case reports")

23) *Lusch v. Matrixx Initiatives, Inc.*, 2007 U.S. Dist. LEXIS 72068, at *10-*11 (D. Or. Sept. 25, 2007) (excluding expert testimony based in part on case reports)

24) *Martinkovic v. Bangash*, 1987 WL 28400, at *2 (N.D. Ill. Dec. 18, 1987) ("Of course the anecdotal reports of alleged adverse reactions are not admissible to prove the truth of the matter declared in the reports")

25) *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1250, 1254 (11th Cir. 2005) ("case reports raise questions, they do not answer them")

26) *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.")

27) *Nelson v. Am. Home Prods. Corp.*, 92 F. Supp. 2d 954, 969 (W.D. Mo. 2000) (AERs "do not demonstrate a causal link sufficient for admission to a finder of fact in court")

28) *Newton v. Roche Labs., Inc.*, 243 F. Supp. 2d 672, 680 (W.D. Tex. 2002) ("many other courts have soundly rejected case reports as an acceptable basis for causation")

29) *Richardson v. Richardson-Merrell, Inc.*, 649 F. Supp. 799, 801 & n.5 (D.D.C. 1986) (AERs "are neither exceptions to the hearsay rule nor data reasonably relied upon by experts in the field of making determinations of causality")

30) *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002) ("while they may support other proof of causation, case reports alone ordinarily cannot prove causation")

31) *Rose v. Matrixx Initiatives, Inc.*, 2009 WL 902311, at *11, *15 (W.D. Tenn. Mar. 31, 2009) (case studies "do not 'provide an adequate scientific basis for general causation'")

32) *Ryman v. Sec'y of Dep't of Health & Human Servs.*, 65 Fed. Cl. 35, 39-40, 43 (2005) ("Vaccine Adverse Event Reporting System . . . evidence is not reliable.")

33) *Saari v. Merck & Co.*, 961 F. Supp. 387, 398 (N.D.N.Y. 1997) (doctor's "report to the FDA was simply a report of what plaintiff told him about what she believed was her reaction to the vaccine")

34) *Salden v. Matrixx Initiatives, Inc.*, 2007 U.S. Dist. LEXIS 18552, at *6 (E.D. Mich. Mar. 16, 2007) (case reports are "merely anecdotal")

35) *Sutherland v. Matrixx Initiatives, Inc.*, 2006 U.S. Dist. LEXIS 96652, at *30 (N.D. Ala. Nov. 7, 2006) ("standing alone" case studies are insufficient "to establish general causation")

36) *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.")

37) *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1453, 1470, 1481, 1483 (D.V.I. 1994) ("anecdotal information of chance associations . . . [has] no epidemiological significance")

38) *Willert v. Ortho Pharm. Corp.*, 995 F. Supp. 979, 981 (D. Minn. 1998) (case reports "do not investigate or explain the mechanism of causation" (internal quotation marks omitted))

39) *Wolf v. Procter & Gamble Co.*, 555 F. Supp. 613, 620 (D.N.J. 1982) (consumer complaints received by company are inadmissible hearsay)

40) *Wyatt v. Matrixx Initiatives, Inc.*, 2007 U.S. Dist. LEXIS 67986, at *14 (N.D. Ala. Mar. 30, 2007) (case study "amounts to anecdotal evidence, not evidence that has been vigorously tested using scientific methodology")

Examples from State Case Law

1) *Cosgrove v. Merrell Dow Pharms., Inc.*, 788 P.2d 1293, 1298-99 (Idaho 1989) (AERs "are anecdotal in nature and should not form the basis for any conclusions, expert or otherwise")

2) *Heckstall v. Pincus*, 797 N.Y.S.2d 445, 447 (N.Y. App. Div. 2005) (AERs are "unverified listings and reporting of adverse reactions" and "are not generally accepted in the scientific community on questions of causation")

3) *Linnen v. A.H. Robins Co.*, 2000 WL 16769, at *10 (Mass. Super. Dec. 14, 1999) ("[C]ase reports alone are not considered reliable scientific evidence of causation.")

4) *Merrell Dow Pharms., Inc. v. Havner*, 953 S.W.2d 706, 720-21 (Tex. 1997) ("[A]necdotal . . . evidence accomplishes no more than a false appearance of direct and actual knowledge of a causal relationship.")

5) *Pauley v. Bayer Corp.*, 2006 WL 463866, at *2 n.2 (Pa. C.P. Phil. Jan. 26, 2006) (AERs "are not proof of the data they contain, and do not directly bear upon the adequacy of label warnings")

6) *Pauling v. Orentreich Med. Grp.*, 787 N.Y.S.2d 311, 312 (N.Y. App. Div. 2005) (under both *Daubert* and *Frye*, "observational studies" by themselves are unreliable)

7) *Peters v. Johnson & Johnson Prods., Inc.*, 783 S.W.2d 442, 444-45 (Mo. Ct. App. 1990) (AERs are inadmissible hearsay as "unsolicited letters and unsubstantiated reports from alleged . . . users do not stand as to their trustworthiness")

8) *Ranes v. Adams Labs., Inc.*, 778 N.W.2d 677, 691-94 (Iowa 2010) (case reports "reflect only reported data, not scientific methodology")

9) *Revels v. Novartis Pharms. Corp.*, 1999 WL 644732, at *4-*5 (Tex. App. Aug. 26 1999) ("[A] study of case reports alone is a scientifically invalid manner in which to form an expert opinion.")

10) *Swallow v. Emergency Med. of Idaho, P.A.*, 67 P.3d 68, 73 (Idaho 2003) (reports of ten adverse events not reliable evidence of causation where "there is no showing that ten adverse cardiac events occurring over eight years to patients . . . is a greater incidence of such events than would be expected to occur by chance")