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 RESPONDENTS

DARREN J. ROBBINS
ERIC ALAN ISAACSON
JOSEPH D. DALEY
SCOTT H. SAHAM
LUCAS F. OLTS
ROBBINS GELLER RUDMAN & DOWD LLP
655 West Broadway
Suite 1900
San Diego, California 92101
(619) 231-1058

SAMUEL H. RUDMAN
DAVID A. ROSENFELD
ROBBINS GELLER RUDMAN & DOWD LLP
58 South Service Road
Suite 200
Melville, New York 11747
(631) 367-7100

DAVID C. FREDERICK
Counsel of Record
SCOTT H. ANGSTREICH
GREGORY G. RAPAWY
EMILY T.P. ROSEN
KELLOGG, HUBER, HANSEN, TODD, EVANS & FIGEL, P.L.L.C.
1615 M Street, N.W.
Suite 400
Washington, D.C. 20036
(202) 326-7900
(dfrederick@khhte.com)

November 5, 2010

QUESTION PRESENTED

Respondents are investors in petitioner Matrixx Initiatives, Inc. who claim that petitioners violated § 10(b) of the Securities Exchange Act of 1934 and Securities and Exchange Commission Rule 10b-5 by misrepresenting and by failing to disclose information about the safety of their drug products, including several independent reports by doctors linking intranasal applications of Matrixx's Zicam products to persistent anosmia (loss of the sense of smell).

Contrary to petitioners' question presented, which asserts that this case concerns "a pharmaceutical company's nondisclosure of adverse event reports even though the reports are not alleged to be statistically significant," this case does not involve "adverse event reports" required by the Food and Drug Administration. Zicam was not subject to the federal reporting requirements at the relevant time. *See infra* pp. 8-9, 55; Br. in Opp. 17-18.

Accordingly, the question presented is:

Whether a securities-fraud complaint adequately can plead materiality and scienter by alleging that defendants received multiple, credible reports from medical specialists that its cold medicine appeared to cause serious, persistent anosmia, omitted disclosure of product-liability litigation concerning that defect, obtained scientific studies linking the drug's key ingredient zinc to anosmia but conducted no follow-up studies, and stated that clinical trials established that its drug did not cause anosmia when in fact it had no basis for any such claim.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

CASES

STATUTES, REGULATIONS, AND RULES

ADMINISTRATIVE MATERIALS

OTHER MATERIALS

INTRODUCTION

Since Justice Story's time, this Court has defined materiality in a wide variety of contexts as a totality-of-the-circumstances inquiry. In *TSC Industries, Inc. v. Northway, Inc.*, 426 U.S. 438 (1976), and *Basic Inc. v. Levinson*, 485 U.S. 224 (1988), this Court adopted that well-settled approach in cases of securities fraud. The inquiry essentially asks whether, in light of the context and circumstances, a reasonable investor would regard a statement or omission as important in making a decision to purchase or sell securities.

Respondents' complaint alleges that, by October 2003, petitioner Matrixx Initiatives, Inc. ("Matrixx") knew of a problem with its flagship drug Zicam. Zicam was a then-popular cold remedy earning millions of dollars per quarter, with rapidly growing sales. But Matrixx had received warnings from several specialists who had diagnosed certain Zicam products as causing a noteworthy number of patients to experience persistent anosmia – loss of the sense of smell. A link between Zicam and that very serious condition posed a major threat to Matrixx's business: it could lead to irreparable damage to the Zicam brand, from which Matrixx derived the predominant portion of its revenues; regulatory action against Matrixx; and costly product-liability suits. Indeed, in October 2003, the first of many suits against Matrixx already had been filed.

Matrixx responded to the warnings of a link between Zicam and anosmia by concealing them. Through baseless threats of legal action, it intimidated a group of medical specialists into removing Zicam's name from a presentation at a national conference. It issued optimistic statements that talked generically about possible product-liability litigation

without mentioning actual litigation already filed against the company. When, in February 2004, allegations that Zicam caused anosmia became public despite Matrixx's efforts, it stated misleadingly that the safety of Zicam had been "well established" by "clinical trials." JA77a-78a (¶ 38).[1] Days later, the doctor whom Matrixx had threatened went to the press with his information linking Zicam to anosmia, and Matrixx's stock dropped 23.8% in a day.

As Matrixx was forced only weeks later to admit, the evidence it had in February 2004 was insufficient (at best) to establish that Zicam was safe. Indeed, the Food and Drug Administration ("FDA") ultimately sent Matrixx a warning letter charging (among other things) that the Zicam products at issue were misbranded because their labeling failed to disclose the risk that they would cause anosmia. Matrixx pulled those products off the market.

Matrixx now seeks from this Court a rule that its statements and omissions in 2003 and 2004 could not, as a matter of law, have defrauded its investors. Matrixx maintains that, unless the number of cases of Zicam-induced anosmia known to Matrixx were statistically significant, no reasonable investor would have cared about the information Matrixx had, and Matrixx could not possibly have acted with scienter.

The unprecedented pleading standards urged by Matrixx would undermine governmental enforcement actions and private securities suits alike. Matrixx seeks to elevate an arbitrary threshold – statistical significance – into a rule of law pursuant to which

---

[1] "JA__a (¶ __)" refers to paragraphs in the operative complaint, reproduced in the Joint Appendix. "App." refers to the appendix to the certiorari petition.

aggrieved investors in drug companies could never survive motions to dismiss unless they had a good-faith basis for pleading that the false statements or omissions rested on information that rose to the level of "statistical significance."

This Court should reject Matrixx's proposed standard. First, it conflicts with the well-settled understanding of materiality in a wide variety of legal contexts. Second, it distorts the uses and purposes of statistical significance, which does not equate to practical significance. Third, it creates a standard divorced from the behavior of actual and reasonable investors, who base investment decisions on a broad variety of useful information rather than limiting themselves to findings based solely on statistics. Fourth, it incentivizes manufacturers to withhold the necessary data from which a statistical analysis could be drawn. And, fifth, it promotes a battle-of-the-statistical-experts at the pleading stage of a case, rather than after factual development. The court below rightly rejected Matrixx's artificial, unworkable, and unprecedented bright-line rule. This Court should as well.

STATEMENT

A. Statutory And Doctrinal Background

Congress enacted the Securities Act of 1933 and the Securities Exchange Act of 1934 ("1934 Act") in response to widespread abuses in the securities industry. To advance the objective of "honest markets," *Basic*, 485 U.S. at 230 (internal quotations omitted), 1934 Act § 10(b) forbids the use of "any manipulative or deceptive device or contrivance" "in connection with the purchase or sale of any security." 15 U.S.C. § 78j(b).

Securities and Exchange Commission ("SEC") Rule 10b-5 implements § 10(b) by prohibiting "(a) . . . any device, scheme, or artifice to defraud, (b) . . . any untrue statement of a material fact or . . . omi[ssion of] a material fact necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading, [and] (c) . . . any act, practice, or course of business which operates or would operate as a fraud or deceit upon any person." 17 C.F.R. § 240.10b-5. A private plaintiff seeking relief for a § 10(b) violation must show "(1) a material misrepresentation or omission by the defendant; (2) scienter; (3) a connection between the misrepresentation or omission and the purchase or sale of a security; (4) reliance upon the misrepresentation or omission; (5) economic loss; and (6) loss causation." *Stoneridge Inv. Partners, LLC v. Scientific-Atlanta, Inc.*, 552 U.S. 148, 157 (2008).

The Private Securities Litigation Reform Act of 1995 ("PSLRA") requires that the complaint in a securities-fraud action alleging a material misstatement or omission "specify each statement alleged to have been misleading, [and] the reason or reasons why the statement is misleading," and provide a particularized basis for any allegations made on information and belief. 15 U.S.C. § 78u-4(b)(1). Where applicable, the complaint also must "state with particularity facts giving rise to a strong inference that the defendant acted with the required state of mind." *Id.* § 78u-4(b)(2). A "strong inference" is one that is "cogent and at least as compelling as any opposing inference of nonfraudulent intent." *Tellabs, Inc. v. Makor Issues & Rights, Ltd.*, 551 U.S. 308, 314 (2007).

The PSLRA does not impose any heightened pleading standard for allegations that a misstatement or omission was material. Materiality allegations are governed by Federal Rule of Civil Procedure 8(a)(2), which requires a civil complaint to contain "a short and plain statement of the claim showing that the pleader is entitled to relief."

B. Nature Of The Action

Respondents seek damages arising from petitioners' securities fraud from October 22, 2003, to February 6, 2004. JA60a (¶ 1). Respondents allege that, during that time, petitioners[2] were aware of important information linking intranasal Zicam products to persistent anosmia, but nevertheless made materially false and misleading statements and omissions concerning Zicam and anosmia that overstated Matrixx's likely future prospects. JA60a-64a (¶¶ 1-10), 98a-99a (¶¶ 58-60).

1. Intranasal application of zinc and anosmia

Zinc gluconate, the active ingredient of Matrixx's Zicam products, is a zinc salt. When dissolved, it releases positively charged zinc ions. *See Handbook of Applied Therapeutics* 2-9 (Mary Anne Koda-Kimble et al. eds., 8th ed. 2007).

Medical researchers long have known that zinc salts can destroy the sense of smell when applied to the olfactory region of the nasal cavity. That effect was first discovered in 1934, through efforts to combat polio. Researchers then believed that persons contracted the polio virus through inhalation into the olfactory cleft and then transmission along

---

[2] Petitioners (collectively "Matrixx") are Matrixx itself and three Matrixx executives. JA65a (¶¶ 16-20).

the olfactory nerves to the victim's spinal cord.[3] The resulting medical mantra became "[p]rotect the nose and prevent polio." Roland H. Berg, *Polio and Its Problems* 38 (1948). Experiments began with various chemicals that might offer protection.

Stanford University researcher Edwin Schultz touted zinc sulfate (a zinc salt) as the "golden chemical" to protect the nose. *Id*. at 37. Schultz believed that zinc caused proteins in the nasal membranes to form a protective coating around the olfactory nerves, preventing them from absorbing the polio virus. *Id*. He further believed that zinc would not create that barrier "unless the protective spray had temporarily destroyed the sense of smell." *Id*. at 39.

Zinc-induced anosmia was not always temporary. During a 1937 polio epidemic in Toronto, Canada, nose-and-throat specialists sprayed some 5,000 children with a zinc sulfate solution. *Id.* at 40. Months later, Schultz began receiving complaints that many of the children "had suffered a complete and evidently permanent loss of the sense of smell." *Id.* at 42. Because the treatment also failed to stop polio, that ended the intranasal application of zinc sulfate in humans.

Animal studies continued on the effect of ionized zinc on the sense of smell. A 1976 *American Journal of Anatomy* article explained that exposing the olfactory epithelium[4] of mice to a zinc sulfate solution

---

[3] *See* E.W. Schultz, *Immunity and Prophylaxis in Poliomyelitis*, 107 J. Am. Med. Ass'n 2102, 2103 (1936); E.W. Schultz & L.P. Gebhardt, *Zinc Sulfate Prophylaxis in Poliomyelitis*, 108 J. Am. Med. Ass'n 2182 (1937).

[4] The olfactory epithelium "lines the olfactory region of the nasal cavity and contains olfactory receptors." *Dorland's Illustrated Medical Dictionary* 644 (31st ed. 2007).

caused severe damage.[5] In 1978, researchers described the "immediate and total loss" of treated mice's ability to smell following nasal irrigation with zinc sulfate.[6] In 1993, researchers reported that applying a zinc sulfate spray to the olfactory mucosa in rats caused anosmia in 80% of the animals within two days.[7]

Studies also determined that the anosmia-inducing effect of zinc sulfate was specifically attributable to the *zinc ions* in the solution (as opposed to the sulfate ions). In 1972, researchers compared the effect of zinc sulfate on sea turtles to the effect of magnesium sulfate and found that only the former caused anosmia, concluding: "The role of Zn^{++} seems crucial." Marion Manton et al., *Chemoreception in the Migratory Sea Turtle* Chelonia Mydas, 143 Biol. Bull. 184, 193 (1972). In 1982, a researcher tested the effect of several salt solutions, including zinc sulfate and zinc chloride, on the olfactory mucosa of catfish. *See* Paul Cancalon, *Degeneration and Regeneration of Olfactory Cells Induced by $ZnSO_4$ and Other Chemicals*, 14 Tissue & Cell 717 (1982). He observed the presence of a "[s]pecific degeneration effect of Zn^{2+} ions" on the mucosa that did not depend on the compound's other chemicals. *Id.* at 729 ("[S]odium sulfate and sodium chloride leave the mucosa intact, [but] . . . zinc sul-

---

[5] *See* Daniel H. Matulionis, *Light and Electron Microscopic Study of the Degeneration and Early Regeneration of Olfactory Epithelium in the Mouse*, 145 Am. J. Anat. 79 (1976).

[6] Joseph W. Harding et al., *Denervation of the Primary Olfactory Pathway in Mice*, 140 Brain Research 271, 271 (1978).

[7] *See* Anne D. Mayer & Jay S. Rosenblatt, *Peripheral Olfactory Deafferentation of the Primary Olfactory System in Rats Using $ZnSO_4$ Nasal Spray With Special Reference to Maternal Behavior*, 53 Physiol. & Behav. 587 (1993).

fate and zinc chloride are equally effective."). Thus, by at least the 1980s, substantial scientific evidence existed that ionized zinc applied intranasally could adversely affect the sense of smell.

2. Matrixx's intranasal zinc products

Matrixx develops, manufactures, and markets over-the-counter pharmaceuticals. JA60a (¶ 2). Matrixx's core brand in 2003-2004 was a line of common-cold products generating 100% of Matrixx's sales. *Id.* The "Zicam Cold Remedy" accounted for approximately 70% of Matrixx's sales overall. *Id.* The over-the-counter remedy had several forms, including an intranasal spray and gel. *Id.*

Matrixx marketed Zicam as a homeopathic[8] medicine. JA77a (¶ 38). Based on that characterization, Zicam did not undergo the rigorous new drug application process that "applie[s] to all other new drugs in the United States" and requires pre-market submission to the FDA of clinical testing data showing a drug's safety and efficacy. Suzanne White Junod, *An Alternative Perspective: Homeopathic Drugs, Royal Copeland, and Federal Drug Regulation*, 55 Food & Drug L.J. 161, 183 (2000); *see id.* (homeopathic regulation "stands in marked contrast to the well-honed new drug application/investigational new drug process"); *compare* 21 U.S.C. § 355 (governing new

---

[8] Homeopathy is a type of alternative medicine based on the "principle . . . that a disease can be cured by a substance that produces similar symptoms in healthy people" and that involves "giving very small doses of highly diluted substances." National Ctr. for Complementary and Alternative Medicine, U.S. Dep't of Health & Human Services, *Homeopathy: An Introduction* 1, *available at* http://nccam.nih.gov/health/homeopathy/homeopathy.pdf (updated Aug. 2010). "[A] number of its key concepts are not consistent with the current understanding of science, particularly chemistry and physics." *Id.*

drug applications) *and* 21 C.F.R. pts. 310, 312, 314 (same) *with* FDA Compliance Policy Guide ("CPG") § 400.400, "Conditions Under Which Homeopathic Drugs May Be Marketed" (rev. Mar. 1995) (formerly CPG § 7132.15).

Between October 2003 and February 2004, manufacturers of drugs not marketed under an approved new drug application had no obligation to report to the government adverse events associated with their products. In 2006, Congress enacted the Dietary Supplement and Nonprescription Drug Consumer Protection Act, extending adverse event reporting requirements to such drugs. That Act now requires companies like Matrixx to submit to the government any report they receive of a "serious adverse event" – such as a death, hospitalization, disability, or birth defect – "associated with [their] drug." 21 U.S.C. § 379aa(a), (b).

3. Information communicated to Matrixx about Zicam and anosmia before February 2004

From before October 2003 through February 2004, Matrixx received credible, non-public information linking Zicam with persistent anosmia.

a. In 1999, Dr. Alan Hirsch, a practicing neurologist who specializes in issues of smell and taste, observed a link between Zicam use and anosmia in a "cluster" of his patients. JA67a (¶ 25). In December 1999, Dr. Hirsch called Matrixx to inquire about the amount of zinc in Zicam's nasal gel. JA67a-68a (¶ 25). He spoke with "a Mr. Laundau" and told him about at least one patient who had developed anosmia after using Zicam in the absence of a cold. JA68a (¶ 25). Dr. Hirsch further advised Laundau that studies had shown problems with the intranasal application of zinc. Laundau responded that he was

unaware of those studies. Dr. Hirsch volunteered to conduct a clinical study on a possible link between Zicam and anosmia, but Matrixx turned him down. *Id.*

b. Three years later, Matrixx contacted a researcher in the taste-and-smell field concerning Zicam. In September 2002, petitioner Timothy Clarot, Matrixx's Vice President of Research and Development, telephoned Dr. Miriam Linschoten of the University of Colorado's Health Sciences Center and Rocky Mountain Taste and Smell Center ("RMTSC"). JA68a (¶ 26). Dr. Linschoten was treating several patients at the RMTSC for loss of smell following Zicam use; one of them had complained to Matrixx. *Id.* Clarot told Dr. Linschoten that Matrixx had received additional, similar complaints from other Zicam users as far back as 1999. *Id.* Dr. Linschoten asked whether Matrixx had conducted relevant studies; Clarot replied that Matrixx had not, but had hired a consultant to review the product. JA68a-69a (¶ 26). Dr. Linschoten mentioned studies linking zinc sulfate to loss of sense of smell, but Clarot "gave her the impression that he had not heard of" such studies. JA69a (¶ 26).

On September 20, 2002, Dr. Linschoten e-mailed Clarot several abstracts of studies on zinc sulfate and anosmia. *Id.* (¶ 27). Clarot then invited Dr. Linschoten to participate in animal studies Matrixx was then planning, but she declined because her focus was on human research. *Id.*

c. In September 2003, Dr. Bruce Jafek of the Department of Otolaryngology[9] at the University of

---

[9] Otolaryngologists are physicians specializing in "diseases and disorders of the ear, nose, throat (ENT), and related

Colorado School of Medicine, along with Dr. Linschoten and another colleague (JA101a (¶ 64)), developed a poster presentation[10] for the American Rhinologic Society[11] meeting on September 20, 2003. The presentation described the observed link between Zicam use and anosmia among numerous individuals. JA69a-70a (¶ 28).[12]

The presentation included a detailed case report on a 55-year-old man who, prior to using Zicam, had normal taste and smell functions. JA70a (¶ 28). Upon spraying Zicam into his nose, however, he experienced severe burning, followed immediately by the loss of his sense of smell. *Id.* By the presentation date, 23 months after the incident, the patient's sense of smell had not returned. The presentation noted nine other Zicam users with similar symptoms. *See* 2003 Presentation.

Dr. Jafek and his colleagues considered and rejected the possibility that the common cold itself had caused the subjects' anosmia. That phenomenon

---

structures of the head and neck." American Academy of Otolaryngology, http://www.entnet.org/healthinformation/AboutOtolaryngology.cfm.

[10] Poster presentations are "a major format for communicating at scientific meetings." Martha Davis, *Scientific Papers and Presentations* 191 (2005).

[11] The American Rhinologic Society is "the world's largest physician organization whose mission focuses upon the medical and surgical treatment of patients with diseases of the nose and paranasal sinuses." American Rhinologic Society, http://www.american-rhinologic.org/.

[12] Matrixx has filed copies of the presentation ("2003 Presentation") in several district court proceedings, including *Hans v. Matrixx Initiatives, Inc.*, No. 3:04-cv-540-TBR (W.D. Ky. filed Feb. 1, 2006) (Dkt. No. 26-19). A more legible copy (provided by Dr. Linschoten) is enclosed in the back pocket herein.

(known as "post-viral anosmia") typically occurs following a *severe* upper respiratory infection ("URI"). The Zicam users discussed in the presentation typically took Zicam "early in the course of a *mild* URI." *Id.* (emphasis added). "Most convincing" in excluding the possibility of post-viral anosmia, the users described "immediate, acute, 'burning' pain" following Zicam use, "followed immediately by persistent hyposmia or anosmia." *Id.*[13]

Before the September conference, Matrixx received the presentation's abstract, which was entitled "Zicam® Induced Anosmia." JA69a (¶ 28). Matrixx sent two warning letters to Dr. Jafek seeking to prevent him from naming either Matrixx or Zicam. JA61a (¶ 4) (asserting that "'as a legal matter' he did 'not have [Matrixx's] permission to use their company name or product trademarks'" in the presentation); *see also* JA70a (¶ 29). Dr. Jafek redacted the Zicam name from the presentation. JA70a (¶ 29).

d. Personal-injury lawsuits also were filed against Matrixx by Zicam users. Between October 2003 and February 2004, 10 Zicam users sued Matrixx, alleging that Zicam had damaged their sense of smell. JA87a-88a (¶ 49) (listing complaints). From late 2003 through October 2004, more than 270 others sued Matrixx, alleging that Zicam had damaged their sense of smell. JA87a-91a (¶ 49). Matrixx since has settled some 300-plus Zicam lawsuits for approximately $12 million. Another 176 suits brought by 671 plaintiffs remained pending in May 2010.[14]

---

[13] "Hyposmia" is a diminished or reduced sense of smell. *See Dorland's Illustrated Medical Dictionary* at 918.

[14] *See* Ken Alltucker, *High court to hear suit of investors vs. drug firm*, Ariz. Republic, June 15, 2010, at A1.

4. Statements by Matrixx to its investors from October 2003 to February 2004

a. In late October 2003, Matrixx announced that the Zicam brand was "poised for growth" in the upcoming cough-and-cold season. JA72a (¶ 32). Matrixx represented that it had "very strong momentum" because of the Zicam line – "[a] product that offers a unique benefit." JA73a-74a (¶ 33). Matrixx further said that it was "extremely well positioned for a successful" cold season and that annual revenues were poised to rise dramatically, "up in excess of 50%." JA74a (¶ 34). Matrixx disclosed nothing about the potential link between Zicam and anosmia, despite the information it had received. JA71a-75a (¶¶ 32-34).

b. On November 12, 2003, Matrixx filed its third-quarter 2003 Form 10-Q with the SEC. JA75a-76a (¶ 35). Matrixx included a statement about adverse reputational and financial consequences from product-liability claims, "even [those] without merit" and those "not proven to be valid." *Id.* Although a lawsuit alleging that intranasal Zicam caused anosmia had been filed on October 14, 2003, JA61a-62a (¶ 5), Matrixx disclosed neither that lawsuit's existence nor any other information about a possible link between intranasal Zicam and anosmia.

c. When news of a possible link between Zicam and anosmia reached the public in early 2004, Matrixx's stock price dropped significantly. On Friday, January 30, 2004, after ordinary trading closed, the Dow Jones Newswires reported that the FDA was looking into complaints that "an over-the-counter common-cold medicine manufactured" by Matrixx "may be causing some users to lose their sense of smell." JA79a-80a (¶ 40). Matrixx's stock price

dropped from $13.55 per share on January 30 to $11.97 per share on Monday, February 2. JA80a (¶ 41).

On February 2, Matrixx responded with a press release proclaiming Zicam's safety. JA77a-78a (¶ 38), 193a. Matrixx claimed that "alleg[ations] that intranasal Zicam products cause anosmia (loss of smell) are *completely* unfounded and misleading." JA77a (¶ 38) (emphasis added). Matrixx also reassured investors that "[i]n no clinical trial of intranasal zinc gluconate gel products has there been a single report of lost or diminished olfactory function (sense of smell). Rather, the *safety* and efficacy of zinc gluconate for the treatment of symptoms related to the common cold have been *well established* in two double-blind, placebo-controlled, randomized clinical trials." JA77a-78a (¶ 38) (emphases added). Following Matrixx's denials, its stock price rose to $13.40 on February 3. JA80a (¶ 41).

Matrixx suggested to its investors that reports of Zicam-induced anosmia could be explained as post-viral anosmia resulting from the common cold. JA78a (¶ 38); *see also* Pet. Br. 8-9 n.3. It did not disclose that the doctors whose research gave rise to those reports had specifically ruled out post-viral anosmia. *See supra* pp. 11-12.

d. On February 6, 2004, the link between Zicam and anosmia was revealed to a nationwide television audience. On the news program *Good Morning America* ("*GMA*") that day, reporter John Ferrugia told viewers about a woman named "Linda" who claimed that Zicam had caused her anosmia. JA80a (¶ 42). Ferrugia noted that Linda's claim was not an isolated one: "Dr. Bruce Jafek has discovered more than a dozen patients with the same troubles as

Linda . . . after using the Zicam product." *Id.* The reporter stated that four lawsuits had been filed alleging that Zicam caused anosmia and that "[o]thers are being prepared, anywhere from California to Michigan." JA81a (¶ 42).

Matrixx responded with more denials, issuing a press release that same day entitled "Matrixx Initiatives *Reaffirms Safety* of Intranasal Zicam® Remedy." JA81a (¶ 44), 201a (emphasis added). It repeated that in "no clinical trial of intranasal zinc gluconate gel products has there been a single report of lost or diminished olfactory function (sense of smell)." JA81a-82a (¶ 44).

Following the *GMA* broadcast, Matrixx's common stock plummeted, dropping 23.8% in one day (from $13.05 per share to $9.94) on unusually heavy trading volume. JA81a (¶ 43).

5. Subsequent developments

On February 27, 2004, Matrixx told the SEC and its investors that, in fact, it did not know whether Zicam could cause anosmia. JA82a (¶¶ 45-46), 206a.[15] In a Form 8-K filing, Matrixx admitted for the first time that it had convened a two-day meeting of "physicians and scientists to review current information on smell disorders" in response to "a poster presentation at the American Rhinologic[] Society in September 2003." JA82a (¶ 45). The panel found "insufficient scientific evidence at this time to determine if zinc gluconate, when used as recommended, affects a person's ability to smell." *Id.* (¶ 46). A contempora-

---

[15] The complaint states that the Form 8-K filing took place on February 19, 2004. JA82a (¶¶ 45-46). The filing itself is dated February 27, but states that an event (presumably, the meeting) it is disclosing took place on February 19. JA205a.

neous ABC News report summarized the situation: "All along, Matrixx Initiatives, the maker of Zicam, said the product was safe. But now it admits there are no studies dealing with the issue." JA84a (¶ 47).

In mid-2004, Dr. Jafek and his colleagues expanded the 2003 Presentation into a peer-reviewed article published in the *American Journal of Rhinology*, then the American Rhinologic Society's official journal. JA101a (¶ 64).[16] An additional peer-reviewed study published in 2006 described 17 additional cases of anosmia observed at the University of California San Diego Nasal Dysfunction Clinic, concluding that 15 were caused by intranasal application of zinc gluconate.[17] More peer-reviewed articles studying zinc gluconate and anosmia have since been published.[18]

---

[16] The district court refused to consider this article because it was "published post-Class Period." App. 42a; *see also* App. 19a n.4 (court of appeals did "not disturb" that ruling). Respondents have argued at every stage of this case that the district court erred in that ruling. The pertinent legal question is only whether respondents have *plausibly* alleged materiality. After-the-fact corroboration of a statement is relevant to that limited question, regardless of whether that corroboration would be admissible at trial. *See infra* p. 31. Matrixx itself invokes (at 7 n.2) post-Class-Period facts to question Dr. Jafek's credibility, including his later expert testimony in product-liability cases involving Zicam and court rulings excluding that testimony from evidence.

[17] *See* Thomas H. Alexander & Terence M. Davidson, *Intranasal Zinc and Anosmia: The Zinc-Induced Anosmia Syndrome*, 116 Laryngoscope 217, 218 (2006).

[18] *Compare* Burton Slotnick et al., *Olfaction and Olfactory Epithelium in Mice Treated With Zinc Gluconate*, 117 Laryngoscope 743, 746-47 (2007) (study funded in part by Matrixx, concluding that zinc gluconate did not cause long-lasting anosmia in mice), *with* Jae H. Lim et al., *Zicam-Induced Damage to*

On June 16, 2009, the FDA issued a warning letter to Matrixx, finding that several Zicam intranasal products "may pose a serious risk to consumers who use them." JA268a.[19] The FDA had received "more than 130 reports of anosmia . . . associated with use of these products." *Id.* In addition to those reports, the FDA was "aware that Matrixx appears to have more than 800 reports related to loss of sense of smell associated with Zicam Cold Remedy intranasal products." JA272a. The FDA found that Matrixx's Zicam intranasal products were misbranded for lack of "adequate warnings regarding the risk of anosmia associated with the product." JA271a.

The letter further stated that the FDA was "not aware of any data establishing that the Zicam Cold Remedy intranasal products are generally recognized as safe and effective for the uses identified in their labeling." JA269a. "On the contrary," the FDA concluded, "there is evidence that these products pose a serious safety risk to consumers," including "evidence in the published scientific literature that various salts of zinc can damage olfactory function in animals and humans." JA269a, 270a.

The letter noted that, although intranasal Zicam was labeled as homeopathic, it could not benefit from the FDA's discretionary enforcement guidelines regarding homeopathic products because "there [was]

Mouse and Human Nasal Tissue, 4 PLoS One e7647, at 5-8 (2009) (study whose authors declared they had no conflicts of interest, concluding that Zicam's effects "contributed to a long-lasting and apparently irreversible olfactory dysfunction in the mouse" and had toxic effects on human nasal tissue).

[19] *See* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm166909.htm, *reprinted at* JA267a-274a ("Warning Letter").

evidence of a safety risk associated with the product." JA270a. The FDA has since described its letter as an "enforcement action to protect consumers from fraudulent alternative medicine products."[20]

After receiving the Warning Letter, Matrixx withdrew from the market its intranasal Zicam products.[21]

C. District Court Proceedings

On April 29, 2004, the first complaint in this action was filed. On March 4, 2005, lead plaintiff NECA-IBEW Pension Fund filed the operative consolidated amended complaint. JA59a-111a. Matrixx moved to dismiss. The district court granted the motion.

Relying upon *In re Carter-Wallace, Inc. Securities Litigation*, 220 F.3d 36 (2d Cir. 2000) ("*Carter-Wallace II*"), the court concluded that, unless Matrixx had known of "statistically significant" information linking Zicam to anosmia, all other information Matrixx had received on that topic was immaterial as a matter of law. App. 44a-50a. The court also held that respondents had not pleaded sufficiently that Matrixx had a "motive" to omit the truth about Zicam, "disbelieved" its public statements about Zicam, or had attempted to "profit" from them. App. 51a-52a. Finally, the court ruled that, unless respondents could show that Matrixx "*knew* there was a definitive and statistically significant

---

[20] FDA, *Alternative Medicine Fraud*, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/ucm207747.htm (last updated Oct. 25, 2010).

[21] *See* Matrixx Initiatives, Inc., *Message to Consumers*, http://www.zicam.com/messagetoconsumers.

link between Zicam and anosmia," any amendment would be futile. App. 54a.

D. The Ninth Circuit's Decision

The Ninth Circuit reversed. It reasoned that *Basic* "rejected the adoption of a bright-line rule to determine materiality because '"[t]he determination [of materiality] requires delicate assessments of the inferences a 'reasonable shareholder' would draw from a given set of facts and the significance of those inferences to him."'" App. 23a (quoting *Basic*, 485 U.S. at 236 (quoting *TSC*, 426 U.S. at 450)) (alterations in original). Courts assessing materiality should engage in a "'fact-specific inquiry.'" *Id.* (quoting *Basic*, 485 U.S. at 240).

Rather than focusing solely on statistical significance, the court continued, a materiality analysis should consider whether reasonable investors would have viewed as significant the information about a Zicam-anosmia link that had been communicated to Matrixx. App. 24a-26a. The court held that respondents' allegations met the PSLRA's pleading standards, as well as the "plausib[ility]" standard of *Bell Atlantic Corp. v. Twombly*, 550 U.S. 544, 570 (2007). App. 26a.

The Ninth Circuit also reversed the district court's scienter holding, listing allegations supporting a strong inference of Matrixx's scienter. App. 28a-33a. By the time of its October 22, 2003 press release and conference call, Matrixx already had received information about a possible link between Zicam and anosmia from Drs. Hirsch, Linschoten, and Jafek. App. 28a-29a. Further, although Matrixx spoke about the reputational and financial risks of potential product-liability claims in its November 2003 Form 10-Q "in the abstract," Matrixx gave no indication

that the risk already had come to fruition (App. 30a), through the filing of a lawsuit.

By the time of Matrixx's February 2, 2004 press release,

> a strong inference can be drawn that [petitioners] knew that the statements alleging a link between Zicam and anosmia were not "completely unfounded and misleading." [Petitioners] allegedly knew about the presentation by Jafek to the American Rhinologic Society, Clarot's conversation with Linschoten, and several lawsuits alleging that Zicam caused anosmia.

App. 31a. In addition, Matrixx's statements in that press release that Zicam's safety had been "well established" by clinical trials conflicted with allegations that

> Clarot told Linschoten in September 2002 that Matrixx had not conducted any studies and asked her to participate in studies. The references in the press release to clinical trials establishing Zicam's safety also conflict with the March 4, 2004, news report that Matrixx did not know if Zicam could cause anosmia and [had] formed a medical advisory panel to conduct studies.

Id.

Viewing respondents' allegations as a whole, the Ninth Circuit concluded that they supported a scienter inference that was "'cogent and at least as compelling' as any 'plausible non-culpable explanation[]'" for petitioners' conduct. App. 33a (quoting *Tellabs*, 551 U.S. at 324) (alteration in original).

SUMMARY OF ARGUMENT

I.A. The standard for materiality in securities-fraud cases is well-settled. Under *TSC* and *Basic*, that standard is a fact-specific inquiry into the likelihood that a reasonable investor would "view[] . . . [particular information] as having significantly altered the 'total mix' of information . . . available." *TSC*, 426 U.S. at 449. It involves the drawing of delicate inferences and is usually a question for the finder of fact. The fact-specific nature of the materiality standard in fraud cases dates back at least to *McLanahan v. Universal Insurance Co.*, 26 U.S. (1 Pet.) 170, 189 (1828), and *McLanahan* itself treated the point as settled by even earlier authority. Materiality is similarly fact-specific in numerous other areas of the law.

B. Applying that settled materiality standard here compels the conclusion that respondents have stated a claim. In pleading materiality, respondents were required by *Twombly* and *Ashcroft v. Iqbal*, 129 S. Ct. 1937 (2009), only to establish a plausible inference of materiality. They did so by pointing to facts including, among others, the expert physicians who had concluded, by October 2003, that a causal link existed between intranasal Zicam use and persistent anosmia; the seriousness of persistent anosmia and the threat it posed to Zicam as Matrixx's principal revenue source; and the actual movements of Matrixx's stock price after the truth came out on February 6, 2004.

Matrixx's responses rely almost entirely on its request that this Court impose a bright-line rule requiring statistical significance for *any* allegation of a failure to disclose information about adverse drug effects to be material under the securities laws.

When that position fails (as it must), respondents should prevail. Matrixx also argues that the doctors who linked Zicam to anosmia in 2003 failed to account for "confounding factors" such as the common cold itself, but the doctors considered and rejected that theory.

C. Respondents also alleged facts sufficient to raise a strong inference of scienter, as required by the PSLRA and *Tellabs*. Matrixx's acts demonstrate that it either intended to deceive or acted recklessly with regard to the truth of its statements. Particularly convincing are its attempt in September 2003 to conceal from the public the presentation to the American Rhinologic Society through baseless legal demands that Dr. Jafek not use its name, and its claim in February 2004 that Zicam already had been proved safe before admitting, a few weeks later, that it had no basis to say one way or the other whether Zicam caused anosmia.

II.A. This Court should reject Matrixx's proposed bright-line rule that would require a showing of statistical significance in all cases involving adverse drug events. Statistical significance is not the same as practical importance, and practical importance is what matters for materiality.

B. *Basic* forecloses a rule that would make any fact, including statistical significance, a categorical prerequisite for materiality in securities-fraud cases. Such a rule would exclude information that a reasonable investor would consider important, and the filtering function of materiality does not permit such a result. Matrixx's argument that disclosure of statistically insignificant information will mislead investors is paternalistic and inconsistent with *Basic*'s core reasoning. The nationwide securities market is

served by many sophisticated analysts and advisors who are fully capable of understanding statistical nuance.

The cases on which Matrixx relies do not help it. The Second and Third Circuit cases did not address the materiality of non-statistical information, such as the expert physicians' opinions present here. Matrixx's other cases all involve the use of statistical significance at the *evidentiary* stages of a case, rather than at the pleading stage. Cases involving use of statistical significance in *proving* causation are inapposite when the question is whether a company has concealed information showing a material increase in the *risk* that causation at some future time would be proved.

C. Depending on the particular facts, a reasonable investor would pay attention to non-statistical evidence of risks to a company's drug products and to statistical evidence that provides useful information even without achieving a standard of "statistical significance." Both types of information have been accepted by courts in appropriate cases.

The argument that statistical evidence is meaningless unless found to be "significant" is based on an incorrect view of statistics. Courts and respected scholars have criticized the overuse of statistical significance: the better approach takes into account the estimated size and practical importance of a possible statistical relationship, rather than focusing solely on the precision of the estimate.

Matrixx's proposed rule has other defects. That rule would not lead to the certainty and determinacy that Matrixx promises because Matrixx shies back from selecting a particular critical value for testing significance, and because Matrixx and its *amici*

suggest leaving open significant exceptions to their proposed standard. Matrixx's rule also would impose unworkable burdens preventing investors from recovering on meritorious claims.

D. Finally, Matrixx mischaracterizes this case by suggesting that it concerns regulatory adverse event reports. The information at issue here was not the product of the FDA's Adverse Event Reporting System ("AERS"), which did not apply to Zicam at the time. Accordingly, Matrixx's arguments that regulatory adverse event reports are unreliable as a class are irrelevant. Also, because regulatory adverse event reports already are made public by the FDA, Matrixx's claim that releasing them will overwhelm the market with information has no weight.

The correct approach under *Basic* looks to whether the particular facts surrounding an adverse event report or group of such reports are material. When properly applied, that test presents no greater difficulty than any other totality-of-the-circumstances inquiry. The Ninth Circuit correctly applied that test, and this Court should affirm its judgment.

ARGUMENT

I. THE COMPLAINT ADEQUATELY PLEADS MATERIALITY AND SCIENTER

A. Materiality Is A Fact-Intensive Determination Based On The Totality Of The Circumstances

1. The long-settled standard for materiality in securities-fraud cases asks whether the misstated or omitted fact "would have been viewed by the reasonable investor as having significantly altered the 'total mix' of information made available." *TSC*, 426 U.S. at 449; *see also Basic*, 485 U.S. at 232 (adopting *TSC*'s standard for Rule 10b-5 cases). That standard requires consideration of all other information that would have been available to the investor. Its purpose is "to filter out essentially useless information that a reasonable investor would not consider significant, even as part of a larger 'mix' of factors to consider in making his investment decision." *Basic*, 485 U.S. at 234.[22]

The materiality standard thus requires "delicate assessments of the inferences a 'reasonable shareholder' would draw from a given set of facts and the significance of those inferences to him." *TSC*, 426 U.S. at 450; *see also Basic*, 485 U.S. at 236 (quoting *TSC*). "[T]hese assessments are peculiarly ones for the trier of fact." *TSC*, 426 U.S. at 450. Both *TSC* and *Basic* were unanimously decided and have been the law for decades. Matrixx does not argue that

---

[22] The standard is the same for common-law misrepresentation, where the test for materiality "cannot be stated in the form of any definite rule, but must depend upon the circumstances of the transaction itself." W. Page Keeton et al., *Prosser and Keeton on the Law of Torts* § 108, at 753 (5th ed. 1984).

either opinion is unworkable or should be revisited now.

2. Precedent dating back centuries confirms that the materiality of an allegedly fraudulent misstatement or omission is to be decided "in the particular case . . . upon its own circumstances." *McLanahan*, 26 U.S. (1 Pet.) at 189. In *McLanahan,* Justice Story discussed in detail the "inquisition into facts" needed to determine whether an omission concerning the time at which a ship sailed was material to an insurance contract. *Id.*[23] The Court held that the facts bearing on this inquiry should be found by the jury after hearing witness testimony. *See id.* at 191 (citing *Maryland Ins. Co. v. Ruden's Administrator*, 10 U.S. (6 Cranch) 338, 339-40 (1810); *New-York Firemen Ins. Co. v. Walden*, 12 Johns. 513 (N.Y. Sup. Ct. 1815) (Kent, Ch.)).

This Court has applied the venerable principle that materiality is fact-specific to more modern cases in a variety of subject areas. In *United States v. Gaudin*, 515 U.S. 506 (1995), for example, this Court applied *TSC*'s and *McLanahan*'s discussion of the factfinder's role to the materiality standard in a criminal prosecution for making false statements to the government: "[O]ur cases have recognized . . . that the materiality inquiry, involving as it does 'delicate assessments of the inferences a "reasonable [decision-

---

[23] Relevant circumstances included "the nature and length of the voyage, the season of the year, the prevalence of the winds, the conformation of the coasts, the usages of trade as to navigation, and touching and staying at port, the objects of the enterprise and other circumstances, political and otherwise, which may retard or advance the general progress of the voyage," all considered in light of "nautical skill, information, and experience." *McLanahan*, 26 U.S. (1 Pet.) at 188.

maker]" would draw from a given set of facts and the significance of those inferences to him . . . [is] peculiarly on[e] for the trier of fact.'" *Id.* at 512 (quoting *TSC*, 426 U.S. at 450) (third through sixth alterations in original).

Similarly, in *Burlington Northern & Santa Fe Railway Co. v. White*, 548 U.S. 53 (2006), this Court described the highly contextual nature of the materiality inquiry for employment discrimination retaliation, noting that "the significance of any given act of retaliation will often depend upon the particular circumstances" and "an act that would be immaterial in some situations is material in others." *Id.* at 69 (internal quotations omitted).

3. To survive a motion to dismiss on materiality grounds under the standards announced by this Court in *Twombly* and *Iqbal*, respondents must satisfy the ordinary requirements of Federal Rule of Civil Procedure 8 by showing that their claims are plausible. *See Iqbal*, 129 S. Ct. at 1949 ("To survive a motion to dismiss, a complaint must contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'") (quoting *Twombly*, 550 U.S. at 570).

In 1995, when Congress imposed higher pleading standards for allegations of falsity and scienter, *see* 15 U.S.C. §§ 78u-4(b)(1) (falsity), 78u-4(b)(2) (scienter), it did not heighten the standard for allegations of materiality. Congress's decision not to heighten the pleading standard for materiality conveys its intent that existing law (under *Basic* and *TSC*) should continue undisturbed, so that materiality remains a fact-intensive question generally to be decided on the evidence, not on the pleadings. *Cf. Patterson v. McLean Credit Union*, 491 U.S. 164, 172-73 (1989)

(statutory *stare decisis* has "special force" because "Congress remains free to alter what we have done").

B. The Complaint Plausibly Alleges That Matrixx Misstated And Omitted Material Facts

1. The complaint's factual allegations meet the foregoing materiality standard. The complaint alleges that Matrixx had undisclosed information in its possession that sufficiently suggested an important risk to its vital Zicam product line. That information was sufficiently significant to be material from a reasonable investor's perspective. Yet Matrixx withheld that information from its investors and made affirmative false and misleading statements about it.

a. By October 2003, the information in Matrixx's possession more than plausibly suggested a link between intranasal Zicam use and persistent anosmia. Matrixx received specific information from multiple reliable medical sources in 1999, 2002, and 2003. JA67a-70a (¶¶ 25-28). Nasal specialists had identified a causal link between intranasal Zicam use and persistent anosmia in multiple patients. Those identifications were not based on a mere correlation of Zicam use with anosmia. Rather, each doctor had found clinical evidence supporting the link. In particular, the patients who had experienced anosmia also reported a specific burning sensation immediately following intranasal Zicam use. JA69a-70a (¶ 28), 70a-71a (¶ 30).

A reasonable investor would have been particularly concerned about the specific information received by Matrixx because background medical research indicated a biologically plausible causal mechanism for a link between intranasal Zicam use and persistent anosmia. Numerous studies from as far back as the

1930s established that intranasally applied zinc could cause anosmia. Matrixx received information about such studies as early as 1999. *See supra* pp. 9-12.[24] Knowledge of those studies would have made a reasonable investor alert to the likelihood that the specific information Matrixx had received reflected a real problem for the company.

Dr. Jafek and his colleagues considered the clinical evidence of a causal link sufficient to justify a presentation to the American Rhinologic Society, a leading medical association for nasal specialists. JA69a-70a (¶ 28). Their findings were later published in the Society's peer-reviewed *American Journal of Rhinology*. Matrixx knew of Dr. Jafek's research findings, but responded only by sending letters improperly demanding that the presentation reference neither the company nor its products. JA70a (¶ 29); *see infra* note 32 (explaining why Matrixx's demand was baseless). Matrixx also knew by October 2003 that it had been sued based on allegations that Zicam caused anosmia. JA87a (¶ 49).[25]

---

[24] Matrixx argues (at 6-7) that the relevant studies involved zinc sulfate, not the zinc gluconate used in Zicam. But scientists' "work with fish in the early [19]80s," JA69a (¶ 27), established that the harmful effects on sense of smell were caused by positive zinc ions. *See supra* p. 8. Reference 6 of the 2003 Presentation cited that research.

[25] Matrixx argues (at 48 n.25) that the product-liability suit already underway in October 2003 was irrelevant to materiality and that the Ninth Circuit did not rely on that suit in its materiality analysis. On the contrary, that court properly considered the undisclosed suit as one of many facts supporting respondents' plausible allegations of material omissions, as well as giving the nondisclosure considerable weight in its scienter analysis. *See* App. 25a-26a, 29a-30a. A reasonable investor would see a difference between Matrixx's generic disclosure that

b. Persistent anosmia is a very serious medical condition.[26] A link between anosmia and intranasal Zicam use would more than plausibly expose Matrixx and its investors to three risks: costly product-liability litigation against Matrixx, some of which was already underway (though undisclosed by Matrixx to investors); future FDA enforcement action; and drastically reduced sales of intranasal Zicam products, as well as reduced sales of other Zicam products through damage to the Zicam brand. The risk of reduced sales was especially acute because many consumers would not buy a cold remedy that could lead to a problem far more serious than the cold itself. The importance of those risks makes it more than plausible that information about a link between intranasal Zicam and anosmia would have been substantially likely to alter the total mix of information available to Matrixx's investors, particularly in light of Matrixx's reliance on its Zicam product line for the lion's share of its revenues.

c. The movements in Matrixx's share price after disclosure of the information linking Zicam to persistent anosmia further support the plausible materiality of Matrixx's misstatements and omissions. After *Good Morning America* reported on the connection between Zicam and persistent anosmia on February 6, 2004, the price of Matrixx's common stock dropped

---

product-liability suits *can* happen and the fact that one already was underway. Further, the materiality of the suit lay not in the effect it individually would have on Matrixx's finances, but in its early indication that Matrixx's flagship drug was now exposed to litigation.

[26] *See* Warning Letter at JA274a n.2 ("[L]oss of sense of smell can have serious consequences. For example, patients with anosmia may not be able to detect the smell of a gas leak, smoke, or spoiled food.").

23.8% on unusually heavy trading volume, from $13.05 per share to $9.94. JA81a (¶ 43). That drop was not a temporary reaction to bad publicity, but a considered market judgment. Not until November 2004 did Matrixx's share price return to $13.05 per share.[27]

d. The FDA's later decision to send Matrixx the Warning Letter, which led Matrixx to remove intranasal Zicam from the market, further supports the plausible materiality of Matrixx's misstatements and omissions. The Warning Letter found that intranasal Zicam was misbranded because its labeling still, in 2009, did not mention the risk that it might cause anosmia. The letter echoed points that Dr. Jafek and his colleagues had made in late 2003; it also relied on additional information to which Dr. Jafek did not have access. *See supra* pp. 17-18.

The FDA's action in 2009 – based on a theory very similar to that of Dr. Jafek and the other doctors that notified Matrixx of the link between Zicam and anosmia between 1999 and 2003 – tends to corroborate those doctors' analysis, as do the later peer-reviewed publications on the topic. Wholly apart from the admissibility of that information as *evidence* of materiality (which respondents need not yet produce), these are among the "facts . . . suggestive enough to render [it] plausible," *Twombly*, 550 U.S. at 556, that the doctors had identified a serious problem that would have influenced a reasonable investor at the time.

e. In addition to omissions of material information, Matrixx made affirmative claims that Zicam

---

[27] *See* Supplemental Request for Judicial Notice, Exh. A, No. 06-15677 (9th Cir. filed June 8, 2009).

had been proved safe. Those statements created a materially misleading impression because of the sparse and cursory nature of the testing that Matrixx had in fact conducted on Zicam. On February 2, 2004, after published reports of the Zicam-anosmia connection, Matrixx went so far as to say that the "safety" of Zicam had been "well established in two double-blind, placebo-controlled, randomized clinical trials." JA77a-78a (¶ 38). That press release purported to rebut "alleg[ations] that intranasal Zicam products cause anosmia" as "completely unfounded and misleading." *Id.* Matrixx's unmistakable intent in issuing its statement was to persuade investors that Matrixx had a reasonable scientific basis for saying that Zicam did not cause anosmia.

Less than a month later, however, Matrixx conceded that "insufficient scientific evidence [exists] at this time to determine if zinc gluconate, when used as recommended, affects a person's ability to smell." JA82a (¶ 46).[28] Indeed, when Matrixx made those statements, Zicam was being marketed "without FDA approval," JA269a, and had not been subject to the FDA's testing and reporting requirements to determine whether it was "safe and effective in its proposed use(s), and whether [its] benefits . . . outweigh [its] risks."[29]

---

[28] Matrixx argues (at 9 n.4) that this statement, in a February 27, 2004 8-K filing with the SEC, is irrelevant. On the contrary, the 8-K filing establishes that, as of February 19, 2004, Matrixx lacked any reasonable basis to say or imply that Zicam had been proved safe in the context of anosmia. Matrixx similarly lacked any such basis weeks earlier when it made its February 2 statements.

[29] FDA, *New Drug Application (NDA)*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDeveloped

2. Matrixx argues (*e.g.*, at 14, 46) that respondents were required to compare, in their complaint, the reports of anosmia known to Matrixx as of late 2003 with the total number of cases of anosmia in the relevant population.[30] No such requirement exists. Respondents were permitted to rely, especially for pleading purposes, on: the opinions of the doctors who reported the cases to Matrixx; the corroborating details in the reports (such as a burning sensation experienced in the nostrils); the background medical literature that strongly suggested zinc exposure could cause anosmia; and the comparative seriousness of the side effect – persistent lost sense of smell – with the affliction purportedly being mitigated, the common cold. Given those allegations, respondents' complaint satisfies the established totality-of-the-circumstances test for materiality.

Matrixx also argues (at, *e.g.*, 46-47) that respondents failed to exclude the possibility of a "co[n]-founding indicator," arguing that the complaint failed to "deny[] or contradict[]" the causal link between anosmia and infections caused by the common cold. But nothing in Rule 8, *Twombly*, or *Iqbal* suggests that a plaintiff bears the burden to anticipate and negate detailed factual counterarguments in a complaint. The issue of possible alternative causes for the reported incidences of Zicam-induced anosmia is

---

andApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm (last updated Aug. 20, 2010).

[30] Matrixx also argues (at 6 & n.1) that the number of reports was 12, rather than the 23 respondents stated in their opposition to certiorari, but states that "[t]he exact figure is irrelevant" for present purposes. Respondents agree with the latter point. The content and context of the information that Matrixx received are the key allegations here, not the precise number of individuals suffering from anosmia.

an evidentiary dispute that should be resolved on summary judgment or at trial, with the benefit of admissible expert opinion.

In any event, the doctors who linked Zicam to anosmia *had* considered, and rejected, the possibility that the subjects of their study were suffering from post-viral anosmia. *See supra* pp. 11-12. They did so because post-viral anosmia typically follows a severe cold, but study subjects typically had experienced mild colds. Further, subjects reported experiencing a burning pain in their nasal cavity followed immediately by persistent hyposmia or anosmia, which also is inconsistent with post-viral anosmia. *See id.*

C. The Complaint's Allegations Support A Strong Inference That Matrixx Acted With Scienter

1. "To establish liability under § 10(b) and Rule 10b-5, a private plaintiff must prove that the defendant acted with scienter, a mental state embracing intent to deceive, manipulate, or defraud." *Tellabs*, 551 U.S. at 319 (internal quotations omitted). Under the PSLRA, respondents must allege sufficient facts to establish "a strong inference that the defendant acted with the required state of mind." 15 U.S.C. § 78u-4(b)(2). Sufficient facts are alleged where "a reasonable person would deem the inference of scienter cogent and at least as compelling as any opposing inference one could draw from the facts alleged." *Tellabs*, 551 U.S. at 324.[31] "[T]he court's job is not to

---

[31] All circuits to consider the issue have held that "a plaintiff may meet the scienter requirement by showing that the defendant acted intentionally or recklessly, though the Circuits differ on the degree of recklessness required." *Tellabs*, 551 U.S. at 319 n.3. Matrixx has not questioned that rule. The Court therefore should assume that respondents may prevail by show-

scrutinize each allegation in isolation but to assess all the allegations holistically." *Id.* at 326. Such scrutiny can reveal a strong inference of scienter despite the "absence of a motive allegation." *Id.* at 325.

2.a. The complaint alleges that, in September 2003, Matrixx attempted to stop Dr. Jafek from publishing his findings – or at least from using either "Matrixx" or "Zicam" in his presentation – through a baseless threat to sue him. JA61a (¶ 4) (asserting that "as a legal matter" Jafek did "not have [Matrixx's] permission to use their company name or product trademarks"); *see also* JA101a (¶ 64) (Dr. Jafek deleted references to Zicam or Matrixx from his poster presentation to avoid "threatened legal action from [Matrixx]").[32] When Dr. Jafek replied to Matrixx's initial letter seeking permission to use the names, Matrixx

---

ing recklessness. In any event, respondents' allegations establish a strong inference even of purposeful deception.

[32] Matrixx lacked any reasonable basis for its claim that, "as a legal matter," Dr. Jafek needed permission to use "the company name or product trademarks," JA118a, in a presentation at a medical conference. A trademark owner has no right to silence criticism of its products that has no conceivable likelihood of "caus[ing] confusion" about the maker of any goods or services. 15 U.S.C. §§ 1114(1)(a), 1125(a)(1)(A); *see also*, *e.g.*, *Utah Lighthouse Ministry v. Foundation for Apologetic Info. & Research*, 527 F.3d 1045, 1052 (10th Cir. 2008) ("The Lanham Act is intended 'to protect the ability of consumers to distinguish among competing producers,' not to prevent all unauthorized uses.") (citation omitted). Matrixx also could not legitimately threaten Dr. Jafek with an action for disparagement or dilution of its trademarks because his speech was plainly noncommercial. *See* 15 U.S.C. § 1125(a)(1)(B) (disparagement action requires use of mark in "commercial advertising or promotion"); *see id.* § 1125(c)(3)(C) (dilution action unavailable for "[a]ny noncommercial use of a mark").

sent another letter refusing to grant permission. JA70a (¶ 29).

Matrixx's actions support a strong inference that its senior officers were well aware of the potential risk that the doctors' findings posed to its products, but intended to respond to that risk not through inquiry and disclosure but instead through concealing information from the public (including Matrixx's investors) for as long as possible. By September 2003, Matrix not only knew of Dr. Jafek's own research and presentation, but also had received two earlier similar reports and had been informed of studies showing the harmful effects of zinc on the sense of smell. *See supra* pp. 9-10.

Matrixx says (at 6-7) that it "attempted to obtain more information about the user complaints reported by Linschoten and Jafek," implying that it responded to those complaints in good faith. The record will not bear that interpretation. Matrixx cites nothing that it did to obtain more information about Dr. Linschoten's patients in 2002 – it merely told her that it had retained a consultant and invited her to participate in animal studies it claimed an intent to conduct. The record does not show, and Matrixx does not say, at what point it *actually* conducted any animal studies. Indeed, Matrixx's statement to Dr. Linschoten about planned animal studies, coupled with a complete absence of any reference to those studies in its 2003 or 2004 public statements, strengthens the inference of scienter by showing that Matrixx knew it needed to do more to have a reasonable basis to make pronouncements about the safety of intranasal Zicam.

As for the "requests" that Matrixx describes in its letter to Dr. Jafek, the doctor rightly perceived

them as threatening legal action rather than seeking information in good faith.[33] In any event, the fact that Matrixx's Vice President and Director of Research and Development personally followed up on communications with Drs. Linschoten and Jafek merely underscores that Matrixx *did* consider their findings a real concern for its business, but nevertheless attempted to conceal those findings until public disclosures forced its hand.

b. Matrixx's February 2004 statements that the "safety" of intranasal Zicam had been "well established" by clinical trials and that contrary allegations were "completely unfounded and misleading" also support a strong inference of scienter. JA77a-78a (¶ 38), 81a-82a (¶ 44). Those statements on their face conveyed the false impression that intranasal Zicam had been tested in clinical trials to determine whether it caused anosmia, when – as Matrixx admitted only a few weeks later – it had no evidence to support those statements. *See supra* pp. 15-16.

The timing of Matrixx's vigorous denials, followed by its reluctant admissions, supports a strong inference that Matrixx knew it lacked a reasonable basis for statements it made during the October 2003-February 2004 period. Did Matrixx have evidence of Zicam's safety in early February 2004 that somehow vanished in the following two weeks? Did the results

---

[33] The letter asked Dr. Jafek to explain his "basis for linking [reports of anosmia] with the use of zinc nasal products" and specified that he should do so "*[p]rior* to [his] presentation next week." JA118a (emphasis added). It cautioned him "not to proceed with a program that does not accurately and fairly portray our company or our products." *Id.* Matrixx thus threatened a defamation suit without expressing genuine interest in learning more from Dr. Jafek.

of the earlier trials it had claimed "established" Zicam's safety change during that time? The inference that Matrixx intended to deceive (or at least spoke recklessly) is more "cogent," *Tellabs*, 551 U.S. at 314, than either of those unlikely scenarios.

3. Matrixx's only argument with respect to scienter is that the "most obvious inference" from the complaint is that "petitioners believed [the reports of Zicam-induced anosmia] were far too few, and too caught up with the confounding cold indicator, to indicate anything meaningful about adverse reactions to use of Zicam." Br. 49. Matrixx makes no attempt to address the information it actually possessed, the timing of its statement, or other facts that support a strong inference of scienter here. As with its materiality argument, Matrixx's argument on scienter thus rises or falls with its request for a bright-line rule requiring allegations of statistical significance before any statement about adverse drug effects can violate Rule 10b-5.

II. THIS COURT SHOULD REJECT MATRIXX'S PROPOSED BRIGHT-LINE RULE

Matrixx seeks a rule that a drug manufacturer has no duty to disclose to its investors information tending to show that its products cause adverse effects unless that information rises to the level of statistical significance. Such a rule would be unprecedented and unwise, and would rest on fundamental misunderstandings about the nature and meaning of the concept of statistical significance.

A. Statistical Significance Is Not The Same As Practical Importance

Researchers use the term "statistical significance" to characterize a result from a test that satisfies a particular kind of test designed to show that the

result is unlikely to have occurred by random chance. *See* David H. Kaye & David A. Freedman, *Reference Guide on Statistics*, *in Reference Manual on Scientific Evidence* 83, 122 (Fed. Judicial Ctr., 2d ed. 2000) ("*Reference Manual*"). The purpose of significance testing in this context is to assess whether two events (here, taking Zicam and developing anosmia) occur together often enough to make it sufficiently implausible that no actual underlying relationship exists between them.

To test for significance, the researcher typically develops a "null hypothesis" – *e.g.*, that there is *no* relationship between using intranasal Zicam and the onset of burning pain and subsequent anosmia. The researcher then selects a threshold (the "significance level") that reflects an acceptably low probability of rejecting a true null hypothesis – *e.g.*, of concluding that a relationship between Zicam and anosmia exists based on observations that in fact reflect random chance. In theory, the significance level the researcher chooses should reflect "contextual considerations" about the particular purpose of the experiment and requires a balancing of the costs of different possible errors: the error of finding a relationship where there is none (a "Type I" error) as opposed to the error of overlooking a relationship where one exists (a "Type II" error). *See* Kenneth J. Rothman et al., *Modern Epidemiology* 153, 155 (3d ed. 2008). In practice, however, significance levels of 0.1 (10%), 0.05 (5%), and 0.01 (1%) often are used in academic and industry research as rules of thumb without any explicit consideration of error costs.

The researcher then calculates a value (referred to as *p*) that reflects the probability that the observed data could have occurred *even if* the null hypothesis

were in fact true. If the *p*-value falls below the pre-selected significance level, the researcher finds a statistically significant result and rejects the null hypothesis. *See id.* at 153. A *p*-value that *exceeds* the significance level, however, does not necessarily lead the researcher to *accept* the null hypothesis; rather, the researcher concludes only that the null hypothesis "cannot [be] reject[ed]." *Id.* at 151-52.

Moreover, as Matrixx concedes (at 35 n.16), neither the *p*-value itself nor a finding of statistical significance at any particular level determines whether a result is practically important. Significance levels and *p*-values do not incorporate either the *magnitude* or the *implications* of a study's result. For example, researchers studying a drug that cures cancer might estimate that 5% of those taking the drug will experience temporary nausea and might find that result statistically significant at the 0.01 level. But regulators, doctors, and patients would view such a finding as a minimal consideration given the drug's great benefits.

By the same token, a causal relationship of potentially great practical importance may not necessarily produce findings that reach the level of statistical significance. For example, researchers studying an anti-nausea drug might estimate that those taking the drug would have a one-third increase in their risk of developing cancer as a result, but might calculate a *p*-value of 0.07 or 0.12 and so not find that result significant at the 0.05 level. Based on such results, researchers would not formally reject a null hypothesis that taking the drug was unrelated to cancer. But doctors likely would not prescribe the drug and patients likely would refuse to take it. The

estimated risk, although uncertain, would be too great relative to the drug's benefits.

B. Adopting Statistical Significance As A Bright-Line Rule For Materiality Would Depart From Well-Settled Precedent

1. In *Basic*, this Court declined to adopt a "usable, bright-line rule" defining information about preliminary merger discussions as immaterial "until 'agreement-in-principle' as to the price and structure of the transaction ha[d] been reached between the would-be merger partners." 485 U.S. at 232-33. The Court's reasons apply here with equal force.

a. *Basic* explained that "[a]ny approach that designates a single fact or occurrence as always determinative of an inherently fact-specific finding such as materiality, must necessarily be overinclusive or underinclusive." *Id.* at 236.[34] That general observation holds true here: requiring a statistical-significance finding as categorically necessary before information about adverse drug effects is deemed material would be underinclusive, authorizing drug companies to conceal information that reasonable investors would consider important.

Matrixx's attempt to reconcile its rule with *Basic* rests on its erroneous assertion that "the statistical significance standard *defines* the information a reasonable investor would consider relevant." Br. 43. In appropriate cases, a reasonable investor would

---

[34] The SEC has followed the same approach in administrative guidance. *See* SEC, Staff Accounting Bulletin No. 99, at 3 (1999) (quoting with approval the position of the Financial Accounting Standards Board that "no general standards of materiality could be formulated to take into account all the considerations that enter into an experienced human judgment"), *available at* http://www.sec.gov/interps/account/sab99.htm.

consider relevant both non-statistical information, such as diagnoses by treating physicians, without the need for statistical support; and statistical information suggesting a causal link without finding statistical significance. *See infra* pp. 47-53.

b. *Basic* also explained that the materiality requirement "filter[s] out essentially useless information that a reasonable investor would not consider significant, even as part of a larger 'mix' of factors to consider." 485 U.S. at 234. That standard has no room for "paternalistic withholding of accurate information" on the ground that investors will act imprudently if they receive it. *Id.*

Matrixx relies upon the types of arguments this Court rejected in *Basic*. For example, Matrixx contends (at 30) that "[i]nvestors generally are not scientists or epidemiologists and cannot be expected to sift significant from insignificant scientific data with ease" and that "disclosure of [adverse event reports about drugs] can mislead investors into undervaluing or prematurely selling a security." Matrixx's paternalistic position is that information should be deemed immaterial not because investors will ignore it, but because investors will *use* it incorrectly and make decisions against their own best interests.

Matrixx also relies heavily (at 3, 30, and 44) on this Court's statement in *TSC* that the materiality standard should not be set so low as to "bury the shareholders in an avalanche of trivial information." 426 U.S. at 448. The *TSC* Court expressed that concern as a reason supporting its "total mix" standard for materiality. When a substantial likelihood exists that a reasonable investor would view information as reasonably altering the total mix of available information, the information is not "trivial" under *TSC*.

No purported concern for overburdening investors justifies withholding it.

Matrixx also inaccurately portrays how the nationwide securities markets assimilate information about public companies. The market's capacity to use information is not limited to an individual lay investor's abilities. *Cf. Flamm v. Eberstadt*, 814 F.2d 1169, 1175 (7th Cir. 1987) ("Disclosures to the market as a whole cannot be limited to what is fit for rubes."). Legions of professional securities analysts and investment advisors make their livelihoods by analyzing massive volumes of information about public companies.

Those professionals can understand nuanced statistical information or obtain expert assistance to assess it. Their analyses affect decisions by their customers and clients, and ultimately affect stock prices. *See Dirks v. SEC*, 463 U.S. 646, 658-59 (1983) (observing that, in a "healthy market," securities analysts "ferret out and analyze information" to obtain a "basis for judgments as to the market worth of a corporation's securities") (internal quotations omitted). That process will not function properly if issuers withhold useful information because lay investors might misinterpret it.

c. *Basic* also admonished that administrative convenience and the "comfort of corporate managers" do not justify depriving investors, analysts, and advisors of material information. 485 U.S. at 236. That part of *Basic*'s holding forecloses Matrixx's argument (at 28) that its bright-line rule is necessary to ensure that corporate managers do not "inoculate themselves against . . . securities-fraud suits" through excessive disclosures. "[T]he Securities Acts and Congress' policy decisions" place on every issuer of

securities a duty to "exercise [its] judgment in the light of all the circumstances" when determining whether to disclose information. *Basic*, 485 U.S. at 236. An issuer genuinely attempting to comply with that duty can rely on the PSLRA (which does not include any heightened materiality standard) to protect it from "frivolous, lawyer-driven litigation." *Tellabs*, 551 U.S. at 322.

2. Matrixx asserts that court of appeals decisions hold 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." Br. 33 (citing *In re Carter-Wallace, Inc. Sec. Litig.*, 150 F.3d 153, 157 (2d Cir. 1998) ("*Carter-Wallace I*"), and *Oran v. Stafford*, 226 F.3d 275, 284 (3d Cir. 2000) (Alito, J.)). Matrixx overstates the holdings of those cases.

Both *Carter-Wallace I* and *Oran* state generally that drug companies "need not disclose isolated reports of illnesses suffered by users of their drugs until those reports provide statistically significant evidence that the ill effects may be caused by . . . use of the drugs." *Carter-Wallace I*, 150 F.3d at 157; *accord Oran*, 226 F.3d at 284. Neither court considered the potential importance of non-statistical information about a drug's effects, such as case studies or clinical opinions formed by physicians, or even mentioned the possibility that such evidence might exist. Matrixx overreads those cases as rejecting the materiality of such evidence.

3.a. Matrixx also relies upon a string of cases (at 35-42) giving weight to statistical significance in products liability, employment discrimination, and other contexts. Those decisions do not help Matrixx,

because every one was rendered at the evidentiary stages of a case, not on the pleadings.

That difference in posture matters. A court weighing evidence (or ruling on its sufficiency or admissibility) may well consider the presence or absence of a finding of statistical significance. What Matrixx seeks is a rule prohibiting a court from permitting the gathering and presentation of evidence unless a finding of statistical significance is first alleged. The Federal Rules "do[] not impose a probability requirement at the pleading stage." *Twombly*, 550 U.S. at 556; *accord Iqbal*, 129 S. Ct. at 1949. Statistical significance is not just a probability requirement, but a very demanding one designed for "scientists search[ing] for certainty," rather than a "trier of fact" determining what is "more likely than not." *Pitre v. Western Elec. Co.*, 843 F.2d 1262, 1269 (10th Cir. 1988).

Castaneda v. Partida, 430 U.S. 482 (1977), and *Hazelwood School District v. United States*, 433 U.S. 299 (1977), on which Matrixx relies (at 35, 39, 41), illustrate *evidentiary* uses of statistical calculations. In *Castaneda*, the Court held that an underrepresentation of a protected class on Texas grand juries that would occur by chance less than 1 time in 10^{140} could establish a *prima facie* case of discrimination. *See* 430 U.S. at 496 n.17. In *Hazelwood*, the Court stated that, depending on its size, a much smaller discrepancy in school-teacher hiring might either support or undermine a case of discrimination. *See* 433 U.S. at 311-12. Neither case held or implied that the absence of a statistically significant underrepresentation would "necessarily exclude discriminatory design as the cause." *Craik v. Minnesota State Univ.*

Bd., 731 F.2d 465, 476 n.13 (8th Cir. 1984) (internal quotations omitted).

b. Further, Matrixx's cases are inapposite because they deal with the role of statistical significance in proving an actual casual link – for example, between a product and an injury, or a plaintiff's race and an adverse employment action. An investor alleging fraudulent misrepresentations or omissions does not need to show that a pharmaceutical manufacturer withheld information that would demonstrate by preponderant evidence that a drug actually had the harmful effects in question. Rather, "[p]robabilities determine the value of stock." *Pommer v. Medtest Corp.*, 961 F.2d 620, 623 (7th Cir. 1992) (Easterbrook, J.). A company's deliberate concealment of information about the probability that a drug will be found to cause harmful effects can be securities fraud if a reasonable investor would regard the probability itself as important, even if the drug remains more likely safe than not.

In this case, Matrixx concealed information showing a heightened risk that the public, the FDA, or the courts ultimately would conclude that intranasal Zicam products caused anosmia. Later, the risk was disclosed to the public and Matrixx's share value dropped. Still later, the risk came to fruition when the FDA concluded that Zicam was misbranded, and Matrixx removed the intranasal Zicam products from the market. A reasonable investor would have been concerned about the risk when Matrixx concealed it – just as Matrixx's actual investors were.

C. A Reasonable Investor Would Not Consider A Finding Of Statistical Significance A Prerequisite To Evaluating Otherwise Useful Information

This case turns on whether (as Matrixx and its *amici* contend) a reasonable investor would disregard any information about a potential problem with a drug except for a statistically significant result. A reasonable investor would not act that way.

1. Information suggesting that a drug might have a yet-unproven adverse effect is information about a "contingent or speculative" future event, *Basic*, 485 U.S. at 238, such as whether the drug subsequently may be the subject of litigation, regulatory action, or consumer disfavor. Assessing the materiality of contingent events requires "'balancing of both the indicated probability that the event will occur and the anticipated magnitude of the event in light of the totality of the company activity.'" *Id.* (quoting *SEC v. Texas Gulf Sulphur Co.*, 401 F.2d 833, 849 (2d Cir. 1968)).

In assessing the risk of a particular drug causing an important adverse effect, a reasonable investor would consider a broad range of different kinds of information. That range would include not only quantitative information about the number of adverse effects reported, but also, among other things, available background scientific and clinical information indicating that a potential problem was biologically plausible or implausible; case reports suggesting the existence of a problem with sufficient detail to be informative; and the opinions of researchers and treating physicians who have studied the drug's effects.

Even with regard to quantitative information, a reasonable investor would not wholly disregard information about the incidence of an adverse effect solely because the information did not incorporate a finding of statistical significance. If information is uncertain but potentially important, investors taking "calculated risks," *Texas Gulf Sulphur*, 401 F.2d at 849 n.10 (internal quotations omitted), will discount it, not discard it. Small changes to the estimated probability that a drug has a serious adverse effect can be important to investors if that drug (as here) provides a significant portion of the company's revenues and if that adverse effect would drastically undermine the drug's value.

2. Matrixx's arguments rest ultimately on a premise that only statistical significance should ever count as evidence of causation in the drug context. Matrixx argues that a complaint failing to "plead facts establishing that [adverse event reports] reflect a statistically significant correlation between use of [a] product and [a] reported adverse event" has "do[ne] *nothing* to show that the [reports] reflect a potentially causal relationship." Br. 42-43 (emphasis added). *Amicus* BayBio makes the same claim: that "[o]nly if a statistically significant connection between use of [a] drug and [an] adverse event is established is there *any meaning* from the incidence of the adverse event." Br. 5 (emphasis added). These claims are incorrect: many types of information other than statistical significance can alert a reasonable investor to a risk that more than "a chance sequence of events," Pet. Br. 25, has led to a cluster of reported problems with a drug.

a. Matrixx essentially ignores the relevance of *non-statistical* information, including clinical reason-

ing.[35] "For the treating physician, '[c]linical reasoning is the essential function of the physician.'" Mary Sue Henifin et al., *Reference Guide on Medical Testimony*, *in Reference Manual* 439, 461 (quoting Jerome P. Kassirer & Richard I. Kopelman, *Learning Clinical Reasoning* 2 (1991)) (alteration in original); *see also* Fed. R. Evid. 703 note (giving the "diagnosis" of a "treating physician" as a paradigmatic combination of expert opinion and first-hand observation). Where specialist researchers conclude that a drug causes serious adverse effects, their views are important information likely to affect decisions made by courts, regulators, and consumers – and, therefore, investors.

Courts have recognized that a physician's differential diagnosis (which identifies a likely cause of certain symptoms after ruling out other possibilities) can be reliable evidence of causation. *See*, *e.g.*, *Turner v. Iowa Fire Equip. Co.*, 229 F.3d 1202, 1208

---

[35] Matrixx concedes (at 44-45 n.22) that courts in numerous cases have "permit[ted] an inference of causation on the basis of scientifically reliable evidence other than statistically significant epidemiological data," but claims that "[t]his case does not present th[at] question" because respondents did not argue it in their brief in opposition. On the contrary, respondents argued that "[p]etitioners mischaracterize th[is] lawsuit as one primarily involving so-called 'adverse event reports'" when, in fact, it involved much more detailed and corroborated information, including "complaints . . . concern[ing] a singular, dramatic reaction – the user's loss of sense of smell following Zicam's application into the nose – that complainants and medical researchers each attributed specifically to Zicam." Br. in Opp. 17-18; *see also id.* at 16 (arguing that petitioners withheld from investors "specific information" that they received through "a variety of channels: otolaryngology researchers, consumer complaints, and personal-injury lawsuits"); *id.* at 2-5 (setting forth the relevant medical evidence in detail).

(8th Cir. 2000) ("[D]ifferential diagnosis is a tested methodology, has been subjected to peer review/ publication, does not frequently lead to incorrect results, and is generally accepted in the medical community."); *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 263 (4th Cir. 1999) ("[A] reliable differential diagnosis provides a valid foundation for an expert opinion."); *Baker v. Dalkon Shield Claimants Trust*, 156 F.3d 248, 252-53 (1st Cir. 1998) (describing differential diagnosis as a "standard scientific technique, widely used in medicine").[36]

Even at the evidentiary phase, courts also have rejected the argument that only statistical significance can be reliable evidence of causation. *See*, *e.g.*, *Westberry*, 178 F.3d at 262 (refusing to require "epidemiological studies" before admitting a doctor's causation opinion); *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 158 (3d Cir. 1999) ("[A] physician's diagnosis, based in part on a strong temporal relationship between symptoms and exposure, need not necessarily be supported by 'a statistically significant correlation.'"); *Ferebee v. Chevron Chem. Co.*, 736 F.2d 1529, 1536 (D.C. Cir. 1984) ("products liability law does not preclude recovery until a 'statistically significant' number of people have been injured").

b. Matrixx and BayBio also advance an erroneous view of statistical information. There is no difference in the *kind* of information conveyed by results of $p = 0.33$, $p = 0.1$, or $p = 0.05$, merely a difference in the degree of certainty. "[T]here is no sharp line between a 'significant' and a 'nonsignificant' difference; significance in statistics . . . varies continuously between extremes." Ralph L. Rosnow & Robert Rosenthal,

---

[36] *See also* 4 *Weinstein's Federal Evidence* § 702.06[2][c][iii], at 702-131 & n.46 (2009 update) (collecting cases).

Statistical Procedures and the Justification of Knowledge in Psychological Science, 44 Am. Psychol. 1276, 1277 (1989). When human lives, or billions of dollars, turn on an uncertain question, a reasonable decision-maker would not stop considering information at the 0.05 level. As Judge Posner wrote in *Kadas v. MCI Systemhouse Corp.*, 255 F.3d 359 (7th Cir. 2001):

> The 5 percent test is arbitrary; it is influenced by the fact that scholarly publishers have limited space and don't want to clog up their journals and books with statistical findings that have a substantial probability of being a product of chance rather than of some interesting underlying relation between the variables of concern. Litigation generally is not fussy about evidence; much eyewitness and other nonquantitative evidence is subject to significant possibility of error, yet no effort is made to exclude it if it doesn't satisfy some counterpart to the 5 percent significance test.

Id. at 362-63.[37]

3. Scholars likewise recognize the overuse of statistical significance as an error:

> Statistical significance is . . . a diversion from the proper objects of scientific study. Significance, reduced to its narrow statistical meaning only, has little to do with a defensible notion of scientific inference, error analysis, or rational decision making. . . . Statistical significance should

---

[37] *See also*, *e.g.*, *MacDissi v. Valmont Indus., Inc.*, 856 F.2d 1054, 1058 n.3 (8th Cir. 1988) ("Even where quantitative evidence does not alone demonstrate discrimination to some judicially created standard of statistical conclusiveness, it is still relevant in conjunction with all other evidence in determining intentional discrimination.").

> be a tiny part of an inquiry concerned with the *size* and *importance* of relationships.

Stephen T. Ziliak & Deirdre N. McCloskey, *The Cult of Statistical Significance: How the Standard Error Costs Us Jobs, Justice, and Lives* 2 (2009) (emphasis added).

A long line of scholarly works agrees. The point has been made by statisticians,[38] epidemiologists,[39] medical researchers,[40] and researchers in other fields.[41] Indeed, in the seminal *Daubert* case, a group

---

[38] *See*, *e.g.*, David A. Freedman, *Statistical Models: Theory and Practice* 70 (rev. ed. 2009) (describing "[s]tatistical significance" as "technical jargon" that has "acquired enormous – and richly undeserved – emotional power"); Frank Yates, *The Influence of* Statistical Methods for Research Workers *on the Development of the Science of Statistics*, 46 J. Am. Stat. Ass'n 19, 32 (1951) (criticizing researchers who give "undue attention to the results of . . . tests of significance . . . and too little to the estimates of . . . magnitude").

[39] *See*, *e.g.*, Rothman, *Modern Epidemiology* at 163 ("[B]ecause statistical hypothesis testing promotes so much misinterpretation, we recommend avoiding its use in epidemiologic presentations and research reports.").

[40] *See*, *e.g.*, Jonathan A C Sterne & George Davey Smith, *Sifting the Evidence – What's Wrong with Significance Tests?*, 322 British Med. J. 226, 226 (2001) (recommending that the "[r]esults of medical research should not be reported as 'significant' or 'non-significant'"); David A. Savitz, *Is Statistical Significance Testing Useful in Interpreting Data?* 7 Reproductive Toxicology 95, 96 (1993) ("[S]tatistical significance testing is not useful in the analysis or interpretation of scientific research.").

[41] *See*, *e.g.*, Larry G. Daniel, *Statistical Significance Testing: A Historical Overview of Misuse and Misinterpretation with Implications for the Editorial Policies of Educational Journals*, 5 Research in the Schools 23, 23-24 (1998) (collecting criticisms of the misuse of statistical significance tests in the field of education research); William W. Rozeboom, *The Fallacy of the Null-Hypothesis Significance Test*, 57 Psychol. Bull. 416, 416-17

of respected epidemiologists warned this Court that, "[w]hen used to evaluate the association between exposure and disease, the concept of statistical significance is often misleading and never descriptive of the magnitude of effect or the precision of measurement" and that a factfinder is misled when "told that a body of data is not 'statistically significant' [and so] made to believe that the data has no value."[42]

4.a. Matrixx's proposed rule has other defects as well. As proposed, the rule would not even draw a bright line. It is impossible to say whether information is statistically significant without pre-selecting a particular critical value for significance. *See supra* pp. 39-40. Matrixx hints (at 35-36) that the Court might adopt a threshold of $p < 0.05$, but ultimately argues only that the level must be "meaningful." With no pre-selected threshold, a statistical significance requirement would not allow companies to determine whether information was material. And to the extent this Court were to accept Matrixx's suggestion and impose a specific threshold, it would be adopting on purely policy grounds an arbitrary statistical threshold far outside its expertise.

Matrixx even suggests in a footnote that statistical significance may not always be required, correctly recognizing that courts have held other forms of evidence to be "scientifically reliable." Br. 44-45 n.22 (citing cases relying on non-statistical evidence, but claiming the argument was waived here); *but see supra* note 35 (rebutting Matrixx's waiver argument).

(1960) (describing the "'null-hypothesis significance test'" as "seldom if ever appropriate to the aims of scientific research").

[42] Brief *Amici Curiae* of Professors Kenneth Rothman et al. at 4, *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993) (No. 92-102), 1992 WL 12006438.

So do several of its *amici*.[43] That suggestion further undermines not only the alleged certainty Matrixx seeks, but also (by turning this case into fact-specific error correction) the basis on which this Court granted review.

b. Matrixx's proposed rule also would decrease "investors' ability to recover on meritorious claims." *Tellabs*, 551 U.S. at 322. Establishing a statistically significant result usually requires expert testimony from an epidemiologist, econometrician, or statistician, based on a developed factual record. Even if investors retained experts for pre-filing investigation (itself a significant and unjustified burden), any pre-filing analysis could well be inconclusive for lack of access to information controlled by defendants. Here, for example, the Warning Letter states that "Matrixx appears to have more than 800 reports related to loss of sense of smell associated with Zicam Cold Remedy intranasal products" that it never sent to the FDA. JA272a. Respondents have no access to those reports and do not know how many describe incidents before February 2004.

---

[43] *See* Consumer Healthcare Products Ass'n et al. *Amicus* Br. 21 (equating "statistical significance" with "sufficient evidence, based on appropriate analysis and other pertinent information, of a causal association"); DRI *Amicus* Br. 33 n.8 (suggesting that the standard include whether reports have been "medically or scientifically substantiated" and whether a company's management has "reached an internal consensus"); PhRMA/BIO *Amicus* Br. 22 ("in certain limited circumstances, statistically insignificant adverse event reports may arise together with *other* information that, when viewed as a whole, establishes that drug sales are threatened").

D. Adverse Events Reports Do Not Require Special Treatment In The Materiality Analysis

Matrixx extensively discusses (at 17-32) adverse event reports, which drug manufacturers provide to the FDA under 21 U.S.C. § 379aa and 21 C.F.R. § 314.80. Much of Matrixx's brief (like those of most of its *amici*) argues that adverse event reports, taken as a class, are not reliable evidence of causation. That argument is a red herring.

1. This case does not even involve adverse event reports in the regulatory sense. No mandatory reporting requirement applied to Zicam in 2003 or 2004. *See supra* pp. 8-9. Instead, this case involves voluntary, unregulated communications from knowledgeable specialists who considered it important to warn Matrixx and their professional colleagues about the effects of Zicam. Matrixx's arguments (at 19-20) about regulatory adverse event reports that must be filed "whether or not [the event is] considered drug related," 21 C.F.R. § 314.80(a), lack any relation to the facts alleged in the complaint. The Ninth Circuit did not hold, and respondents have never argued, that all adverse event reports are material. Respondents were required only to allege plausibly that the particular information at issue in this case was material.

2. Further, Matrixx's arguments about the low probative value of adverse event reports generally do not justify treating all adverse event reports as lacking useful information.[44] "Context matters." *Burlington*, 548 U.S. at 69. Whether the reports

---

[44] Matrixx's argument (at 23-24) that such reports are hearsay is irrelevant because the question here is what investors regard as material, not what is admissible evidence at trial.

come from respected clinicians or individual patients, identify serious or trivial side effects, reflect a plausible biological causal relationship, or are corroborated by other information available to an issuer are all relevant to materiality. Indeed, Matrixx itself defines (at 17) "AERs" (*i.e.*, adverse event reports) to include "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." It never explains why the differences among those types of information do not matter for materiality.

Matrixx also lists in the addendum to its brief a number of cases ruling that adverse event reports, or case reports more generally, are unreliable evidence of causation. As with Matrixx's cases on the evidentiary weight to be given statistical significance, *see supra* pp. 44-46, those cases have little import here because they were all decided at the evidentiary stages of the case, rather than on the pleadings, and all addressed what was needed for actual causation, rather than to plead materiality to investors.

3. Matrixx argues (at 29, 44) that the difficulty of making case-by-case determinations about information concerning adverse drug effects is so great that, without a bright-line rule, "companies would have a strong incentive simply to disclose all the AERs they receive." That concern is exaggerated, because corporate managers have a stronger incentive to manage public perceptions of their company. Most pursue that goal through appropriate judgments about which risks are material, often with the aid of counsel.

Matrixx also warns (at 30) that "[e]xcessive disclosure" of adverse event reports will confuse the market. The concern is an odd one – as Matrixx's *amici* PhRMA and BIO acknowledge (at 16), "most adverse event data are already made available to the public by the FDA."[45] If that raw information could somehow impair the functioning of the market, it already would be doing so. The information at issue in *this* case, of course, was not subject to mandatory reporting and publication. *See supra* pp. 8-9.

4. Matrixx challenges respondents to say (at 48-49) whether "20," or "18," or "12," or "11, or seven, or four" adverse event reports, "[o]r just one," would be material, arguing that a bright-line rule based on statistical significance is the only solution. That challenge misunderstands a totality-of-the-circumstances test. "[A] tyro thinks to puzzle you by asking you where you are going to draw the line . . . . But the theory of the law is that such lines exist." Oliver Wendell Holmes, *Law in Science and Science in Law*, 12 Harv. L. Rev. 443, 457 (1899). Under *Basic*, the correct answer is that it depends upon the nature of the reports and other relevant facts. A hundred unverified reports of a headache accompanying drug use might not be material. Ten well-documented reports of a deadly illness could well be: six reports of death from the rare condition aplastic anemia were deemed immaterial in *Carter-Wallace I*, but 10 were enough to take the drug in that case off the market. *See* 150 F.3d at 155.

---

[45] *See* FDA, *The Adverse Event Reporting System (AERS): Latest Quarterly Data Files*, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm.

The line-drawing problem is far more troublesome for Matrixx's theory, because Matrixx seeks to ignore facts that should make a difference. Suppose 10 patients had reported an important adverse side effect for a drug – but each had been examined by a different, well-reputed specialist, and all 10 doctors had concluded independently that the drug caused the problem. Matrixx's attempt to "confin[e] materiality to a rigid formula," *Basic*, 485 U.S. at 236, would prevent courts from even considering allegations about such expert conclusions – contrary to precedent, actual investor behavior, and common sense.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

DARREN J. ROBBINS
ERIC ALAN ISAACSON
JOSEPH D. DALEY
SCOTT H. SAHAM
LUCAS F. OLTS
ROBBINS GELLER RUDMAN
& DOWD LLP
655 West Broadway
Suite 1900
San Diego, California 92101
(619) 231-1058

SAMUEL H. RUDMAN
DAVID A. ROSENFELD
ROBBINS GELLER RUDMAN
& DOWD LLP
58 South Service Road
Suite 200
Melville, New York 11747
(631) 367-7100

DAVID C. FREDERICK
Counsel of Record
SCOTT H. ANGSTREICH
GREGORY G. RAPAWY
EMILY T.P. ROSEN
KELLOGG, HUBER, HANSEN,
TODD, EVANS & FIGEL,
P.L.L.C.
1615 M Street, N.W.
Suite 400
Washington, D.C. 20036
(202) 326-7900
(dfrederick@khhte.com)

November 5, 2010