Statistically Insignificant Deaths: Disclosing Drug Harms to Investors (and Patients) Under SEC Rule 10b-5

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Abstract

This Article, using statistical tools and theory in conjunction with more standard legal approaches, argues that pharmaceutical manufacturers should disclose all cases of illness or injury associated with their products because this data is material to patients and their doctors, and therefore to Securities and Exchange Commission Rule 10b-5's "reasonable investor." Patient and investor interests complement each other in this context, so each will benefit from disclosures that interest the other. Because individuals process more information than traditional statistical tests convey, they act reasonably in expanding their treatment and investment criteria beyond statistical data. Moreover, two sets of expert intermediaries—doctors and professional investors—will be involved. Their expertise will contribute to a more accurate assessment of the risks that adverse-event reports may suggest a drug presents, and of the significance of these risks to shareholders. The Supreme Court's reasons for not requiring full disclosure are out of place in the context of adverse-event reporting given Rule 10b-5's pro-disclosure mandate and the fact that even seemingly singular and unconnected facts can substantially move investors' and patients' opinions about a drug's safety, and thus its maker's viability. A full-disclosure rule would place the determination of which facts are important into the hands of parties with "skin in the game" rather than regulators or self-interested drug makers.

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INTRODUCTION

Anti-inflammatory drug Vioxx's first five years were its best, and its last. Between May 1999 and September 2004, Vioxx's maker Merck & Co. booked $10 billion in sales[1] on 105 million prescriptions[2] of its new wonder drug for osteoarthritis pain. But things were not as rosy for Vioxx and Merck as these figures imply. Evidence emerged that Vioxx caused heart attacks and death.[3] On September 30, 2004, Merck announced a worldwide withdrawal of the drug.[4] Merck stock plummeted twenty-seven percent in one day, shedding $27 billion in market capitalization.[5] The harm to Vioxx users was of course far greater. A massive study by a U.S. Food and Drug Administration ("FDA") director ultimately found that Vioxx likely caused the deaths of tens of thousands of its users.[6]

Soon after the drug's withdrawal, facts came to light suggesting that Merck knew in 1996 that Vioxx might interfere with heart function, and that it had persuasive evidence[7] as early as 2000 that Vioxx

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1 MERCK & CO., INC., ANNUAL REPORT 2003, at 19 (2003 sales of $2.5 billion); MERCK & CO., INC., ANNUAL REPORT 2002, at 24 (2002 sales of $2.5 billion, an increase of "8% over 2001"); Melody Petersen, *Increased Spending on Drugs Is Linked to More Advertising*, N.Y. TIMES, Nov. 21, 2001, at C1 (2000 sales of $1.5 billion, 1999 sales of $330 million); *Pharmaceutical Sales 2004*, DRUGS.COM, http://www.drugs.com/top200_2004.html (last visited Nov. 9, 2013) (2004 sales of $1 billion).

2 MERCK & CO., INC., ANNUAL REPORT 2004, at 21.

3 *See infra* notes 106–07 and accompanying text.

4 *Id.* at 20.

5 John Simons, *Will Merck Survive Vioxx?*, FORTUNE, Nov. 1, 2004, at 90, 90. It took two years for Merck's stock to recover to pre-withdrawal levels. *See Merck & Co., Inc.*, YAHOO! FIN., http://finance.yahoo.com/echarts?s=MRK+Interactive#symbol=mrk;range=20040927,20061030;compare=;indicator=volume;charttype=area;crosshair=on;ohlcvalues=0;logscale=off;source=undefined (last visited Nov. 9, 2013).

6 *See infra* notes 106–07 and accompanying text.

7 This Article uses "evidence" differently from "proof." As Part II shows, a great deal of information can be evidence of a drug's adverse effects, but relatively little or none is incontrovertible proof of harm.

caused heart attacks and death.[8] Merck appears to have engaged in questionable behavior to avoid directly confronting and disclosing to the public the link between its drug and the fatalities.[9] With its blockbuster drug on the line and billions to lose, Merck certainly had motive to do so.

Although one might expect the FDA to be the natural conduit for bringing a drug's dangers to light, this Article suggests an alternative avenue: the securities laws.[10] The interests of investors, patients, and doctors acting on behalf of their patients complement each other in the drug-disclosure context because they are each other's proxies. Investors will stay away from a company that makes medications that potential patients are afraid to use or doctors are unwilling to prescribe, and patients will benefit from investors' acumen in ferreting out a drug's dangers. Their treatment and investment choices can in-

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8 *See infra* Part I.B.

9 *See infra* Part I.B.

10 This Article does not intend to suggest that the FDA should not warn the public of drugs' dangers. However, the FDA could benefit from some help. *See infra* Part I.B–C; note 24; note 319 and accompanying text. More relevant to the securities laws, investors have an interest in information about drug harms and should not be deprived of such information when making investment decisions. While this Article suggests that an analysis under the FDA umbrella may lead to the same conclusions about disclosure, an analysis under the securities laws maintains a direct nexus to investor concerns. That robust disclosure to investors would have the likely effect of saving lives (because patient well-being is relevant to investors) is a nice side effect.

Three key FDA failures contributed to the Vioxx tragedy. First, the FDA's standard three-phase procedure focuses on testing the drug's safety (as opposed to its efficacy) on healthy volunteers—i.e., not necessarily on those with the condition(s) the drug is to treat. *See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA, http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm (last updated May, 1, 2012). In Vioxx's case, the drug was most likely to injure exactly the osteoarthritis sufferers it was intended to treat. *See* Ronald M. Green, *Direct-to-Consumer Advertising and Pharmaceutical Ethics: The Case of Vioxx*, 35 HOFSTRA L. REV. 749, 754 (2006); Eric J. Topol, *Failing the Public Health—Rofecoxib, Merck, and the FDA*, 351 NEW ENG. J. MED. 1707, 1707 (2004). Second, the FDA approved Vioxx for market based on Merck-supplied data that was not peer reviewed. The first peer-reviewed study of Vioxx, which strongly implicated Vioxx's dangers, came out eighteen months after the FDA's decision. Topol, *supra*, at 1707; *see infra* Part I.B.3 (VIGOR study). Third, after it had nontrivial clues of Vioxx's heart risks, the FDA did not immediately evaluate or order a study of the risks despite its power to do so. Topol, *supra*, at 1707; *see also* Margaret Gilhooley, *Vioxx's History and the Need for Better Procedures and Better Testing*, 37 SETON HALL L. REV. 941 (2007); Amanda J. Dohrman, Note, *Rethinking and Restructuring the FDA Drug Approval Process in Light of the Vioxx Recall*, 31 J. CORP. L. 203 (2005).

Further, this Article focuses on drug-harm disclosure, not drug control. Decisions about allowing a drug to market despite its risks or keeping it from market are in the domain of the FDA. This Article touches on drug control issues inasmuch as it discusses how differently situated patients may or may not want to use potentially risky drugs. *See infra* Part II.B.2.d; note 213 and accompanying text; text accompanying note 219; text following note 290; and note 356. Some of these insights may be relevant to the FDA's drug-control role.

form each other and, it is hoped, lead to more accurate decisionmaking.

Merck would eventually face thousands of product liability lawsuits as a result of the Vioxx fall out.[11] A class action lawsuit alleging securities law violations, including violations of section 10(b) of the Securities Exchange Act of 1934 ("'34 Act")[12] and Securities and Exchange Commission ("SEC") Rule 10b-5,[13] is ongoing.[14]

Section 10(b) and Rule 10b-5 require a public company to disclose facts that would materially influence an investor's decision to purchase its securities.[15] A fact is material if a reasonable investor would view it as "significantly alter[ing] the 'total mix' of information made available."[16] Such facts include information that a drug harms its users, which affects the drug's marketability and its manufacturer's financial health. The prevailing legal standard while Vioxx was on the market, however, did not consider cases of drug harm—"adverse events" or "adverse event reports" ("AERs")[17]—suffered by a drug's users to be material unless there were a "statistically significant"[18] number of cases.[19] Lack of statistical significance meant that Merck

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11 *See, e.g.*, Alex Berenson, *Merck Is Said to Agree to Pay $4.85 Billion for Vioxx Claims*, N.Y. TIMES, Nov. 9, 2007, at A1.

12 Securities Exchange Act of 1934, Pub. L. No. 73-291, 48 Stat. 881 (codified as amended at 15 U.S.C. §§ 78a–78pp (2012)).

13 17 C.F.R. § 240.10b-5 (2013).

14 *See In re* Merck & Co., Inc. Sec., Derivative & "ERISA" Litig., Nos. 05-1151 (SRC), 05-2367 (SRC), 2011 WL 3444199, at *6 (D.N.J. Aug. 8, 2011).

15 Basic, Inc. v. Levinson, 485 U.S. 224, 226, 231 (1988); *see* 15 U.S.C. § 78j(b) (2012); 17 C.F.R. § 240.10b-5; *infra* Part A.

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

17 Adverse events occur both within and outside of clinical trials. The latter are referred to as "adverse event reports" ("AERs") and originate from health-care professionals and consumers. *FDA Adverse Event Reporting System (FAERS) (formerly AERS)*, FDA, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm (last updated Sept. 10, 2012).

18 The term "statistically significant" is commonly, but incorrectly, thought to mean something akin to "measurable" or "observable." Quite the opposite is the case. Part II.B, *infra*, explains its meaning in detail. For now, the following example illustrates the concept well. Suppose that, in a drug trial, ten deaths among subjects taking the drug would be expected purely by chance, and that the likelihood of getting more than twenty-five deaths purely by chance is below some threshold probability, typically five percent. If there are twenty-five deaths, the result is considered statistically significant. But if there are only twenty-four fatalities, which might have a seven percent probability of occurring by chance, the company would not have had to disclose that there were any fatalities at all because the number of deaths failed to cross the threshold of statistical significance.

19 *See* N.J. Carpenters Pension & Annuity Funds v. Biogen IDEC Inc., 537 F.3d 35, 58 (1st Cir. 2008); Oran v. Stafford, 226 F.3d 275, 284 (3d Cir. 2000); *In re* Carter-Wallace, Inc. Sec. Litig., 150 F.3d 153, 157 (2d Cir. 1998).

did not have to disclose Vioxx's dangers to the investing community. It likewise allowed Merck to treat the deaths and heart attacks as if they did not exist *at all* for drug-safety purposes.[20] The materiality standard of the time—the least disclosure-friendly since Rule 10b-5's enactment—thus allowed Merck to withhold what it had learned of Vioxx's dangers and created incentives for Merck not to learn more.

In 2011, the Supreme Court heard *Matrixx Initiatives, Inc. v. Siracusano*,[21] a Rule 10b-5 case considering whether the drug company Matrixx Initiatives, Inc. had to disclose a statistically insignificant number of reports that its Zicam Cold Remedy, a nasal spray, caused loss of smell (a condition known as anosmia).[22] Importantly, the Court held that statistical significance was not a prerequisite for materiality. Rather, it held that the materiality inquiry is contextual and thus could, but need not, involve statistically significant data.[23] The Court, however, concluded that Rule 10b-5 did not require disclosure of all AERs.[24] It also implied that its holding may have been different had Matrixx conducted significance tests to disprove the anosmia connection.[25] As this Article shows, this still-lenient ruling gave drug makers a great deal of discretion to withhold drug harms from the public.

This Article argues that, although the Supreme Court correctly held that statistically insignificant data could materially alter a reasonable investor's perception of a company's market prospects, pharmaceutical manufacturers should have to disclose *every* adverse event. *Matrixx* did not fully account for the nuances of what statistical significance signifies. For example, it overlooked statistical theory's instruction that because not all probabilistic judgments are quantifiable,

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20 *See infra* Part II.B.2.b (discussing the "existence-nonexistence dichotomy").

21 Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309 (2011).

22 *Id.* at 1313–14; *see also infra* Part I.C (discussion of the *Matrixx* case).

23 *Matrixx*, 131 S. Ct. at 1321.

24 *Id.* As a strict matter, AERs are available from the FDA via quarterly data files that may be downloaded from its website or via a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552 (2012). *See FDA Adverse Event Reporting System*, *supra* note 17. But the information is not helpful, because the data files are all but impossible for lay people to decipher. For example, a FOIA request by the author to the FDA asking for 800 AERs withheld by Matrixx was answered with a messy data file containing 3284 AERs without the requested 800 marked and with no additional information. *See infra* note 148 and accompanying text. The Supreme Court presumably agreed that current AER availability does not amount to disclosure because *Matrixx*'s language implicitly assumes that such reports to the FDA are not disclosures under Rule 10b-5. *See Matrixx*, 131 S. Ct. 1309.

25 *See id.* at 1322–23 (noting that Matrixx had not conducted its own research relating to anosmia and so had no basis for rejecting findings of a causal link between Zicam and anosmia).

nonstatistical criteria properly inform inherently subjective decisions like choosing a medicine or investing in its maker.

Even a seemingly isolated AER, when combined with a decisionmaker's subjective knowledge and ordinary reasoning, can substantially influence a patient's, doctor's, or investor's opinion about a drug's safety, and thus its manufacturer's financial viability. Doctors and professional investors, and even patients and individual investors (who generally can obtain the benefit of these experts' advice should they want to),[26] certainly are better positioned than a conflicted drug company, an overworked (and perhaps captured) regulator, or a court to determine which AERs matter to them. Their decisions will be influenced by personal factors, including medical conditions specific to particular patients, risk tolerance, and available treatment or investment alternatives. An information-forcing rule would thus shift a key component of drug-use and investment decisions—determining whether a given adverse event is important enough to act on—to those whose health and wealth the decisions ultimately impact.

The Article also argues that the commonly espoused information overload and excessive burden justifications for not requiring complete disclosure are relatively weak in the pharmaceutical context.[27] For example, the too-much-at-once problem at the heart of the information overload concern should be mitigated if AERs are released to the market as they happen, rather than only when a statistically significant number of them accumulate. Relatedly, the fact of many AERs being released at once is itself material to patients, doctors, and investors. The excessive burden justification is less persuasive when it comes to disclosing drug harms because both the data to be disclosed and the infrastructure for disclosing it—the Internet[28]—already exist; disclosure of AERs would not require great amounts of additional time and resources to achieve, as might the disclosures required under other regulatory regimes.

This Article proceeds in three parts. Part I describes the legal and factual background that frames the subsequent statistical and disclosure-oriented discussions. Part II focuses on the use of probability and statistics in making judgments about causation, showing that de-

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26 Note, however, that the ability of laypeople to gather and process information should not be discounted. *See infra* Part II.B–C.

27 *See infra* Part III.B.2.

28 This Article is agnostic as to requiring disclosure of adverse-event reports in periodic regulatory filings. Such disclosures would have many of the deficiencies in informing the marketplace as does the current partial-disclosure system.

spite the shortcomings of significance testing, other aspects of statistics can properly inform the discussion of what drug manufacturers should have to disclose. Part III concludes that, when it comes to adverse events, full disclosure is the best policy and properly fits within the framework of Rule 10b-5.

I. Materiality and Statistical Significance

This Part begins by delineating the evolution of Rule 10b-5's materiality standard from one close to a "philosophy of full disclosure" to a more paternalistic and overly company-protective one that requires historically little disclosure to the public. It then uses two real-world case studies—Merck's actions with respect to the dangers of its Vioxx painkiller, and Matrixx's actions with respect to its Zicam Cold Remedy—to discuss how a drug company might abuse a heightened materiality standard to avoid having to make public relevant information about the effects of its drugs.

A. A Brief History of Materiality

Since its initial promulgation, Rule 10b-5's materiality standard has developed from an investor-protective, disclosure-friendly standard to one that is, historically speaking, both paternalistic and firm-friendly.

1. The '34 Act and Rule 10b-5

Congress passed the '34 Act in the midst of the Great Depression to protect the nation from the "social and economic evils which have affected the security and prosperity of the entire country."[29] Market participants could not be trusted to curtail the "evasions, suppressions, distortions, exaggerations, and outright misrepresentations practiced by corporations with intent to cloak their operations and to present to the investing public a false or misleading appearance as to financial condition."[30] Seventy years later, the pharmaceutical industry would engage in similar practices when drug makers habitually failed to disclose their products' risks.

Section 10(b) of the '34 Act makes it "unlawful . . . [t]o use or employ, in connection with the purchase or sale of any security . . . any manipulative or deceptive device or contrivance in contravention of"

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29 S. Rep. No. 73-792, at 3 (1934).

30 *Id.* at 11; *see also id.* at 4–5, 8–11.

rules set forth by the SEC.[31] In 1942 the SEC promulgated Rule 10b-5, making it

> unlawful . . . [t]o make any untrue statement of a material fact or to omit to state a material fact necessary in order to make the statements made . . . not misleading . . . in connection with the purchase or sale of any security.[32]

Although courts initially enforced a robust disclosure requirement, they eventually drifted towards a looser standard that allowed some of the abuses the '34 Act was meant to remedy.

2. Court Interpretations

Because the drafters of Rule 10b-5 offered only a general sense of the evils they intended the rule to remedy,[33] it was left to the courts to define its contours. Perhaps recognizing that investors will have the best view of the image a firm endeavors to convey to the market, and are in the best position to recognize when they have been misled, the courts soon read a private right of action into the rule.[34]

a. The Original Standard

From as early as 1938, Section 10(b) was understood to extend firms' disclosure obligations beyond those needed to withstand common law fraud or deceit claims because "the frauds to be suppressed may take on more subtle and involved forms than those in which dis-

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31 15 U.S.C. § 78j (2012).

32 17 C.F.R. § 240.10b-5 (2013). The entire Rule reads:

> It shall be unlawful for any person, directly or indirectly, by the use of any means or instrumentality of interstate commerce, or of the mails or of any facility of any national securities exchange,
>
> (a) To employ any device, scheme, or artifice to defraud,
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> (b) To make any untrue statement of a material fact or to omit to state a material fact necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading, or
>
> (c) To engage in any act, practice, or course of business which operates or would operate as a fraud or deceit upon any person,
>
> in connection with the purchase or sale of any security.

33 *See* Milton V. Freeman, *Administrative Procedures*, 22 BUS. LAW. 891, 922 (1967). The rule was said to be "casual[ly]" drafted, with almost no discussion. Blue Chip Stamps v. Manor Drug Stores, 421 U.S. 723, 767 (1975) (Blackmun, J., dissenting).

34 *See* Superintendent of Ins. of N.Y. v. Bankers Life & Cas. Co., 404 U.S. 6, 13 n.9 (1971); J.I. Case Co. v. Borak, 377 U.S. 426, 432 (1964) ("Private enforcement . . . provides a necessary supplement to Commission action."); Kardon v. Nat'l Gypsum Co., 69 F. Supp. 512, 514 (E.D. Pa. 1946) (first private-right-of-action case). This is not to say that private class-action securities litigation is without its problems or immune to abuse. *See, e.g.*, THOMAS LEE HAZEN, THE LAW OF SECURITIES REGULATION § 7.17 (5th ed. 2005).

honesty manifests itself in cruder and less specialized activities."[35] The '34 Act proscribed not only lies but half-truths and omissions—"inequality of knowledge" was key.[36]

In the 1968 landmark case of *SEC v. Texas Gulf Sulphur*,[37] in which a mining firm's employees denied news of a promising drill core before trading in the firm's securities, the Second Circuit nicely summarized the materiality standard's development since Rule 10b-5's enactment:

> This is not to suggest . . . that "the test of materiality must necessarily be a conservative one . . ." solely . . . measuring the effect the knowledge of the facts would have upon prudent or conservative investors. . . . "The basic test of materiality . . . is whether a *reasonable* man would attach importance. . . ." This, of course, encompasses any fact "which in reasonable and objective contemplation *might* affect the value of the corporation's stock or securities." The speculators and chartists of Wall and Bay Streets are also "reasonable" investors entitled to the same legal protection afforded conservative traders. Thus, material facts include . . . those facts which affect the probable future of the company and those which may affect the desire of investors to buy, sell, or hold the company's securities. . . . [W]hether facts are material . . . [depends on] 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."[38]

On this point, the court elaborated that a "more than marginal" possibility of the discovery of a large mine was material because it "might well have affected the price of Texas Gulf Sulphur stock and would certainly have been an important fact to a reasonable . . . investor."[39]

Despite the decades-long development of a materiality threshold based on the reasonable investor who *might* view a fact as influencing

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35 Hughes v. SEC, 174 F.2d 969, 975 (D.C. Cir. 1949); *see also* Kohler v. Kohler Co., 319 F.2d 634, 636–37, 638 (7th Cir. 1963); A.A. Berle, Jr., *Stock Market Manipulation*, 38 COLUM. L. REV. 393 (1938).

36 List v. Fashion Park, Inc., 340 F.2d 457, 461 (2d Cir. 1965); Mansfield Hardwood Lumber Co. v. Johnson, 268 F.2d 317, 327 (5th Cir. 1959) (quoting Am. Guaranty Co. v. Sunset Realty & Planting Co., 23 So. 2d 409, 449 (La. 1945)); *Hughes*, 174 F.2d at 973–74.

37 SEC v. Tex. Gulf Sulphur Co., 401 F.2d 833 (2d Cir. 1968), *cert. denied sub nom.* Coates v. SEC, 394 U.S. 976 (1969).

38 *Id.* at 849 (internal citations omitted).

39 *Id.* at 849–50.

his or her investment decision, and its seeming adoption by the Supreme Court,[40] the Court recast the standard to one that assumes that the reasonable investor is both less interested in the events befalling the companies in which he or she invests and less capable of determining what information is important.

b. The Current Standard

In 1976, the Supreme Court explicitly rejected the might-affect standard in *TSC Industries, Inc. v. Northway, Inc.*[41] It created a new test under which a fact was material if there was a "substantial likelihood" that it would "significantly alter[ ] the 'total mix' " of available information.[42] In ratcheting up the standard, the Court reasoned that anything less would both cause investors to be overloaded with information and be unfair to firms.

The Court reaffirmed its *TSC Industries* standard in 1988 in *Basic, Inc. v. Levinson*,[43] where it reiterated its concern about overdisclosure leading to an "overabundance of information."[44] The Supreme Court thus adjusted the materiality standard to one where the expected impact of a fact had to be very high to be considered material.[45] Contradictorily, the decision also rejected the argument that investors would be "overwhelmed by excessively detailed and trivial information" because (1) it "assumes that investors are nitwits" who cannot adequately process information or make "probabilistic" assessments, and (2) remedying lack of "full disclosure," rather than enforcing "paternalistic withholding of accurate information," was the goal of the '34 Act.[46] The subsequent treatment of the ratcheted-up standard by circuit courts raised (perhaps unbeknownst to the courts) the standard even further in the context of adverse event reporting.

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40 Affiliated Ute Citizens of Utah v. United States, 406 U.S. 128, 151, 153–54 (1972); Mills v. Elec. Auto-Lite Co., 396 U.S. 375, 384 (1970) (interpreting section 14(a) of the '34 Act, which contains a materiality requirement substantially like that of Rule 10b-5).

41 TSC Indus., Inc. v. Northway, Inc., 426 U.S. 438, 441 (1976) (interpreting section 14(a) of the '34 Act).

42 *Id.* at 445–46, 449.

43 Basic, Inc. v. Levinson, 485 U.S. 224 (1988).

44 *Id.* at 230–32. *Basic* was brought under section 10(b) of the '34 Act and its corresponding Rule 10b-5.

45 *See id.* at 238 (describing the probability-versus-magnitude test); *see supra* text accompanying note 38.

46 *Basic*, 485 U.S. at 233–34 (quoting Flamm v. Eberstadt, 814 F.2d 1169, 1175 (7th Cir. 1987); SEC v. Capital Gains Research Bureau, Inc., 375 U.S. 180, 186 (1963)).

c. *Materiality and Statistical Significance Before* Matrixx

Two cases solidified the place of statistical significance in Rule 10b-5 jurisprudence. In 1998, in *In re Carter-Wallace, Inc. Securities Litigation*,[47] Carter-Wallace touted both the safety of its epilepsy drug and its substantial contribution to revenues while becoming aware of at least fifty-six drug-related AERs, including ten deaths.[48] The Second Circuit held that Carter-Wallace's untempered positive statements were not misleading because "[d]rug companies need not disclose isolated reports of illnesses suffered by users of their drugs until those reports provide statistically significant evidence that the ill effects may be caused by—rather than randomly associated with—use of the drugs."[49]

In the similar case of *Oran v. Stafford*,[50] American Home Products ("AHP") was sued under Rule 10b-5 for making positive statements about its diet drug fen-phen in SEC filings while it knew of, but did not disclose, fifty-five cases of heart-valve damage and "hundreds" of reports of heart and lung problems among fen-phen users.[51] AHP acknowledged that "these symptoms were reactions to the drug[ ]."[52] In a wholesale adoption of the *Carter-Wallace* standard, the court affirmed the complaint's dismissal because there was no "statistically significant causal relationship" between AHP's products and heart-valve damage at the time of its SEC filings.[53] In other words, despite AHP's admission that its drug caused hundreds of injuries, it did not have to disclose this to the market because, the court would have one believe, any conclusions based on these data would have been so "purely speculative" as to be of no interest to investors.[54]

Although most courts generally adopted statistical significance as a brightline prerequisite, even where no obvious study was done by the manufacturer,[55] others resisted its harsh implications. Some held

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47 *In re* Carter-Wallace, Inc. Sec. Litig., 150 F.3d 153 (2d Cir. 1998).

48 *Id.* at 155; Joseph B. Kadane, Matrixx v. Siracusano*: What Do Courts Mean by "Statistical Significance"?*, 11 L., Probability & Risk 41, 42 (2011).

49 *In re Carter-Wallace, Inc.*, 150 F.3d at 157.

50 Oran v. Stafford, 226 F.3d 275 (3d Cir. 2000).

51 *Id*. at 279–81 (Alito, J.). Then-Judge Alito would later join the *Matrixx* decision.

52 *Id.* at 279.

53 *Id.* at 283–84.

54 *Id.* at 286.

55 *See, e.g.*, N.J. Carpenters Pension & Annuity Funds v. Biogen IDEC, Inc., 537 F.3d 35, 41, 44, 50 (1st Cir. 2008); Masters v. GlaxoSmithKline, 271 F. App'x 46, 50 (2d Cir. 2008) (Sotomayor, J.) (Then-Judge Sotomayor would eventually author *Matrixx*); *In re* Alliance Pharm. Corp. Sec. Litig., 279 F. Supp. 2d 171, 189 (S.D.N.Y. 2003); Kadane, *supra* note 48, at 46 (stating that no "obvious statistical studies" were done by Carter-Wallace or Biogen). It would

that statistical significance, although evidential of materiality, was not necessary for its proof.[56] Meanwhile, at least one court implied that statistical significance was insufficient for materiality.[57] Part II explains in detail why the last two categories of cases, which essentially predicted the *Matrixx* rule, were correct for two seemingly contradictory reasons. In some ways statistical significance is too high a threshold—certainly higher than the *might* standard, and, as the *Matrixx* court would eventually hold,[58] higher than the *substantially likely* standard.[59] In other ways, statistical significance is too low a standard, primarily because it does not measure the practical importance or magnitude of a measured effect.[60]

Parts I.B and C below describe situations in which any standard requiring only partial disclosure, including one requiring a statistically significant number of adverse events, might be abused by drug companies to keep relevant data from investors, patients, and their doctors.

B. Case #1: Merck and Vioxx

The law of materiality moved to a standard that embodied statistical significance as its core principle. This Part offers a case study of how a drug manufacturer aware of such a standard might game the system to keep a dangerous drug on the market while avoiding a securities lawsuit.[61] This scenario involves a series of carefully orchestrated clinical trials (or a reluctance to conduct the appropriate trials,

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be difficult for anyone other than the company to conduct the type of study required to make a determination of statistical significance. *See infra* text following note 146; *infra* Part II.B.1.

56 *See, e.g.*, *In re* Elan Corp. Sec. Litig., 543 F. Supp. 2d 187, 210 (S.D.N.Y. 2008); *In re* Bayer AG Sec. Litig., No. 03 Civ. 1546, 2004 WL 2190357, at *8–10 (S.D.N.Y. 2004) (holding, on the day of Vioxx's withdrawal, that a statistically insignificant number of AERs could be material when coupled with other information).

57 *See* Avon Pension Fund v. GlaxoSmithKline PLC, 343 F. App'x. 671 (2d Cir. 2009). Although the court upheld dismissal of the complaint because it pleaded "no facts indicating that the test results were even statistically significant," the plaintiffs did plead "myriad findings of statistical significance." *Id.* at 672. Indeed, one of the "meta-analyses" on which the court focused found a statistically significant correlation between GlaxoSmithKline's diabetes drug, Avandia, and heart attack. Kadane, *supra* note 48, at 44, 46 (citing Steven E. Nissen & Kathy Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes*, 356 NEW ENG. J. MED. 2457 (2007)); Nissen & Wolski, *supra*, at 2459 (showing a *p*-value of three percent for heart attack); *see infra* Part II.B.1, II.B.2.a (discussing the meaning of "*p*-value").

58 *See infra* Part I.C.

59 *See infra* Part II.B.2.c.

60 *See infra* Part II.B–C.

61 To protect the innocent, no actual accusations are made.

as it were). Part I.C offers a complementary case study in which there were few or no relevant clinical trials.

1. Manipulating the Game: The 1996 Kidney Study

Based on the results of a kidney function study, Merck knew of Vioxx's potential to interfere with heart function as early as 1996. The study's doctors believed that Vioxx increased the ratio of a clotting agent in the study subjects' blood, which in turn increased the risk that Vioxx users would experience cardiovascular problems.[62] The doctors drafted an article abstract and summary that unequivocally stated that Vioxx use resulted in a higher clotting-agent ratio.[63] Exercising their veto rights, Merck personnel pressured the doctors to water down their abstract to make it more equivocal, and altogether refused to clear the summary.[64] Despite the doctors' protests, Merck insisted that they weaken their conclusions in the final article to make it sound as if Vioxx's effect on synthesis of the anticlotting agent was a vague possibility.[65]

2. The 1997 Gastrointestinal Study That Never Was

In 1997, Merck wanted to test (and advertise) the gastrointestinal side effects of Vioxx, which it believed to be lower than the nonsteroidal anti-inflammatory drugs ("NSAIDs") with which it intended Vioxx to compete. While planning the trial, company scientists exchanged emails implying that they feared that Vioxx use would result in heart problems because NSAIDs might have cardioprotective effects (the "naproxen hypothesis"), or that Vioxx was cardio-harmful.[66] One email exchange, initiated by the drafter of a trial protocol, contained the following:

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62 Fifth Amended Complaint at 44–45, In re Merck & Co., Inc. Sec., Derivative & "ERISA" Litig., Nos. 3:05-CV-01151, 3:05-CV-02367, 2009 WL 1468968 (D.N.J. Mar. 10, 2009) [hereinafter FAC]; JOHN S. MARTIN, JR., DEBEVOISE & PLIMPTON LLP, REPORT OF JOHN S. MARTIN, JR. TO THE SPECIAL COMMITTEE OF THE BOARD OF DIRECTORS OF MERCK & CO., INC. CONCERNING THE CONDUCT OF SENIOR MANAGEMENT IN THE DEVELOPMENT AND MARKETING OF VIOXX, app. A at 49–51 (2006).

63 MARTIN, *supra* note 62, app. A at 133.

64 *Id*. app. A at 133–38.

65 FAC, *supra* note 62, at 41–42; MARTIN, *supra* note 62, app. A at 138–55;.

66 FAC, *supra* note 62, at 46–49, 56–57. Not surprisingly, the explanation of the e-mails depends on who is asked. *Compare* MARTIN, *supra* note 62, app. A at 33–39 (describing Merck employees' explanations), *with* FAC, *supra* note 62, at 46–49 (describing the Vioxx plaintiffs' perspective). The distinction is irrelevant for this Article's purposes because both have negative implications for Vioxx's commercial success. Nonetheless, Merck has relied expansively on this distinction in defending its actions. *See, e.g.*, *In re* Vioxx Class Cases, 103 Cal. Rptr. 3d 83, 89 (Ct. App. 2009).

> Do we want to allow high [cardiovascular] risk patients in the study given the risks we have discussed? I think [excluding such patients] will definitely make enrollment more difficult but I am still concerned that the NSAID group will be getting cardioprotection that the [Vioxx] group will not.[67]

In response to the protocol draft, an Associate Director at Merck replied that he "[w]ould allow low-dose aspirin—I know this has been discussed to death, but real world everyone is on it, so why exclude AND without Cox-1 inhibition [caused by aspirin] you will get more thrombotic events and kill [the] drug."[68] The protocol draft's author responded:

> Low Dose Aspirin—I HEAR YOU! This is a no win situation! The relative risk of [gastrointestinal problems with] even low dose aspirin may be as high as 2–4 fold. Yet, the possibility of increased [cardiovascular] events is of great concern—(I just can't wait to be the one to present those results to senior management). What about the idea of excluding high risk [cardiovascular] patients . . . ? This may decrease the [cardiovascular] event rate so that a difference between the [Vioxx and non-Vioxx] groups would not be evident.[69]

Another doctor remarked that "[i]t is clear to me that the program will be severly [sic] hurt if the megatrial shows a win in [gastrointestinal problems] and a loss in [heart attacks and stroke]. That is what we are setting up by not allowing [aspirin]."[70] Yet another Merck doctor opined that if "aspirin prophylaxis is not permitted" in the study to mitigate Vioxx's dangers to the heart, there could be many more cardiovascular adverse events observed in the Vioxx group as compared to the NSAID group.[71]

Merck ultimately proposed to the FDA a study which would exclude patients taking aspirin and those with a history of heart problems—i.e., those patients who, without the cardio-protection afforded by aspirin, would most likely be injured by Vioxx, and thus

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67 MARTIN, *supra* note 62, app. A at 34 (citations omitted) (quoting a comment typed into the draft protocol) (internal quotation marks omitted).

68 *Id.* app. A at 35. COX-1 inhibits the production of the clotting agent discussed *supra* in Part I.B.1. By inhibiting COX-1 production, aspirin thus prevents clotting, and is therefore cardio-protective. FAC, *supra* note 62, at 103. Thrombotic events are those related to blood clots.

69 FAC, *supra* note 62, at 41–42; MARTIN, *supra* note 62, app. A at 38.

70 FAC, *supra* note 62, at 42; MARTIN, *supra* note 62, app. A at 39.

71 MARTIN, *supra* note 62, app. A at 30–31.

were most likely to make "a difference between the two groups . . . evident."[72] Merck canceled the study, however, ostensibly because the FDA planned to require that Vioxx be packaged with a warning about gastrointestinal effects irrespective of the proposed study's ultimate outcome, Vioxx's gastrointestinal benefits could be proven in other ways, and the study would have been expensive.[73] It is easy, however, to interpret Merck's actions as being a manipulation of circumstances aimed at ensuring that it had no statistically significant findings, and thus nothing to disclose.[74]

3. The VIGOR Gastrointestinal Study, Turned on Its Head

In January 1999, four months before Vioxx was approved, Merck began the Vioxx Gastrointestinal Outcomes Research ("VIGOR") study to compare the gastrointestinal effects of Vioxx and naproxen, the NSAID painkiller in Aleve.[75] The published study showed that patients taking Vioxx were four times as likely to suffer a heart attack as patients taking naproxen.[76] It also noted that thirty-eight percent of the heart attacks occurred in the four percent of the study group that had a history of heart trouble and for whom aspirin therapy was recommended, but who were not taking aspirin during the study—that is, exactly the group that Merck proposed be excluded from the study that it contemplated in 1997.[77] The increased risk among the Vioxx group barely received mention in the published study, which explained it away by attributing it to naproxen's supposed "coronary protective effect."[78] In other words, Vioxx was not more dangerous to the heart to a statistically significant degree, but naproxen was that much safer. The paper concluded that Vioxx was safer from a gastrointestinal standpoint to a statistically significant degree.[79] It never ad-

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72 *Id.* app. A at 38, 40–41; *see also* Green, *supra* note 10, at 753–54 (describing this as a high-risk group and noting that arthritis patients—Vioxx's target consumers—are prone to cardiac problems); Topol, *supra* note 10, at 1707 (same).

73 MARTIN, *supra* note 62, app. A at 43–44.

74 Stated differently using statistical insights, *see infra* Part II, the increased risk for patients using a particular drug is necessarily measured against a baseline comparison group. By carefully choosing the test and comparison groups, a dishonest company can make the relative risk of using its drug seem small or nonexistent.

75 *See* Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520, 1520, 1522 (2000).

76 *Id.* at 1520, 1523, 1526.

77 *Id.* at 1523; *see supra* text accompanying notes 66–73.

78 *Id.* at 1523–24, 1527.

79 *Id.* at 1520, 1527.

dressed the question of why, *as a matter of drug safety or commercial viability*, it was acceptable for a new drug to be four times as dangerous as one it intended to replace, whatever the reason for the difference.

It would eventually surface that VIGOR's authors omitted three heart attacks suffered by Vioxx patients, raising the relative risk of heart attack for Vioxx patients to five-to-one.[80] The *New England Journal of Medicine* published an "Expression of Concern" in which it cited evidence implying that at least some of the authors were aware of the additional adverse events and purposely omitted them from their November 2000 article.[81] Merck's stock fell almost five percent upon publication of the correction.[82] The *Journal* reaffirmed its Expression of Concern two months later, and added that the authors omitted from their original article that the prevention of sixty-five gastrointestinal adverse events came at a cost of twenty-seven additional serious cardiovascular events.[83] According to the study's authors, the VIGOR study was nonetheless a success.[84] Stated differently, a statistically significant improvement in the gastrointestinal area beat out statistically insignificant (per the authors) worsening of heart attacks, strokes, and death.[85] Although the improvement in the former category may outweigh the worsening in the latter for an otherwise healthy patient with stomach problems, a doctor is unlikely to advise a patient with a strong stomach but weak heart to switch from naproxen. This decision is most properly each patient's to make.

Notwithstanding VIGOR's implications and FDA pressure not to overstate Vioxx's heart safety, Merck declined to study either Vioxx's

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80 Gregory D. Curfman et al., *Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis,"* 353 NEW ENG. J. MED. 2813, 2813 (2005).

81 *Id.* at 2813–14.

82 Alex Berenson, *Medical Journal Criticizes Merck Over Vioxx Data*, N.Y. TIMES, Dec. 9, 2005, at A1.

83 Gregory D. Curfman et al., *Expression of Concern Reaffirmed*, 354 NEW ENG. J. MED. 1193, 1193 (2006).

84 *See* Bombardier et al., *supra* note 75, at 1520, 1527.

85 *See id.*; *see also infra* note 90 and accompanying text.

or naproxen's hypothesized effects on the heart.[86] Merck continued its stance that "Vioxx was safe, unless proved otherwise."[87]

4. The ADVANTAGE Gastrointestinal Study, Sans Three Heart Attacks

In 2000, Merck conducted another gastrointestinal study comparing Vioxx and naproxen. Merck's marketing department pushed the study as a promotional tool to introduce Vioxx to a group of doctors.[88] The published study showed five heart attacks among Vioxx subjects versus one among naproxen subjects.[89] Despite the five-to-one relative risk, the result was statistically insignificant, and thus unworthy of mention in the article's Results section—it could be *ignored entirely*.[90]

Evidence revealed in lawsuits after Vioxx's withdrawal, however, showed that eight, not five, Vioxx patients suffered heart attacks; eight heart attacks *was* statistically significant.[91] One of the three victims (all of whom died) was a seventy-three-year-old woman whose family

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86 Green, *supra* note 10, at 757–59; Topol, *supra* note 10, at 1707; Alex Berenson et al., *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES, Nov. 14, 2004, at N1;; Warning Letter from Thomas W. Abrams, Dir., Div. of Drug Mktg., Adver., and Commc'ns, FDA, to Raymond V. Gilmartin, President & CEO, Merck & Co., Inc. (Sept. 17, 2001), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166383.pdf. *But compare* Green, *supra* note 10, at 758 ("a clinical trial aimed directly at assessing Vioxx's risks was ethically and legally out of the question"), *with* Topol, *supra* note 10, at 1707 (stating that the "FDA has the authority to mandate that [such] a trial be conducted," and that it could have been conducted "at any point").

87 Berenson et al., *supra* note 86, at 1.

88 Alex Berenson, *Evidence in Vioxx Suits Shows Intervention by Merck Officials*, N.Y. TIMES, Apr. 24, 2005, at A1 [hereinafter Berenson, *Evidence Shows Intervention*].

89 Jeffrey R. Lisse et al., *Gastrointestinal Tolerability and Effectiveness of Rofecoxib Versus Naproxen in the Treatment of Osteoarthritis*, 139 ANNALS OF INTERNAL MED. 539, 539, 543 (2003) (ADVANTAGE stood for "Assessment of Differences between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness").

90 *Id.* at 539, 543 (showing a *p*-value of 0.2); *see also id.* at 545 ("[N]o significant differences were observed in . . . cardiovascular . . . adverse events."). Part II.B, *infra*, discusses both the meaning of "*p*-value" and its common misinterpretations.

When a result is "statistically insignificant," it means that given a population in which the true effect is really zero, and a perfectly designed study, it would be possible to find as many heart attacks as were found or more purely by chance with a typically less than five-percent probability. It is incorrect to say that that a statistically insignificant estimate is zero. The best estimate of the true heart attack rate is the actual number measured in the study. *See infra* Part II.B.

91 STEPHEN T. ZILIAK & DEIRDRE N. MCCLOSKEY, THE CULT OF STATISTICAL SIGNIFICANCE: HOW THE STANDARD ERROR COSTS US JOBS, JUSTICE, AND LIVES 29, 30 (2007); Berenson, *Evidence Shows Intervention*, *supra* note 88.

brought the discrepancy to light.[92] Merck emails showed that a company doctor's "clinical judgment" suggested that the woman died of a heart attack, but that he could be "persuaded to say" that her cause of death was unknown.[93] His superior swiftly replied, "I think this should be called an unknown cause of death," and asked whether the woman's death was "included in the [heart attack] only analysis or not? (hopefully not)." A few hours later, she added, "I would prefer unknown cause of death so we don't raise concerns."[94] The cause of death was classified as unknown.[95]

The article's lead author later admitted:

> Merck designed the trial, paid for the trial, ran the trial. . . . Merck came to me after the study was completed and said, 'We want your help to work on the paper.' The initial paper was written at Merck, and then it was sent to me for editing.[96]

He said that he was never provided the background surrounding the woman's death, and that "I went with the cardiovascular data that was presented to me."[97]

One can speculate as to why Merck left the three deaths out of the study, but the law of the time would have rewarded a dishonest company for covering up three heart attacks with the nondisclosure of all eight because five heart attacks did not cross the threshold of statistical significance, whereas an honest disclosure of eight heart attacks would have.[98]

5. The APPROVe Colon Study: No Avoiding Statistical Significance This Time . . . for the Most Part . . . Until Later

In 2004, after a five-year run with Vioxx, Merck could neither avoid a statistically significant finding that the drug was responsible for an increase in cardiovascular events, nor could it explain it away using the naproxen hypothesis. The APPROVe study compared Vioxx to a placebo to test its effect on colon polyps.[99] It showed to a

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92 ZILIAK & MCCLOSKEY, *supra* note 91, at 29; Berenson, *Evidence Shows Intervention*, *supra* note 88.

93 Berenson, *Evidence Shows Intervention*, *supra* note 88.

94 *Id.* (internal quotation marks omitted).

95 *Id.*

96 *Id.*

97 *Id.*

98 *See supra* note 18.

99 Robert S. Bresalier et al., *Cardiovascular Events Associated with Rofecoxib in a*

statistically significant degree that Vioxx patients were 2.80 times more likely to suffer cardiac adverse events and 2.32 times more likely to suffer strokes than patients taking a placebo.[100] With naproxen out of the picture (Vioxx's effects were compared to those of a sugar pill), there was no escaping the conclusion that Vioxx was independently responsible for the increase in cardiovascular incidents.[101] Merck withdrew the drug worldwide three days later.[102]

The study's authors asserted that the increased risks appeared only for those taking Vioxx for longer than eighteen months. Those taking it for a shorter period were eighteen percent more likely to suffer a cardiovascular event than those on a placebo, but because this rate was different to a statistically significant degree from the post-eighteen-month rate, it was ignored.[103] Merck would rely on this eighteen-month cutoff in thousands of lawsuits[104] until criticism forced it to admit in 2006 that the distinction was incorrect.[105]

6. After Vioxx's Withdrawal

A study lead-authored by an FDA Director concluded that not only was naproxen not cardio-protective, but it increased the incidence of heart problems.[106] Vioxx use resulted in "an estimated 88,000–140,000 excess cases of serious coronary heart disease" in the

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Colorectal Adenoma Chemoprevention Trial, 352 NEW ENG. J. MED. 1092, 1093 (2005) (APPROVe stood for "Adenomatous Polyp Prevention on Vioxx").

100 *Id.* at 1096.

101 *See id.* at 1092.

102 *See generally* Press Release, FDA, FDA Issues Public Health Advisory on Vioxx as Its Manufacturer Voluntarily Withdraws the Product (Sept. 30, 2004), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108361.htm.

103 Bresalier et al., *supra* note 99, at 1092, 1097, 1098 (showing *p*-values of 0.01 and 0.07). See Part II.B, *infra*, for the meaning of "*p*-value."

104 *See, e.g.*, Alex Berenson, *Medical Journal Retracts Part of a Paper on Vioxx*, N.Y. TIMES, June 27, 2006, at C13; Alex Berenson, *Jury to Start Deliberation in Two Vioxx Injury Cases*, N.Y. TIMES, Apr. 4, 2006, at C4.

105 *Correction*, 355 NEW ENG. J. MED. 221 (2006); Stephen W. Lagakos, *Time-to-Event Analyses for Long-Term Treatments—The APPROVe Trial*, 355 NEW ENG. J. MED. 113, 116 (2006) (correction criticizing the Merck scientists' methods); Alex Berenson, *Merck Admits a Data Error on Vioxx*, N.Y. TIMES, May 31, 2006, at C1.

106 David J. Graham et al., *Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cyclo-Oxygenase 2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs: Nested Case-Control Study*, 365 LANCET 475, 480 (2005). The study was enormous, covering 1,394,764 subjects. *Id.* at 477; *see also In re* Vioxx Class Cases, 103 Cal. Rptr. 3d 83, 89 (Ct. App. 2009).

United States; at a fatality rate of forty-four percent, that translates into 38,720 to 61,600 deaths.[107]

A 2006 follow-up study by Merck examining the effects of Vioxx on APPROVe patients a year after they stopped taking the drug showed that they were at a sixty-four percent greater risk of developing cardiovascular problems than patients taking a placebo.[108] But because the study showed that there was an 11.5% chance that the same relative risk would have shown up had those patients taken a placebo,[109] Merck began its press release of the study by asserting: "[T]here was not a statistically significant difference in the risk of confirmed . . . cardiovascular events in patients who had previously taken VIOXX compared to those who had previously taken placebo."[110]

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107 Graham et al., *supra* note 106, at 480; *see also* Topol, *supra* note 10, at 1708 ("tens of thousands" of additional "major adverse events").

108 MERCK & CO., INC., APPROVE OFF-DRUG EXTENSION: PRELIMINARY ANALYSES OF THROMBOTIC CARDIOVASCULAR SAFETY 3 (2006); Alex Berenson, *Follow-up Study on Vioxx Safety Is Disputed: Other Researchers Say Merck Should Monitor Patients*, N.Y. TIMES, May 13, 2006, at C3.

109 MERCK & CO., INC., *supra* note 108, at 3 (showing a *p*-value of 0.115). See Part II.B, *infra*, for the meaning of "*p*-value."

110 Press Release, Merck & Co., Inc., Merck Announces Preliminary Analyses of Off-Drug Extension of APPROVe Study (May 11, 2006), *available at* http://online.wsj.com/public/resources/documents/WSJ_060512-ReleasewReport-final.pdf.

An article published on the eve of this Article's being sent to print strongly suggests that Merck has not changed its practices based on its Vioxx experience. *See* Marie Brenner, *Danger in the Ring*, VANITY FAIR, Jan. 2014, at 56. The company acquired the rights to the NuvaRing contraceptive device in 2009 by purchasing the firm that then produced it. *Id.* at 59. The circumstances surrounding the marketing of the NuvaRing device are frighteningly reminiscent of those surrounding Vioxx.

Like Vioxx, NuvaRing looked to be a blockbuster drug, earning $440 million in 2008 and $623 million in 2012. *Id.* at 59–60. Studies done well before NuvaRing's introduction to the market suggested that the type of hormones used in the device, third-generation progestins, are about twice as likely to cause blood clots as earlier forms of progestin used in other contraceptive devices. *Id.* at 60. Studies done in 2007 and 2011 showed increased risks of 60% and 56%, respectively. *Id.* "To this day, no test has been made of NuvaRing after it leaves the factory," even though there may have been reason to believe that storage of an unused device at an improper temperature could cause it to release a "life-threatening surge of estrogen." *Id.* at 62. A 2012 study found that the risk that users of devices like NuvaRing will develop a certain type of blood clot that can travel to the lungs is 550% greater compared to those who are not using a hormonal contraceptive, and 90% greater compared to users of oral contraceptives containing earlier forms of progestin. *Id.* at 60. Even as the FDA allowed NuvaRing onto the market, it questioned the device's safety. *Id.* at 61; *cf. supra* note 10. As with Vioxx, Merck worked to minimize the warnings about the device's risk of causing blood clots, including sometimes-fatal pulmonary embolisms. *Id.* at 60–63, 109–10; *cf. supra* text accompanying notes 72–73.

More than 100 lawsuits had been filed over NuvaRing at the time Merck acquired the rights to the device. *Id.* at 59. As of this printing, over 1000 lawsuits have been filed against Merck over the device, *id.* at 59, and checking for the presence of NuvaRing appears to have become

C. *Case #2: Matrixx and Zicam*

Certain situations allow a drug's manufacturer plausibly to game the statistical-significance materiality standard in the context of clinical studies. Matrixx's potential Zicam-related gaming arose in a different context.[111] It involved primarily external data, mainly AERs from patients and their doctors. Nonetheless, the undisclosed data is information that would have interested rational patients wanting to make informed treatment decisions, their doctors making treatment recommendations, and ultimately investors making investment choices.[112]

The following sections highlight Matrixx's actions before and after the suit. By way of partial introduction to the statistical concepts in Part II and the full-disclosure discussion in Part III, this Section discusses why Matrixx's actions were material to patients and investors.

1. *Matrixx's Actions Through the End of the Class Period*

Matrixx Initiatives, Inc. introduced Zicam in its intranasal forms to the market in 1999.[113] The new cold remedy propelled Matrixx from an organic-vitamin company with mediocre profits to a successful firm which earned seventy percent of its revenues from the new flagship product.[114] Soon after its introduction, however, Matrixx began receiving AERs and other clues that Zicam might be causing smell loss.[115] Nonetheless, the company did not temper its positive statements about its future, and even worked to counter the anosmia-related news that reached the marketplace.[116]

The following information is known or alleged to have been available to Matrixx as of the end of the class period in the securities lawsuit, all of which has been documented without the benefit of discovery.[117] In December 1999, the neurological director of the Smell

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the standard practice of at least some health professionals who observe symptoms of pulmonary embolism in female patients, *id.* at 58.

111 As before, no actual allegations are made.

112 *See infra* Parts II and III.

113 MATRIXX, http://www.matrixxinc.com (last visited Nov. 9, 2013).

114 Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309, 1314 (2011).

115 *See infra* notes 117–24 and accompanying text.

116 *See Matrixx*, 131 S. Ct. at 1314–17.

117 The Private Securities Litigation Reform Act of 1995 ("PSLRA") stays discovery in private securities-fraud cases until after a motion to dismiss. 15 U.S.C. § 78u-4(b)(3) (2006). Plaintiffs therefore must make out a claim of materiality based solely on public information and information that they are able to gather on their own at their expense.

& Taste Treatment and Research Foundation, Ltd., informed Matrixx that a "cluster of his patients" may have lost their smell from Zicam, "at least one" of his patients who did not have a cold developed anosmia after Zicam use, and "previous studies" had suggested that intranasal zinc (a Zicam component) could be dangerous.[118] Moreover, the same director offered to conduct a clinical study to evaluate Zicam's effects on smell, but his offer was declined.[119]

In September 2002, Matrixx's Vice President for Research and Development called a doctor at the University of Colorado after one of the doctor's patients called Matrixx to complain of anosmia after Zicam use.[120] The vice president informed the doctor that other customers had made similar complaints, and the doctor said that she had treated several patients for loss of smell after Zicam use.[121] During this call, the Colorado doctor again informed Matrixx's vice president of "previous studies" linking zinc to anosmia.[122] Matrixx's vice president replied that his company had not done any studies to evaluate Zicam's effect on its users' sense of smell.[123] Sometime later, after having been sent the previous studies mentioned above, Matrixx's vice president asked the doctor whether she would be interested in doing animal studies, but she declined because she focused on human studies.[124]

A year later, another Colorado doctor observed eleven cases of anosmia following Zicam use.[125] Both doctors prepared a presentation to the American Rhinologic Society in which they planned to detail the case of a man "with previously normal taste and smell who experienced severe burning in his nose, followed immediately by a loss of smell, after using Zicam."[126] Matrixx learned of the presentation and informed the doctors that, "as a legal matter, [they did] not have [Matrixx's] permission to use [its] company name or product

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118 *Matrixx*, 131 S. Ct. at 1314.

119 Siracusano v. Matrixx Initiatives, Inc., 585 F.3d 1167, 1170 (9th Cir. 2009); Consolidated Amended Complaint at 6, Siracusano v. Matrixx Initiatives, Inc., Civ. No. 04-0886-PHX-DKD (D. Ariz. Mar. 4, 2005) [hereinafter CAC].

120 *Matrixx*, 131 S. Ct. at 1314; CAC, *supra* note 119, at 6.

121 *Matrixx*, 131 S. Ct. at 1314; CAC, *supra* note 119, at 6. It is unclear from the record in the case whether the Colorado doctor informed the Matrixx vice president of the "several" other cases. She did, however, express her concern that Zicam did not adequately warn of the danger of smell loss. CAC, *supra* note 119, at 6.

122 *Matrixx*, 131 S. Ct. at 1314; CAC, *supra* note 119, at 6.

123 *Matrixx*, 131 S. Ct. at 1314.

124 *Id.* at 1314–15.

125 *Id.* at 1315.

126 *Id*.

trademarks," after which the doctors removed references to Zicam.[127] Nine plaintiffs filed four product-liability lawsuits alleging that Zicam damaged their sense of smell.[128]

On February 6, 2004, the news program Good Morning America reported the findings that were presented by the Colorado doctors, but with Zicam's name attached.[129] It also mentioned the four lawsuits.[130] Matrixx's stock price fell twenty-six percent and a class-action 10b-5 suit followed.[131]

Matrixx defended in court that the AERs it received were unreliable because (1) they did not by themselves show the rate of anosmia among Zicam users, which rate must be compared to the base rate of anosmia in the population to determine whether a difference is statistically significant; (2) they were anecdotal; (3) they were hearsay; and (4) they did not consider potential alternative causes of anosmia, like the common cold which Zicam was intended to treat.[132] Because investors would not base their decisions on "unreliable speculation," argued Matrixx, a high threshold—statistical significance—should be required before it had to disclose AERs.[133]

Matrixx also asserted that it had conducted two placebo-controlled randomized clinical trials with no reported cases of anosmia,[134] and defended itself with the "nitwit" argument disfavored in *Basic* that investors would be unable to make "reasoned" decisions if every AER was disclosed.[135] Implicit in its defense was the notion that disclosing all AERs would be overly burdensome to the company.[136]

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127 Petition for Writ of Certiorari app. D.1 at 117a–18a, Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309 (2011) (Letter from Timothy L. Clarot, Dir. of Research and Dev., Matrixx Initiatives, Inc., to Bruce Jafek, M.D. (Sept. 13, 2003)); CAC, *supra* note 119, at 24;.

128 *See* Christensen v. Matrixx Initiatives, Inc., No. 4:03-cv-0146-HWB (W.D. Mich. Oct. 14, 2003); Sutherland v. Matrixx Initiatives, Inc., No. CV2003-1635-WHR (Ala. Cir. Ct. Dec. 18, 2003); Bentley v. Matrixx Initiatives, Inc., No. CV2004-001338 (Ariz. Super. Ct. Jan. 23, 2004); Nelson v. Matrixx Initiatives, Inc., No. YC048136 (Cal. Super. Ct. Dec. 8, 2003); *see also* CAC, *supra* note 119, at 17.

129 *Matrixx*, 131 S. Ct. at 1316.

130 *Id.*

131 *Id.*

132 Brief for Petitioners at 13, 15, 17–27, Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309 (2011) (No. 09-1156). *But see supra* text accompanying note 118.

133 Brief for Petitioners, *supra* note 132, at 17–49. Part II.B.2.c, *infra*, explains how statistical significance is a high standard.

134 Brief for Petitioners, *supra* note 132, at 5, 8. Matrixx also issued a press release to this effect. *Matrixx*, 131 S. Ct. at 1316.

135 *See* Brief for Petitioners, *supra* note 132, at 26, 28–31; *supra* text accompanying note 46.

136 Petition for Writ of Certiorari at 12, Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309 (2011) (No. 09-1156); J. Robert Brown Jr., Matrixx v. Siracusana*: Revisiting the Materiality Standard (Part 3)*, RACE TO THE BOTTOM (June 23, 2010, 6:00 AM), http://www.theracetothebot

Matrixx continued to sell the intranasal forms of Zicam for five years. As the following Section illustrates, this decision came with serious consequences for unknowing investors and patients.

2. *Tips of an Iceberg: Why It Was All Material*

Within two months of the Good Morning America report, the two University of Colorado doctors together encountered over 165 cases of anosmia that followed Zicam use.[137] One of the doctors consistently observed that her patients complained of an "immediate, severe burning" following Zicam use, which was followed by the loss of smell.[138] The FDA also began receiving AERs of patients who had lost their sense of smell after Zicam use, and began investigating the drug's side effects.[139]

In a turn of events reminiscent of those surrounding Vioxx, Matrixx's reliance on its two placebo-controlled studies began to fall apart. Although neither study revealed anosmia adverse events, both were very small—one looked at 213 patients and the other at 80.[140] By way of comparison, the smallest of the Vioxx studies involved 2586 patients.[141] Because the rates of adverse events can be low, such sample sizes are too small to properly test the occurrence of most side effects because there may not be even a single adverse event, much less enough events to determine the relative riskiness of the drug to a statistically significant degree. Because the consequences can be high—death, heart attacks, anosmia—measuring relative risks is important. Both studies also showed an increase in burning sensations in the zinc over the placebo group, but not to a statistically significant degree.[142]

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tom.org/securities-issues/matrixx-v-siracusana-revisiting-the-materiality-standard-par-2.html; *cf.* Brief for Petitioners, *supra* note 132, at 13, 26 (suggesting that requiring companies to disclose all AERs would flood the market with unnecessary information).

137 CAC, *supra* note 119, at 8. Shortly thereafter, the doctors published their findings. *See* Bruce W. Jafek et al., *Anosmia After Intranasal Zinc Gluconate Use*, 18 AM. J. OF RHINOLOGY 137 (2004).

138 CAC, *supra* note 119, at 8.

139 *FDA Reviewing Complaints Whether Nasal Spray Causes Loss of Smell*, DENVERCHANNEL.COM (Oct. 6, 2004), http://www.thedenverchannel.com/news/fda-reviewing-complaints-whether-nasal-spray-causes-loss-of-smell.

140 *See* Michael Hirt et al., *Zinc Nasal Gel for the Treatment of Common Cold Symptoms: A Double-Blind, Placebo-Controlled Trial*, 79 EAR, NOSE & THROAT J. 779 (2000); S.B. Mossad, *Effect of Zincum Gluconium Nasal Gel on the Duration and Symptom Severity of the Common Cold in Otherwise Healthy Adults*, 96 Q. J. MED. 35 (2003).

141 Bresalier et al., *supra* note 99, at 1092.

142 *See* Hirt et al., *supra* note 140, at 780 (1.14 times more likely in the zinc group); Mossad, *supra* note 140, at 41 (2.5 times more likely in the zinc group).

It is thus not surprising that in one of its regulatory filings Matrixx admitted that "there is insufficient scientific evidence at this time to determine if zinc gluconate, when used as recommended, affects a person's ability to smell."[143] Matrixx quickly said that it would conduct animal and human studies, the results of which would be available a year later.[144] In the meantime, it continued to sell Zicam.

One can only speculate why Matrixx had not studied Zicam's effect on its users' sense of smell given previous studies tying zinc to smell loss, AERs starting in 1999, offers by outside scientists to conduct such studies, and the fact that it was administered nasally. But the statistical-significance materiality standard (and the scientific practice of ignoring statistically insignificant results) would easily explain Matrixx's disinclination to examine the question further.

Matrixx's position suggests that *no number* of AERs received from outside patients and doctors would ever be material, no matter how serious the information.[145] Matrixx correctly noted that statistical significance would be determined by comparing the rate of adverse events in a test group taking a drug to the rate of that adverse event in the relevant population not taking the drug.[146] Thus, a plaintiff that wanted to plead a material—i.e., statistically significant—number of AERs would have to conduct a large-scale study to estimate the rate of anosmia in the general population of cold sufferers, and a similar study to estimate the rate of anosmia among Zicam users. Such a task is very difficult. Moreover, because companies have a great deal of discretion in whether and what studies they initiate, they can delay definitive judgment about a product for a long time.

In 2009, the FDA sent Matrixx a Warning Letter after having received 130 Zicam-related AERs of anosmia, compared with "few [such] reports" related to other intranasal cold remedies.[147] The Letter also disclosed that the FDA was aware of an additional 800 similar AERs that were withheld by Matrixx.[148] The same day, the FDA advised consumers not to use intranasal Zicam, and Matrixx withdrew the products.[149] Since 2005, Matrixx has been named a defendant in

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143 Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309, 1316 (2011) (form 8-K).

144 *FDA Reviewing Complaints*, *supra* note 139.

145 Brief for Petitioners, *supra* note 132, at 46.

146 *See id*. at 13, 21–22, 25, 33, 46.

147 Letter from Deborah M. Autor, Dir., Office of Compliance, FDA, to William J. Hemelt, Acting President, CFO & COO, Matrixx Initiatives, Inc. (June 16, 2009), *available at* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm166909.htm.

148 *Id.*

149 News Release, FDA, FDA Advises Consumers Not to Use Certain Zicam Cold Reme-

nearly 500 product liability lawsuits in federal courts alone, with most coming after Zicam's withdrawal.[150] Matrixx stock would fall as much as seventy-three percent before being bought and taken private by a private-equity firm.[151]

The Vioxx and Zicam case studies show how the statistical significance standard both allows for the nondisclosure of obviously relevant adverse event data, and incentivizes drug makers to actively avoid testing the safety of their products or to manipulate their studies to prevent the number of adverse events from reaching the threshold of statistical significance in order to avoid disclosure altogether. Knowledge of even an isolated instance of bad news is important to investors, drug users, and prescribers because it may be the tip of a larger iceberg of problems to which they may or may not react based on their individual situations and preferences.[152] Both stakeholders and patients may very well care that adverse events have been experienced by a "cluster" of patients, "at least one" patient, "other customers," patients from "previous studies," and so on.[153]

Part II employs the statistical theory behind significance testing to explain and expand on the notion that reasonable investors, patients, and their caregivers will attach significance to isolated AERs for their potential to warn of future dangers. Part III then applies the findings of Part II to show that the common arguments against requir-

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dies: Intranasal Zinc Product Linked to Loss of Sense of Smell (June 16, 2009), *available at* http://www.fda.gov/Newsevents/Newsroom/PressAnnouncements/ucm167065.htm; News Release, Zicam, Message to Consumers: Matrixx Initiatives Voluntarily Withdraws Zicam Cold Remedy Swabs, Zicam Cold Remedy Nasal Gel (June 16, 2009) (on file with The George Washington Law Review).

150 BLOOMBERG FINANCE L.P., BLOOMBERG LAW COMPANY REPORT: MATRIXX INITIATIVES, INC. 7 (2012) (custom report generated Mar. 26, 2012; on file with The George Washington Law Review). A Bloomberg Law docket listing showed eighty-eight state cases, a large majority of which asserted products liability claims. BLOOMBERG LAW, DOCKET SEARCH (May 7, 2012), http://www.bloomberglaw.com/dockets/search/results/e02bb52037cfb944202b5938d52d3c27.

151 BLOOMBERG LAW COMPANY REPORT, *supra* note 150, at 3, 38.

152 Even Matrixx acknowledged this concept. *See* Brief for Petitioners, *supra* note 132, at 22 ("The 'great utility' of AERs thus is not that they establish an association between a drug and an adverse event, but rather that they may 'generate signals of potential problems that warrant further investigation.'" (quoting FDA, THE CLINICAL IMPACT OF ADVERSE EVENT REPORTING 6 (1996)). The great value of an isolated piece of bad news lies in its potential to be combined with additional knowledge unique to the decisionmaker. *See infra* Part II.

153 *See supra* text accompanying notes 118–28. The FDA estimates that it receives reports of fewer than one percent of AERs, and has found that more than three AERs for otherwise rare conditions warrant further investigation. FDA, *supra* note 152, at 5, 7. Learning of individual AERs is also especially important to investors who are limited by the PSLRA in their ability to seek ex post recompense for securities fraud. *See supra* note 117.

ing full disclosure are unavailing in the context of adverse-event reporting.

II. EVERY INJURY MATTERS—PROBABILITY, STATISTICS, AND JUDGMENT

Statistics is about knowledge and power. It is used to establish truths about *what is real* by attempting to make sense of complex facts. Significance testing is one of the most common forms of statistical analysis; it dominates the field of drug regulation.[154] Significance testing, however, cannot reveal as much as is commonly believed for at least three reasons. First, as already shown, study design determines what data is collected.[155] Second, as this Part highlights, and especially relevant if one values statistical tests for their ability to provide objective knowledge, a properly interpreted significance test conveys only a narrow fact about data consistency, rather than causation. Third, despite significance testing's goal of objectivity, a great deal of subjectivity is involved in statistical inference.

This Part draws on the philosophy of statistics to inform the discussion of what adverse-event information should be disclosed. The discussion begins by describing different types of probabilities, and the ability of statistics to measure each. It then describes significance testing, focusing on what knowledge it can and, importantly, cannot (but is commonly believed to) convey. It describes what "statistical significance" means, and why it is both an over- and under-inclusive standard. This Part concludes by utilizing tenets from the Bayesian approach to statistical thought—which accommodates subjective knowledge—to show that even apparently singular adverse events are important because they inform the background against which treatment and investment decisions are made. Any adverse-event report has the potential, when combined with other knowledge held by the decisionmaker (and, possibly, by no one else), to sizably increase the likelihood that he or she will choose a different (and, as will be argued, more likely to be correct) course of action.

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154 *See* Stephen Senn, *Bayesian, Likelihood, and Frequentist Approaches to Statistics: A Comparison of Methods*, APPLIED CLINICAL TRIALS, Aug. 2003, at 35, 35.

155 Relatedly, the way in which study outcomes are interpreted can have a large impact on how study results are used. *See supra* Part I.B.3. In other words, researchers have a great deal of power to influence study results.

A. Types of Probability

Probability statements can be classified into three categories: theoretical probability, empirical probability, and personal probability.[156] Theoretical, or "true," probabilities are those based on mathematical models that, if the inputs are correct, are always right.[157] For example, the statement "If I flip a fair coin, there is a fifty percent chance that it will come up heads" is a statement of a theoretical probability—the coin is fair, and a coin has two sides, so it is equally likely that either side will come up.

Empirical probabilities are determined by repeatedly observing an event's outcome.[158] Empirical probabilities are experience-based, and the results of the experiments on which they are based are objectively verifiable. They may, however, be unreliable because the probability obtained may be the result of random chance. Indeed, unless an experiment is observed an infinite number of times, the true probabilities[159] of its various outcomes cannot be known for certain.[160] This method of determining probabilities is called the "frequentist" approach because it is based on observing long-run frequencies of possible outcomes.[161] Returning to the coin example, one might test whether a coin is fair by flipping it 100 times. If it comes up fifty heads and fifty tails, one might be satisfied that it is fair, but if comes up 100 heads and no tails, one might reject the notion that it is fair. These are reasonable assumptions, even though a fair coin could conceivably come up 100 heads in 100 flips, and a biased coin could similarly come up exactly fifty heads and fifty tails. For a result between these two extremes, the decisionmaker must either pick a threshold number of heads above which he or she will reject the idea that the coin is fair, or simply refrain from deciding.

Personal probabilities, often called subjective or Bayesian probabilities, are based on neither mathematical models nor long-run

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156 RICHARD D. DE VEAUX ET AL., INTRO STATS 367–70 (3d ed. 2009). Different terms are sometimes used for these concepts. *See, e.g.*, David W. Barnes, *Too Many Probabilities: Statistical Evidence of Tort Causation*, 64 LAW & CONTEMP. PROBS. 191, 192–93 (2001) (using "fact probability," "sampling error probability," and "belief probability," respectively).

157 DE VEAUX ET AL., *supra* note 156, at 368. If a model's inputs are wrong—e.g., if not all coins are in fact fair—then the probabilities it generates will also be wrong. Doubting a model's accuracy—e.g., a coin's fairness—relates to personal probability. *See* Barnes, *supra* note 156, at 192; *see also infra* Part II.C.

158 DE VEAUX ET AL., *supra* note 156, at 367.

159 Or, if you will, the probability in God's eyes.

160 *See id.*

161 Sarah B. Lawsky, *Probably? Understanding Tax Law's Uncertainty*, 157 U. PA. L. REV 1017, 1031 (2009); Senn, *supra* note 154, at 37–38.

frequency observations. Rather, they are subjective, reflecting one's personal degree of belief about the likelihood of a given outcome. These probabilities are based on factors like one's intuition and personal qualitative knowledge of circumstances, including knowledge based on experience.[162] They are beliefs arising from "some particular individual's internal state."[163] Personal probabilities are special in that they can influence the degree to which one trusts an empirically obtained probability, thus resulting in a different probability assessment for the decisionmaker.[164] Using the coin-flipping example again, one might observe that another flipping of a coin 100 times came up with fifty-five heads and forty-five tails. An ordinary onlooker might believe that this is close enough to an even number of outcomes to infer that the coin is fair. Now imagine that the person flipping the coin has placed a bet with another onlooker that more heads would come up than tails and that he has previously been thrown out of a number of casinos on suspicion of cheating. The assessment of the coin's fairness by an observer who knows about the bet and the casino incidents is likely different from that of the ordinary onlooker, and with good reason.[165]

Closely related to theoretical and empirical probabilities are the concepts of direct and inverse probabilities, respectively. Direct probability statements rely on the underlying theoretical probabilities of the possible outcomes of an event or experiment to determine the likelihood that a given outcome will occur.[166] A pair of questions illustrates direct probability determinations well. If a fair coin is flipped 100 times, what is the probability of getting exactly forty heads?[167] Knowing that the coin is fair—that the true probability is fifty percent—the probability of forty heads can be precisely calculated.[168] Similarly, if the true probability of a drug causing injury is two percent, the probability that the drug injured 19,800 or fewer of its 1,000,000 users can be calculated.[169]

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162 Senn, *supra* note 154, at 37.

163 Lawsky, *supra* note 161, at 1031.

164 *See* Senn, *supra* note 154, at 37–38. They can also modify one's belief in a theoretical probability.

165 A Bayesian would call your two pieces of information "prior knowledge" and argue that it would be a mistake to ignore that information in deciding whether the coin is biased. *See infra* Part II.C.

166 *See* Senn, *supra* note 154, at 36.

167 *See id.*

168 The probability is 1.084%.

169 The probability is 7.77%.

Inverse probabilities come into play when the true probability of an occurrence is unknown (in real life, this is roughly always). Restating the questions from the previous paragraph to remove knowledge of true probabilities would read as follows: If a coin is flipped 100 times and comes up forty heads, what is the probability that it is fair?[170] Similarly, if 19,800 of a drug's 1,000,000 users received an injury, what is the probability that it was caused by the drug? Unlike direct probability questions, these are impossible to answer because, rather than using a true probability to calculate the likelihood of the observed outcome, they are effectively trying to determine their underlying true probabilities. Nonetheless, as explored in the next section, it is inverse probability questions that significance testing attempts to approach, though not (when used properly) definitively answer.[171]

B. "Statistical Significance"

Whether the frequency of a given event is statistically significant is determined by significance testing. The next two Sections describe the significance-testing procedure and the knowledge that it imparts, with a focus on its use in drug trials, as well as the weaknesses of this approach to show what it does not reveal.

1. Null Hypothesis Significance Testing

Imagine that a pharmaceutical manufacturer wants to bring a new drug, "Flubegone," to market. It suspects that Flubegone can reduce the duration of the common flu. In the process of conducting a study to test this suspicion, it notices that a larger proportion of the patients taking the drug are having heart attacks than are patients taking a placebo—three percent and one percent, respectively.[172] The manufacturer wants to know whether the disparity is caused by Flubegone or if it is merely a result of natural randomness. To answer such a question, it would ordinarily conduct a "hypothesis test."

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170 *See* Senn, *supra* note 154, at 36.

171 *See id.* at 36, 37–38; Bruno Lecoutre et al., *Uses, Abuses and Misuses of Significance Tests in the Scientific Community: Won't the Bayesian Choice Be Unavoidable?*, 69 INT'L STAT. REV. 399, 412 (2001).

172 This example assumes that Flubegone is compared to a placebo. It may also be compared to another cold remedy, or the heart-attack rate among Flubegone patients may be compared to a known base rate of heart attacks in the population or among people who share characteristics of those in the trial. *See supra* text accompanying note 146. For this Article's purposes, these tests are substantively the same.

To test whether the difference between heart attack rates of Flubegone and placebo patients is large enough to warrant concern, the researcher develops a "null hypothesis" about the effects of Flubegone. Typically, the null hypothesis is that the drug in question has no effect—that Flubegone does not affect heart attack rates.[173] The null hypothesis is a working assumption that is tentatively taken as true. Its validity is assessed by comparing it to the observed increase in heart attack rates among Flubegone patients.[174] If Flubegone use is indeed unrelated to heart attacks, one would expect that its users would suffer heart attacks at the same rate as placebo patients. Thus, the null hypothesis is that Flubegone users suffer heart attacks at a rate of one percent.

The magnitude of the difference in heart attack rates is then run through a model known to approximate the distribution of such differences of varying magnitudes.[175] The model yields a "*p*-value," the

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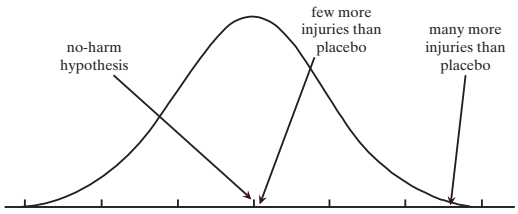
173 *See* DE VEAUX ET AL., *supra* note 156, at 512, 523, 532; David H. Kaye & David A. Freedman, *Reference Guide on Statistics*, *in* FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 83, 122 (2d ed. 2000); *see also* Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309, 1319 n.6 (2011).

174 *See* DE VEAUX ET AL., *supra* note 156, at 509, 524–25; ZILIAK & MCCLOSKEY, *supra* note 91, at 12. Note that the validity of a no-harm hypothesis, not a harm hypothesis, is tested. *See infra* Part II.B.2.c.

175 DE VEAUX ET AL., *supra* note 156, at 513. One distribution that may be used is the familiar bell curve:



The difference in rates is translated into statistical terms and plotted along the distribution. The center of the curve corresponds to the null hypothesis of no difference in rates. The area to the right of the center represents a greater heart attack rate among Flubegone users. The area to the left of the center would correspond to a lower heart attack rate. The shape of the curve confirms what would be expected: if there really is no difference between treatments, most experiments would yield a difference in rates between Flubegone and the placebo that would cluster around the center. Each point on the curve corresponds to a probability of randomly getting a difference in heart attack rates as extreme as, or more extreme than, the observed difference, assuming the truth of the null hypothesis that there is no difference in rates. This probability is called a *p*-value. *See infra* text accompanying note 176.

Another critical input into the model is the sample size—the number of patients being tested. Both the proportion and absolute number of cases that make a result statistically significant varies between surveys. For example, depending on the rate at which the injury normally occurs in the population, say thirty percent, 90 of 300 patients receiving an injury may be enough to establish statistical significance in one study, but neither thirty percent nor ninety patients

probability of randomly getting a difference in heart-attack rates equal to or larger than that observed, assuming the truth of the null hypothesis that Flubegone does not affect heart attack rates.[176] A smaller *p*-value is stronger evidence against the no-effect theory.

The *p*-value is next compared to a predetermined significance level—almost universally five percent, including in medicine.[177] If the *p*-value is lower than this threshold, meaning that the result is less than five percent likely to occur randomly assuming the truth of the null hypothesis, then the difference is said to be "statistically significant."[178] In this case, one "rejects the null hypothesis" on the ground that the observed difference in heart attack rates would be unlikely if Flubegone really had no adverse effect.[179] If the *p*-value is higher than the significance level, one "fails to reject" the null hypothesis, and the result is not statistically significant.[180]

In light of the basic process and logic of significance testing, the next section highlights some of its key shortcomings, and discusses the ways in which these weaknesses are relevant to evaluating whether individual adverse events are material to treatment and investment decisions.

2. A Limited Discourse

The dimensions along which significance testing may not convey knowledge may nevertheless be important to investor, patient, and doctor decisionmakers. The "significance test controversy" has been debated in nonlegal fields for some time,[181] but has received little attention in the legal arena. A legal and legal policy approach elucidates significance testing's weaknesses by using patients' and investors' overlapping concerns as the catalyst, bringing into focus the elements that go into their decisionmaking. It begins with issues related to the null hypothesis.

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may be enough in another. *See supra* text accompanying notes 140–42; *infra* note 235 and accompanying text.

176 DE VEAUX ET AL., *supra* note 156, at 511; Kaye & Freedman, *supra* note 173, at 122.

177 *E.g.*, ZILIAK & MCCLOSKEY, *supra* note 91, at 10–13, 23–32, 111; Michael D. Green et al., *Reference Guide on Epidemiology*, *in* FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 358 (2d ed. 2000). Occasionally, other levels, especially ten percent and one percent, are used.

178 DE VEAUX ET AL., *supra* note 156, at 538–39.

179 *See id*.

180 *See id.* at 511, 538. This Article uses "statistically insignificant" and "statistically nonsignificant" interchangeably to signify that a result is not statistically significant.

181 *See, e.g.*, ZILIAK & MCCLOSKEY, *supra* note 91; Lecoutre et al., *supra* note 171, at 400–01.

a. Interpreting the Results

Recall that the null hypothesis of the fictional drug company in Part II.B.1 assumed that Flubegone had no adverse effect. That significance testing looks at an inverse probability is the source of its first limitation: the *p*-value is not the probability that Flubegone is not harmful.[182] It cannot be because from the start it *assumes* that Flubegone is not harmful.[183] Neither is it the probability that Flubegone is safe given the data. Rather, it is the probability of seeing as many injuries as observed, or more, *if* Flubegone is safe.[184] The inability to translate the probability of the observed data given the hypothesis into the probability of the hypothesis given the data[185] makes it impossible to calculate the probability that the drug causes (or, in typical null hypothesis terms, does not cause) harm. It would be ideal if a significance test yielded a conclusive probability, but it cannot.[186] Significance testing must therefore rely on somewhat inverted reasoning. Rather than directly addressing the question of whether Flubegone is harmful because it causes heart attacks, a hypothesis test approaches the issue of whether it is harmful by determining whether it can "falsify" the hypothesis that Flubegone is harm*less*. That is, if the odds of seeing a certain number of injuries or more is low enough (typically, five percent) given the truth of the null hypothesis, then it is assumed that the injuries did not occur by chance, but instead were caused by Flubegone.[187] As is gospel in statistics, "the null hypothesis is never proved or established, but it is *possibly* disproved."[188] Although scientists may be comfortable with this methodology because it is mathematically clean, it is unlikely to assuage the fears of "real-world" drug users.

A significance test determines the extent to which the observed data is consistent, or compatible, with the null hypothesis that the drug causes no harm.[189] Unfortunately, any number of alternate hy-

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182 *See* DE VEAUX ET AL., *supra* note 156, at 513.

183 Kaye & Freedman, *supra* note 173, at 122.

184 David H. Kaye & George F. Sensabaugh, Jr., *Reference Guide on DNA Evidence*, *in* FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 485, 535–36 (2d ed. 2000).

185 *See* ZILIAK & MCCLOSKEY, *supra* note 91, at 17, 39, 41, 103, 155–56, 176.

186 *See infra* Part II.C.

187 This is the best that the underlying mathematics allow in an inverse-probability situation. *See supra* text accompanying notes 170–71. Falsification is an approach to understanding an observation by disproving—falsifying—possible explanations for the observation. *See infra* text accompanying notes 191, 196–97.

188 R.A. FISHER, THE DESIGN OF EXPERIMENTS 16 (8th ed. 1966) (emphasis added).

189 *See* DE VEAUX ET AL., *supra* note 156, at 511; ZILIAK & MCCLOSKEY, *supra* note 91, at 133; Kaye & Freedman, *supra* note 173, at 122; David E. Adelman, *Scientific Activism and Re-*

potheses could be equally consistent with the observed data.[190] For example, even though the observed data may yield a very high *p*-value for a hypothesis of no harm, another hypothesis corresponding to some potentially high level of harm—for example, four times as many heart attacks—might have an identical *p*-value, indicating that such harm is equally consistent with the observed data as the no-harm hypothesis.[191] Likewise, even 100 percent consistency between the observed data and the null hypothesis does not prove the absolute truth of the null hypothesis; it shows only that the result could be entirely compatible with the null hypothesis, as it may be with other hypotheses.[192]

One can thus never prove conclusively—i.e., accept completely—the hypothesis that Flubegone is benign; the best that one can do is fail to reject the hypothesis that it is benign.[193] A *p*-value above the statistically significant level means only that there is not enough evidence, based on the selected significance level, to reject the assumption that a drug has no harmful effects.[194] As acknowledged by the authors of a basic statistics text, "[t]hat's a pretty weak conclusion, but it's all we're entitled to."[195] At the same time, one can never disprove the null hypothesis because a significance test can never falsify it with total certainty.[196] The best that can be said is that the observed data are unlikely to have appeared by chance if the null hypothesis is true, and no intervening forces caused the data to appear.[197]

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straint: The Interplay of Statistics, Judgment, and Procedure in Environmental Law, 79 NOTRE DAME L. REV. 497, 513 (2004).

190 DE VEAUX ET AL., *supra* note 156, at 511; Adelman, *supra* note 189, at 527, 550, 552 n.230.

191 Charles Poole, *Beyond the Confidence Interval*, 77 AM. J. PUB. HEALTH 195, 197 (1987).

192 *Cf.* DAVID TABAK & FREDERICK J. LEE, NAT'L ECON. RES. ASSOCS., THE MATRIXX OF MATERIALITY AND STATISTICAL SIGNIFICANCE IN SECURITIES FRAUD CASES 3 (2010), *available at* http://www.nera.com/nera-files/PUB_Materiality_Matrixx_1210.pdf (showing that, in testing whether a coin is fair, a result of one head and one tail has a *p*-value of 100%, indicating complete consistency with the null of an equal distribution of flips, but does not prove that the coin is fair because even unfair coins can show the same result).

193 *See* DE VEAUX ET AL., *supra* note 156, at 511–12; Lecoutre et al., *supra* note 171, at 402; Joseph S. Rossi, *Statistical Power of Psychological Research: What Have We Gained in 20 Years?*, 58 J. CONSULTING & CLINICAL PSYCHOL. 646, 646 (1990).

194 *See* DE VEAUX ET AL., *supra* note 156, at 512; Rossi, *supra* note 193, at 646.

195 DE VEAUX ET AL., *supra* note 156, at 511.

196 Mark Parascandola, *Epistemic Risk: Empirical Science and the Fear of Being Wrong*, 9 L., PROBABILITY & RISK 201, 203, 207 (2010).

197 DE VEAUX ET AL., *supra* note 156, at 511; Kaye & Freedman, *supra* note 173, at 122. It is exceedingly difficult to completely insulate an experiment from intervening causes, or so-called "confounding variables."

The analysis is akin to that surrounding the presumption of innocence in U.S. criminal law. If the evidence fails to establish a defendant's guilt beyond a reasonable doubt, he or she is said to be "not guilty." We do not say that the defendant is "innocent," because he or she may have nonetheless committed the crime, and in fact, may have more likely than not committed the crime. In other words, although consistency or lack thereof is evidential, it cannot prove causation. Decisionmakers need the ability to allocate degrees of belief among competing hypotheses.

"Failing to reject" is not an assertion that changes patients' and investors' minds. Unfortunately, statistical significance and insignificance are often treated as a concrete disproof and proof, respectively, of the null hypothesis.[198] As discussed above[199] and in the following section, this practice has allowed drug makers to ignore, for medical and therefore Rule 10b-5 disclosure purposes, adverse events whose number does not rise to the standard five percent significance level.[200] Nonetheless, they could be considered material by investors, doctors, and patients, who use additional criteria for their decisionmaking.

b. The Existence-Nonexistence Dichotomy

Statistical significance and insignificance have become de facto stand-ins for the disproof and proof of inverse probability questions. Significance levels were originally conceived to serve as evidence of the relative consistency between data and competing hypotheses.[201] When searching for potential explanations of an observation, a very low *p*-value for one hypothesis and a high *p*-value for another implied that the former was better. Either *p*-value could be greater or lower

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198 *See generally* Ziliak & McCloskey, *supra* note 91; Lecoutre et al., *supra* note 171, at 401, 402; *see also infra* Part II.B.2.c.

199 *See supra* Parts I.B.4, I.B.6.

200 *See supra* note 177 and accompanying text.

201 *See, e.g.*, Raymond Hubbard & M.J. Bayarri, *Confusion over Measures of Evidence (*p*'s) Versus Errors (*a*'s) in Classical Statistical Testing*, 57 AM. STATISTICIAN 171 (2003); Paul Meier et al., *What Happened in* Hazelwood*: Statistics, Employment Discrimination, and the 80% Rule*, 9 AM. B. FOUND. RES. J. 139, 151 (1984); Parascandola, *supra* note 196, at 206. There is some debate as to the extent to which R.A. Fisher, a founder of modern statistics and the person who popularized the *p*-value, intended that it serve as a decision rule in addition to a measure of evidence. *See, e.g.*, DE VEAUX ET AL., *supra* note 156, at 538, 549; Lecoutre et al., *supra* note 171, at 399–400; Meier et al., *supra*, at 151; Parascandola, *supra* note 196, at 206. *See also generally* ZILIAK & MCCLOSKEY, *supra* note 91; Hubbard & Bayarri, *supra*. In any case, "the wide use of Fisher's statistical tables at a time before computers were widely available, combined with the need for a 'rule of behaviour' as identified by Neyman and Pearson [two prominent statisticians of Fisher's time], helped to institutionalize the emphasis on a common numerical threshold of significance." Parascandola, *supra* note 196, at 207.

than five percent, indicating significance or a lack thereof under today's status quo.[202] The five percent level is used as a bright-line decision rule under which significant results are accepted and insignificant ones are ignored entirely.[203]

This cut-off is problematic because, as scholars and at least one court have acknowledged, any universal level for statistical significance is arbitrary.[204] An event is supposed to be "statistically significant if we don't believe that it's likely to have occurred only by chance," which in turn depends on one's "tolerance for believing that rare events can happen [to him or her]."[205] In other words, it is a choice variable that an individual must select based on his or her unique life circumstances. Patients, doctors, and investors do not leave the confines of reasonableness by requiring different levels of certainty to make something significant, and thus material to their treatment or investment decisions.[206] Unfortunately, the personal, subjective judgment of individuals has been replaced with a rigid convention of social science.

Commentators have described this status quo of the bright-line statistical-significance standard as creating a "game or a fight . . . within which only the significant results win, while nonsignificant ones are (theoretically) only statements of ignorance, and thus perceived as failures."[207] Unfortunately, because the status quo "inhibit[s] critical discussion,"[208] it is also a convenient way to ignore otherwise relevant, but often unseemly, results. Adopting such a rule of law can have unintended consequences. Merck appears to have adopted this standard, making it easy for the company to ignore increases in heart attack rates among Vioxx users by relying on statistical insignificance.[209]

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202 *See supra* note 177 and accompanying text.

203 *See, e.g.*, DE VEAUX ET AL., *supra* note 156, at 519 (discussing the "absolute nature of the hypothesis test decision"). *See also generally* ZILIAK & MCCLOSKEY, *supra* note 91.

204 *See, e.g.*, Kadas v. MCI Systemhouse Corp., 255 F.3d 359, 362–63 (7th Cir. 2001) (Posner, J.); DE VEAUX ET AL., *supra* note 156, at 491, 538; Adelman, *supra* note 189, at 545; Meier et al., *supra* note 201, at 152; Poole, *supra* note 191, at 197; *see also supra* note 201 (noting how the five percent level is at least partially the result of historical accident).

205 DE VEAUX ET AL., *supra* note 156, at 337, 338.

206 *See infra* Part II.C.

207 ZILIAK & MCCLOSKEY, *supra* note 91, at 112; Lecoutre et al., *supra* note 171, at 400. Institutional rigidity is another cause of the dichotomy. *See* ZILIAK & MCCLOSKEY, *supra* note 91, at 238–44.

208 Poole, *supra* note 191, at 196.

209 *See* MARTIN, *supra* note 62, ex. 3 at 1–2; ZILIAK & MCCLOSKEY, *supra* note 91, at 28–31; *see also supra* Part I.B.

Recall that Merck's 2004 ADVANTAGE study showed (even without the three fatal heart attacks that were revealed later) a five-fold increase in heart attacks among Vioxx patients with a *p*-value of twenty percent.[210] This meant that, assuming the truth of the null hypothesis of no difference between Vioxx and naproxen, there was a twenty percent chance that the heart attack rate would have been at least five times higher among Vioxx patients. Stated differently, if the Vioxx patients had instead taken naproxen, there was one chance in five that they would have suffered five times as many, or more, heart attacks. Stated yet another way, there was an eighty percent chance that in the general population, the heart attack rate among Vioxx users would have been higher than that of naproxen users. But according to Merck, "no significant differences were observed in . . . cardiovascular . . . events" because only a ninety-five percent chance that Vioxx would have caused an increase in heart attacks in the general population is convincing enough under the status quo.[211] It is hard to imagine that these "insignificant" deaths would have been immaterial to a Merck investor or to a patient seeking pain relief. In ignoring statistically insignificant harm, not proving lack of harm, taking lack of harm as having been proven, and continuing to sell Vioxx, Merck allowed uninformed people to die.[212] Although some patients may have assumed the risk of Vioxx's dangers, Merck deprived them of a fully informed choice. Essentially, very real-life side effects of products can disappear into statistical insignificance.[213]

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210 *See supra* notes 90–91 and accompanying text; *see also supra* Part I.B.4.

211 Lisse et al., *supra* note 90, at 545; *see also* text accompanying notes 108–10 (describing similar behavior in Merck's study of patients who stopped taking Vioxx).

212 *See supra* text accompanying note 107.

213 Another drawback of a hard cut-off is that very promising results can remain unexplored. A 2001 study of the effects of the St. John's wort plant on major depression yielded a number of statistically insignificant results. In the entire sample of patients, those taking St. John's wort were forty-two percent more likely to respond positively to a predetermined minimum level than those taking a placebo with a *p*-value of fifteen percent. Richard C. Shelton et al., *Effectiveness of St. John's Wort in Major Depression: A Randomized Controlled Trial*, 285 J. AM. MED. ASS'N 1978, 1979, 1983 (2001) (showing a response in 26.5% of the group taking the herb and 18.6% in the placebo group; because of the nature of the statistical test performed, *p*-values were calculated for values other than that of no effect.); *see also* KENNETH J. ROTHMAN, EPIDEMIOLOGY: AN INTRODUCTION 124 (2002). Additionally, among patients who remained in the trial for its maximum eight-week duration, those taking St. John's wort were ninety percent more likely to experience a remission of their depression than those taking a placebo with a *p*-value of seven percent. Shelton, *supra*, at 1982–83. Among patients with relatively less severe depression, those taking St. John's wort were twice as likely to experience a remission of their depression than those taking a placebo with a *p*-value of twenty percent. *Id.* at 1983. But despite the herb's appearing to have been forty-two percent more likely to produce a positive response, and roughly twice as likely to lead to remission, the authors asserted that "St John's

These examples reveal that one of the main problems with significance testing is that it begins with the presumption of no effect. The next Section shows how such a default position might be misused.

c. Excessive Skepticism

A maxim of statistical testing is: "Don't make your null hypothesis what you want to show to be true."[214] But no effect is precisely what the maker of a potentially harmful drug wants to find.[215] The same is true of a pharmaceutical company that wants to show that a potentially market share-stealing natural remedy is ineffective.[216]

Although a high burden of persuasion may very well be appropriate in the context of subjecting someone to a criminal penalty,[217] it is not the approach patients and investors are likely to take in their decisionmaking. Neither is it always desirable. Yet the standard tack of testing a hypothesis of no effect (and rejecting the no-effect hypothesis only if there is a very small chance that the results would have appeared by chance) is a skeptical position by design. "The essential attitude for a hypothesis tester is skepticism. . . . [T]he burden of proof is on the unusual claim."[218] But as one commentator put it, this is often the backward position: "Usually, as we have seen, the statistical test is not of an efficacy of treatment so much as *inefficacy*, that is, a

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wort was not effective for treatment of major depression." *Id.* at 1978. In other words, depression sufferers were told that a cure that might double their chances of escaping their disease was ineffective because there was a seven to twenty percent chance that their symptoms would have abated had they taken the placebo. It is reasonable to posit that many sufferers would take that risk and spend a few dollars on a bottle of the herb. An outside scientist examined the original study and calculated *p*-values for a range of relative remission ratios for the less-depressed group. He found that "the data [were] equally compatible with values of 1.0 and 4.1." ROTHMAN, *supra*, at 125. In other words, the data equally supported the study authors' conclusion of "not effective" and the alternate conclusion of "4.1 times as effective." *See id*. at 127; *see also supra* text accompanying notes 190–91.

214 DE VEAUX ET AL., *supra* note 156, at 523.

215 Adelman, *supra* note 189, at 515–16 ("[T]hey . . . place the scientific burden of proof on those seeking to demonstrate risks to the environment or human health.").

216 *See supra* note 213; *cf.* Shelton, *supra* note 213, at 1985 (stating that thirteen of the St. John's wort study's sixteen authors "received funding from Pfizer and other pharmaceutical companies" and that the "study was funded as an independent research grant to the principal investigator by Pfizer Inc., manufacturers of antidepressants and St. John's wort extract"). It is fair to assume that Pfizer's antidepressant revenues substantially exceed its St. John's wort revenues.

217 *See supra* text following note 197.

218 DE VEAUX ET AL., *supra* note 156, at 511–12, 523, 564 ("[T]he null hypothesis is the status quo, the nothing-is-strange-here position a skeptic would take."); Adelman, *supra* note 189, at 550; *see also* Parascandola, *supra* note 196, at 206.

[presumption] of No Effect from which the [researcher] wants to conclude that there *is* an effect."[219]

A default position of doubt rather than belief is certainly appropriate under some circumstances, but it is the *less* cautious position when looking for a drug's dangers, or when a patient has little to lose (either because he or she is otherwise certain to die, or because a potential cure has few or no side effects). Risk-averse investors with many investment options will likewise prefer to err on the side of caution—that is, be less skeptical—by presuming harm.[220]

Methods are available to test the nonskeptical, but more cautious, position of presuming harm. Indeed, the degree of consistency of the data with any degree of harm (or benefit) of a drug can be deduced.[221] It remains the case, however, that "[b]ecause significance testing does not quantify directly the probability that a hypothesis is valid, qualitative judgments—not quantitative assessments—of the support for a hypothesis must be made."[222] The next Section discusses some of the additional information upon which informed investment and treatment decisions are based.

d. Practical Significance—Does It Really Matter?

Quantitative measures of the consistency of data with hypotheses are not only insufficient for informed decisionmaking, but are also unnecessary. Statistical significance is a measure of "Type I error": the probability of mistakenly rejecting a true null hypothesis—a so-called false positive.[223] It does not speak to the probability of "Type II errors": the probability of mistakenly failing to reject a false null hypothesis—a false negative.[224] When testing a hypothesis of no harm, a false negative error thus occurs when the drug in fact causes heart attacks, but not enough of them are observed to make the result statis-

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219 ZILIAK & MCCLOSKEY, *supra* note 91, at 138.

220 *See infra* Part III.B.1.

221 Poole, *supra* note 191, at 197; *see also* ROTHMAN, *supra* note 213, at 117–28; *supra* text accompanying notes 190–91.

222 Adelman, *supra* note 189, at 563.

223 DE VEAUX ET AL., *supra* note 156, at 543–44. As discussed, significance testing is imperfect. The significance level chosen as the threshold for statistical significance is the probability of a Type I error under the strict assumption that the null hypothesis is true. Parascandola, *supra* note 196, at 206. Each can have a similar Type I error, making the measure substantially less useful, because various hypotheses can have the same *p*-values. *See supra* text accompanying notes 190–91.

224 DE VEAUX ET AL., *supra* note 156, at 543–44. Type I and II errors are inversely correlated. The lower the chosen significance level, the greater the probability of a Type II error. *Id.* at 543–49.

tically significant using the standard five percent significance level. This type of error also occurs when an herb reduces depression symptoms, but the hypothesis that it has no effect is accepted because it did not reduce them enough.[225]

Although false negatives are often more important than false positives, very few studies mention the reliability with which they avoid them.[226] The consequences can be shocking where a large chance of missing an important effect is classified as statistically insignificant. For example, a drug that was found to cause only a statistically insignificant (and thus, per practice, to-be-ignored) reduction in heart attack rates was shown to have had a seventy-seven percent chance of reducing its would-be patients' mortality by twenty-five percent, and a forty-two percent chance of reducing it by half.[227] The problem is not isolated, and it does not appear to be improving.[228]

The rate of false negatives is not calculated for an entire study, but for a given effect size—a given magnitude of departure from the no-effect hypothesis.[229] The smallest effect (in increased chance of heart attack, lessened depression, etc.) with which a patient will be concerned is important. One can then perform a calculus resembling the Hand formula, where the costs of false positives and false negatives are discounted by their probabilities.[230] Favoring the minimization of false positives, as does significance testing, at the cost of neglecting false negatives, can be less prudent and more risky.[231] Stated differently, "'statistically significant' does not mean 'actually

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225 *See supra* text accompanying notes 210–12 & note 213. Recall that a null hypothesis can never properly be accepted. *See* DE VEAUX ET AL., *supra* note 156, at 511; text accompanying note 193.

226 ZILIAK & MCCLOSKEY, *supra* note 91, at 172.

227 Jennie A. Freiman et al., *The Importance of Beta, The Type II Error and Sample Size in the Design and Interpretation of the Randomized Control Trial*, 299 NEW ENG. J. MED. 690, 691 (1978).

228 *See* ZILIAK & MCCLOSKEY, *supra* note 91 at 136–39 (showing that the articles in a psychology journal had an overall seventy-six to eighty-three percent chance of missing a small effect, a forty-six to fifty-two percent chance of missing a medium effect, and a fifteen to seventeen percent chance of missing a large effect, and observing that "if you were dying of cancer, you might not view a [seventeen] percent chance of needlessly dying as satisfactory" (internal quotation marks omitted)); *see also id.* at 178–86 (citing examples in various fields); Rossi, *supra* note 193 (little or no improvement).

229 Freiman et al., *supra* note 227, at 691.

230 See *supra* text accompanying notes 38 and 45 for the use of this test in materiality analysis. Statisticians refer to this as a "loss function." *See, e.g.*, Lester V. Manderscheid, *Significance Levels—0.05, 0.01, or ?*, 47 J. FARM ECON. 1381, 1383–84 (1965).

231 Parascandola, *supra* note 196, at 208. The same is true when dealing with potential harm to the environment. *See* Adelman, *supra* note 189, at 544–45, 550–53.

important' or 'meaningful,' even though it . . . sounds that way."[232] A declaration of statistical significance does not answer the question "Does it matter?" because it ignores the gravity, and thus the *practical significance*,[233] of the observed effect.

Imagine that a miracle pain reliever is suspected of causing both mild colds and instant death. If mild colds and instant death occur with the same frequency, their significance levels are identical. Although many a pain sufferer might risk the former, most would forgo relief rather than risk the latter. Some, however, may find their pain so unbearable, and may be on the verge of passing on from, say, the cancer causing their pain, that they may be willing to risk instant death. The decision to use a drug (or a natural remedy)[234] that is less certain to have an effect, or has only a small effect, requires an individualized, necessarily subjective, determination.[235] What matters depends entirely on the situation of the patient, not the researcher or, worse, the drug company, doing the testing.

Practical significance is the true measure of a drug's impact on patients' life and health decisions, and thus on investors' financial decisions. As the Vioxx and Zicam examples illustrate, risks which are statistically insignificant but practically very real can be highly relevant to investors. Although this is certainly true in cases where the risks are related to a large portion of the drug maker's sales, the securities laws do not require such a connection—they require only a potential impact on an investor's decision to buy a company stock, and such decisions can be based on many factors.[236]

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232 DE VEAUX ET AL., *supra* note 156, at 539, 601; ZILIAK & MCCLOSKEY, *supra* note 91. Unfortunately, "a very frequent error consists in mistaking statistical significance for scientific significance: [believing that] the more significant a result is, the more scientifically interesting it is, and/or the larger the true effect is." Lecoutre et al., *supra* note 171, at 400. The conflation of statistical with practical significance appears to be getting worse. ZILIAK & MCCLOSKEY, *supra* note 91, at 88; *see also id.* at 72, 75, 81; Lecoutre et al., *supra* note 171, at 406.

233 Practical significance is also referred to as "economic," "substantive," or "scientific" significance.

234 See *supra* notes 213, 216, and 219 for an example citing St. John's wort.

235 A small enough sample size will make any observed difference in rates of harm statistically insignificant, and a large enough sample will make any observed difference statistically significant. DE VEAUX ET AL., *supra* note 156, at 539; Meier et al., *supra* note 201, at 155, 160. Neither case implies practical significance. In the former, the harm may be great enough that even one instance of it matters. In the latter, the difference in effect from the no-change presumption may be so small as to be irrelevant.

236 SEC v. Jakubowski, 150 F.3d 675, 681 (7th Cir. 1998) (stating that materiality covers "whatever is important enough to reasonable participants in an investment decision to alter their behavior," including factors unrelated to stock price); *see also supra* Part I.A.2 (describing the historical and current standards).

C. Personal Probabilities Matter

There are serious shortcomings in the common method of assessing pharmaceutical safety, as seen by the different types of probabilities and the ways in which each is relevant to decisionmaking. Significance testing is deficient—both because of its inherent limitations and the ways in which it is applied—in its ability to illumine information useful to judgments about pharmaceutical safety. It is useful primarily when combined with a patient's individual situation. The philosophy of Bayesianism shows that subjective, personal knowledge can and should be combined with objective knowledge, like that obtained in an empirical test, in decisionmaking.[237] Ultimately, there are many ways to explain a set of facts other than by comparing the relative frequencies of different outcomes. Knowledge external to experiments, like the fact that everyone who suffered anosmia did so immediately after feeling a burning sensation following Zicam use, matters. Bayesians welcome outside knowledge, using it to form a "prior probability" that, say, a drug is unsafe.

A prior, or subjective, probability is an individual's estimate of probability that is formed independently of the observed experimental results.[238] It is based on one's general knowledge and understanding of the situation and it can stand alone or modify the experimentally observed probability of harm.[239] It is possible, though unlikely, that one has no prior estimate of an outcome. For example, even though one may have no knowledge of a new disease or a new drug intended to treat it, everyone knows that some drugs sometimes have side effects. This subjective knowledge is less reliable than that of one who has studied the disease, but it is nonetheless relevant to one's decision. An important characteristic of subjective probabilities is that they are updated as additional information becomes available—say, as more heart attacks or cases of anosmia become public.[240]

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237 *See* Senn, *supra* note 154, at 37.

238 *See* Adelman, *supra* note 189, at 508 n.37, 568–69. Technically, a prior probability can also be a precise theoretical, or even empirical, probability. *See* Charles Yablon, *The Meaning of Probability Judgments: An Essay on the Use and Misuse of Behavioral Economics*, 2004 U. ILL. L. REV. 899, 913, 927–28 & n.167. In practice, they are subjective because studies are done in the first instance because theoretical or empirical data on a drug's safety do not exist. *See* Senn, *supra* note 154, at 36–37.

239 Adelman, *supra* note 189, at 508 n.37, 568–69; *see supra* note 167 and accompanying text.

240 Adelman, *supra* note 189, at 508; Lawsky, *supra* note 163, at 1059 n.130; *cf.* text following note 197 (discussing the need for "degrees of belief").

Bayesian statistics thus approaches knowledge by asking the question that really matters: Given my observations, what is the probability that the drug causes harm?[241] A criminal-law illustration is instructive.[242] Imagine that a defendant in a city of 100,000[243] is arrested for shooting his wife. He argued with and beat his wife earlier in the day and on other occasions, and he once shot at someone. A gun with a partial print was found near the body. An expert testifies that only one person in a thousand, including the defendant, has such a print. What is the significance of these findings? Based on the print alone, and at first blush, it would seem that the defendant looks rather guilty because he is 1000 times more likely to have left the print than a random member of the population. But the comparison with the population sample is all but irrelevant: a juror's job is not to weigh the defendant's guilt against *one* random member of the population, but against the probability that *anyone* else did it. Based again only on the print, the defendant is actually ninety-nine times more likely innocent than guilty, and ought to be acquitted.[244] However, a juror may have the prior knowledge that the defendant had a violent history with his wife and that he shot at someone. The jury's final estimate of the defendant's guilt is the statistical probability (based on the print) modified by the necessarily subjective probability (based on the prior violence) that he did it. As this example shows, the empirical probability can be vastly different from the final modified probability. Normally insufficient statistical evidence can become sufficient if paired with data that forms the basis for a prior estimate.

Medical decisions embrace information that is both external and internal to the individual. The former include data like AERs, effect sizes, false negatives, and indeed, consistency with a no-harm hypothesis.[245] The latter include known susceptibilities (e.g., heart attacks by

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241 *See* DE VEAUX ET AL., *supra* note 156, at 536 n.4; Yablon, *supra* note 238, at 913 ("Bayes's Theorem is a mathematical rule for combining a prior probability distribution for some individual property or event *A*, with . . . the general likelihood of *A* given the observance . . . of *B*. Bayes's Theorem enables us to compute the . . . probability of *A* . . . after an observation of event . . . *B*."). A recitation of the mathematical formula for Bayes's theorem is unnecessary for this Article.

242 This example is adapted from MICHAEL O. FINKELSTEIN, QUANTITATIVE METHODS IN LAW 87–90 (1978). *See supra* text following note 197.

243 Assume that this is the relevant population of which the defendant is a part.

244 If only one person of a thousand could have left the print, then in a city of 100,000, there are only 100 suspects: the defendant, and ninety-nine others.

245 *See generally supra* Part II.B.2.

arthritis patients),[246] the severity of symptoms, and personal risk tolerances.[247]

The ultimate question under Rule 10b-5 is how investors process information, both on their own and in the shoes of potential users of a drug. They care about pecuniary—practical—significance. After all, if doctors refuse to prescribe, or patients refuse to use, a drug, the company that makes the drug will make that much less profit.[248] Investors' reactions to news like the revelation about Zicam on Good Morning America show that decisions are not made through the hyper-objective, substance-purged method of common significance testing, but instead are made subjectively.[249] Rightly or wrongly in any situation, they use the "mind's internal detector"[250] to process statistical evidence in light of background knowledge. "Rational belief-formation . . . is holistic; it is the amalgamation of frequency data with the other (theoretical or observational) grounds of belief that produces experts', assessors', and regulators' Bayesian probabilities."[251] Both professionals (professional investors and doctors) and laypeople (retail investors and patients) alike use the richness of information conferred by ordinary and experienced recognition,[252] viewing information in context. They care that cold sufferers lost their sense of smell immediately after using Zicam. They care more about instant death than mild colds.

Significance testing only addresses the effect of sampling error—the possibility that the sample being tested is not representative of the population from which it is randomly drawn.[253] Unfortunately, it is widely employed to make broader mathematical claims about the operation of the world, and thus over- or understates things. In addition,

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246 *See supra* note 72 and accompanying text.

247 *See supra* Part II.B.2.d; *see also* Yablon, *supra* note 238, at 902–03, 909, 927–28. This is not to suggest, of course, that medical decisions should be based on anecdote alone.

248 *See* Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309, 1323 (2011). Patients may also benefit from the signals given by analysts who digest and act on information about a drug's safety. *See infra* text accompanying notes 304–07; 345–49.

249 *See, e.g.*, Stephen Figlewski, *Market "Efficiency" in a Market with Heterogeneous Information*, 86 J. POL. ECON. 581, 584–85 (1978); Milton Harris & Artur Raviv, *Differences of Opinion Make a Horse Race*, 6 REV. FIN. STUD. 473, 474 (1993) ("[D]isagreements can arise either because speculators have different private information or because they simply interpret commonly known data differently.").

250 ZILIAK & MCCLOSKEY, *supra* note 91, at 148.

251 Matthew D. Adler, *Against "Individual Risk": A Sympathetic Critique of Risk Assessment*, 153 U. PA. L. REV. 1121, 1216 (2005).

252 *See* Joshua D. Wright & Douglas H. Ginsburg, *Behavioral Law and Economics: Its Origins, Fatal Flaws, and Implications for Liberty*, 106 Nw. U. L. REV. 1033, 1071, 1072 (2012).

253 *See supra* Parts II.B.1, II.B.2.a.

significance testing depends on an accurate sampling model. When there is systematic manipulation of data,[254] the sampling model will be wrong by definition, making the results of significance tests meaningless.

Significance testing attempts to "test the significance of numbers 'in their own terms,' objectively, without regard for human purposes."[255] But in attempting to eliminate judgment, it truncates the reasoning process by removing relevant facts from consideration.[256] It kills data flow to those who can make the best use of it, or at the very least, have a right to it.

The good news is that the law need not reject, and with *Matrixx*, has not entirely rejected, the use of personal judgment. In reaching the correct decision, however, *Matrixx* appears to have missed the point in some areas. The next Part offers some suggestions for the future of pharmaceutical disclosures by building on the material discussed thus far.

III. Drug Trials and Speed Skating: The Case for Complete Disclosure

In light of the inadequacies of significance testing shown in Part II, this Part offers a justification for a new standard of complete disclosure. It further argues that the information-overload and excessive-burden reasons for not requiring full disclosure of adverse events do not withstand scrutiny.

A. Matrixx Was (Mostly) Right

The Supreme Court in *Matrixx* reached half of the result suggested by the previous analysis, holding that the plaintiffs did not have to plead a statistically significant number of AERs for those reports to

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254 *See supra* Part I.B–C.

255 Ziliak & McCloskey, *supra* note 91, at 12; *see also* Adler, *supra* note 251, at 1142 ("[S]cientists and, traditionally, statisticians have eschewed the suggestion [of using Bayesian methods], because it makes essential reference to *minds*—to beliefs—and thus has seemed too subjective for scientific purposes."). Interestingly, there is evidence that when scientists know they are being evaluated, they do not abide by the existence-nonexistence dichotomy, implying that the system's participants may not fully believe in it. *See* Lecoutre et al., *supra* note 171, at 402–04, 406–08.

256 *Cf.* Yablon, *supra* note 238, at 928 (discussing how a clinician, when determining the likelihood of suicide in a particular patient, would know more about that patient than simply that he or she was depressed—they would also know the "specific characteristics" of that patient's psychological state).

be material.[257] Relying primarily on the premise that a bright-line rule would artificially exclude criteria that would matter to investor trading decisions, the Court held that the materiality inquiry was necessarily contextual.[258] There were reliable indicia, other than a statistically significant number of adverse events, indicating that Zicam use caused injury, and enough of them were plausibly shown by the plaintiffs to survive a motion to dismiss.[259]

The Court also ruled that statistically significant data are evidential, but not dispositive.[260] In the case before it, enough facts were available to lead to a "substantial likelihood" that they would have "*significantly* altered" a reasonable investor's assessment of the "total mix" of information available in the market.[261] It was key that Zicam made up seventy percent of Matrixx's sales and that other cold remedies were readily available to consumers.[262]

Nevertheless, the Court explicitly gave drug manufacturers a great deal of discretion to withhold news of adverse events from the market: adverse events, without "something more," need not be disclosed.[263] In particular, it expressed concern over "bury[ing] shareholders in an avalanche of trivial information."[264] Implicit in its holding is a fear of burdening companies with excessive disclosure.[265] But as the case studies in Part II demonstrated, even a bare AER, without any quantitative clothing, can be very useful in making investment and treatment decisions. In effect, the "something more" is supplied by the decisionmaker.

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257 Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309, 1318, 1323 (2011). For the relevant facts of the case, see *supra* Part I.C.

258 *Matrixx*, 131 S. Ct. at 1319, 1321.

259 *Id.* at 1319–20 & n.9, 1322–23.

260 *Id.* at 1321.

261 *Id.* at 1318, 1321, 1323 (internal quotation marks omitted).

262 *Id.* at 1323.

263 *Id.* at 1321.

264 *Id.* at 1318 (quoting Basic, Inc. v. Levinson, 485 U.S. 224, 231 (1988)) (internal quotation marks omitted).

265 *See id.* at 1321; TSC Indus., Inc. v. Northway, Inc., 426 U.S. 438, 448 (1976) ("[I]f the standard of materiality is unnecessarily low, . . . the corporation and its management [may] be subjected to liability for insignificant omissions or misstatements."); Kenneth C. Fang & Brad Jacobs, *Clarifying and Protecting Materiality Standards in Financial Statements: A Review of SEC Staff Accounting Bulletin 99*, 55 BUS. LAW. 1039, 1062 (2000); James Harlan Koenig, *The* Basics *of Disclosure: The Market for Information in the Market for Corporate Control*, 43 U. MIAMI L. REV. 1021, 1064–65 (1989); Brown, Jr., *supra* note 136 (Matrixx's argument that its "only safe alternative would be to provide investors with every adverse event report . . . is an argument that disclosure would be burdensome to the company").

Moreover, the Court stated that a firm does not have an affirmative duty to disclose adverse events if it makes no positive statements about itself elsewhere that would otherwise be misleading given the existence of bad news.[266] In this case, the statement would have to be tempered so as not to be misleading.[267] In other words, complete silence about adverse events would be acceptable as long as no countervailing positive statements were made.[268]

Finally, despite its rejection of bright-line rules, the undercurrent in *Matrixx* is that a significance test failing to reject the hypothesis that Zicam was harmless would have been sufficient to relieve Matrixx from its duty to disclose any AERs. The Court observed that Matrixx "had not conducted any studies of its own to disprove" the "link between Zicam's key ingredient and anosmia," despite the evidence that it had available.[269] But even if Matrixx had such studies "disproving" a connection between Zicam and anosmia, they would have been significance tests that failed to disprove beyond the standard five percent level the assumption that Zicam was harmless. As discussed in Part II, these studies would have been relatively meaningless to patients and doctors, and their investor counterparts.[270]

B. Full Disclosure

Ultimately, the only materiality standard that would provide investors, and their doctor and patient proxies, the information they need while remaining true to the spirit of the '34 Act is one of full disclosure.

For the first fifty years of its existence, Rule 10b-5's materiality standard was much more investor-protective and less paternalistic than it has been since *Basic*.[271] It was concerned with "subtle and involved" frauds (presumably including the abuse of statistical tools), "inequality of knowledge," information that "*might*," "may," or has a "more than marginal" probability of influencing an investment deci-

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266 *Matrixx*, 131 S. Ct. at 1321.

267 *Id.*

268 *Id.* at 1322 ("Even with respect to information that a reasonable investor might consider material, companies can control what they have to disclose under these provisions by controlling what they say to the market.").

269 *Id.* at 1323; *see also id.* at 1319, 1321. *But compare supra* text accompanying notes 134, 140–42 (Matrixx relying on a clinical trial intended to test Zicam's effectiveness as a cold remedy), *with supra* text accompanying note 123 (Matrixx acknowledging that it did not test Zicam's effect on smell).

270 Recall also that even a statistically significant finding only shows causation in a weak sense, inferring it from data consistency. *See supra* Part II.B.2.a.

271 *See supra* Part I.A.2.

sion[272]—it was intended to protect the lowest common denominator of investor, ranging from the speculator to the conservative trader.[273] This earlier standard fits better with what statistical theory predicts will matter to investors. Disclosure facilitating informed decisionmaking was truly the cornerstone of the regulatory regime. It forced those who had to air their laundry to keep it clean.

The lessons from Vioxx and Zicam support the proposition that, in the unique context of the pharmaceutical industry, a broader conception of materiality deserves to be revisited. This may be accomplished either by returning to the pre-*Basic* standard for adverse-event reporting, or by understanding the *Basic* standard to require disclosure of all adverse events.[274] As the following Sections show, investor (and patient) risk aversion, when combined with low switching costs, support the conclusion that all adverse-event news is material. The information-overload and excessive-burden justifications for eschewing a rule that classifies all drug harms as material are unpersuasive. Also unpersuasive are the courts'—and particularly the Supreme Court's—concerns for which these justifications may be straw men.[275]

1. Risk Aversion and Switching Costs

Imagine that you are an Olympic speed skater. At the 2006 Olympic speed-skating competition, it seemed that the outer lane was faster than the inner.[276] In the women's 1500 meter race, the racer who started in the outer lane won ten of seventeen races, and the average margin by which she won was nearly 0.5 seconds—a large margin by speed-skating standards. A significance test of the hypothesis that the inner and outer lanes were equal yielded a *p*-value of thirty-nine percent. The authors concluded, "Events that happen more than a third of the time are not remarkable. So, even though there is an observed difference between the lanes, [one] can't conclude that it isn't due simply to random chance. . . . There's insufficient evidence to declare any lack of fairness."[277] Maybe so, but given a choice, a ra-

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272 *See supra* Part I.A.2.a.

273 *See supra* text accompanying note 38.

274 This Article is agnostic as to the means of returning to the pre-*Basic* standard or reunderstanding the *Basic* standard—whether it is by court decisionmaking, SEC rulemaking, or Congressional action.

275 *See infra* Part III.B.3.

276 This example is from DE VEAUX ET AL., *supra* note 156, at 650–51, 652, 655–57.

277 *Id.* at 657. Recall that, assuming no outside influences and a strict interpretation, the *p*-value is the probability of seeing data at least as extreme as that observed given the truth of the null hypothesis. *See supra* notes 176, 197, 223 and accompanying text.

tional skater would always choose the outer lane, even with a thirty-nine percent chance that its times were 0.5 seconds faster merely from random variation.[278]

The same is true of investors, who are generally risk averse, preferring the highest possible expected return given their particular tolerance for risk,[279] have very low switching costs,[280] and are interested in monetary returns from a security rather than the security itself.[281] Each disclosed adverse event has the effect of increasing the risk associated with a security and reducing its expected return. If and when a security's risk-return blend, as indicated by adverse events and other news, worsens enough to offset the cost of switching—which essentially consists of a minor commission; possible capital-gain taxes if the sale is at a profit, which it may not be if it is prompted by bad news; and the time required to place the trades—an investor will switch to another investment that fits his or her taste for risk.[282] With today's very low switching costs and with "so many substitutes for any one firm's stock that the effective demand curve is horizontal,"[283] investors should switch based on a low threshold of bad news. They would not wait for bad news to reach the level of statistical significance, or the lower, but still very high, level set forth in *Matrixx*. In addition, with no discovery available,[284] AERs may be the only evidence of a drug's dangers; they are only the tips of an iceberg of larger problems that will eventually surface all at once.

In addition, each investor has a different risk tolerance,[285] a unique view of a company's financial future, and a unique set of sub-

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278 The result would be different if the skater had to "pay" for use of the outer lane by having some number of seconds added to her race time. In this case, she would have to evaluate, using both the calculated statistic and her subjective knowledge about the track and the other skaters, how much the outer lane was worth.

279 Janet E. Kerr, *Suitability Standards: A New Look at Economic Theory and Current SEC Disclosure Policy*, 16 PAC. L.J. 805, 814, 821 (1985); Donald C. Langevoort, *The SEC, Retail Investors, and the Institutionalization of the Securities Markets*, 95 VA. L. REV. 1025, 1047 (2009).

280 Samuel Issacharoff, *The Vexing Problem of Reliance in Consumer Class Actions*, 74 TUL. L. REV. 1633, 1650 (2000); Lynn A. Stout, *Are Stock Markets Costly Casinos? Disagreement, Market Failure, and Securities Regulation*, 81 VA. L. REV. 611, 633–35 (1995).

281 West v. Prudential Sec., Inc., 282 F.3d 935, 939 (7th Cir. 2002).

282 *See* Kerr, *supra* note 279, at 808, 812 & n.46, 816; Langevoort, *supra* note 279, at 1043 (noting that "rational actors weigh all available information in a Bayesian search process" in which they update their view of a drug and its maker as additional information is made available); *supra* text accompanying note 240.

283 *West*, 282 F.3d at 939.

284 *See supra* note 117 and accompanying text.

285 *See* Clive W.J. Granger, *Some Comments on Risk*, 17 J. APPLIED ECONOMETRICS, 447,

jective knowledge.[286] Each will thus react differently to news as it is released. This results in a range of tipping points of when investors deem it appropriate to switch out of an investment,[287] but a disclosure regime that waits for a critical mass of news to accumulate will cause a sudden (and presumably undesirable to a market that values gradualness and predictability) change in securities prices.[288]

Like investors, most patients are likely to be risk-averse and generally have low switching costs.[289] Thus, they will want to know—or at least want their doctors to know—about individual adverse events, especially if they have something in common with the person to whom the purportedly irrelevant event happened. The commonality may be as simple as a naproxen user declining to switch to Vioxx after learning that Vioxx patients suffered five times as many heart attacks. Indeed, interviewed jurors in various Vioxx product liability cases roundly showed their disgust with Merck's nondisclosure of the drug's dangers.[290] Each patient will be uniquely positioned to determine, with his or her doctor's help, whether a drug, given its adverse-event history, is right for him or her. Some may not care about any AERs while some may switch based on one, but the decision properly belongs to the patient, not the drug company.

2. Justifying Partial Disclosure

The two major justifications for a relatively narrow understanding of materiality under the securities laws are that investors will be flooded with so much information that they will be unable to digest it, and that companies would be unfairly burdened with disclosures if the standard were too loose. This Section discusses each of these reasons, and argues that they are inapposite in the pharmaceutical disclosure context.

450–51 (2002); Jonathan Ingersoll, *Multidimensional Security Pricing*, 10 J. FIN. & QUANTITATIVE ANALYSIS 785, 788 (1975).

286 *See supra* Part II.C.

287 Modern portfolio theory might suggest that rational investors would not care about AERs because they are idiosyncratic risks that have been diversified away, but investors do in fact trade on released news. *See supra* note 249 and accompanying text.

288 *Cf.* Langevoort, *supra* note 279, at 1041 n.49.

289 *See, e.g.*, Matrixx Initiatives, Inc. v. Siracusano, 131 S. Ct. 1309, 1323 (2011) (noting many alternative cold remedies to Zicam). Patients and doctors may, however, be brand loyal.

290 Alex Berenson, *For Merck, the Vioxx Paper Trail Won't Go Away*, N.Y. TIMES, Aug. 21, 2005, at 1, 25; Alex Berenson, *Jury Calls Merck Liable in Death of Man on Vioxx*, N.Y. TIMES, Aug. 20, 2005, at A1.

a. Information Overload

There is a fair amount of debate over whether and to what extent market participants can accurately digest even material information.[291] Some argue that investors are rational and will make better decisions when given additional data, but others hold that behavioral and psychological factors prevent investors from behaving rationally once a critical mass of information has been absorbed.[292] The primary criticism of more, rather than less, mandatory disclosure is that too much data *at once* on a given choice will overburden the cognitive capacities of information consumers.[293] That is not to say that additional information is always bad, but only that "as a decision maker is given more information, decision quality initially increases; once the information level reaches a certain point, however, the decision maker's decision quality decreases if [he or] she is given additional information."[294] In addition, critics argue, although professional investors likely can assimilate more data than retail investors, they are not immune to information overload.[295]

i. Doubting Information Overload

There are significant hurdles that must be overcome before accepting information overload as a reason to protect investors from themselves. As a general matter, and as now-SEC Commissioner Parades[296] acknowledges, we are not "ready to toss aside the [investor-

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291 *See* Troy A. Paredes, *Blinded by the Light: Information Overload and its Consequences for Securities Regulation*, 81 WASH. U. L.Q. 417, 417, 443 (2003). See *supra* Part II for the argument that every adverse event is material. Paredes, *supra*, is one of the preeminent and most recent references on this topic, citing scores of sources and covering most major arguments on either side. Although it favors the view that overload is probably a problem in securities regulation, it ultimately argues for more empirical research on the topic. *Id.* at 420, 483–85. It does not focus on the particular regulatory needs of any specific industry, including the pharmaceutical industry.

For a recent extensive work arguing that overdisclosure is a problem where expert intermediaries are not involved, as they are in the securities regulation area discussed herein, see Omri Ben-Shahar & Carl E. Schneider, *The Failure of Mandated Disclosure*, 159 U. PA. L. REV. 647, 659, 732 (2011). This Article suggests that the ability of laypeople to gather and process information should not be underestimated. *See supra* note 24 and accompanying text; *infra* Part II.C; *infra* Part III.B.

292 *See, e.g.*, Paredes, *supra* note 291, at 420, 421 n.11, 443 & nn.120–21, 456–57.

293 Paredes, *supra* note 291, at 441; Susanna Kim Ripken, *The Dangers and Drawbacks of the Disclosure Antidote: Toward a More Substantive Approach to Securities Regulation*, 58 BAYLOR L. REV. 139, 160 (2006).

294 Paredes, *supra* note 291, at 441.

295 *Id.* at 453–55.

296 *SEC Biography: Commissioner Troy A. Paredes*, SEC, http://www.sec.gov/about/commissioner/paredes.htm (last updated July 17, 2012); *see* Paredes, *supra* note 291.

]rationality assumption completely."[297] As a threshold matter, a great deal of the data suggesting that cognitive deficiencies impede rational decisionmaking has been gathered under artificial experimental conditions, rather than in a functioning marketplace.[298] Some cognitive errors that appear in experimental settings do not "survive exposure to real-world settings."[299]

There is also insufficient evidence to know the extent to which investors are susceptible to information overload, and if they are, where retail or professional investors are in relation to the overload point.[300] The effect on investors of receiving less information is likewise unknown.[301] There is general agreement, ranging from epidemiologists to securities law scholars, that putting information into an understandable form is perhaps most important in ensuring that it is useful.[302] In any case, a key problem in curtailing disclosure is determining which disclosures should be cut—and more importantly, who should make such a determination—to make the remaining available data more digestible.[303]

No information should be more important to investors, doctors, and patients than that a pharmaceutical company's bread-and-butter products—pharmaceuticals—are injuring patients. This is especially so when the injuries are deadly or otherwise permanent.[304] Even disclosure minimalists agree that having "skin in the game" motivates information processing.[305] Combined profit *and* health incentives working together in this context (i.e., doctors/patients informing inves-

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297 Paredes, *supra* note 291, at 445, 483 ("[I]t is not clear that information overload leads to the kind of systematic biases often associated with behavioral finance.").

298 Wright & Ginsburg, *supra* note 252, at 1045.

299 *Id.* This finding is not surprising given that it is very difficult to design experiments that account for all result-affecting outcomes, while unfettered decisionmakers will use all information available to them. *See supra* Part II.

300 Paredes, *supra* note 291, at 450, 473.

301 *Id.* at 450, 458 ("After all is said and done, we might learn that [professionals]—because they have greater ability and incentive to 'get it right'—make very good investing decisions in the face of vast quantities of information and that reducing the level of disclosure would not meaningfully improve their decisions.").

302 Paredes, *supra* note 291, at 447, 475; Poole, *supra* note 191, at 197; Ripken, *supra* note 293, at 146–47; *see also* Jonathan R. Macey & Geoffrey P. Miller, *Good Finance, Bad Economics: An Analysis of the Fraud-On-The-Market Theory*, 42 STAN. L. REV. 1059, 1083 (1990).

303 Paredes, *supra* note 291, at 420, 459–62.

304 One might argue that profits should be most important to drug companies, even at the expense of drug safety. Leaving aside the obvious moral and ethical deficiencies of this view, putting dangerous drugs onto the market is not likely to benefit a manufacturer beyond the short term.

305 Paredes, *supra* note 291, at 455; *see also* Wright & Ginsburg, *supra* note 252, at 1070–72.

tors informing doctors/patients informing investors and so on) may very well lead to better information processing than would the sum of its parts. It is sufficient for each group to be interested in and act on enough data that a group's action serves as a signal to another. In addition, compared with, say, earnings reports, which "require a large investment in information-gathering to decode,"[306] the fact of an injury is immediately understood as something that elicits caution.[307] Thus, the nature of the information and its consumers raises questions about whether drug harms are the type of data that will easily overload.

In addition, the too-much-at-once concern is less acute in the pharmaceutical context. Very little adverse-event data is revealed, so not only is there little chance of overloading on it, but it would also be more likely to substantially move one's opinion about a drug's safety.[308] Even assuming investors are overloaded because they receive other data on a drug maker, patients interested in their specific susceptibilities are less likely to be. Relatedly, the continuous disclosure advocated herein would cause information consumers to receive information steadily, presumably allowing for easier digestion, rather than all at once. And if there are so many AERs appearing at once that one might consider them overwhelming, they should have to be disclosed despite any potential overload because the simple fact of an overwhelming number of injuries is itself informative.[309] Information overload is concerned not with individuals' ability to understand data, but with their cognitive ability to process too much of it at once.[310] In the present context, the presence of too much information (i.e., many adverse events) is itself a very valuable fact.

ii. Disclosure Even Assuming Some Overload

Because each patient and investor is uniquely situated, no two will digest the same information identically, nor necessarily be inter-

306 Macey & Miller, *supra* note 302, at 1085.

307 Of course, as discussed previously, this is not to say that a patient will not decide, based on his or her circumstances, to use the drug despite notice of the injury.

308 *See supra* Parts II.C, III.B.1; *cf.* Letter from Lucian A. Bebchuk et al. to Elizabeth M. Murphy, Sec'y, SEC 1, 7–8 (Aug. 3, 2011) (on file with The George Washington Law Review) (advocating, on behalf of some commentators who believe that information overload may be a problem, that the SEC "develop rules to require public companies to disclose to shareholders the use of corporate resources for political activities" because, inter alia, "the Commission's current rules do not require public companies to give shareholders detailed information on corporate spending on politics").

309 *Accord infra* text accompanying note 336.

310 Paredes, *supra* note 291, at 440–41.

ested in the same information.[311] *Someone*—an analyst paying attention to a given company, or perhaps a patient or potential patient, most likely advised by his or her doctor—will very likely care about any given injury associated with a drug. It is unfair to punish that someone with information deprivation because of another's inability or disinterest in reviewing or analyzing a disclosure.[312] The Second Circuit correctly recognized that the securities laws were for the benefit of all investors, from the prudent and conservative to the chartist and speculator, all of whom are "'reasonable' investors entitled to the same legal protection."[313]

But disclosure is warranted in this case even if truth does not "find relatively quick acceptance on the market"[314] and investors (and patients) might in some contexts benefit from "paternalistic withholding of accurate information."[315] As the Vioxx and Zicam examples show, and given the consequences for patient health, it is more sensible, and more consistent with the pro-disclosure tilt of section 10(b) of the '34 Act and Rule 10b-5, to allow the market (for treatment and securities) to determine what data are important. Although drug companies may in principle be better positioned to know what data is practically significant, giving them the option to withhold it on this ground invites gaming of the process given their financial incentive to control the disclosure of negative information.[316] Drug companies therefore cannot be trusted to make the evaluation honestly and disclose the data,[317] and the judgment should not be left to them.[318]

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311 *See* Paredes, *supra* note 291, at 459; *supra* Part I.B–110.

312 *See* Wright & Ginsburg, *supra* note 252, at 1052; *cf.* Paredes, *supra* note 291, at 460–61 (discussing various scaled-back disclosure options, all of which involve either making disclosures better suited to one group at the expense of another or eliminating them entirely).

313 SEC v. Tex. Gulf Sulphur Co., 401 F.2d 833, 849 (2d Cir. 1968), *cert. denied sub nom.* Coates v. SEC, 394 U.S. 976 (1969); *see also* Flamm v. Eberstadt, 814 F.2d 1169, 1175 (7th Cir. 1987); *supra* note 38 and accompanying text.

314 *Cf. Texas Gulf Sulphur*, 401 F.2d at 859 (asserting that "truth *does* find relatively quick acceptance on the market" (emphasis added)).

315 Basic, Inc. v. Levinson, 485 U.S. 224, 234 (1988).

316 *See supra* Part I.

317 *See* David L. Ratner, *The SEC at Sixty: A Reply to Professor Macey*, 16 CARDOZO L. REV. 1765, 1767–68 (1995) (arguing that disclosure requirements protect the less informed from the better informed); Ripken, *supra* note 293, at 155 ("Ultimately, disclosure decreases investor risks and protects the public interest. It can be seen as a way of remedying the social and economic wrongs that occur when those with greater information exploit those with less information."). Of course, drug companies may disclose any positive news that they want, however immaterial.

318 Fraud would certainly still be possible under the full-disclosure rule proposed herein. There would, however, no longer be a system in place that magnifies the effect of a given fraud—e.g., hiding three heart attacks to get the benefit of not having to disclose eight. *See*

An overworked or captured government agency is also a bad candidate for determining what should be disclosed.[319] The same is true of courts, which can only adjudicate a matter after the fact. Even if courts are able to properly decide whether certain adverse events should have been disclosed, and there were no costs involved with using the court system, there are still patients in the equation here for whom permanent injuries can rarely, if ever, be adequately compensated ex post.[320]

iii. Giving Investors and Patients What They Need While Giving the Company Some Say

If one still fears that investors, especially nonprofessional ones, would not be able to sift out important data, or that full disclosure would be unfair to pharmaceutical companies,[321] a potential solution that preserves full disclosure is to require only Internet disclosure while permitting pharmaceutical manufacturers to classify drug harms into two categories: one for what it considers a minor event and one for what it considers to be of more serious concern.[322] Both categories, or buckets, would be available to everyone who sought them out.

In addition, the minor bucket would have the effect of serving as a spam filter of sorts; one often ignores what is in his or her spam folder, but a look is sometimes worthwhile. If one seeks a reason to dismiss an AER, a good reason is that the report is in the minor

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supra Part I.B.4. Presumably, it would be more difficult to hide eight heart attacks than three, in turn making it more difficult to keep from alerting the market. Further, if an adverse event is discovered, there will be no question that it should have been disclosed. There should therefore be less incentive to cover it up because there is no plausible reason that can be given later for not having disclosed it, such as a claimed belief at the time that it was immaterial.

319 Roberta Romano, *Empowering Investors: A Market Approach to Securities Regulation*, 107 YALE L.J. 2359, 2366, 2378 (1998) ("[N]o government entity can know better than market participants what regulations are in their interest. . . . The institutional investors who dominate today's markets have far greater ability, as well as financial incentives, to process information . . . than does the SEC staff."); *see also* Paredes, *supra* note 291, at 452 n.157. It is also questionable whether an overworked or captured agency is able or willing to assist data consumers. *See supra* note 24.

320 Mark A. Geistfeld, *Placing a Price on Pain and Suffering: A Method for Helping Juries Determine Tort Damages for Nonmonetary Injuries*, 83 CAL. L. REV. 773 (1995); Lisa J. Laplante, *Negotiating Reparation Rights: The Participatory and Symbolic Quotients*, 19 BUFF. HUM. RTS. L. REV. 217, 224, 248–51 (2013) (discussing the incommensurability problem in the human-rights context).

321 *See infra* Parts III.B.2.b, III.B.3.

322 This is essentially a take on tiered disclosure, under which "one set of disclosures [is] available to experts, and a different set . . . to lay investors." Paredes, *supra* note 291, at 461, 478–79. Further, firms already have substantial control over the form of their disclosures, and this proposal is consistent with that policy.

bucket. But sometimes, one has special reason to look for more detailed data than under the usual course of business. In this case, the data would be available.

Such a system would serve multiple functions. First, it would provide each uniquely situated patient with reason to care about a given type of adverse event access—directly or via his or her doctor—to data that would otherwise be unavailable. Next, it would promote investor autonomy by allowing the market—which is to say, professional investors with a superior ability and resources to accurately process news and set market prices,[323] and whose actions benefit retail investors as well[324]—rather than the drug manufacturer, to decide whether the data are worth acting on. In addition, consumers of adverse-event data would have to actively pull it from the website where it is posted, because it would not be pushed to them. It may very well be that those who pull it will do so because they are able to process it. Finally, it provides drug manufacturers with a semi-official say in how their adverse-event disclosures are packaged, allowing the company to express an opinion on the importance of a given harm and leaving the ultimate decision on whether and how to react to patients and investors.[325]

b. Excessive Burden

Another implicit argument against full disclosure is that it would create an excessive burden for the disclosing company.[326] But in this context, the marginal burden of requiring all adverse events to be disclosed is, indeed, marginal.[327] The drug companies by definition al-

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323 *See* Wright & Ginsburg, *supra* note 252, at 1045, 1073.

324 *See* Frank H. Easterbrook & Daniel R. Fischel, *Mandatory Disclosure and the Protection of Investors*, 70 VA. L. REV. 669, 693 (1984); Paredes, *supra* note 291, at 431–33, 452–53; Romano, *supra* note 319, at 2366 & n.17, 2369, 2378; *infra* notes 355–56 and accompanying text.

325 One complaint about this two-bucket system might be that drug makers will put everything into the minor bucket, perhaps leading to lawsuits. It should be an easy matter, however, to provide the makers with a safe harbor for such misclassifications. Firms that place all disclosures into the minor bucket will have their categorizations ignored by the market, making their say in the matter less meaningful. Additionally, professionals watching a particular company who know what to look for and decide to search the minor bucket will find bad news hidden there and, directly or upon hearing of the bad news, trade on it to correct the market price. *See* Macey & Miller, *supra* note 302, at 1990; Romano, *supra* note 319, at 2378; *infra* notes 355–56 and accompanying text; *see also* DeMarco v. Lehman Bros. Inc., 222 F.R.D. 243, 246 (S.D.N.Y. 2004).

326 *See supra* note 265.

327 Putting the adverse events into a format more digestible than what currently exists and disclosing them as they happen, *see supra* note 24, would carry some additional cost. It would, however, be minor when compared with the cost of developing the drug.

ready have all the adverse events available to them, and they must already disclose the events to the FDA.[328] This situation is unlike the frameworks created by Sarbanes-Oxley[329] and Dodd-Frank,[330] which forced companies to research and create new information at substantial cost.

Not only does the data to be disclosed already exist, but so does the infrastructure for disclosing it. The Internet is the ideal mechanism for making this data public, and its use is already sanctioned by the SEC in Regulation FD for direct communication with the market.[331] In other words, it takes little more than a *click* to make AERs available.[332] In fact, the pharmaceutical industry has already said that it would disclose more of its drugs' effects on the Internet, but the great majority of firms are not keeping their word.[333]

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328 21 C.F.R. § 314.80(c) (2013); *see supra* note 24.

329 *See, e.g.*, SEC, OFFICE OF ECON. ANALYSIS, STUDY OF THE SARBANES-OXLEY ACT OF 2002 SECTION 404 INTERNAL CONTROL OVER FINANCIAL REPORTING REQUIREMENTS 37–56 (2009); Robert Prentice, *Sarbanes-Oxley: The Evidence Regarding the Impact of SOX 404*, 29 CARDOZO L. REV. 703, 726–33 (2007); Roberta Romano, *Does the Sarbanes-Oxley Act Have a Future?*, 26 YALE J. ON REG. 229, 252–53 (2009) (focusing on impact on small firms); *see also* Donald C. Langevoort, *Internal Controls After Sarbanes-Oxley: Revisiting Corporate Law's "Duty of Care as Responsibility for Systems,"* 31 J. CORP. L. 949, 968 (2006) (discussing the "labor-intensive formalism" of Sarbanes-Oxley's reporting systems); *A Price Worth Paying?*, ECONOMIST, May 21, 2005, at 71.

330 Jody Freeman & Jim Rossi, *Agency Coordination in Shared Regulatory Space*, 125 HARV. L. REV. 1131, 1148 (2012); Eric Dash, *Feasting on Paperwork*, N.Y. TIMES, Sept. 9, 2011, at B1; *The Dodd-Frank Act: Too Big Not to Fail*, ECONOMIST, Feb. 18, 2012, at 35.

331 Selective Disclosure and Insider Trading, 65 Fed. Reg. 51,716, 51,717, 51,723 (Aug. 24, 2000).

332 Very recent anecdotal evidence shows that sophisticated investors are indeed very interested in AERs and will go to great lengths, including making complicated FOIA requests, to obtain them. *See* Brody Mullins & Christopher Weaver, *Open-Government Laws Fuel Hedge-Fund Profits*, WALL ST. J., Sept. 23, 2013, at A1. Such requests can take months to be processed, however, and the information may ultimately not be helpful. *See supra* notes 24, 299, 307. Immediate Internet disclosure is more efficient from this standpoint. It will also help to avoid sudden price movements that FOIA-based disclosure does not appear to alleviate, *see* Mullins & Weaver, *supra*; *see also supra* note 265 and accompanying text, and please those who favor disclosing information to the entire market at once whenever possible, *see, e.g.*, Selective Disclosure and Insider Trading, 65. Fed. Reg. at 51,716 (explaining the selective disclosure of nonpublic information by issuers to market insiders before disclosing to general public "leads to a loss of investor confidence in the integrity of our capital markets"); STEPHEN M. BAINBRIDGE, SECURITIES LAW: INSIDER TRADING 148–49 (1999) (discussing popular view that notions of fairness justify prohibition on insider trading); Mullins & Weaver, *supra* (stating that FOIA-based disclosure is "an irritant to those who say all investors should get [information] at once"). Finally, while large investors apparently have the sophistication and financial ability to exploit the FOIA system to get information (and then keep it secret until the market changes), *see* Mullins & Weaver, *supra*, the doctors and patients who are an integral part of the ongoing information exchange described throughout this Article are likely not so fortunate.

333 Alex Berenson, *Despite Vow, Drug Makers Still Withhold Data*, N.Y. TIMES, May 31,

Another burden, of sorts, is that "[d]isclosure could provide information to competitors and potential future customers which would be to the detriment of the disclosing corporation."[334] In the pharmaceutical context, potential future customers—patients—are the point. Although competitors may indirectly benefit from knowing the side effects of a firm's drugs, they may be put on alert that their competing drugs-in-progress have the potential to cause similar harm.[335] If this notice causes them to minimize those harms before they reach patients, disclosure again has a net benefit.

Even assuming a minor additional burden, disclosure of every AER would be sensible. If there are few of them, disclosure should be easy. If there are so many that disclosure is no longer easy, especially given that the information and disclosure infrastructure exist, there is very likely enough bad news that it should have to be disclosed despite the burden.[336]

3. Behind-the-Scenes Concerns?

With the overload and burden arguments for allowing companies to limit disclosure of drug harms being less than convincing, what might the Court (and others) really be saying by not requiring full disclosure? Perhaps it fears an overreaction to something that might be trivial, causing a company to take a financial hit despite the reasonable investor's (or patient's) concerns.[337] This potential fear is related to the fact that investors (and patients) can generally switch investments (and treatments) relatively easily.[338] Another possibility is that the Court fears disproportionate harm to the company caused by the wrapping of minor bad news in the formality of a statutorily required disclosure.[339] A related concern specific to the pharmaceutical context may be that the Court fears that a full-disclosure standard might make drug companies more averse to clinical testing, thereby inhibiting innovation.

2005, at A1, C3. As of the time of the article, Eli Lilly was the laudable exception, posting almost all its studies. *Id.* Merck and Pfizer disclosed "none" and "a few," respectively. *Id.*

334 *In re* Veriphone Sec. Litig., 784 F. Supp. 1471, 1483 (N.D. Cal. 1992).

335 *Cf.* Paula J. Dalley, *The Use and Misuse of Disclosure as a Regulatory System*, 34 FLA. ST. U. L. REV. 1089, 1111–12 (2007) (citing Sharon Begley, *In Switch, Scientists Share Data to Develop Useful Drug Therapies*, WALL ST. J., Jan 20, 2006, at A9).

336 *Accord supra* text accompanying note 309; *infra* note 353.

337 *Cf.* Brief for Petitioners, *supra* note 132, at 29–30.

338 *See supra* Part III.B.1.

339 *Cf.* Brief for Petitioners, *supra* note 132, at 30.

Succumbing to these and similar fears kills data flow, making the disclosure and information dissemination process less efficient. An apt analogy is litigation, where a litigant cannot hold back an admission against interest that is harmful to his or her case no matter how unreliable it is.[340] Requiring robust disclosure—including not only adverse events with details about the patients to whom they occurred, but also what testing was done on a product (so as to illuminate what testing was *not* done)—would make it more difficult for pharmaceutical companies to abuse the current system that, even post-*Matrixx*, is based on significance testing.[341] Creating an environment in which it is clear to the market what testing was not done should motivate firms to conduct rigorous trials or risk losing investors and patients to their more thorough competitors. Of course, the disclosed information would also be available to the FDA, which could order more trials as it deems fit.[342] Full disclosure, by its very nature, would also absolve the firms from nondisclosure liability.[343]

The Supreme Court espoused a policy of uncovering abuse by means of securities disclosures in *Dirks v. SEC*.[344] Dirks, an investment analyst, uncovered massive fraud at an insurance company where employees reportedly held "forgery parties," at which they passed around and signed fake insurance contracts.[345] During his in-

340 4 CHRISTOPHER B. MUELLER & LAIRD C. KIRKPATRICK, FEDERAL EVIDENCE § 8:44 (3d ed. 2003). While jury confusion is a valid ground for excluding from trial an admission against interest, that concern is all but irrelevant in an environment where sophisticated professionals do the vast majority of trading and can quickly set a correct market price with their trading, and where patients know their own subjective situations best. At trial, a jury is deciding the fate of the defendant; here, investors and patients are making decisions that impact themselves.

341 *See supra* Part I.B–C; text accompanying notes 269–70. While this Article focuses on the materiality aspect of Rule 10b-5, the abuses described herein should also qualify as a "device, scheme, or artifice to defraud" and an "act, practice, [and] course of business which operates . . . as a fraud." 17 C.F.R. § 240.10b-5(a), (b) (2013); *see also* Speed v. Transamerica Corp., 99 F. Supp. 808, 812–28 (D. Del. 1951).

One might ask whether Rule 10b-5 should be understood to require the disclosure of any minutia that any investor could ever care about, such as the CEO's political views. This Article deals with the pharmaceutical context because it is one in which there is a coincidence of factors suggesting that adverse-event data can be both processed properly by the market and disclosed at only marginal cost. Further, drugs are at the center of what a drug company does, while issues like the CEO's political views are not and do not generally affect the company's performance or its products' effectiveness. That is not to say that sometimes such collateral items, or collections of them, are not disclosure-worthy, but only that, unlike in the adverse-event context, the presumption should not be that they are in every situation.

342 *See* Topol, *supra* note 10, at 1707; *see also supra* note 10.

343 *See infra* notes 357–58 and accompanying text.

344 Dirks v. SEC, 463 U.S. 646 (1983).

345 WILLIAM A. KLEIN, J. MARK RAMSEYER & STEPHEN M. BAINBRIDGE, TEACHER'S

vestigation, Dirks shared his findings with a number of his clients, who sold their shares in the insurer.[346] After the fraud was exposed, the SEC thanked Dirks by leveling insider trading charges against him.[347] The Court would have none of it, stating that it was beneficial for markets to have analysts "uncover[ ] . . . startling information."[348] "But for Dirks' efforts, the fraud might well have gone undetected longer."[349]

In the pharmaceutical context, full disclosure would have the double effect of making available information that investors, doctors, and patients may use to uncover something big. As discussed, these constituencies are superb proxies for each other in this context—investors will care that a drug's sales decline because patients sense danger, while patients will benefit from investors' skill in ferreting out a drug's dangers.[350] Although not every patient, doctor, and investor will want to sift through the disclosed data, full disclosure would give each the ability to do so if he or she has a special reason to want the information. That the stakes in this context involve health in addition to money makes it all the more important. The actions of doctors, patients, and investors (and, for that matter, the previously unresponsive FDA) following the Good Morning America report about Zicam show how effective curious individuals with an interest in a drug's safety can be in causing information to be disseminated to various constituencies.[351]

Market overreaction is also not likely to be a grave concern.[352] If all adverse events must be disclosed, they will become more commonplace and not be a cause for investor alarm in and of themselves.[353] At

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MANUAL FOR BUSINESS ASSOCIATIONS: AGENCY, PARTNERSHIPS, AND CORPORATIONS 328 (7th ed. 2009). The fraud was so massive that the Wall Street Journal initially did not believe it and refused to publish the story when given the details by Dirks. *Dirks*, 463 U.S. at 649–50.

346 *Id.* at 649.

347 *Id.* at 650–51.

348 *Id.* at 658–59 & n.18. The Court added that it was irrelevant that Dirks uncovered "information that required no analysis or exercise of judgment as to its market relevance." *Id.* at 658 n.18.

349 *Id.* at 658 n.18.

350 *See supra* Part I.

351 *See supra* Part I.C.2.

352 *See supra* text accompanying notes 298–99.

353 Matrixx admits as much in its certiorari petition. Petition for Writ of Certiorari, *supra* note 136, at 15 ("Any reasonably sophisticated investor buying shares in a pharmaceutical company must realize that consumers will, from time to time, experience adverse events after using the company's product."). There may be a transition period during which the market gets used to receiving this type of information. If there are still so many adverse event reports that they cause alarm, alarm is likely proper. *Accord* text accompanying notes 309, 336.

the same time, patients with specific susceptibilities or similarly situated with someone who suffered a supposedly irrelevant adverse event can benefit greatly.[354] To the extent that there is an initial overreaction, professional investors, who do the "great bulk of trading"[355] and are used to interpreting the newly disclosed data, can be expected swiftly to take advantage of the price discrepancy and correct the overreaction.[356]

There are potential benefits to the disclosing company as well. First, most private 10b-5 suits allege lack of disclosure where there should have been.[357] But if the allegedly bad news has already been disclosed, such cases become nonstarters. This in turn frees firms from the costly burden of constantly defending totality-of-the-circumstances class-action suits.[358]

Finally, the disclosure of even a single event can have a leveling effect on "blogosphere rumor" and other speculation about what is not being disclosed in a total absence of unfavorable news.[359] In statis-

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354 *See, e.g.*, *supra* text accompanying notes 66–77 (discussing known susceptibilities to Vioxx in certain patients).

355 Ratner, *supra* note 317, at 1779; *see also* THE EMBEDDED FIRM: CORPORATE GOVERNANCE, LABOR, AND FINANCE CAPITALISM 48, 262, 285, 461 (Cynthia A. Williams & Peer Zumbansen eds., 2011).

356 West v. Prudential Sec., Inc., 282 F.3d 935, 938, 940 (7th Cir. 2002) (Easterbrook, J.); DeMarco v. Lehman Bros., Inc., 222 F.R.D. 243, 246 (S.D.N.Y. 2004); Robert G. Newkirk, *Sufficient Efficiency: Fraud on the Market in the Initial Public Offering Context*, 58 U. CHI. L. REV. 1393, 1409 (1991). Indeed, the overreaction is likely to be by a professional investor who gets the data first and quickly trades on it. Thus, retail investors should be relatively unaffected by a sudden unwarranted change in a security's price because of the disclosure of negative drug information. If a retail investor does quickly trade on irrelevant news, his or her trades will likely be too small to affect the price. *West*, 282 F.3d at 938.

Doctor and patient overreaction to minor events is likewise not likely to be a concern. First, a supposed overreaction to an adverse event may in fact be an accurate reflection of patient risk tolerances. *See* Wright & Ginsburg, *supra* note 252, at 1052. After all, when it comes to, say, heart attack death, even a very small chance is a Pascal's wager for anyone save perhaps a terminally ill patient. As discussed, doctors and patients have the best subjective information to make the react/don't-react determination. There is also good reason to believe that doctors should be able to determine when an adverse event is cause for alarm. Second, the overreaction problem, like the overload problem, deals not with an inability to understand data, but with a cognitive inability to properly process it. There is good reason to believe, however, that adverse-event data can be processed properly. *Cf.* Part III.B.2.a.i.

357 *See* Brief for Petitioners, *supra* note 132, at 28 (citing N.J. Carpenters Pension & Annuity Funds v. Biogen IDEC, Inc., 537 F.3d 35, 47 (1st Cir. 2008)).

358 *See id.*; Kevin E. Noonan, *Supreme Court Increases Disclosure Burdens on Pharma Companies*, PATENT DOCS: BIOTECH & PHARMA PATENT LAW & NEWS BLOG (Mar. 24, 2011, 11:59 PM), http://www.patentdocs.org/2011/03/supreme-court-increases-disclosure-burdens-on-pharma-companies.html.

359 *See* Ripken, *supra* note 293, at 154 ("With full disclosure, the price of a given security can be expected to shift less drastically because there is more accurate public information about

tical language, disclosure makes the subjective knowledge more precise, allowing for a better estimation of a drug's safety and its maker's future. In the absence of the additional knowledge, one may naturally be prone to assume the worst.[360] The tobacco industry's dispute with state governments illustrates well how investors prefer a known quantity to an unknown one. After multi-billion dollar settlements, tobacco company stocks rose.[361] Thus, in the final analysis, even pharmaceutical companies may benefit from being more forthright with the marketplace.

CONCLUSION

The current systems of medical testing and securities disclosure have resulted in a situation where patients, their doctors, and investors are unable to make informed decisions. The market for investment and treatment decisions is getting bad information because it puts the on-off switch for publicizing drug harms largely into the hands of the pharmaceutical industry. The information-forcing rule suggested herein would disincentivize drug makers from making profit-loss calculations about their disclosures. It also favors investor autonomy and decisions based on the collective judgment of the market over conflicted drug companies, cumbersome judicial review, and overworked (and perhaps captured) government agencies. The best way to allow the market to decide what information is worth acting on is to give it all the information and let it decide. The health and wealth of a great many can benefit. Future Supreme Court Justice Louis D. Brandeis expressed it well when he famously said, "Publicity is justly commended as a remedy for social and industrial diseases. Sunlight is said to be the best of disinfectants; electric light the most efficient policeman."[362]

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the security floating in the market and therefore less of a need to rely on rumor and speculation.").

360 Put differently, one can say that the release of information moves one from a state of uncertainty (knowing that a drug may be harmful, but not knowing the chances that it is) toward, but not to, one of risk (knowing the chances that it is harmful). *See* Lawsky, *supra* note 163, at 1026. Uncertainty is more dangerous to one's welfare, and thus requires more assumption of the worst, than risk. *See generally* Matthew D. Adler, *Risk, Death and Harm: The Normative Foundations of Risk Regulation*, 87 MINN. L. REV. 1293 (2003).

361 *E.g.*, *Business Digest: Cigarette Companies in Big Florida Accord*, N.Y. TIMES, Aug. 26, 1997, at D1; Constance L. Hays, *For Tobacco Stocks, a Session of Surges*, N.Y. TIMES, Nov. 24, 1998, at C8.

362 LOUIS D. BRANDEIS, OTHER PEOPLE'S MONEY AND HOW THE BANKERS USE IT 92 (1914). Justice Brandeis's reference to diseases is especially apt in this context.