No. 09-1156

IN THE
Supreme Court of the United States

MATRIXX INITIATIVES INC., ET AL.,

Petitioners,

v.

JAMES SIRACUSANO AND NECA-IBEW PENSION FUND,

Respondents.

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

BRIEF FOR THE CONSUMER HEALTHCARE PRODUCTS ASSOCIATION AND THE COUNCIL FOR RESPONSIBLE NUTRITION AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF AMICI CURIAE

The Consumer Healthcare Products Association (CHPA) is the not-for-profit association representing the makers of over-the-counter (OTC) medicines and nutritional supplements and the consumers who rely on these healthcare products.[1] CHPA is one of the oldest trade associations in the United States. It has more than 70 active members that manufacture or market OTC medicines and nutritional supplements, as well more than 120 associate members that provide goods and services to the active members. CHPA is committed to promoting the increasingly vital role of OTC medicines and nutritional supplements in America's healthcare system through science, education, and advocacy. Among its many activities, CHPA shares information with partners across the globe to promote the safe and responsible use of OTC medicines. CHPA also monitors legal issues that affect its members, as well as the entire industry, and offers its perspectives in cases that raise such issues.

The Council for Responsible Nutrition (CRN) is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN has more than 70 members that produce a large portion of the dietary supplements marketed in

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[1] Pursuant to Rule 37.6, *amici* confirm that no counsel for a party authored this brief in whole or in part, and no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici* made a monetary contribution to its preparation or submission. The parties have consented in writing to the filing of this brief.

the United States and around the world. CRN members manufacture popular national brands; store brands marketed by major supermarkets, drug stores, and discount chains; and products marketed through natural food stores and mainstream direct selling companies. In addition to complying with federal and state regulations governing dietary supplements, CRN members adhere to voluntary guidelines for manufacturing and marketing and CRN's Code of Ethics.

This case presents the question whether a plaintiff can state a claim under § 10(b) of the Securities Exchange Act and SEC Rule 10b-5 based on a company's nondisclosure of adverse event reports even if the complaint contains no allegation that the reported adverse events are statistically significant. That issue is important to the many CHPA and CRN members that are, or may become, publicly traded companies. Because hundreds of thousands of adverse events are reported each year, the Ninth Circuit's approach could lead to a flood of securities litigation. A company could protect itself from such litigation by disclosing all adverse event reports in its securities filings, even if there is no evidence that the adverse events are causally related to the company's product. But such undifferentiated disclosures would not be useful to investors, and would make it more difficult to identify meaningful information about adverse events associated with a company's products. Undifferentiated disclosures also could prompt consumers and health care providers to stop using a product based on unsubstantiated concerns about adverse event

reports while obscuring important, validated adverse event information.

SUMMARY OF ARGUMENT

1. Adverse event reports play an essential role in identifying potential safety issues with OTC medicines and dietary supplements, but they have significant limitations. Most importantly, adverse event reports, standing alone, do not establish a causal relationship between a product and an adverse event. Adverse events may occur for a variety of reasons that are unrelated to the product. Moreover, adverse event reports are of variable quality and are often incomplete. Because consumers are permitted to use OTC medicines and dietary supplements without the supervision of a physician, adverse event reports for these products are more likely to be submitted by consumers, and may be less informative and medically precise than adverse event reports submitted by health care providers.

2. To determine whether adverse event reports suggest a causal association between an adverse event and a product, it is necessary to analyze the adverse event data. A wide range of factors may be relevant to this analysis, including the frequency of the adverse event among consumers who are using the product and the frequency of the adverse event among consumers who are *not* using the product. Even after careful analysis of adverse event reports, it may be necessary to conduct additional studies to assess whether there is a causal relationship between an adverse event and a product. The U.S. Food and Drug Administration's internal process for determining whether to act on adverse event reports

confirms that inferences of causation must be based on careful analysis of the data.

3. The statistical significance standard recognized by most courts of appeals appropriately recognizes that adverse event reports, standing alone, are not "material" for purposes of federal securities laws. The statistical significance standard addresses the quality of the evidence of a relationship between an adverse event and a product, and therefore it is not the kind of "bright-line" rule that this Court rejected in *Basic Inc. v. Levinson*, 485 U.S. 224 (1988).

4. The Ninth Circuit's rejection of a statistical significance standard is detrimental to investors and consumers. Under the Ninth Circuit's standard, companies have an incentive to disclose all adverse event reports without regard to whether there is any evidence of a causal connection between the adverse event and the product. As a result, the Ninth Circuit's approach is likely to bury investors "in an avalanche of trivial information – a result that is hardly conducive to informed decisionmaking." *Basic*, 485 U.S. at 231 (citation and internal quotation marks omitted). In the analogous context of warnings in prescription drug labeling, the Food and Drug Administration has recognized that "overwarning" has the effect of not warning at all, because the reader stops paying attention to excess warnings. Undifferentiated disclosures also could cause consumers to stop using beneficial medications based on unfounded concerns based on adverse event reports, and could decrease appropriate responses to real safety issues.

ARGUMENT

I. Adverse Event Reports Do Not Establish A Causal Relationship Between An Adverse Event And A Product.

In order to understand the issue in this case, it is necessary to understand the nature and limitations of adverse event reports. Spontaneous adverse event reporting by health care providers (HCPs) and consumers is entirely voluntary. The U.S. Food and Drug Administration (FDA) encourages consumers and HCPs to report adverse events directly to FDA through its MedWatch program, and provides a form, Form 3500, to gather information about adverse events.[2] Although the form requests a wide range of information, adverse event reports are of variable quality and are often incomplete.[3]

Instead of, or in addition to, reporting an adverse event to FDA, consumers and HCPs may report adverse events to the manufacturer, packer, or

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[2] *See* Form 3500, *available at* http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm. Reports can be submitted online (at www.fda.gov/medwatch), by telephone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by regular mail.

[3] Form 3500 requests information about: the patient (e.g., age, gender, weight); the adverse event (e.g., type of event, outcomes attributed to the adverse event, dates of the event and the report, description of the event, relevant tests/laboratory data, other relevant clinical history); the suspect product(s) (e.g., name, strength, and manufacturer; dosage, frequency and route of administration; dates of use; diagnosis or reason for use; whether the event abated after the dose was stopped or reduced; whether the event reappeared after reintroduction); and other medical products used and dates of use.

distributor listed on the label of the product. In turn, that entity has obligations to report some adverse events to FDA.[4] For non-prescription products such as the product at issue in this case, and for dietary supplements, the entity's reporting obligations depend on how the product is regulated.[5]

For an OTC drug that is marketed under a monograph, a homeopathic drug, or a dietary supplement, the manufacturer, packer, or distributor whose name appears on the label (the "responsible person") must report to FDA all serious adverse events associated with the product when used in the United States, whether or not the responsible person believes the events are related to the product. Federal Food, Drug, and Cosmetic Act (FDCA) §§ 760(b)(1), 761(b)(1), 21 U.S.C. §§ 379aa(b)(1), 379aa-1(b)(1). A "serious adverse event" is defined as an adverse event that results in death, a life-threatening experience, inpatient hospitalization, persistent or significant disability or incapacity, or congenital anomaly or birth defect; or that requires,

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[4] A reportable adverse event may include, in addition to a side effect of a product, an occurrence due to an accidental overdose, abuse, withdrawal, or failure of expected pharmacologic action. Federal Food, Drug, and Cosmetic Act (FDCA) §§ 760(a)(1), 761(a)(1), 21 U.S.C. §§ 379aa(a)(1), 379aa-1(a)(1).

[5] Most OTC drug products are marketed under an OTC monograph that specifies the conditions under which a drug product is considered to be generally recognized as safe and effective. Other OTC drug products (including some drug products that previously were marketed as prescription drugs, such as ibuprofen) are marketed based on new drug applications that FDA reviewed and approved prior to market entry.

based on reasonable medical judgment, a medical or surgical intervention to prevent one of these outcomes. FDCA §§ 760(a)(3), 761(a)(2), 21 U.S.C. §§ 379aa(a)(3), 379aa-1(a)(2). The responsible person must report serious adverse events within 15 business days and submit certain new medical information related to a submitted serious adverse event report within 15 business days of receiving the new information.[6] Non-serious adverse events need not be reported to FDA, but the responsible person must maintain records of all adverse event reports, subject to inspection by FDA, for six years. FDCA §§ 760(e), 761(e), 21 U.S.C. §§ 379aa(e), 379aa-1(e).[7]

Congress clearly understood that an adverse event report does not necessarily indicate a causal relationship between a product and an adverse event. The FDCA expressly provides that submission of any adverse event report shall not be construed as an admission that the product caused or contributed to the adverse event. FDCA §§ 760(g), 761(g), 21 U.S.C. §§ 379aa(g), 379aa-1(g). The legislative history of the FDCA states emphatically: "The committee emphasizes that adverse events are communicated from consumers regarding events that

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[6] This reporting requirement for new medical information applies to information that the responsible person receives within one year of the initial report. FDCA §§ 760(c), 761(c), 21 U.S.C. §§ 379aa(c), 379aa-1(c).

[7] Congress recognized that a broader reporting requirement would be counterproductive: "[A]ny broader reporting system could overburden manufacturers, consumers, and the agency alike, generating information that may not be useful to the public health system at tremendous cost to all involved." S. Rep. No. 109-324 at 6 (2006).

may be associated with the use of a dietary supplement or nonprescription drug. The fact of a report of an adverse event is not determinative that the event occurred or that the event was caused by a consumer's use of the product." S. Rep. No. 109-324 at 6 (2006).

The reporting requirements for an OTC drug marketed under a new drug application (NDA) are somewhat broader. If a serious adverse drug experience is unexpected (i.e., not in the current labeling for the product), the NDA holder ("applicant") must submit an "alert report" to FDA as soon as possible, but within 15 calendar days.[8] The applicant also must submit follow-up reports within 15 calendar days of receiving new information or as requested by FDA. 21 C.F.R. § 314.80(c)(1). These requirements apply whether the serious and unexpected adverse drug experience is domestic or foreign. Adverse drug experiences that are not required to be reported as 15-day alert reports must be included in periodic reports to FDA.[9]

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[8] An adverse drug experience is "[a]ny adverse event associated with the use of a drug in humans, *whether or not considered drug related*," including adverse events occurring in the course of the use of a drug product in professional practice or from overdose (whether accidental or intentional), abuse or withdrawal, or failure of expected pharmacological action. 21 C.F.R. § 314.80(a) (emphasis added).

[9] These periodic reports are required at quarterly intervals for three years from the date of approval of the NDA, and at annual intervals thereafter, except that FDA may upon written notice require that the applicant submit reports at different intervals. 21 C.F.R. § 314.80(c)(2).

Although adverse event reports play an essential role in identifying potential safety issues, they have significant limitations.[10] Most importantly, adverse event reports, standing alone, do not establish a causal relationship between the adverse event and the product. Adverse events can occur for a variety of reasons that are unrelated to the product. For example, an adverse event could be a manifestation of a patient's underlying health condition or a side effect of another medication that a consumer is taking. At a recent meeting convened by the Institute of Medicine, a senior FDA official noted, "The main question is: is there a causal association? Many results from such signals will not be replicated by additional research; some will."[11]

An additional limitation of adverse event reports is that the number of reports does not reflect the actual frequency of the event. Raw adverse event data are not gathered in any systematic fashion. Instead, they are the result of spontaneous, voluntary reports. The rate at which adverse events

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[10] *See, e.g.,* Lanh Green, Pharm.D., M.P.H., Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, FDA, *Postmarketing Pharmacovigilance Practice at FDA*, presented at Drug Information Association 42nd Annual Meeting, Slide 9 (June 21, 2006), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm119101.pdf.

[11] Janet Woodcock, M.D., Director, CDER, FDA, *Studying the Safety of Marketed Drugs: Ethical and Design Issues*, presented at the first meeting of the Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs, Slide 2 (June 7, 2010), *available at* http://www.iom.edu/~/media/Files/Activity%20Files/Quality/DrugSafetyPostMarket/2010-JUN-07/Woodcock.ashx.

are reported has been shown to depend on many factors, including the time since product launch, safety-related regulatory activity, media attention, and the use of the product. FDA, *Guidance for Industry: ICH E2E Pharmacovigilance Planning* 11 (Apr. 2005). To further complicate matters, more than one report may be filed about the same adverse event.[12]

As a result, determining the incidence of an adverse event based on adverse event reports is not a straightforward process. In the words of an FDA official, "the numerator is uncertain" and "the denominator can only be projected."[13] The "numerator" (the number of occurrences of an adverse event among consumers taking the drug) must be estimated based on a relatively small set of adverse event reports that were collected in a non-systematic manner. The "denominator" (the number of consumers who are using a drug product) must also be estimated, because product sales data do not necessarily equate to product use.[14]

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[12] Green, *supra* note 10, Slide 9.

[13] *Id*.

[14] FDA, *FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration* (May 2010) at 18. Adverse events that occur in the context of clinical trials — rather than in general use — are collected and analyzed more systematically, and companies report these adverse events to FDA under a separate reporting system. These types of adverse events are distinct from the spontaneous adverse event reports that are at issue in this case.

Still another limitation of adverse event reports is that they are often incomplete. As an FDA drug safety official has noted, "one of the limitations of spontaneous reports is that, in general, they are poorly documented, and the evaluator may need to contact the event reporter . . . in order to secure follow-up information."[15] FDA Guidance advises caution in interpreting adverse event reports because the data accompanying them are often incomplete.[16]

The limitations of adverse event reports are particularly pertinent for non-prescription products and dietary supplements. Because consumers are permitted to use these products without the supervision of a physician or other HCP, adverse events reports for these products are more likely to be submitted by consumers rather than HCPs. A consumer's adverse event report may be less informative than an HCP's report. For example, the description of the adverse event may not be as medically precise as the one that an HCP would give, and a consumer may not provide the relevant

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[15] Syed Ahmad, M.D., M.P.H., Division of Drug Risk Evaluation, Office of Drug Safety, Center for Drug Evaluation and Research, FDA, *Adverse Drug Event Monitoring at the FDA*, 18 J. Gen'l Internal Medicine 57, 58 (2003).

[16] FDA, *Guidance for Industry: ICH E2E Pharmacovigilance Planning* 11 (Apr. 2005); Adverse Event Reporting System description, *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm. The Adverse Event Reporting System (AERS) is a computerized information database designed to support FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. FDA uses AERS to monitor for new adverse events and medication errors that might occur with these marketed products.

medical history that would help put the adverse event in context.

In sum, adverse event reports are important and useful, but they have significant limitations. Standing alone, adverse event reports do not establish a causal relationship between an adverse event and a product.

II. Adverse Event Data Must Be Analyzed To Determine Whether An Adverse Event Is Causally Related To A Product.

To determine whether adverse event reports suggest a causal association between an adverse event and a product, it is necessary to analyze the raw adverse event data. A wide range of factors may be relevant to the analysis, including:

- The temporal relationship between exposure to the product and the adverse event,
- The clinical and pathological characteristics of the event,
- Whether there is a plausible biological or pharmacologic mechanism that could account for the adverse event,
- Whether the event or related event has been reported previously for the product or a related product,
- Whether other medication(s) taken at the same time or prior to the product could have caused the event,
- Whether an underlying condition could have caused the event,

- Whether the adverse event subsides when the product is stopped or reduced in dosage,
- Whether the adverse event reappears when the product is re-introduced or the dosage is increased,
- The frequency of the adverse event among consumers who are using the product, and
- The frequency of the adverse event among consumers using the product, compared to the frequency of the adverse event among similar consumers who are not using the product.

See generally Stephens' Detection of New Adverse Drug Reactions 331-34 (John Talbot & Patrick Walker eds., 5th ed. 2004).

A number of analytical techniques may be useful to assess potential causality from adverse event reports, including unrestricted evaluation/global introspection, structured algorithms, and Bayesian probabilistic analysis. *See id*. at 337.

Even after careful analysis of adverse event reports, it may be unclear whether there is a relationship between a product and an adverse event. In such cases, it may be necessary to conduct additional studies that are designed specifically to assess the potential relationship.

> If the cases are scanty and most are associated with reasonable alternative explanations, then a watching brief is likely to be the most appropriate course. At the other extreme, a well-documented series of cases of a particular suspected [adverse drug

> reaction] without obvious alternative explanation and/or with evidence of a possible mechanism should rapidly lead to consideration of both what further investigation may be warranted and what action is needed to minimize the risks. Many issues come between these extremes, and this requires careful consideration of evidence from various sources and of the possible ways in which any issue might be investigated further.

Id. at 354.

As additional data become available (for example, from specifically designed studies or other pertinent sources, such as the medical literature), these data can be considered in the context of the previously available adverse event data. Assessing evidence from multiple sources of information can be complex. A commonly-used framework for this type of assessment, known as the Bradford-Hill criteria, considers a range of factors: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy.[17]

FDA's internal process for determining whether to act on adverse event reports reflects the need for careful analysis of the data as a basis for drawing inferences of causation. As described above, FDA

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[17] For a brief explanation of the Bradford-Hill criteria, *see Stephens' Detection of New Adverse Drug Reactions* at 338-39.

receives adverse event information from two primary sources: voluntary adverse event reports submitted by HCPs and consumers, and mandatory adverse event reports from responsible parties. Clinical reviewers at FDA evaluate the adverse event reports. If the reviewers identify a potential safety concern — often referred to as a "safety signal" — they will search for additional, related events in the Adverse Event Reporting System (AERS) or the medical literature, and may check with foreign regulatory agencies to determine whether they can discern a common trend, causal relationship, or pattern of events. A reviewer may look for indicators such as a temporal association (i.e., the product was taken before the adverse event), consistency with existing information or biological plausibility, a similar event in products of the same class, dose-response relationships, and the specificity and consistency of the association.

If the safety signal appears to be real, FDA may take steps to confirm it, including epidemiologic studies in large databases that link prescriptions with adverse outcomes, queries to foreign regulatory agencies about whether similar adverse events have been reported to them, and/or analyses of a World Health Organization database that collects adverse drug reactions data from over 60 countries. *See* Ahmad, *supra* note 15, 58.

Based on its further evaluation of the potential safety signal, FDA may take a range of actions to inform consumers and HCPs and protect the public health. FDA's course of action depends on the strength of the evidence linking an adverse event to a particular product. For example:

- On a quarterly basis, FDA publishes Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS).[18] In this publication, FDA is careful to note that although it has identified a potential safety issue, it has not necessarily identified a causal relationship between the drug and the listed risk: "[i]f, after further evaluation, FDA determines that the drug is associated with the risk, it may take a variety of actions including requiring changes to the labeling of the drug, . . . or gathering additional data to better characterize the risk . . . FDA will complete its evaluation of each potential signal/new safety information and issue additional public communications as appropriate."
- FDA also publishes Drug Safety Communications that alert the public to important safety information,[19] including situations in which FDA is continuing to review new information to evaluate the

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[18] Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System, *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Surveillance/AdverseDrugEffects/ucm216272.htm.

[19] Drug Safety Communications, *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm199082.htm. These communications are also indexed by drug product. *See* Index to Drug-Specific Information, *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111085.htm.

relationship between reported adverse events and a product, and where FDA recommends that HCPs and patients continue to use the medications according to the recommendations in the label.[20]

- Where there is more convincing evidence of an association between an adverse event and a product, FDA may require updates to a product's labeling information, restrict use of the product, issue communications to HCPs and/or consumers, and in the most compelling instances, remove the product from the market.

Even after rigorous evaluation and analysis of adverse event reports and other efforts — including additional studies — to confirm whether a signal is "real," it is not always clear whether there is a causal association between a product and an adverse event. Indeed, a senior FDA official noted at a recent Institute of Medicine meeting that the biomedical community "lack[s] a consensus on the quantity and quality of data that . . . convincing[ly]" shows a causal association.[21]

The example of calcium channel blockers (CCBs) demonstrates that initial signals can prove to be illusory. CCBs are prescription drugs used to treat

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[20] *See, e.g.,* FDA Drug Safety Communication: Ongoing safety review of oral biphosphonates and atypical subtrochantic femur fractures, *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203891.htm

[21] Woodcock, *supra* note 11, Slide 2.

high blood pressure and other cardiovascular indications. In the mid-1990s, a series of epidemiologic studies suggested that CCBs could be associated with serious adverse events, including heart attacks, death, cancer, and suicide. A subsequent series of epidemiologic studies in the late-1990s found no increased risk of these same adverse events. Ultimately, in large randomized, controlled trials that were designed to test specifically for these adverse events, these events were not observed.

III. Requiring Plaintiffs To Plead Statistical Significance Reflects The Reality That Adverse Event Reports, Standing Alone, Do Not Indicate A Causal Relationship.

As described above, epidemiologists and regulators do not take a collection of adverse event reports at face value. Recognizing the limitations of raw adverse event data, they analyze the reports, and frequently seek additional information, to determine whether there is a relationship between the adverse event and the product.

The statistical significance standard established in *Carter-Wallace I and II* recognizes that raw adverse event reports, standing alone, are not material: "Drug companies need not disclose isolated reports of illnesses suffered by users of their drugs until those reports provide statistically significant evidence that the ill effects may be caused by — rather than randomly associated with — use of the drugs and are sufficiently serious and frequent to affect future earnings." *In re Carter-Wallace, Inc., Sec. Litig.*, 150 F.3d 153, 157 (2d Cir. 1999) ("*Carter Wallace I*"). This standard requires the plaintiff to

allege that there is sufficient evidence, based on appropriate analysis, that there may be a causal association between a product and an adverse event, such that the adverse event would be material information to the reasonable investor. Without evidence of a statistically significant association between a product and an adverse event, a plaintiff cannot reasonably allege that a company (or its officers or directors) failed to disclose an adverse event with the requisite scienter, because the company did not have reason to regard the adverse event as material.

Contrary to the Ninth Circuit's suggestion, the statistical significance requirement is not a "bright-line" rule of the kind that this Court rejected in *Basic Inc. v. Levinson*, 485 U.S. 224 (1988). In *Basic*, the Court rejected an argument that the existence of preliminary merger discussions is not material information until the parties have reached an agreement-in-principle, noting that "[a]ny approach that designates a single fact or occurrence as always determinative of an inherently fact-specific finding such as materiality must necessarily be overinclusive or under-inclusive." *Id.* at 236.

Respondents' assertion that the statistical significance standard is a "bright-line rule" of the type rejected in *Basic* mischaracterizes the statistical significance standard. That standard does not adopt any pre-determined metric, such as a fixed number of adverse events. As *Carter-Wallace II* made clear, the statistical significance standard does not rely on specific numbers, but instead on the quality of the evidence of a relationship between the adverse event and the drug:

> The complaint describes the adverse reports received by Carter-Wallace and concludes that the 'adverse events . . . were extremely serious and the number of incidences was . . .statistically unacceptable.' This allegation is based, like much of the appellants' arguments, on the sheer number of adverse reports — 57 — before July 1994.
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> We do not believe that the existence or the number of such reports is problematic . . . [T]he receipt of an adverse report does not in and of itself show a causal relationship . . . Some adverse events may be expected to occur randomly, especially with a drug designed to treat people that are already ill.

In re Carter-Wallace, Inc., Sec. Litig., 220 F.3d 36, 40-41 (2d. Cir. 2000) ("*Carter-Wallace II*").

As described above, the analytic process for evaluating whether there is a relationship between an adverse event and a product is fact-specific. The process involves numerical analysis, but it also involves complex medical judgments based on a relatively small number of adverse event reports that are often incomplete and of uneven quality, weighing evidence from multiple sources of information, and assessing the totality of available data against multiple criteria. This process is not properly characterized as a "bright-line rule." Instead, the statistical significance standard distinguishes complaints that allege only the existence of some number of adverse event reports from complaints

that allege sufficient evidence, based on appropriate analysis and other pertinent information, of a causal association between that product and an adverse event.

IV. The Ninth Circuit's Approach Is Detrimental To Investors And Consumers.

FDA received almost 600,000 adverse event reports in 2009. Based on the number received in the first quarter of 2010, it is likely to receive more than 600,000 reports this year.[22] Under the Ninth Circuit's approach, a plaintiff can allege a violation of Section 10(b) and Rule 10b-5 merely by alleging that the defendant failed to disclose some number of adverse event reports. Such a permissive pleading standard could lead to a flood of meritless securities litigation. Unless plaintiffs are required to allege a statistically significant link between a product and adverse events, claims based on randomly associated adverse events will be permitted to proceed to discovery.[23] As this Court has recognized, discovery

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[22] Reports Received and Reports Entered into AERS by Year, *available at* http://www.fda.gov/Drugs/GuidanceCompliance RegulatoryInformation/Surveillance/AdverseDrugEffects/ ucm070434.htm.

[23] The district court in *In re Pfizer Inc. Securities Litigation*, 584 F.Supp.2d 621 (S.D.N.Y. 2008), like the Ninth Circuit in *Matrixx*, refused to require statistical significance as a threshold for materiality at the motion to dismiss stage. The court determined that statistical significance was a fact issue for the jury. *Id.* at 635-36. The court thus left the issue of materiality for determination at summary judgment. As a result, Pfizer has been forced to expend millions of dollars to conduct discovery and defend the case.

costs alone create significant pressure to settle even meritless claims, particularly in class action litigation. *See, e.g., Dura Pharm., Inc. v Broudo*, 544 U.S. 336, 347 (2005).

Companies faced with an onslaught of securities litigation under the Ninth Circuit's standard have an incentive to disclose *all* adverse event reports, without regard to whether there is any evidence of a causal connection between the adverse event and the product. Such an undifferentiated listing of all adverse events that occurred during a securities filing period will defeat the purpose of the materiality standard by burying meaningful information in an avalanche of essentially meaningless information. This Court's concern about inundating investors with too much information was the basis for the materiality standard articulated in *TSC Industries* and adopted in *Basic*: "[T]he Court was careful not to set too low a standard of materiality; it was concerned that a minimal standard might bring an overabundance of information within its reach, and lead management 'simply to bury the shareholders in an avalanche of trivial information — a result that is hardly conducive to informed decisionmaking.'" *Basic*, 485 U.S. at 232 (citing *TSC Indus., Inc. v. Northway, Inc.*, 426 U.S. 438, 448-49 (1976)).

The detrimental effect of an overinclusive listing of adverse events has been recognized in the analogous context of warnings in prescription drug labeling. To reduce exposure to tort liability based on failure to warn, prescription drug companies have an incentive to include a broad set of warnings in labeling, even if some of those warnings have not

been scientifically established. When labeling includes too many warnings, however, the warnings tend to lose their effectiveness. As FDA has recognized, "[o]verwarning has the effect of not warning at all. The reader stops paying attention to excess warnings."[24] Research on risk communication underscores the importance of limiting disclosures to significant information, since "extraneous information distracts" and "erodes ability to remember key points."[25]

Undifferentiated disclosure of adverse events may also be harmful to consumers. As a result of such disclosures, consumers might stop taking beneficial medications based on concerns about adverse events that are unrelated to the medications. FDA officials have raised this concern in connection with its proposal to disclose more adverse events information to the public. As a senior FDA official noted, disclosure of adverse events without appropriate context can harm public health because patients and HCPs may overreact to potential safety signals (e.g.,

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[24] Center for Devices and Radiological Health, FDA, *Write it Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care* 7 (1993), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070771.pdf

[25] Kala L. Paul, M.D., *Learnings from Consumer Research in Risk Communication*, presented at FDA hearing on Medication Guides, Slide 12 (June 12-13, 2007), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/UCM173468.pdf.

by stopping their medicines).[26] In addition, the FDA official warned that patients and HCPs could become desensitized to safety information: "[O]ver-response to eventual false positives will cause unnecessary concern and drug cessation [and] potentially decrease appropriate responses to real safety issues in the future."[27]

For each of these reasons, the Ninth Circuit erred in rejecting the statistical significance requirement adopted by other federal courts of appeals.

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[26] *FDA Seeks IOM's Help in Setting Threshold for Post-Market Drug Safety Action*, FDA Week (June 22, 2010). FDA proposes to address this concern by accompanying adverse event data with a clear disclaimer to ensure that concerns associated with disclosure of adverse event data do not override the benefits of those disclosures.

[27] Woodcock, *supra* note 11, Slide 4.

CONCLUSION

The decision of the Ninth Circuit should be reversed.

Respectfully submitted,

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