

2011 1

2011 ASA JSM Late-Breaking Session

US Supreme Court
Matrixx Initiatives, Inc., v. Siracusano,
Docket No. 09-1156

*Statistical Significance
is not Necessary
For Causation*

August 3, 2011
ASA JSM Miami, FL

2011 2

Fisher on Significance

“It is usual and convenient for experimenters to take 5 per cent. as a standard level of significance, in the sense that they are prepared to ignore all results which fail to reach this standard, and, by this means, to *eliminate from further discussion* the greater part of the fluctuations which chance causes have introduced into their experimental results.”

Fisher 1935 [1960], p. 13, italics supplied.

MATRIX Matrixx Initiatives, Inc.
ZICAM Home

Matrixx (Nasdaq: MTXX): changing the way consumers use healthcare products.
Sales (2008): \$120 million, (2009): \$80 million

2004 Lawsuit 2009 FDA

2011 4

Matrixx sold Zicam

Zicam: \$48 million/yr, 40% of net 2008 sales

Zicam: a homeopathic remedy clinically proven to reduce the duration and severity of the common cold.

Active ingredient:
zinc gluconate.

ZICAM Cold Remedy
Get over your cold faster
Reduces the duration and severity of cold symptoms
Nasal Gel
0.50 FL. OZ./15mL Homeopathic

2011 5

Pre-Market Clinical Trials

Matrixx conducted two published double-blind, placebo-controlled, randomized clinical studies of intranasal application of zinc gluconate.

In both studies, “[t]he overall incidence of adverse events associated with zinc gluconate treatment was extremely low, with **no statistically significant difference between the adverse event rates for the treated and placebo subsets.**”

2011 6

Anosmia: Loss of Smell

1999: Matrixx advised that a doctor was aware of “at least one” user who complained of anosmia after using Zicam.

2002: Matrixx contacted by a user with anosmia.

2003: Colorado doctors prepare a poster claiming ten reports of anosmia after using Zicam.

2004: January 30, Dow Jones Newswire reported that three lawsuits were filed against Matrixx. Matrix shares dipped.

2011 7

Matrixx Press Release: 2/2/2004

... “Statements alleging that intranasal Zicam products cause anosmia (loss of smell) are completely unfounded and misleading.”

... Matrixx received no reports of anosmia during the premarket clinical trials.

... Anosmia is frequently caused by the common cold—the very condition Zicam is used to treat. Users might report an erroneous association between Zicam and anosmia.

2011 8

Respondents Allege Fraud

Matrixx “touted the growth of business” based primarily on “the increased success of [the] Zicam cold remedies” and made several statements concerning the safety of Zicam ...

These Zicam-related business-growth and safety statements were false and misleading, because Matrixx failed to disclose that “large numbers [sic] of Zicam users had lost their sense of smell.”

Respondents alleged securities fraud: 5/19/04.

2011 9

Securities Fraud

To claim securities fraud, plaintiff must allege

- (1) misrepresentation/omission of **material fact**
- (2) **made with scienter**: intent to deceive or defraud.

2011 10

District Court

Matrixx moved to dismiss the complaint. District court agreed. Respondents failed to plead materiality and scienter.

- Materiality: court invoked the *Carter-Wallace* requirement of **statistical significance**
- Scienter: Respondents failed to plead facts establishing that Matrixx knew of a “definitive **and statistically significant** link between Zicam and anosmia ...”

Respondents appealed to the 9th Court of Appeals

2011 11

FDA and Court of Appeals

2009: FDA issues a warning letter (June).

2009: 9th Circuit Court of Appeals (Aug) rejects *Carter-Wallace* statistical significance requirement

2011 12

Supreme Court Argument

2010: Matrixx argues (Oct 20):

Adverse event reports (AERs) that do not reveal a **statistically significant** increased risk of adverse events from product use are not material.

- A. Reasonable investors would not make investment decisions on the basis of *isolated* adverse event reports (AERs).
- B. **Statistical significance** should be required as a *threshold element of materiality* in § 10(b) cases based on undisclosed AERs.

2011 13

US Supreme Court (3/2011)

Statistical Significance is Unnecessary for Causation

Organizer & Chair: Milo Schield
Speakers:

1. Steven T. Ziliak, Roosevelt University
2. Joseph "Jay" Kadane, Carnegie Mellon U.
3. Donald Rubin, Harvard University
4. Daniel T. Kaplan, Macalester College

2011 14

Conclusion

Statistical educators should give **a more nuanced presentation** on the relationship between statistical significance and causation.

2011 15

Confounding by Indication

Confounding by Indication: Where a known cause of the reported event is the very condition for which the drug is indicated.

```
graph TD; Cold["Cold"] -.-> ZICAM; Cold -.-> Anosmia;
```

When a drug is claimed to cause the very symptoms for which it is a designated treatment, determining the direction of causation is difficult at best.