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cerulean's
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Competitive compliance insights and strategies for executives and decision-makers

Dear Client:

This month we start with an analysis of a US Supreme Court ruling with profound implications for regulatory affairs professionals—the Matrixx Decision.

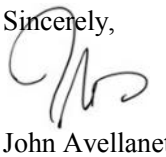
Guest contributor Dan O'Leary reviews the case and discusses five critical steps to undertake in the wake of this Court ruling. As he succinctly points out, the risk to a company's bottom line as a result of failure by regulatory affairs (and medical affairs) professionals has significantly increased because of the Matrixx Decision.

We then turn to several recent trends and regulatory publications along with our recommendations for how you can take advantage in our monthly Trend Watch.

And in our Enforcement Analysis section, we look at a recent Warning Letter and what it reveals about FDA expectations for CAPAs and records integrity (the subject of a May 23rd compliance alert).

Best wishes.

Sincerely,



John Avellanet
Managing Director

BONUS DOWNLOADS

- **OIG Audit Process Handbook**
- **IPEC Quality by Design Checklist for Suppliers**
- **IPEC Quality by Design Checklist for Excipients**
- **IPEC Quality by Design FAQS for APIs**
- **FDA Guidance: Summary Bioequivalence Data for ANDAs**

… and more

INSIDE

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Matrixx Decision: What It Means for You

An exclusive article from Dan O'Leary, President of Ombu Enterprises based in Swanzey, New Hampshire. Dan is an expert on risk management and operational excellence in manufacturing. He can be reached at Dan@OmbuEnterprises.com.

On March 22, 2011 the US Supreme Court decided a case that links adverse event reporting to securities reporting regulations. The unanimous Court decision, written by Justice Sotomayor, concludes that adverse event reports do not have to be statistically significant to be material to a reasonable investor. This has serious implications for life science firms—both pharmaceutical and device companies—and especially for professionals and executives in regulatory affairs.

Matrixx v. Siracusano

The case, *Matrixx Initiatives, Inc., et al. v. Siracusano et al.*[1] involved an alleged connection between Zicam Cold Remedy, a leading Matrixx product, and the loss of smell (a medical condition called anosmia).

The plaintiffs claimed that Matrixx did not disclose the potential linkage and, as a result, mislead investors. Matrixx claimed that without a statistically significant number of adverse events from which to draw the connection, it was not obligated to report the potential linkage to investors.

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The investors, in a class action suit, claimed that Matrixx did not disclose a possible connection between Zicam's active ingredient, zinc gluconate, and loss of sense of smell. During the period in question (about 3½ months starting in late October 2003), the investors noted that Matrixx made statements related to revenues and product safety and that the statements were misleading because Matrixx did not disclose known adverse events to the investors. The investors assert this was misleading and violated the securities law and regulations[2], especially since Zicam represented about 70% of Matrixx's sales.

The case came from the Ninth Circuit who held that the investors could proceed with the suit against Matrixx. The US Supreme Court affirmed the decision, stating that statistical significance is not the test, but rather how the sum total of information available to an investor might influence a decision.

"Failure to disclose adverse events is a violation of securities law"

Background

During the time in question, manufacturers of over the counter (OTC) drugs did not have to report adverse events to the US Food and Drug Administration (FDA). In 2006, the US Congress changed the law to require OTC drug manufacturers to report a serious adverse event within 15 days.[3]

In 1999, Dr. Alan Hirsch, neurological director of the Smell & Taste Treatment and Research Foundation, Ltd., contacted the Matrixx customer service line after discovering a possible connection between Zicam nasal gel and loss of smell in some of his patients. Dr. Hirsch told a Matrixx employee that some previous studies showed that intranasal use of zinc could be problematic.

In September 2002, Timothy Clarot, the Matrixx Vice President for Research and Development, contacted Miriam Linschoten, Ph.D., at the University of Colorado Health Sciences Center because Matrixx received a compliant of anosmia from a patient. Linschoten asked Clarot about previous studies and got the impression that Clarot didn't know about them. She subsequently sent abstracts of the earlier studies to Clarot.

By September 2003 a colleague of Linschoten at the University of Colorado, Dr. Bruce Jafek, had observed 10 patients who suffered anosmia after using Zicam. Linschoten and Jafek decided to present a poster at the American Rhinologic Society. Matrixx learned of the planned poster and Clarot sent a letter to Dr. Jafek advising him that he did not have permission to use the Matrixx name or the name of any of its products. Dr. Jafek presented the poster without a reference to Zicam.

By February 6, 2004, the end of the class period, nine plaintiffs had filed four product liability lawsuits alleging Zicam damaged their sense of smell.

Misleading Information

Given this information, the investor lawsuit claimed that Matrixx made a series of public statements that were misleading.

In October 2003, after Dr. Jafek's poster session, Matrixx stated that Zicam was "poised for growth in the upcoming cough and cold season" and the company had "very strong momentum."

On January 30, 2004 Dow Jones Newswires reported that the FDA was looking into the loss of smell problem based on lawsuits. On February 2, 2004, Matrixx issued a press release stating, "Matrixx believes statements alleging that intranasal Zicam products caused anosmia (loss of smell) are completely unfounded and misleading."

On February 6, 2004 Good Morning America broadcast Dr. Jafek's findings reporting that he had more than a dozen patients who suffer from anosmia after using Zicam and that there were four product liability law-

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suits. In response, Matrixx issued another press release largely repeating its February statement.

After the Dow Jones Newswires report, the Matrixx stock price dropped from $13.55 to $11.97 (USD). After the Matrixx February press release, the stock rose to $13.40. Then, after the Good Morning America report, the stock again fell, this time to $9.94.

Three days after the Good Morning America report, Matrixx informed the Securities and Exchange Commission (SEC) that it had convened a panel of physicians and scientists for a two-day meeting to review current information on smell disorders. The Matrixx panel concluded there was insufficient scientific evidence to determine that zinc gluconate, when used as recommended, affects a person's ability to smell.

The Issues

The issues in the case hinged on two points:

1. Did Matrixx make a material misrepresentation or omission?
2. Did Matrix act with a mental state embracing intent to deceive, manipulate or defraud (scienter)?

Matrixx argued that "adverse event reports that do not reveal a statistically significant increased risk of adverse events from product use are not material information". In other words, unless there is statistically significant evidence, adverse event reports are just anecdotes; reasonable investors would not consider them relevant.

The US Supreme Court disagreed.

The Court stated that statistically significant data are not always available. For example an adverse event may be subtle or rare. Moreover, ethical considerations may prohibit a randomized clinical trial. In addition, medical experts may have other methods, lacking statistically significant data, to infer a link between a product and an adverse event.

FDA does not limit the evidence it needs to assess causation and take regulatory action. FDA considers such factors as "temporal relationship of product use and the event", "evidence of a dose-response for the effect", "biologic plausibility", etc.[4] As a result, the FDA may act on information that suggests, but does not prove, causation. For example, manufacturers of OTC drugs must revise their labeling "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have to be proved."[5]

On June 16, 2009 FDA issued a Warning Letter to Matrixx stating, "FDA has concluded that these products may pose a serious risk to consumers who use them. Specifically, FDA has received more than 130 reports of anosmia, (loss of sense of smell, which in some cases can be long-lasting or permanent), associated with use of [Zicam Cold Remedy intranasal products]."[6]

Matrixx argued that because it did not have statistically significant evidence of causation, it was not reckless. "Rather the most obvious inference that [Matrixx] did not disclose the [reports] simply because [Matrixx] believed there were far too few … to indicate anything meaningful about adverse reactions to use of Zicam."

The Conclusion

The Court disagreed with Matrixx, citing the two-day meeting, the prevention of Jafek's use of the trade names in the poster session, and the press release suggesting that Zicam does not cause anosmia when the panel had actually concluded there was insufficient evidence concerning causation.

The Court inferred that Matrixx did not release the adverse event reports because

"FDA issued a Warning Letter to Matrixx in 2009"

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Trend Watch

Behind-the-scenes insights from conferences, journals, news and blogs around the world

Data Mining Adverse Events

Rand researchers have confirmed that data mining publicly available medical literature accurately uncovers major side effects earlier than any other known method. (InformationWeek)

Recommendation: By excluding articles and studies that did not test for adverse events, researchers were able to consistently detect and predict those adverse events that would cause product liability lawsuits, market withdrawals and black-box warnings—in some cases, more than three years before a lawsuit was filed or a recall issued. *SmarterCompliance*™ subscribers will want to consider conducting a periodic a meta-review of medical literature through PubMed (www.ncbi.nlm.nih.gov/pubmed/), the online portal for the National Library of Medicine, and then filtering out any article that mentions of your medicine (or active pharmaceutical ingredient) but does not specifically test for adverse events. See the related "Matrixx Decision: What It Means for You" in this issue.

"FDA has started recommending firms hire third-party experts to help with record integrity"

Device Trial Costs Rise

Venture capitalist analysis shows that medical device clinical trials have risen to approximately $20 million (USD) in order to obtain results meaningful to potential partners and to regulatory health agencies such as the FDA. (StarTribune)

Recommendation: Potential device and pharma partners increasingly scrutinize clinical trial data to evaluate—and price—new technologies. Subscribers will want to download a copy of the 2008 article "Record Integrity & Licensing Your Intellectual Property" from the Cerulean website. Then, consider drafting a procedure and set of controls around data handling in your environment. This is particularly important if you planning or currently undertaking clinical trials. Retrospective data integrity tends to be viewed skeptically by FDA reviewers. In a March 2011 Warning Letter, FDA suggested to a firm that they hire a third-party to help them put in place data integrity controls (see related "Enforcement Analysis" and the Warning Letter at www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm249425.htm).

Quality by Design Checklists

The International Pharmaceutical Excipients Council (IPEC) has published three documents to help firms incorporate quality by design into drug development. (GMP News)

Recommendation: Subscribers may download all three documents upon login. The first, a checklist for manufacturers and suppliers of active pharmaceutical ingredients (APIs), is perfect for adoption into API contract manufacturer and supplier due diligence. The second, a checklist for excipients users (*e.g.*, final manufacturers and contract manufacturers), can be quickly tailored to auditing your manufacturing environment as well as a contract manufacturer. And the third, a set of FAQs, is an excellent training tool.

EMA Issues FAQs for Annex 11

The European Medicines Agency (EMA) just published a series of frequently asked questions for computerized systems under GMP regulations. (LabCompliance)

Recommendation: Annex 11 is Europe's more modern approach to the US regulation 21 CFR 11. The EMA's FAQs for Annex 11 can be viewed online, along with other FAQs for the GMPs, at the EMA site: http://www.ema.europa.eu/ema/index.jsp; click through to Human Medicines, Inspections, GMP/GDP compliance, and then Q&A, or simply by clicking here.

Enforcement Analysis

Review of recent FDA enforcement activities

Ningbo Smart Pharmaceutical Co. Warning Letter

At the end of March 2011, 2011, the FDA issued a Warning Letter to a API manufacturer in China citing four key issues:

1. Failure of the quality department to ensure raw materials are tested
2. Failure of the quality department to ensure the facility is GMP-compliant
3. Complete lack of records integrity—from raw data to finished documents
4. Failure to perform at least one identity test of each batch of incoming raw materials.

Amongst the recommendations is a clarifying statement regarding FDA expectations of corrective and preventative action: "Please provide a comprehensive corrective action plan that describes your commitment, procedures, actions, and controls to ensure data integrity. This plan should include training to all managers, supervisors, and quality unit personnel…."

Implications

1. The FDA is increasingly concerned about electronic records integrity.
2. FDA expects that CAPAs to include documentation and verification of new/updated "commitments, procedures, actions, and controls" and training.
3. FDA wants to see a documented records retention program with specific records archival and destruction procedures. For more on FDA records requirements, see ceruleanllc.com/specialized-consulting-services/fda-records-management-compliance/

"FDA told a firm in a March Warning Letter to implement a records retention program"

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company executives understood the likely impact on the market, not because they believed the adverse event reports were meaningless

The Court concluded that statistical significance of adverse event reports is not necessary for material significance in the financial sense. The Court concluded that, given the nature of drugs and devices, the mere existence of adverse event reports may not be material; just because a user experienced an adverse event does not mean the product caused the outcome. Therefore, while the mere existence of adverse event reports is not enough to trigger a public disclosure in a financial report, there must be something more.

The key, according the US Supreme Court, is that the "something more" does not need to rise to the level of statistical significance. Instead, the Court suggests a contextual inquiry that "may reveal in some cases that reasonable investors would have viewed reports of adverse events as material even though the reports did not provide statistically significant evidence of a causal link."[7]

"Firms need to undertake contextual reviews of complaints and adverse events"

Your Next Steps

Given that both device and drug manufacturers maintain complaint files, this is a good opportunity to review your procedures and the records you keep.

There are five steps to consider as quickly as possible:

1. Review complaint handling processes
2. Verify adverse event reporting rules
3. Conduct regular contextual analyses of complaints and adverse events
4. Implement blackout controls
5. Review inputs for financial reporting

Complaint Handling and File Review

Complaint files are the basis for any subsequent analysis, so be sure you capture all the complaints regardless of how you may have received them. As the Matrixx case makes clear, the source of a complaint could range from a call to customer service, a poster or paper at a professional society meeting, or even, in today's environment, a social media posting.

Device manufacturers, in particular, need to analyze complaints to identify existing and potential causes of nonconforming product or other quality problems, and employ appropriate statistical methodology to detect recurring quality problems.[8]

To this point, the FDA issued a Warning Letter to Howard Instruments, Inc. on May 12, 2009 citing the firm for lack of data collection and analysis procedures as well as a failure to analyze complaints.[9] The firm responded to the FDA 483 and FDA, in the Warning Letter, says, "We reviewed your responses to these observations and concluded they are inadequate. We disagree with your assertion it is impossible to conduct a trend analysis based on the limited number of complaints received. A trend analysis is an essential aspect of risk assessment and is not limited to findings which are statistically significant."

Adverse Event Reporting Verification

Second, make sure your Adverse Event Reporting to FDA follows the regulations. Be conservative, reporting if there is any doubt.

These are public records and could establish a case in your favor in the event of stockholder questions. (Recall that Matrixx did not have to report adverse events during the time frame in question.)

Contextual Analysis

Third, as part of your quarterly reports and any discussion with analysts, be sure to review the complaint files and your reports

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to the FDA.

This will require you to establish a procedure for a contextual inquiry to determine if complaints (adverse events) may be material. Do not rely on statistical significance alone. Be sure the review extends over a long time period (years), not just the current quarter. Leave a record of the analysis and the reasons for not disclosing information.

> [*Editor's note*: consider conducting this type of meta-analysis as part of your firm's annual quality system management review (QSMR); for more information on QSMR best practices, see the recorded webinar on the Cerulean website.]

Blackout Controls

Fourth, recognize that employees who handle complaints and FDA reports have knowledge that could influence the stock price. Apply appropriate controls, such as blackout periods, for these employees and document your decision and the factors that led to it.

If your firm has outsourced complaint handling, or is considering doing so, discuss with your legal team contractual terms to limit your public disclosure risk by the outsourced vendor's personnel.

Financial Reporting Inputs

Fifth, since complaints and adverse events could impact financial reports, meet with your financial department to review the process and control decisions you made implementing Sarbanes-Oxley (SOX), especially the internal controls in Section 404.

Verify that regulatory affairs (and/or medical affairs) department management will be included in upcoming financial disclosure plans. Pulling together a contextual analysis of adverse event reports and complaints can take time if it has not been conducted on a regular basis.

Final Thoughts

The Matrixx decision brings together two aspects of a company that usually remain separate: adverse events and financial reporting.

Clearly analysis of product reports can show problems in the post-market surveillance phase of the life cycle. The population of people using the product is considerably larger than the clinical testing environment, and could include subpopulations that may react differently. Monitoring these issues and taking action is important for a safe and effective device. The same analysis may be material to investors. The prudent executive will be conscious of both aspects.

Email the author directly at *Dan@OmbuEnterprises.com* with any questions or feedback

"The Matrixx decision gives regulatory affairs direct impact to the bottom line"

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[1] No. 09-1156, 563 U.S. ___, slip op. (Mar 22, 2011) ("Slip op.")

[2] 17 CFR §240.10b-5, which says in part, "It shall be unlawful … 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."

[3] 21 USC §§379aa(b), (c)

[4] FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005)

[5] 21 CFR §201.80(e)

[6] Warning Letter to Matrixx Initiatives, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm166909.htm (2009)

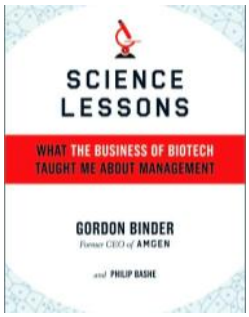
[7] Slip op. at 16

[8] 21 CFR §820.100(a)(1)

[9] Warning Letter to Howard Instruments, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm162732.htm (2009)

Featured Reading

Wherein we highlight books with relevance to leadership, compliance strategies and competitiveness



Gordon Binder's Science Lessons (2008) is his look back at his time starting with Amgen when it consisted of three people, a business plan, and no product or patents, and then all the way through his retirement as CEO of a $50 billion firm.

While the book is mainly a series of company snapshots, stories, and lessons learned along the way, Binder provides readers with four fundamental challenges present in 21st century medicinal product development and compliance:

1. There is never enough money;
2. Complicated risks compound across an organization, from boardroom discussions to quality system SOPs;
3. Everyone tends to know the right thing to do—they just don't want to be the first to say it out loud; and
4. Competition is always present—even from current business partners.

Binder makes clear that these four hurdles exist regardless of company size, from tiny startups to global companies.

Sadly, one lesson readers will learn is that even when business partnerships have the best of intentions, if one partner succeeds and the other struggles, such partnerships can rapidly devolve into lawsuits wherein innocent (and largely forgotten) discussions are used as accusation fodder. It's enough to make one fear success.

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for more advice on lean compliance, improving productivity, and FDA records management

Next month: turning harmonization to your benefit in preparing for regulatory inspections … and more

Calendar and News

Upcoming activities, workshops, events and new publications

KEYNOTE 8 JUNE—FDA and Life Sciences in India. Cerulean's John Avellanet delivers the keynote address at a three-day executive conference on new drug development, generics and the FDA. *Hyderabad, India*

WORKSHOP 10 JUNE—FDA & AMDM Meeting. The AMDM has coordinated a public meeting with the FDA to discuss current regulatory science associated with OIVD. Learn more: www.amdm.org *Silver Spring, Maryland*

CONFERENCE 13-14 JUNE—US-China Food and Drug Law. The FDLI hosts FDA and Chinese counterparts discussing current legal and regulatory requirements for food, drugs, cosmetics, and medical devices in US and China. Learn more: www.fdli.org *Beijing, China*

SPEECH 24 JUNE—Role of IT in Effective Regulatory Compliance. The VCU School of Business hosts John Avellanet presenting lessons learned on from a career in compliance and IT. *Richmond, Virginia*

TELECONFERENCE 28 JUNE—Document Retention: What FDA Expects You to Keep and What to Throw Away. FOI Services hosts records management expert John Avellanet, along with Nancy Singer and other former FDA officials to discuss best practices for document retention—from SOPs to emails. *Learn more: www.foiservices.com*

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