Ethics Forum: VIOXX

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Merck

- Number of employees worldwide: 59,800
- Sales: $24.2 billion
- Net income: $3,275.4 million
- Merck products are sold in more than 140 countries
- Largest-selling product: Singular®
  - $4.3 billion in sales
- $4.9 billion invested in research and development
VIOXX Background

- Vioxx is a non-steroidal anti-inflammatory drug to treat arthritis and other acute pain conditions
- The FDA approved Vioxx in May of 1999
- Vioxx was marketed in more than 80 countries
  - Sales totaled $2.5 billion in 2003
- Some reports suggesting that Vioxx increased the chances of cardiovascular problems
- Between February 2001 and April 2002
  - Recommended that FDA require a label warning of the possible link to cardiovascular problems.
  - The FDA warns Merck to stop misleading doctors about Vioxx's effect on the cardiovascular system.
  - The FDA tells Merck to add information about cardiovascular risk to Vioxx's label.
August 25, 2004: Dr. Graham presents results of a database analysis of 1.4 million patients

- Study concludes that Vioxx users are more likely to suffer a heart attack or sudden cardiac death than those taking other NSAIDs.
- Linked Vioxx to more than 27,000 heart attacks or sudden cardiac deaths nationwide from the time it came on the market in 1999 through 2003.

September 23, 2004: Merck says it learned this day that patients taking Vioxx in a study were twice as likely to suffer a heart attack or stroke as those on placebo.

September 30, 2004: Merck voluntarily withdraws Vioxx from markets worldwide
Journals

- Editors are now accusing Merck of withholding crucial study data that showed the drug heightened the risk of heart attacks
- Evidence of three heart attacks that occurred in low risk people was erased
  - Discredit the study's primary conclusion that Vioxx only increases heart attack risk in those already at high risk.
- Did not learn about this until after Vioxx was pulled from the market

Court Cases

- In 2007 Merck has agreed to pay $4.85 billion to settle nearly 27,000 lawsuits
- Many court rulings are being reversed during the appeal process
- Out of 16 Vioxx cases that have completed trials so far, only three have resulted in victories by plaintiffs
Ethical Issues

- Told FDA that difference in cardiovascular effects was due to “protective effect”
- Merck did not disclose all data to the FDA or NEJM
- Ineffective regulation by the FDA
New England Patriots coach Bill Belichick insists nothing more to come on Spygate

Associated Press

Updated: April 2, 2008, 12:09 PM ET

PALM BEACH, Fla. -- Bill Belichick insists there are no new revelations to come about Spygate. "I think they've addressed everything they possibly can address," the New England Patriots coach said Tuesday.

Belichick, speaking during the AFC coaches breakfast at the NFL meetings, said he was interviewed again after the Super Bowl about allegations that former team employee Matt Walsh had illegal tapes. Those tapes presumably included a walkthrough by the St. Louis Rams on the day before the 2002 Super Bowl, a game the Patriots won.

"I've addressed so many questions so many times from so many people I don't know what else the league could ask," Belichick said.

Commissioner Roger Goodell confirmed that the NFL spoke again with Belichick and other Patriots employees after the Super Bowl loss to the New York Giants. The league has been negotiating an agreement with Walsh that it hopes will get Walsh, a golf pro in Hawaii, to come forward with what he has.

"We followed up on other things because certain things had been tossed out," Goodell said of the added round of interviews with Belichick and other members of the Patriots front office.

This was the first time anyone disclosed that Belichick and other Patriots staffers were reinterviewed after the Super Bowl, when the Walsh allegations surfaced. The first interviews actually came the day before the Super Bowl with player personnel director Scott Pioli, Sherry Khan, a team employee who handled Walsh's contract, and Walsh.

More NFL Headlines

- Glenn expresses desire to remain with Cowboys
- Bengals' Johnson has surgery, expected for camp
- Raiders' Walker released from hospital after attack
- Cards' Arrington charged with disorderly conduct
- Specter says he's ending pursuit of Spygate probe

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### Evidence of cardiovascular implication

**Table 2. Data on Myocardial Infarctions Including the Three Events.**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Person-Years of Exposure</th>
<th>No. of Myocardial Infarctions</th>
<th>Relative Risk</th>
<th>95% CI</th>
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</thead>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2698</td>
<td>20</td>
<td>5.00</td>
<td>1.68 to 20.1</td>
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<tr>
<td>Naproxen</td>
<td>2699</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aspirin indicated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
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<td>8</td>
<td>$\infty$</td>
<td>1.66 to $\infty$</td>
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<tr>
<td>Naproxen</td>
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<td>0</td>
<td></td>
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<tr>
<td><strong>Aspirin not indicated</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Rofecoxib</td>
<td>2593</td>
<td>12</td>
<td>3.00</td>
<td>0.91 to 12.7</td>
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<tr>
<td>Naproxen</td>
<td>2597</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Relative risks were estimated by Poisson regression; confidence intervals were calculated by the exact method.
Outcomes

- For victims…
  - Many patients may have had heart attacks due to using Vioxx. Overall rates were increased, but it is hard to prove a single case in which Vioxx caused a heart attack.

- For Merck and plaintiffs…
  - Only 3/16 lawsuits resulted in clean victories for the plaintiffs, while 2 others had plaintiff victories. Merck settled a large 4.85 billion lawsuit that involved 27,000 lawsuits.
  - Merck’s image may have taken a hit

- For FDA
  - No real sanctions against the FDA
Consequences and Outcomes: FDA – Merck Issues

- Too much trust and hope on VIOXX?
  - Six month Priority Review on VIOXX
  - Advisory Committee vs internal FDA reviewers
- VIGOR study results not given enough attention
  - Cardioprotective effects of Naproxen?
  - Many people prescribed with VIOXX after VIGOR study
  - Physicians misinformed
    - Merck's field representative training strategy: Ordered not to discuss VIGOR study with physicians
- Cardiovascular Card: Preapproval affects of VIOXX which do not reflect VIGOR study results
Consequences and Outcomes: General Issues: Drug Approval Process

- Science of drug approval process?
- Prescription Drug User Fee Act: “Who's Using whom?”
  - September 2007 approval for 5 more years
  - Pressure on FDA to faster process drug approvals
  - FDA responsibility to drug companies?
- Advisory Committee
  - Commercial Conflicts of interest?
Costs to Society: A controversial view

- “Regarding your “Vindicating Vioxx” (May 31), I wish the vindication of Vioxx would go one step further. I am an 87-year-old man who was very active until Vioxx was taken off the market. Now I can hardly walk even after trying many types of medication including steroid injections to my left foot. I, as well as many other patients, would gladly give up a few days of life if we could live them without pain. Many of the doctors have also said that for some people Vioxx is the only medication that works...” - The Wall Street Journal. June 14, 2008

- Moral Hazard
  - Medicare, etc., coverage left to society if person gets a heart attack
recommendations

- stronger action should probably be taken to make sure this type of mistake cannot occur again.
  - the fda as well as merck should be held accountable for their mistakes

- there were warning signs, along with ethical mistakes that (primarily) merck committed, and the financial penalty for merck may or may not teach them their lesson to be more careful with marketing and researching a drug in the future.

- there should be better regulation of studies and reporting of results
Sources

- http://www.merck.com/newsroom/
- http://www.organicconsumers.org/politics/merck060216.cfm
- Avorn, Jerry. Keeping Science on Top in Drug Evaluation. NEJM. 357;7
- VIGOR Study Group. Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis. NEJM.343:1520-8
Questions?