POLITICS OF MEDICINE PART II

THE FDA: PIMPING FOR BIG PHARMA

By

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> **Secrecy enforced by repression in scientific agencies is a severe threat to public health and safety, because it sustains the approval of life-threatening drugs when those decisions couldn't be defended if they were made in the light of day.**
>
> **Tom Devine[1]**

FDA Approval

Most Americans misunderstand what FDA drug approval means. They believe that the FDA only approves drugs that are effective and safe, and that advertising of pharmaceuticals on television and in print has been approved by the FDA as well. Ironically, this couldn't be farther from the truth. The only meaning of FDA approval is that an approved drug is considered to have some benefit – even if it's minor -- that outweighs harm, a fact the FDA and the pharmaceutical industry would rather you not know. It doesn't matter if the drug is virtually identical to 10 other drugs already on the market, if the drug has no clinical benefit, if the drug has serious side effects, or if they simply don't know that the drug won't kill you!

The drug approval process changed completely in 1992 with the passage of the **Prescription Drug User Fee Act (PDUFA)** which allows drug companies to pay the FDA to review their drugs for approval. Since PDUFA, the allocation of resources at the FDA has been altered,

causing a tremendous imbalance in the functions necessary to protect the public from dangerous drugs: 80 % of the resources now go to the approval of new drugs, and 20% is for everything else -- drug safety, arguably the most important of all the departments, commands only about 5%.[2] As a direct result of the PDUFA legislation, the FDA no longer works for the American public: it now works for the pharmaceutical industry and the difference shows. Once the funding started coming from the drug companies they started calling the shots, threatening not to provide money unless the FDA helped them bring new drugs to market. The FDA has basically served this master ever since. We have turned health care over to business, but businesses are only interested in maximizing profits and preparing for the next quarterly report. We have been betrayed by the FDA, and that is the only way to put it.

Relenza: Dying for One Less Day of Flu Symptoms

When the flu drug Relenza (GlaxoSmithKline) was up for approval in 1999, the FDA's Antiviral Drugs Advisory Committee was not impressed. The studies showed that it was no more effective than a placebo, and in fact was potentially unsafe for anyone with a respiratory problem like asthma.[3] The Committee voted 13-4 to reject the drug. But Glaxo complained bitterly about unfair bias, so the director of the antiviral drug division, Heidi Jolson, approved the drug anyway despite the recommendations of the Advisory Committee. She agreed that Relenza had not proved effective for patients over 65 or for those with respiratory, cardiovascular, or other medical conditions, and said that special precautions were warranted, but approved it because "some patients could expect modest benefit."[4] Relenza went on to cause numerous deaths, and the FDA finally had to backtrack and issue a public health advisory to physicians warning them to limit the use of Relenza. But is it still on the market? Of course. And so is the competing and more popular Tamiflu. Does the average American know that Relenza is a drug that might harm

or even kill them? No – to the contrary, we've been told to stockpile this drug and Tamiflu in case of pandemic flu or bioterrorism! What happened to the reviewer who was most opposed to Relenza? Dr. Michael Elsahoff was sternly upbraided by his superiors for his negative review and lost the right to make presentations to the advisory committee. Ultimately, he resigned. Elsahoff was quoted at the time as saying. "Before I came to the FDA I guess I always assumed things were done properly. I've lost a lot of faith in taking a prescription medicine."[5] And where is Heidi Jolson today? She works for **3D Communications**,[6] a high-priced company that helps drug manufacturers win FDA approval, so her hard work was clearly rewarded.

Yaz and Yasmin: Ignoring all the Evidence

In a more recent example, the FDA held an advisory committee meeting in December 2011, to review whether Bayer's birth control medications, Yaz and Yasmin, should remain on the market. At issue was a series of studies which found that users of these best-selling contraceptives have an increased risk of blood clots, leading to deep vein thrombosis, pulmonary embolism, stroke, heart attack, and death. Thousands of women have filed lawsuits against Bayer claiming injury from one or the other of the medications. Despite the serious health risks, the committee voted 15-11 to keep both drugs on the market. It used to be that you weren't allowed to have any financial benefits from the drug companies if you were on the advisory board or a member of the FDA or the CDC, but that's not the case anymore. At least four of the voting members of the committee had worked for Bayer or received funding from them – a clear conflict of interest. The FDA did not have a problem with this. What it did object to, however, was Dr. Sydney Wolfe, voting member and editor of *Worst Pills, Best Pills*. Because his newsletter had recommended against using either of the two contraceptives, Dr. Wolfe was prevented from voting due to an "intellectual conflict of interest."[7] So obviously, the FDA

believes it is a greater conflict to be informed on the science and have an opinion than to have received money from a corporation under review – you're not allowed to think for yourself, but it's okay if your opinions are influenced by money from the pharmaceutical companies! The committee also had refused to enter information into evidence for the hearing that Bayer had withheld their own research findings that Yaz and Yasmin cause an increase in blood clots. Although Bayer faces more than 10,000 lawsuits over injuries caused by the contraceptives, these two drugs brought in $1.58 billion in sales for 2010.[8] In their risk/benefit ratio Bayer evidently believes that it can afford to lose quite a few more lives before seriously considering removing the drugs from the market.

Vioxx: It's Better to Kill the Patient than to Kill the Drug

The story of Merck's arthritis drug, Vioxx, remains perhaps the best-documented and most chilling tale of financial interests dominating over the health and safety of the public. This non-steroidal anti-inflammatory drug came to market in May 1999, touted as being far superior to other aspirin-like products by causing fewer GI problems, and accompanied by a massive advertising campaign featuring such celebrities as Olympic champion figure skater, Dorothy Hamill, and Olympic Decathlon gold medal winner, Bruce Jenner. Reportedly, Merck spent $160 million annually to advertise Vioxx in direct-to-consumer advertising and to physicians. The media blitz paid off. By the end of 1999, doctors had written more than five million prescriptions for Vioxx—slightly more than 22,200 prescriptions *each day*![9] Merck's 1999 Annual Report opened with the following headline: **"Vioxx: Our biggest, fastest, and best launch ever."** By the time Vioxx was withdrawn by Merck on September 30, 2004, this very expensive drug's annual sales were $2.5 billion, accounting for over 10% of Merck's yearly revenue.[10]

But what happened that a mere 5 years after the premier of this blockbuster drug the company had to yank it from the market? By September 2004, Merck could no longer deny the ample evidence that Vioxx was responsible for more than 100,000 heart attacks and 60,000 deaths. Merck claimed ignorance: they didn't know there was a problem with Vioxx until September 2004, when a 2600-person study showed a drastic increase in heart attacks among participants receiving Vioxx compared to naproxen and was terminated early.[11] But is it true that Merck was in the dark about Vioxx?

The allegations against Merck and the FDA were serious enough that Senator Charles Grassley, member of the Senate Finance Committee, convened hearings in November 2004, with the title: ***FDA, Merck and Vioxx: Putting Patient Safety First?*** In testimony, Dr. Gurkipal Singh MD, Professor of Medicine at Stanford University, refuted Merck's claim that they acted immediately once the information about heart attacks became known, and stated that Merck's own documents showed that their scientists were seriously concerned back in **November 1996** – two and a half years **prior** to FDA approval -- that Vioxx had an association with an increased risk of heart attacks. Dr. Singh also gave evidence that there were many internal discussions within Merck about this concern. The entire selling point of Vioxx was that it caused fewer GI bleeding events and thus was ostensibly a safer drug than the 30 other NSAIDS already on the market.[12] But Vioxx was never found to be more effective than its competitors, so if the stomach safety of the drug were negated by an increased risk of heart attacks, physicians might not be willing to make that trade-off. Instead of engaging in this dialogue or designing studies that would have evaluated the heart attack risk more carefully, Merck's scientists created study designs that would exclude people with known heart problems so that the heart attack issue would be less

evident. In fact, the studies were designed purposefully to maximize any GI benefit of Vioxx while hiding the cardiovascular risk.[13]

When reviewing the original new drug application (NDA) for Vioxx, FDA reviewer, Dr. Villalba, noticed that there was an increase in risks of heart attacks compared to placebo, and asked for a larger database to resolve the safety issues.[14] But instead of demanding more studies from Merck or acting to protect the health of Americans, the FDA approved Vioxx on May 20, 1999, after a brief 6-month priority review. Senator Breaux questioned the acting head of the Office of New Drugs, Dr. Sandra Kweder, about this priority review:

> … this person (Dr. Villalba) who is a scientist is telling me that we need a larger database to answer this and other safety comparison questions, i.e. does it cause a greater risk of heart attacks. Yet you approved it at the same time. How can that possibly be?

Dr. Kweder responded:

> First, it is not unusual, when a drug goes on the market, to have ongoing concerns about a particular aspect of its safety, because we have learned from experience that clinical trials do not uncover many events for a variety of reasons. So that is not an unusual circumstance … We also knew that we were likely to, over the course of time, be able to have additional data to bring to the table.[15]

So Kweder actually admitted that the FDA approves drugs without adequate safety testing, and that the clinical trials are insufficient to prove a drug is safe! Dr. Kweder also implied in this statement that the data gathered after approval is taken seriously. But Dr. David Graham, Associate Director for Science and Medicine in FDA's Office of Drug Safety, made it clear in his testimony before the Senate Finance Committee that any concern of the Office of Drug Safety (ODS) must go back to the Office of New Drugs (OND), which has the final word on drug approval, labeling, and restrictions. According to Dr. Graham, the Office of New Drugs tends to deny or downplay safety issues -- they considered a drug safe unless a reviewer can

show with 95% or greater certainty that it is not safe, which is virtually an insurmountable barrier to protecting the American public.[16]

Results of another study, called VIGOR, were made public in May 2000, and showed a **500% increase** in heart attacks for patients using Vioxx vs. naproxen![17] Surely this information should have been sufficient to prompt some action on the part of the FDA – **BUT IT WASN'T**. It took the FDA **two full years** to do anything while they negotiated back and forth with Merck officials, who were opposed to any mention of the cardiovascular risk of Vioxx. Eventually, in what amounts to less than a slap on the wrist, the FDA allowed Merck to add a misleading warning to the label implying that there is a cardiovascular issue with Vioxx because it does not have the anti-platelet activity of other NSAIDS, instead of admitting the inherent heart attack risk of Vioxx itself. Further, the company was allowed to hide this information in the "Precautions" section of the label instead of placing it in the "Warning" section where it belonged, so few physicians were even aware of the change or that there was in fact a significant heart attack risk associated with Vioxx. And to top it all off, the FDA at the same time approved Vioxx for use in rheumatoid arthritis without admonishing Merck for having marketed Vioxx for this indication illegally during the previous three years![18] So the two year stall produced a win for Merck, and a loss for even more Americans. The problem, according to both Dr. Singh and Dr. Graham, is that drug labels are negotiated between the FDA Office of New Drugs and the manufacturer, instead of the FDA simply using its authority to insist that proper warnings be available to the public.

A year after the release of the VIGOR study results, Merck issued a press release on May 22, 2001, entitled **Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx** , which actually stated:

> Extensive review of data from the completed osteoarthritis trials and on-going clinical trials with Vioxx, as well as post-marketing experience with Vioxx, have shown no difference in the incidence of cardiovascular events, such as heart attack, among patients taking Vioxx, other NSAIDs and placebo.[19]

In the Senate Finance Committee hearings, Senator Breaux questioned the head of Merck, Raymond Gilmartin, about this obfuscation of the cardiac risk of Vioxx:

> **Breaux**: I do not understand how Merck could have concluded in the press release that was released in 2001 confirming a favorable cardiovascular safety profile of Vioxx. It seems to me that, looking at the VIGOR study, you are looking at something that showed as much as 5 times increase in the risk of cardiovascular problems for the group taking Vioxx as opposed to the group taking naproxen. Then Merck says this somehow proves that Vioxx has a favorable safety profile.
> **Gilmartin**: The favorable safety profile referred to the entire profile of the drug, which included the impact on GI events.
> **Breaux**: Oh no. But the headline says, "Favorable Cardiovascular Safety Profile." That is the headline!
> **Gilmartin**: Well, that is also because we had data against placebo and we had data against other naproxen NSAIDS. Now, the FDA sent us a letter on that press release.
> **Breaux**: They went crazy.[20]

The FDA sent an unequivocal warning letter to Mr. Gilmartin following the press release stating that "your claim in the press release that Vioxx has a 'favorable cardiovascular safety profile,' is simply incomprehensible, given the rate of MI and serious cardiovascular events compared to naproxen … in fact, serious cardiovascular events were twice as frequent in the Vioxx treatment group as in the naproxen treatment group in the VIGOR study."[21] So even in this official Senate hearing, the head of Merck -- the same man who issued the press release and received the FDA warning letter in response -- continued to deny the fact that Merck had attempted to obscure the cardiovascular risk of Vioxx, and acted as if the FDA warning letter were somehow unrelated to the very real danger of this drug.

And what happened to those intrepid scientists and researchers who attempted to uncover the truth about Vioxx or protect the American public? Dr. Singh had trouble obtaining answers from Merck to his questions about the VIGOR study, but persisted until Merck warned him that they would make his life difficult at Stanford and elsewhere if he didn't stop asking questions.[22] In fact, they called several of his supervisors at Stanford to complain, and tried to intimidate him. Dr. David Graham's experience was even worse:

> Prior to my Senate testimony in mid-November of 2004, there was an orchestrated campaign by senior-level FDA managers to intimidate me so that I would not testify before Congress. Our acting center director contacted the editor of the Lancet, the prestigious medical journal in the United Kingdom, and intimated to the editor that I had committed scientific misconduct, or that I may have committed scientific misconduct, and that they shouldn't publish a paper that I had written showing that Vioxx increases the risks of heart attack. The second was that other high level FDA officials contacted Senator Grassley's office and attempted to get Senator Grassley and his staff to not support me, to not believe me, and to not call me as a witness. Senior FDA officials contacted Tom Devine, my attorney at the Government Accountability Project, and attempted to convince him that he should not represent me because I was a bully, a demagogue, that I was guilty of scientific misconduct, that I was just a terrible person, that I couldn't be trusted, and these people were posing as whistleblowers themselves. But it turns out that they were senior FDA officials -- some of them were in my supervisory chain -- who were involved in a coordinated attempt to discredit me and to smear my name, and to prevent me from giving testimony. The week before I testified, the acting commissioner of the FDA invited me to his office and offered me a job in the Commissioner's office to oversee the revitalization of drug safety for FDA. Obviously he had been tipped off by people in the Senate Finance Committee, who are sympathetic to FDA's status quo, that I was going to be called as a witness. And so to preempt that, he's offering me this job which basically would have been exile to a fancy title with no real ability to have an impact.[23]

Later it also came out that Merck had created a hit list of doctors, mainly researchers and academics, who had to be 'neutralized' or discredited because they criticized the anti-arthritis drug or Merck, and officials emailed each other about recommended courses of action.[24]

The Vioxx catastrophe has been dissected and analyzed to a fine degree. Most people have at least a passing awareness that this was a dangerous drug responsible for hundreds of thousands of cardiac events, and that the FDA was found seriously remiss in its responsibility to protect the public safety. The FDA got a humiliating dressing down by the Senate Finance Committee, and promised to have the Institute of Medicine come in and tell them how to improve. But eight years later, has anything changed? Is the American public any better protected from another Vioxx today?

Senator Grassley continues to be very concerned about the risks facing users of pharmaceuticals as well as the risks facing those who attempt to bring information about dangerous drugs or medical devices to the public's attention. We contacted Senator Grassley's office to see if any of the issues raised at the Senate Finance Committee's Vioxx hearings in November 2004 led to policy changes within the FDA. We were told by one of Senator Grassley's staff that following the hearings, Senator Grassley pursued legislative reforms to improve post-marketing surveillance, and fought hard to enact regulations that would put the Office of Drug Safety on an equal footing with the Office of New Drugs and, in fact, give it the independence which would allow it to have some clout in its role of protecting Americans from dangerous drugs. He has been especially anxious to reign in PDUFA – which is up for renewal again in 2012 -- and has sought to limit the influence of the drug companies over the FDA. Unfortunately, Senator Grassley has found shockingly little support among his colleagues in the Health Committee to force changes in the current system.[25] If you consider how much money is available from the pharmaceutical industry lobbyists to influence opinion on the Hill, it probably isn't surprising that most Senators and Congressmen are more concerned about their wallets than about who might die from a dangerous drug. In the end, Merck never admitted any responsibility for the

harm caused by Vioxx. They have fought every lawsuit and appealed every court decision against them, all the while maintaining that "Merck puts patients first."[26]

New Paradigm – Or Prescription for Disaster?

Unfortunately, there are indications that things are about to get much worse. In fact, the FDA just announced on February 28, 2012, that they are looking for ways to get drugs into the hands of patients more quickly. They will be holding a two-day public meeting this month on March 22nd and 23rd, to evaluate whether to reclassify medications for high blood pressure, cholesterol, migraines and asthma so that patients can get them **without a prescription**, thus eliminating one of the few remaining levels of protection against dangerous drugs! The FDA is proposing a "new paradigm" in which consumers use kiosks or other technological aids in pharmacies or on the internet to self-diagnose for a particular disease or condition, determine whether a particular medication is appropriate, and decide whether specific medication warnings contraindicate use of a drug, all without any physical exam, consultation, or advice from a physician! They further suggest that if blood monitoring is important for a certain medication, a pharmacist would be able to assess results and whether or not it is safe for someone to continue on a medication.[27] In other words, the FDA plans to eliminate the physician and the need for a prescription so that there will be no barrier at all protecting the public from direct-to-consumer advertising. How will the next Vioxx ever get taken off the market without physicians noticing that their patients are sick or dying and making the connection to a drug? There won't even be a paper trail or a record entry to show that the patient was ever on the drug in the first place. And without a prescription there won't be any insurance reimbursement for these medications, so the insurance industry will gain financially and the consumer will lose.

Other aspects of the paradigm include "encouraging" drugmakers to develop antibiotics, and expanding the FDA's woefully inadequate accelerated approval program (the fast track program) to allow drugs which don't meet current standards for effectiveness to be rushed to market. AIDS and cancer drugs already can be approved based on **relaxed (i.e. reduced) standards for effectiveness,** but the FDA's expansion of this program would include drugs for infection, Alzheimer's disease, and what the FDA terms "rare" conditions. This would permit the FDA to fast track even more drugs without the manufacturer having the burden of proving efficacy. If this "new paradigm" goes into action, then there truly will be no brakes at all on the pharmaceutical industry. So don't be surprised if the new drug approval process continues to get shorter until it really is only a rubber stamp – just like the FDA itself.

ENDNOTES

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