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Does the FDA Need to be Overhauled?

By **John Mack**

The Vioxx withdrawal put the Food and Drug Administration (FDA) under the spotlight. There were allegations that the FDA was in cahoots with Merck in keeping Vioxx problems under wraps (see, for example, "Will COX-2 Inhibitors Crash and Burn?"). A *New York Times* story reported that "Members of Congress, an internal F.D.A. whistleblower and prominent medical journals have said the agency is incapable of uncovering the perils of drugs that have been approved and are in wide distribution." ("At F.D.A., Strong Drug Ties and Less Monitoring," *NYT*, December 6, 2004).

Other critics, such as Dr. Marsha Angell, have broader issues with the FDA (see "The Truth About the Drug Companies: What To Do About It").

In January and February, 2005, Pharma Marketing News hosted a survey of pharmaceutical professionals, healthcare professionals, and the general public to get a better idea which reforms, if any, they would like to see implemented at FDA. It should be noted that the great majority of respondents (67%) disagreed with the statement that said "The FDA should not be forced to change how it regulates the drug industry. It is doing a good job right now."

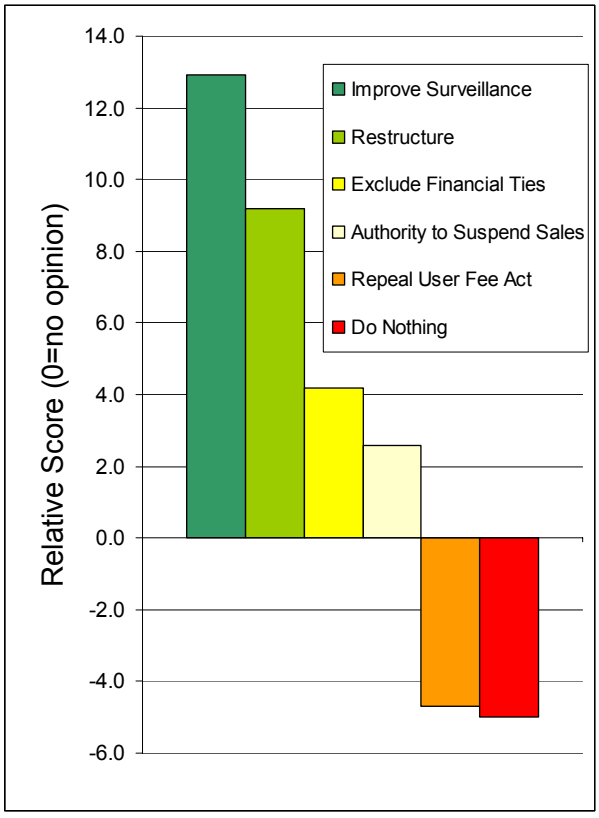
Among the suggestions for revamping the FDA are the following general reforms:

1. **Repeal the Prescription Drug User Fee Act**, which authorizes drug companies to pay fees to FDA for each drug reviewed. In the 2003 fiscal year, the industry gave the FDA $200 million. Meanwhile, Congressional support has shrunk and the agency has made cuts in all its operations except for new drug reviews. "In the past 11 years," reports the *New York Times*, "spending on the reviews has increased to more than four-fifths of the budget of the agency's drug center from about half."

While the FDA has cut drug safety surveillance as one of its priorities, repealing the Drug User Fee Act would not guarantee a concomitant increase in drug safety review, which is arguably the most pressing issue raised by recent drug withdrawals (see below).

Survey Says!

Aside from the option to do nothing to change the FDA, repealing the Prescription Drug User Fee Act was the least desirable option according to respondents to our survey. Only 28% agree or strongly agree that the User Fee Act should be repealed.



2. **FDA advisory committees should not include experts with financial ties to the drug industry**. It is easy to imagine critics increasing the call for this reform in light of a new rule issued by the Department of Health and Human Services and the Office of Government Ethics (5 C.F.R. §5501.109) that prohibits National Institutes of Health (NIH)

employees from consulting with pharmaceutical and other medical products firms. A summary of the rule states that all NIH employees are forbidden from accepting "all compensated or uncompensated employment, including consulting and advisory or other board service, and compensated speaking, writing or editing," for "substantially affected organizations (defined to include biotechnology, pharmaceutical, medical device companies and others with similar interests)." Many NIH employees are also forbidden to own stock in these organizations as well.

Survey Says!
A majority of survey respondents agree (19%) or strongly agree (39%) with this reform idea, whereas 75% of pharma company respondents disagreed, but not strongly.

A respondent from a Pharmacy Benefit Management (PBM) firm noted "I believe there is a need for some improvements. Eliminating anyone who has ties to the drug industry seems harsh - many people have equities, etc."

Drug Safety Monitoring
Other aspects of the Pharma Marketing News survey concerned reforming how the FDA monitors drug safety. FDA whistleblower David Graham, told a Senate committee on Nov. 18, 2004, that America is "virtually defenseless" against another "terrible tragedy and a profound regulatory failure" like Vioxx, (, "FDA whistleblower claims he'll be forced from post," 11/25/2004; http://www.usatoday.com/news/health/2004-11-25-fda-graham_x.htm). Graham, in his written testimony, stated:

"When it comes to safety, the OND (Office of New Drugs) paradigm of 95% certainty prevails. Under this paradigm, a drug is safe until you can show with 95% or greater certainty that it is not safe. This is an incredibly high, almost insurmountable barrier to overcome. It's the equivalent of "beyond a shadow of a doubt." And here's an added kicker. In order to demonstrate a safety problem with 95% certainty, extremely large studies are often needed. And guess what. Those large studies can't be done.

"There are 2 analogies I want to leave you with to illustrate the unreasonableness of CDER's standard of evidence as applied to safety, both pre- and post-approval. If the weather-man says there is an 80% chance of rain, most people would bring an umbrella. Using CDER's standard, you wouldn't bring an umbrella until there was a 95% or greater chance of rain. The second analogy is more graphic, but I think it brings home the point more clearly. Imagine for a moment that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets into those chambers. The gun represents a drug and the bullets represent a serious safety problem. Using CDER's standard, only when you have 95 bullets or more in the gun will you agree that the gun is loaded and a safety problem exists. Let's remove 5 bullets at random. We now have 90 bullets distributed across 100 chambers. Because there is only a 90% chance that a bullet will fire when I pull the trigger, CDER would conclude that the gun is not loaded and that the drug is safe."

Among the suggestions for revamping the FDA are the following reforms specifically aimed at drug safety monitoring:

3. **Restructure the FDA** to separate the job of monitoring safety of approved drugs from the job of approving drugs in the first place.

Dr. Graham, in his testimony before Congress, stated "The organizational structure within CDER is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division approves a new drug, it is also saying the drug is 'safe and effective.' When a serious safety issue arises post-marketing, their immediate reaction is almost always one of denial, rejection and heat. They approved the drug so there can't possibly be anything wrong with it. The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest."

Survey Says!
A large majority (84%) of our survey respondents agreed or strongly agreed that the job of monitoring safety approval should be separated from that of approving drugs. Pharma respondents also favored this approach with 50% agreeing somewhat and 25% agreeing strongly.

Mario Cavallini, Senior Analyst at Simstar, a relationship marketing company located in Princeton, NJ, commented that "Balkanization of FDA functions into separate agencies would just increase inefficiency. The main problem is budgetary: because of the User Fee program creating a (presumably unintended) priority on NDA evaluation, post-approval monitoring has gotten short rations and hand-me-downs. Rectifying the resource distribution problem would go a long way."

4. **FDA should seek additional authority to suspend the sale of drugs already on the market**.

Dr. Graham, in his testimony before Congress, stated "the Office of Drug Safety has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs."

Senator Christopher Dodd (D-Conn.) has announced plans for a proposed Patient Protection Act of 2005. His proposal calls for establishing a new Office of Patient Protection (OPP), which would remain in the FDA but would report directly to the FDA commissioner. OPP would have independent authority to act to protect patients, according to Dodd's announcement. The bill creates a new "watchdog office in the FDA" that could pull drugs off the shelf if they are deemed to be unsafe for patients, he said. Dodd would appropriate $100 million annually to fund OPP.

Dr. Janet Woodcock, Acting Deputy Commissioner for Operations, FDA, discussing the situation with NewsHour Health Correspondent Susan Dentzer, said "FDA doesn't have the authority to require additional studies once a drug is on the market. Our authority is limited to either taking a drug off the market or perhaps having the bully pulpit and saying these studies should be done, or something like that. But we do not have the authority to simply order additional studies to be done."

Survey Says!
Survey respondents were somewhat split on this issue with 45% agreeing and 31% disagreeing (25% had no opinion). Most (50%) of pharma company respondents disagreed somewhat.

5. Improve safety surveillance of approved drugs (e.g., establish patient registries and/or require drug companies to undertake new safety tests once a drug is approved).

On January 24, 2005, Senator Edward Kennedy (D-Mass.) introduced The Affordable Health Care Act (S. 16), which would authorize HHS to require drug sponsors to conduct post-approval studies (so-called Phase IV studies) if a significant safety issue arises regarding the drug or the class of drugs. These safety issues could be triggered through FDA's MedWatch postmarket surveillance system, epidemiological studies or scientific literature. A civil penalty "may be assessed for each day the completion of a required study of a drug is delayed in an amount that is not more than 3 times the gross revenue received by the sponsor for the average sales of the drug in a day."

Survey Says!
This was the most popular FDA reform suggestion amongst our survey respondents with 87% agreeing (57% strongly agreeing) and only 8% disagreeing to any degree. A majority (75%) of Pharma company respondents also agreed with this reform measure.

Fix DTC and Drug Safety Surveillance Too
At least one respondent made the connection between the excess hype of DTC and the problem of drug safety liability issues for the industry. Terry Nugent, VP Marketing at MMS, a medical list broker, said "Perhaps the biggest problem is DTC, [which] accelerates uptake well beyond FDA's ability to keep pace with adverse events. Either they need to step up monitoring or ratchet down DTC. … Over hyping [drugs] with Dorothy Hamill and such will only increase the liabilities for litigation, particularly in the case of drugs like Vioxx and Celebrex where the condition treated is far from life threatening, particularly off label."

DTC is a double-edged sword. It is effective in getting market share for new drugs quickly after launch, but its mere presence shines a light on issues like high prices and safety. Given the extraordinary liability Merck now faces due in large part to the fact that it ran Vioxx DTC advertising even while it knew about its safety issues, pharma companies may welcome some form of increased DTC regulation that would lessen the liability.

In a recent post to the Pharma Marketing Blog, I suggested a way that the FDA can "fix" the DTC problem Mr. Nugent refers to and at the same time improve post-launch drug safety surveillance (see "How the FDA Can Fix DTC").

FDA Offers New Communication Channels
In a newly-announced "culture of openness," the FDA proposed the following new communication channels to provide the public with better and more prompt information about prescription drugs.

The Drug Watch Web Page. At the direction of the new Drug Safety Oversight Board, this page will include emerging information for both previously and newly approved drugs about possible serious side effects or other safety risks that have the potential to alter the benefit/risk analysis of a drug, affect patient selection or monitoring decisions, or that can be avoided through measures taken to prevent or mitigate harm. The agency will enhance access to this information and call for assistance in prioritizing and further evaluating potential adverse health concerns.

Healthcare Professional Information Sheets. One-page information sheets for healthcare professionals for all drugs on FDA's Drug Watch and all drugs with Medication Guides (FDA-approved patient labeling) containing the most important new information for safe and effective product use, such as known and potential safety issues based on reports of adverse events, new information that may affect prescribing of the drug, and the approved indications and benefits of the drug.

Patient Information Sheets. One-page informa-tion sheets for patients containing new safety information as well as basic information about how to use the drug in a consumer friendly format for all products on Drug Watch.

"The FDA is an icon of trust, a certifier of safety, an enabler of innovation and a repository of information," Secretary Leavitt said. "We will keep the promise of the FDA brand by putting in place more rigorous oversight and collecting and sharing important and emerging information about drug safety and effectiveness."

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