Drug Approvals and Deadly Delays

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Truth can be stranger than fiction, and bureaucracy can be stranger than metaphor.

In 1984 a man named John Nestor became notorious in Washington, D.C., for his unusual driving habits on the Capitol Beltway. Nestor had the unique habit of getting into the leftmost lane with his cruise control set at 55 mph, the posted speed limit. He would drive at this speed regardless of what came up behind him. Cars would zoom up close to his rear bumper; drivers would flash their lights and blast their horns, some swerving around him on the right while giving him the finger—none of this fazed Nestor in the least. As he explained it, 55 mph was the law, and he had a right to drive in whichever lane he chose: "Why should I inconvenience myself for someone who wants to speed?"[1]

John Nestor's story stirred a huge amount of public reaction, some supportive, most of it as outraged as the drivers who encountered him on the road. The term "Nestoring" was coined to mean adhering to the precise details of the rules. To me, John Nestor was a good metaphor for the U.S. Food and Drug Administration and its painstakingly slow approval process for drugs and devices.

But it turned out that John Nestor wasn't just a metaphor for FDA; he worked there. In fact, in 1972 he had been transferred out of FDA's cardio-renal-pulmonary unit because that division "had approved no new chemical entities…from 1968 to 1972, an experience that contrasted with the experience of every other medical [sic] modern nation and with the experience of other divisions of the FDA."[2, p 195]

But while John Nestor's inactivity at FDA made him a villain to some, it made him a hero to others. Ralph Nader's Health Research Group argued that Nestor "had an unassailable record of protecting the public from harmful drugs" and helped Nestor eventually overturn his transfer.[3, pp 33-34] When Nestor died in 1999, his *Washington Post* obituary fittingly read: "FDA Official Renowned for Strict Driving Habits."[4]

FDA is one of the most powerful federal agencies, regulating products that account for approximately one of every four consumer dollars. No new medical drug or device can be marketed until the agency has approved its safety and effectiveness.

History of the Current Approval Process

FDA's approval process took its current form in the wake of the thalidomide tragedy. In 1957, thalidomide was introduced in Germany as a sedative with remarkably few side effects. It quickly became available in more than 40 countries, and was especially popular among pregnant women for controlling morning sickness. Its U.S. licensee filed for FDA approval in 1960. The application was handled by Dr. Frances Kelsey, who withheld approval while she investigated possible peripheral nerve damage from the drug. But during the course of her investigation, the drug became linked to severe fetal deformities, which soon resulted in its worldwide withdrawal. Dr. Kelsey was hailed as a hero for preventing thalidomide's widespread use in the U.S. and received the Presidential Gold Medal for Distinguished Service. In September 2010, she became the first recipient of a new FDA award named in her honor.

In retrospect, it's unclear whether it was investigative skill or luck that led Dr. Kelsey to hold up the thalidomide application. For one thing, she was investigating peripheral neuritis, not fetal deformities; her subsequent claim that the two were related is dubious. Moreover, other countries with regulatory approval processes, such as Sweden and Canada, had approved the drug.[2, pp 38-39]

The thalidomide episode spurred the congressional transformation of FDA into the agency it is today. Before then, FDA's basic responsibility was to certify the safety of new drugs prior to marketing. But the 1962 Kefauver amendments added drug efficacy to FDA's responsibilities, even though, ironically, the problem with thalidomide involved safety, not efficacy.

But whether the issue is safety or efficacy, the thalidomide episode illustrated a basic precept—when it comes to approving new drugs, waiting may well be the best course of action. As one commentary noted, the honors bestowed on Dr. Kelsey demonstrated to many others at FDA that "there is no credit to be gained for lives saved due to speedy regulatory action."[5, p118]

The Invisible Victim

The power of that precept stems from the fact that, as a government agency, FDA is a political entity, subject to intense pressure from Congress and media. The precept is also strengthened by the huge difference between the FDA's two

choices in approving new therapies:[6, pp 9-13] If FDA approves a drug that turns out to be disastrous, people will suffer; if it delays or denies a needed drug, people will also suffer. Both mistakes are medically harmful.

But from a political standpoint, there is a huge difference between them. Those injured by an incorrectly approved drug will often know that they are victims of FDA mistakes. Their stories make riveting news, and their testimony, or that of their surviving families, is powerful. But for victims of incorrect FDA delays or denials, who are prevented from using drugs that could have helped them, the situation is far different. All they know is that their doctors told them that nothing more could be done to help them. Only a fraction of these people will understand the reason for this—namely, that a useful drug was bottled up at FDA.

Unlike in the first scenario, these people do not realize that they too are victims of FDA mistakes. Their suffering or death is simply viewed, by them and others, as reflecting the state of medicine rather than the status of an FDA drug application. In short, victims of incorrect FDA approvals are highly visible, while victims of incorrect FDA delays or denials are practically invisible.

For example, consider FDA's incredibly long delay in approving beta-blockers to reduce the risk of second heart attacks. By the mid-1970s this had been documented in clinical trials, and a number of beta-blockers were approved for this use in Europe. But in the U.S., FDA imposed a moratorium on beta-blocker approvals due to the drugs' carcinogenicity in animals. (Among the staffers involved in this delay was that fastidious driver, John Nestor.[2, p 195]) In effect, FDA was denying needed cardiac drugs to people at high risk of heart attacks because of the unproven possibility that those drugs might cause cancer years in the future.

Finally, in 1981 FDA approved the first such drug, boasting that it might save up to 17,000 lives per year. That meant, of course, that as many as 100,000 people may have died waiting for FDA to act[5, p 118]—an explosive point, but one that very few journalists pursued. For all practical purposes, these people were invisible in a very literal sense—we've all seen photographs of thalidomide victims, but I suspect that not one of us has ever seen a photograph of someone who suffered or died because of FDA's beta-blocker moratorium.

Similarly, in the early 1990s it took FDA more than 3 years to approve interleukin-2 as the first therapy for advanced kidney cancer. By the time FDA acted, the drug was available in nine European countries. In clinical trials, the drug had produced remissions of 6 months or longer in 15 to 20 percent of patients. Then why did FDA delay so long? Its attention was occupied by the drug's toxicity; it resulted in the death of approximately five percent of those who took it. This concern obscured the fact that metastatic kidney cancer has the even worse side effect of killing 100 percent of its victims. If we roughly estimate that the drug might have helped 10 percent of those who otherwise die of kidney cancer, then FDA's delay might have contributed to the premature death of more than 3,000 people.[3, p 39] Have we seen any photographs of them?

These episodes clearly illustrate the political and journalistic differences between the opposing goals of avoiding both incorrect approvals and incorrect delays and denials. Medically, both types of agency action are harmful, but politically there is no comparison between them. One has impact; the other doesn't. In the words of FDA Commissioner Alexander M. Schmidt: "In all of FDA's history, I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them…. The message to FDA staff could not be clearer."[6, p 5]

He went on to note: "Congressional pressure for our negative action on new drug applications is, therefore, intense. And it seems to be increasing, as everyone is becoming a self-acclaimed expert on carcinogenesis and drug testing."

Schmidt made that statement in 1974. Fifteen years ago it seemed that the tide had turned, as FDA's handling of drug and device applications improved somewhat with staff increases, and with a growing recognition of the need to streamline approvals, reflected in the 1997 FDA Modernization Act. But in recent years that trend has been reversed. FDA has come under increasing assault by outside groups, from media, and from the Democrat-controlled Congress. Those same groups have enabled dissenters within FDA to gain more clout as well, resulting in "a culture…at FDA…in which agency employees who dislike a regulatory decision are able to keep raising the issue and, if they don't like the results, to go outside established agency procedures…to enlist support from members of Congress and their enabling lapdogs in the media."[7]

In the view of these critics, every unanticipated side-effect from a new drug demonstrates that FDA has become too cozy with industry and too sloppy in reviewing new applications. As Dr. Sidney M. Wolfe, longtime head of Health Research Group, puts it, FDA is controlled by "spineless and gutless" officials infected with a "please the industry" attitude and interested only in getting drug applications out the door.[8] Wolfe is highly dubious about most new pharmaceuticals; most of the drugs recommended in his book *Worst Pills, Best Pills*[9] are older drugs.

If Wolfe were practicing medicine, he would be free to apply these views in treating his patients; advocating them as national policy, however, is another matter. These are the same distinctions as between FDA approvals and denials: When the agency approves a drug, no one is forced to use it; when it disapproves a drug, no one is able to use it. The ethical gap between the two is huge.

What critics such as Wolfe are demanding is pharmaceutical omniscience in advance of widespread use.

But testing new drugs on hundreds or thousands of people will only rarely reveal all the side effects that might occur when those drugs are subsequently used by millions of people. The only way to guarantee zero unexpected side effects is to have zero new drugs, period. That, however, would result in a public health disaster dwarfing all side effects combined.

In response to these critics, FDA itself has imposed new regulatory burdens, ranging from Risk Evaluation and Management Strategies (REMS), which severely restrict the use of certain drugs after they are approved, to a severe tightening of its medical device approval procedures, to high-profile reconsiderations of certain previous approvals. And in one sign of the times, last year Wolfe joined FDA's Drug Safety and Risk Management Committee.[10]

Is There a Remedy?

Most physicians' views of FDA are significantly different from Wolfe's. Over the last 15 years, the Competitive Enterprise Institute has conducted six surveys of physicians on their views of FDA. In each survey, an overwhelming majority of respondents viewed FDA as being too slow in approving new drugs and devices.

Each survey involved a different medical specialty, ranging from oncologists to cardiologists to emergency room physicians and, most recently, orthopedic surgeons. On the basic question of FDA approval speed, those viewing FDA as too slow ranged from 61 to 77 percent. In our most recent survey, of orthopedic surgeons in 2007, 76 percent took this view, and 78 percent believed that FDA has hurt their ability to give patients the best possible care.[11] By the way, 80 percent would like to have Vioxx available again.

But when it comes to influencing FDA, the views of practicing physicians carry far less weight than those of "public interest" advocates and politicians. Given the skewed incentives to which it is subject, is there any hope of FDA reform?

The short answer is yes. For one thing, with the rise of the Internet, information about new pharmaceutical developments is becoming far more widespread; the same is true about information on where such new drugs can be obtained. For important but unapproved therapies, it may be much harder in the future for people to be kept complacently in the dark.

One simple but apparently radical approach would be to leave the agency's safety and effectiveness standards in place, while simply removing its veto power. In effect, FDA would become a certifying agency. Rather than being banned outright, as they are now, uncertified therapies would be available under medical supervision, with informed consent documentation of their uncertified status.

For those doctors and patients who trust FDA, nothing would change; they would simply continue to use FDA-approved therapies. But patients who, in consultation with their doctors, wish to go beyond such therapies, would now have new options.

As for FDA itself, it would no longer be the only game in town. Instead of enjoying its monopoly status, it would now come under competitive pressure to issue timely and credible evaluations, knowing that failure to do so would make it irrelevant to many physicians.[12]

And while this approach may sound radical, it isn't. Most of the physicians in each of our surveys indicated that they would favor it. As for where they would go for information about such unapproved therapies, their answers were to be expected: medical journals, approval status in other medically advanced countries, and the views of their colleagues.[11, p 37]

But if doctors have this view of FDA, why don't their patients?

Whenever FDA announces its approval of a major new drug or device, the question that needs to be asked is: If this drug will start saving lives tomorrow, then how many people died yesterday waiting for the agency to act? As our surveys indicate, many doctors already have this question on their minds. Getting the word out to patients, and to the public at large, may well be the key to truly reforming FDA.

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