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FDA's Bad Medicine

How the Dispersed Knowledge Problem Affects Drug Safety Analysis

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The Food and Drug Administration's (FDA) regulation of drugs and medical devices has long been characterized by three major problems: excessively long approval times, excessive costs, and flawed decision making.¹ The last includes not only approving drugs that are later found to have serious side effects, but also failing to approve useful drugs, and inappropriately removing drugs from the market or restricting the use of approved drugs during post-approval surveillance.

Numerous reports over the past 30 years have found problems with FDA's approval process and post-market drug surveillance programs, and experts have recommended changes to both. Nevertheless, the problems persist. The agency's judgment and its ability to learn from its own experience or from outside advisors are compromised by its organizational structure and its value system. These problems are compounded by grandstanding politicians, plaintiff attorneys, crusading journalists, and "consumer" groups. Ultimately, like all central planners, FDA faces the fundamental social problems of interest or bias and of dispersed knowledge.²

FDA's bias results from its organizational structure as an arm of the federal government, which makes the agency inherently subject to political pressure. If it approves a drug that later is found to be unsafe in any way, the news media, the public, and politicians blame FDA for the error. But if the agency delays when reviewing applications, the patients who need innovative new treatments are worse off, and some may even die waiting for FDA to act.

In both cases, people are hurt, but FDA is only criticized for approving medicines viewed as "too risky"—never for keeping beneficial ones off the market. As a result, the agency has developed an entrenched, progressively more risk-averse culture, so that it now requires longer clinical trials, stricter post-marketing monitoring, and quicker drug

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withdrawals. All of these decrease patient options, contribute to raising drug prices, and lead to unnecessary suffering and death.

Even if that bias problem could be resolved, FDA still faces the problem of dispersed knowledge. Every day, thousands of physicians and patients make myriad choices from available drug options. They take into account differences in effectiveness, side effects, and drug interactions for each individual patient. FDA scientists may know a lot about the drugs they evaluate and their average effects on thousands of users, but they know nothing about the individualized physiology of each patient. On the other hand, intensively trained clinical physicians, who do have knowledge of individual patients, are best able to advise them if a drug is appropriate.

FDA's regulatory authority operates under a one-size-fits-all model, but *every patient is different*. This means that every decision to approve or withhold approval for drugs or medical devices will necessarily be seen as reckless by some patients, and too risk-averse by others. Of course, only when FDA keeps products off the market is decision-making power taken out of the hands of doctors and their patients. Those who have concerns about approved drugs or devices need not use them.

This paper takes a close look at FDA's knowledge problem, and the effects it has had on its decision making regarding drug safety. It concludes that a market-based approach to drug safety information, combined with technological advances in diagnostic science, will lead to a more vibrant medical marketplace—and better outcomes for patients.

The Approval and Monitoring Challenge. When FDA considers approving a new drug or medical device, it carefully sifts through data on the product's safety and effectiveness collected during clinical testing in, at most, a few thousand patients. After a drug is approved, FDA continues to monitor safety by evaluating adverse drug reaction reports, new clinical trials conducted by independent researchers or by the drug's manufacturer, and observational studies (which monitor the use of the drug in ongoing medical care).

Unfortunately, no drug is 100 percent safe. And, because some potentially harmful side effects will arise in fewer than one in 100,000 users, those are often detected only after a drug has been approved. When deciding whether any given drug should be approved in the first place or remain on the market, FDA considers the drug's medical utility—the extent of its use, the severity of the disease or diseases being treated, the drug's efficacy in treating those diseases, and the availability of other drugs to treat the same diseases.

When making such evaluations, the FDA's challenge is to determine the appropriate balance between patient safety and drug effectiveness. But studying drugs more thoroughly during pre- or post-approval clinical trials has weaknesses. Trials are expensive, generally cannot include enough subjects to detect rare side effects, and often are too short in duration to identify long-term side effects. Perhaps most importantly, large clinical trials involve diverse populations with many subgroups that are not easy to identify. Important genetic differences between individuals within each subgroup—such

as those that affect how quickly certain compounds are absorbed into the blood stream or metabolized by the patient's body—can dramatically affect the probability of benefiting from, or being harmed by, the drug. Furthermore, the results of a clinical trial can be biased against approval by the occurrence of a handful of adverse events in a relatively small number of high-risk patients, even though most of the patients studied will experience great benefit and relatively low risk.

The alternative, population-based observational studies conducted after approval, are notorious for their weaknesses, which include the presence of unrecognized confounding factors and a predisposition to attribute any adverse health outcomes to the medicine being taken. However, these weaknesses are unavoidable because there is no reasonable way to pair the population using the drug with an adequate control population not using the drug, but which are similar in all other relevant ways. Still, FDA may be called upon to issue warnings or withdraw a drug from the market based solely or primarily on this highly suspect information, with politicians and the news media demanding that the agency “err on the side of caution.”

Risk of Overreaction. There is a real danger that FDA will overreact to medical risks discovered during post-approval surveillance. A few individual adverse events do not necessarily mean that a drug is inherently unsafe—any given adverse event may not have been caused by the drug, or if it is, the effect may be confined to small subpopulations. Consequently, the agency must carefully evaluate all the emerging safety information and determine whether the post-marketing event is drug-related, whether there are any common trends or risk factors, and how frequently the event occurs among the population exposed compared with its frequency in a population not using the drug. Then the agency must decide whether the emerging data are strong enough to require a change in labeling or whether physicians who have prescribed the drug should be notified of the newfound side effects.

The agency may also take a more drastic approach, such as withdrawing the drug from the market or restricting distribution of the drug by using Risk Evaluation and Mitigation Strategies (REMS)—formerly known as Risk Minimization Action Plans (RiskMAPs). Labeling changes and warning letters are often preferred because REMS and RiskMAPs, which currently are used for around 30 drugs, tend to be excessive and punitive because they restrict which physicians may prescribe, and which pharmacies may dispense, which drugs. That, in turn, limits which patients may obtain access to potentially life-saving medication.

It may seem counterintuitive, but more harm can be caused by issuing an early warning about a drug that later turns out not to be dangerous than by leaving a dangerous drug too long on the market. Withdrawing a drug, because a relatively small number of patients have adverse reactions, imposes a hidden cost in quality and years of life lost for the large number of patients who could benefit from the drug and who will not experience the side effect. Although waiting too long to withdraw the drug can jeopardize the health of those patients who experience the side effect, acting too soon will unfairly deprive the vast majority of patients of the drug's benefits. Some of them will remain ill longer, and,

depending upon the seriousness of the medical condition and the effectiveness of alternative treatments, some may even die.

Case Study: Vioxx. The drug Vioxx (rofecoxib) provides an illustrative example. In 1999, Vioxx was marketed as an improved anti-arthritis drug that would cause fewer gastrointestinal side effects than conventional non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, acetaminophen, and ibuprofen. Vioxx was one of a new class of drugs called Cox-2 Inhibitors that selectively block an enzyme responsible for triggering the pain and swelling of arthritis inflammation, but without causing acid irritation of and damage to the stomach lining as conventional NSAIDs do. Vioxx was a so-called “me-too” drug that, on average, only had marginal benefits over other existing Cox-2 drugs. Still, Vioxx rapidly became a best seller, largely because it gave many individuals much better pain relief than other drugs in its class.

In 2004, after a post-approval study sponsored by Merck, Vioxx’s manufacturer, showed that patients who took Vioxx for more than 18 months were at an increased risk for heart attacks and strokes, the company withdrew the drug from the market. During its four years on the market, over 100 million prescriptions had been filled in the U.S., and the drug *may* have contributed to fatal or other very serious heart problems for several hundred patients.

Another Cox-2 drug and numerous conventional NSAIDs remained on the market following its withdrawal, but many patients who had taken Vioxx could not find a satisfactory substitute.³ Many doctors and patients continue to believe that Vioxx’s ability to relieve pain far outweighs its risks in many cases. A Competitive Enterprise Institute survey released in January 2007, for example, found that 80 percent of the orthopedic surgeons polled would like to have Vioxx available again.⁴ In author Jerome Arnett’s own practice of Internal Medicine, many patients would choose to resume its use, with informed consent about its side effects. Just as “me-too” drugs like Vioxx and other Cox-2 Inhibitors often have slightly different unwanted side effects for different people, they also have subtle but important intended benefits that will affect different patients differently.

FDA’s Real Safety Record. Following the Vioxx recall, Sen. Charles Grassley (R-Ia.) and Rep. Joe Barton (R-Tex.) asked the Government Accountability Office (GAO) to evaluate FDA’s oversight of drug safety. Its report, published in 2006, found FDA’s post-market safety decision-making process to be “complex and iterative,”⁵ and concluded that the agency’s decision-making process was limited by a lack of clarity, insufficient oversight by management, and data constraints. It recommended that FDA revise its decision-making process for major post-marketing safety actions, improve its process to resolve disagreements over safety decisions, and systematically track post-marketing drug safety issues.

FDA also commissioned the National Academies’ Institute of Medicine (IOM) to evaluate its drug safety system, including its oversight of post-marketing drug safety. In a 2006 report, the IOM concluded that FDA approves drugs too quickly and is too slow to

remove them from the market when they prove inordinately risky.⁶ As a result of these two reports, FDA created the Drug Safety Oversight Board to provide the agency with advice on drug safety issues. It also increased its use of RiskMAPs and REMS, increased its staff working in post-marketing surveillance, and extended safety studies to 18 months following a drug's approval.

Unfortunately, neither the GAO nor IOM report sufficiently accounted for the very real harm to patients that would result from approving drugs more slowly or removing them from the market more rapidly, so the recommended expansion of FDA's regulatory powers will not solve that agency's problems.

The agency has a long history of making bad decisions that keep good treatments off the market. For example, its 1988 ban on advertising aspirin to the general public to prevent a first heart attack is estimated to have resulted in tens of thousands of needless heart attack deaths each year it was in effect.⁷ Its 10-year delay (1968-1978) in approving the beta-blocker propranolol for use in treating angina and hypertension—during which time it was available in other countries—caused an estimated tens of thousands of additional deaths.⁸ Its 1992 shutdown of Physio-Control Corporation, a manufacturer of cardiac defibrillators, largely because of paperwork infractions, likely caused up to 1,000 deaths.⁹ Its tragic 1992 recall of Bunnell, Inc.'s Life Pulse High Frequency Jet Ventilator for premature infants (for which there was no effective substitute), because of paperwork violations, may have caused up to several hundred infant deaths.¹⁰ And the list could go on and on.

Conclusion. Who should decide whether a drug's risks outweigh its benefits? The conventional rationale is that consumers can never have sufficient information or expertise to weigh all the benefits and risks, so the FDA must make those choices for patients.¹¹ But this ignores two important facts about the real-world practice of medicine.

- First, doctors are providers of expert advice and judgment who are not merely capable of, but tasked with helping patients determine which course of treatment is best for them.
- Second, each patient is necessarily different from all others, both in terms of physiology and in preference for risk taking. Not only will a drug like Vioxx affect each patient slightly differently, but each patient will place a different value on the benefit of improved pain management and the attendant risks associated with the treatment.

This dispersed-knowledge problem makes FDA ill-equipped to choose which risks are worth taking to achieve which benefits for which patients. That is why so many physicians increasingly believe that FDA's role should simply be to certify that drug manufacturers conduct appropriate testing and to supply that information to the public so doctors and patients can make informed choices. In a series of six surveys of medical specialists conducted between 1995 and 2007, large majorities of physicians said they favored changing the law to give doctors access to unapproved medicines if they carry a warning about their unapproved status—including 68 percent of oncologists, 69 percent

of emergency room physicians, 70 percent of orthopedic surgeons, and 73 percent of neurologists.¹²

Moreover, the ability for physicians to make fine distinctions about which drugs will work best for which patients is becoming much easier as our knowledge of human genetics increases. The new science of pharmacogenomics tells us how genetic differences cause drugs to be metabolized differently in different groups of patients, and gives us a greater ability to fine tune treatment to individual patients.¹³

Different genes encode drug-metabolizing enzymes, drug transporters, and drug targets (receptors). More than 30 families of drug-metabolizing enzymes have been discovered to date and more than 25 examples of genetic variation in drug targets, or receptors, have been found that alter the individual patient's response to drugs. Genaissance Pharmaceuticals, for example, has found 29 biomarkers that affect patients' clinical response to each of four different "statin" drugs. And the company already has developed tests to identify genetic factors that alter patients' responses to medicines for asthma and congestive heart failure.¹⁴

Personalized medicine is here. This rapidly increasing ability of physicians to identify differences among patients is making FDA's role as pharmaceutical gatekeeper less, not more, important. Pharmacogenomics will put more—and more specialized and individualized—patient information in the hands of clinical physicians, while lessening any claim to specialized knowledge by FDA scientists.

Market forces, combined with technological and scientific advances, soon will allow physicians to bypass the FDA's harmful one-size-fits-all drug regulation by identifying the right drug and the right dose for each individual patient. That will help us all live healthier, wealthier, and longer lives.

Notes

¹ See, for example, Ronald W. Hanson, "FDA Regulation of the Pharmaceutical Industry," in Robert Higgs, Ed., *Hazardous to Our Health? FDA Regulation of Health Care Products* (Oakland, Cal.: The Independent Institute, 1995), pp. 13-27; Henry I. Miller, *To America's Health: A Proposal to Reform the Food and Drug Administration* (Stanford, Cal.: Hoover Institution Press, 2000).

² Friederich A. Hayek, "The Use of Knowledge in Society," *American Economic Review*, Vol. 35, No. 4 (September, 1945), pp. 519-30; Randy E. Barnett, *The Structure of Liberty: Justice and the Rule of Law* (Oxford, UK: Oxford University Press, 2000), p. 3.

³ January W. Payne, "Withdrawal Symptoms: Patients, Doctors Explore Alternatives to Vioxx For Arthritis Relief—Very Carefully," *The Washington Post*, November 23, 2004, p. H1; Richard Lottfield, "Vioxx Helped Me Live a Lot Better And I'd Like It Back," *The Wall Street Journal*, June 14, 2008, p. A-10.

⁴ *A National Survey of Orthopedic Surgeons Regarding the Food and Drug Administration and the Availability of New Therapies* (Washington, D.C.: Competitive Enterprise Institute, January 2007).

⁵ Government Accountability Office, "Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process," GAO-06-402 (Washington, D.C., GAO, March 2006).

⁶ Institute of Medicine Committee on the Assessment of the U.S. Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, Alina Baciuc, Kathleen Stratton, and Sheila P. Burke, Eds. (Washington, D.C.: National Academies Press, 2006).

⁷ Paul H. Rubin, "FDA Advertising Restrictions: Ignorance is Death," in Higgs, Ed., *Hazardous to Our Health?*, pp. 29-53.

⁸ Dale H. Gieringer, "The Safety and Efficacy of New Drug Approval," *Cato Journal*, Vol. 5, No. 1 (Spring/Summer 1988), pp. 177-201.

⁹ Robert Higgs, "FDA Regulation of Medical Devices," in Higgs, Ed., *Hazardous to Our Health?*, pp. 55-95.

¹⁰ *Ibid.*

¹¹ Robert Higgs, "Diminishing the Harm?" in Robert Higgs, Ed., *Hazardous to Our Health?*, pp. 97-101.

¹² *A National Survey of Orthopedic Surgeons*, Competitive Enterprise Institute, 2007.

¹³ William E. Evans and Howard L. McLeod, "Pharmacogenomics—Drug Disposition, Drug Targets, and Side Effects," *New England Journal of Medicine*, Vol. 348, No. (February 6, 2003), pp. 538-549; Dan M. Roden, Russ B. Altman, Neal L. Benowitz, et al., "Pharmacogenomics: Challenges and Opportunities," *Annals of Internal Medicine*, Vol. 145, No. 10 (November 21, 2006), pp. 749-757.

¹⁴ Robert Goldberg and Paul Howard, "Vioxx Backlash Could Derail Future of Medicine," *Health Care News*, January 1, 2005, <http://www.heartland.org/Article.cfm?artId=16134>.