

HEALTH CARE POLICY

Gaps, Tensions, and Conflicts in the FDA Approval Process: Implications for Clinical Practice

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Despite many successes, drug approval at the Food and Drug Administration (FDA) is subject to gaps, internal tensions, and conflicts of interest. Recalls of drugs and devices and studies demonstrating advantages of older drugs over newer ones highlight the importance of these limitations. The FDA does not compare competing drugs and rarely requires tests of clinical efficacy for new devices. It does not review advertisements before use, assess cost-effectiveness, or regulate surgery (except for devices). Many believe postmarketing surveillance of drugs and devices is inadequate. A source of tension within the agency is pressure for speedy approvals. This may have resulted in “burn-out” among medical officers and has prompted criticism that safety is ignored. Others argue, however, that the agency is unnecessarily slow and bureaucratic. Recent reports identify conflicts of interest (stock ownership, consulting fees, research grants) among some members of the FDA’s advisory committees. FDA review serves a critical function, but physicians should be aware that new drugs may not be as effective as old ones; that new drugs are likely to have undiscovered side effects at the time of marketing; that direct-to-consumer ads are sometimes misleading; that new devices generally have less rigorous evidence of efficacy than new drugs; and that value for money is not considered in approval. (J Am Board Fam Pract 2004;17:142–9.)

The process of drug development and approval by the United States Food and Drug Administration (FDA) was recently reviewed by Lipsky and Sharp.¹ Using clinical literature and web sites addressing FDA procedures, that review concisely described the FDA’s history, the official approval process, and recent developments in drug approval. However, it did not delve into common misconceptions about the FDA, tensions within the agency, or conflicts of interest in the drug approval process. The rapidly growing business of medical device development, distinct from the drug approval process, also was not addressed. Although most aspects of the FDA review process are highly successful, its limitations

deserve careful consideration, because they may have important implications for choosing treatments in practice.

Recent recalls of drugs and devices call attention to limitations of the approval process.^{2–4} Recent news about complications of hormone replacement therapy^{5,6} and new data supporting the superiority of diuretic therapy over newer, more expensive alternatives for hypertension⁷ emphasize gaps in the process. Clinicians should be aware of regulatory limitations as they prescribe treatments and counsel patients, so they have realistic ideas about what FDA approval does and does not mean.

Because controversies relating to internal conflicts or political issues are infrequently reported in scientific journals, this discussion draws not only on scientific articles, but also internet resources, news accounts, and interviews. The goal was not to be exhaustive, but to provide examples of tensions, conflicts, and gaps in the FDA process.

As Lipsky and Sharp noted, the FDA approves new drugs and devices (as well as assuring that foods and cosmetics are safe). It monitors over \$1 trillion worth of products, which represents nearly a fourth of consumer spending.¹ In the medical

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arena, the basic goal of the FDA is to prevent the marketing of treatments that are ineffective or harmful. However, the agency faces limitations that result from many factors, including the agency's legal mandate, pressures from industry, pressures from advocacy groups, funding constraints, and varied political pressures.

Common Misconceptions

Many consumers and physicians may have misconceptions about the FDA approval process. For a new drug to win approval, the FDA does not require it to be better than products already available—only that it be effective (better than nothing) and fairly safe. For high-risk devices, demonstration of safety and efficacy are also required. But for moderate risk devices, only safety and “substantial equivalence” to a previously marketed device are required. The benefit of a new drug or device must be judged to outweigh the risks. This is all Congress has allowed the FDA to require.

In some cases, the definition of “effective” is narrow and may not address the end results of therapy. A drug that achieves a “surrogate outcome” may be approved if it lowers cholesterol, lowers high blood pressure, or improves heart rhythm—without knowing if it improves life expectancy.

In some cases, approved drugs were later found to increase rather than decrease mortality. The antiarrhythmic drugs encainide and flecainide were examples. The company-sponsored trials that led to their approval showed they were effective in suppressing ventricular arrhythmias. However, by one estimate, these drugs produced a death toll of 50,000 before their toxicity was demonstrated in a large National Institutes of Health-sponsored clinical trial, in which the mortality with active treatment was twice that with placebo.^{8,9} Furthermore, studies used for drug approval are not designed with sufficient statistical power for detecting important but infrequent safety problems.

Drug approval generally requires rigorous testing of clinical efficacy, in the form of at least 2 randomized controlled trials. However, the regulations for medical devices are quite different. Medical devices include anything from contact lenses to cardiac pacemakers and MRI scanners. Most new devices are approved by demonstrating “substantial equivalence” to a product that was marketed more

than 25 years ago (before 1976). For this type of approval, a device need only do technically what it claims and be reasonably safe. A device that delivers electric current to the skin can be considered “effective” without asking if it relieves symptoms. Devices that do not claim substantial equivalence to an older device (a tiny fraction of new submissions) are required to undergo more rigorous review. This may or may not require randomized trials.

Things the FDA Does Not Do

There are some potentially valuable functions the FDA does not perform. For example, it does not approve old drugs and devices. Some medical products in wide use were marketed before FDA approval was required, and their use is “grandfathered” in.

The FDA makes no judgment about the value for money of a new drug or device. Dr. Larry Kessler, Director of the Office of Science and Technology in FDA's Center for Devices and Radiologic Health, says if a manufacturer wanted to market “a gold-plated biliary stent that costs a million dollars a pop—works great—FDA has to approve it. It's a lousy buy because the \$127 version works almost as well. But FDA has to approve it. Medicare may decide it's not cost-effective and refuse to pay for it, but FDA cannot address cost-effectiveness” (L. Kessler, personal communication). In truth, even Medicare cannot make reimbursement decisions based on cost-effectiveness, although private health plans and state Medicaid programs can.

The FDA does not determine whether one blood pressure drug is better than another for reducing the risk of blood pressure complications (like strokes and congestive failure). It does not require that drugs prove this effect, nor does it require head-to-head comparisons of competing drugs or devices. Dr. Kessler says, “The reason is that we could be seen as favoring product A over product B. And FDA always, always, always shies away from that” (L. Kessler, personal communication).

Some consequences of this policy were illustrated by results of recent clinical trials. In the ALLHAT trial, diuretic therapy was found to be more effective at preventing cardiovascular complications of hypertension than were calcium channel blockers or angiotensin-converting enzyme (ACE)

inhibitors.⁷ Because no adequate comparisons were previously available, and because the newer drugs were heavily marketed, diuretics had come to be used in only a minority of patients, whereas calcium channel drugs and ACE inhibitors (at 10 to 20 times the cost) had steadily gained market share.¹⁰ Similarly, a recent study demonstrated no advantage of ticlopidine over aspirin for preventing recurrent strokes among African Americans, despite ticlopidine's substantially higher price and its risk of serious adverse events.¹¹

The FDA does not approve every use to which a medical product might be put. A drug can be marketed after approval for treating one condition, and doctors can legally use it for others. Gabapentin (Neurontin) for example, is approved as an adjunct for treating seizures and for management of post-herpetic neuralgia, but many physicians use it to treat long-term pain and psychiatric problems. Unfortunately, there may be little if any scientific evidence to support off-label uses. "When you routinely recommend some off-label use for your patients—for which there aren't data to prove this is the right thing—when does that really become experimentation without informed consent?" asks Dr. Kessler (L. Kessler, personal communication).

The FDA does not approve television or magazine ads for new drugs before they are aired or printed, although companies are required to submit ads to the agency at the time they are first disseminated. Because of their wide exposure, direct-to-consumer broadcast ads are all reviewed, although some print ads are not.¹² FDA can only request that a company pull ads that are judged misleading after they are already in use. In late 2001, the Department of Health and Human Services instructed FDA not to issue regulatory letters until they are reviewed by the agency's Office of the Chief Counsel. This has delayed letters from 2 to 12 weeks: long enough in some cases for misleading ads to complete their planned broadcast life cycle. FDA cannot verify that it receives all new ads from drug companies and has issued 6 regulatory letters since 1997 citing companies for failing to submit ads when they were first disseminated.¹²

FDA has few resources for routine monitoring of ads and often issues warning letters only after competitors complain. For the interval 2000 to 2002, The FDA web site lists 222 letters to drug makers for warnings or violations of advertising rules. The agency has repeatedly contacted several

companies, including Pfizer, Schering-Plough, Merck, and Glaxo Wellcome (now GlaxoSmith-Kline) for violations. These include improper claims and minimizing drug risks.¹² The agency cannot levy fines, and several drug companies have aired new misleading ads even after being cited for violations, according to a 2002 report by the Congressional General Accounting Office.¹²

The FDA recalls drugs or devices if new evidence emerges suggesting they are unsafe. However, it generally does not recall drugs or devices because of accumulating evidence they do not work. The marketplace is judged sufficient to accomplish this goal, and it sometimes does. But if this process is slow, tests and procedures may continue in use for years after they have been found to be ineffective or inferior to alternative products.

The FDA does not regulate new surgical procedures in any way. It does regulate devices, such as surgical implants. Examples would be metal hip replacements or cardiac pacemakers. It also regulates new surgical instruments, such as the fiberoptic scopes that are increasingly used for minimally invasive surgery. But if a surgeon develops a new approach or technique that does not involve a new device, it falls outside the jurisdiction of the FDA.

Medical Devices

The FDA's approach to approving medical devices differs substantially from the approach to drugs, being in some ways both more complex and less stringent.¹³ The FDA's authority over devices dates only to 1976. Device legislation was a response, in part, to public outcry over some well-publicized device failures. The most prominent was the Dalkon Shield—an intrauterine contraceptive device associated with serious infections.¹⁴ In contrast, the FDA's authority over drugs dates to 1938, although it existed in weaker form starting in 1906.¹⁵

With few exceptions, given the timing of the FDA's authority, devices introduced before 1976 were never required to undergo rigorous evaluation of safety and efficacy. With the huge volume of "things" that suddenly fell under its purview, the FDA had to prioritize its resources and efforts.

One way of prioritizing was to focus first on safety. Evaluation of effectiveness, in many cases, was reduced to engineering performance: does the

device hold up under its intended uses, does it deliver an electric current as advertised? The potential benefits for relieving pain, improving function, or ameliorating disease did not generally have to be demonstrated.

Another way of prioritizing was to assign categories of risk associated with the devices. Rubber gloves seemed less risky than cardiac pacemakers, for example. So the agency assigned devices to 1 of 3 levels of scrutiny. Class I devices have low risk; oversight, performed mainly by industry itself, is to maintain high manufacturing quality standards, assure proper labeling, and prevent adulteration. Latex gloves are an example.

At the other extreme, class III devices are the highest risk. These include many implantable devices, things that are life-supporting, and diagnostic and treatment devices that pose substantial risk. Artificial heart valves and electrical catheters for ablating arrhythmogenic foci in the heart are examples. This class also includes any new technology that the FDA does not recognize or understand. New components or materials, for example, may suggest to FDA that it should perform a more formal evaluation. In general, these devices require a “premarket approval,” including data on performance in people (not just animals), extensive safety information, and extensive data on effectiveness. This evaluation comes closest to that required of drugs. In fact, Dr. Kessler says, these applications “look a lot like a drug applications: big stacks of paper. They almost always require clinical data—almost always. And they often require randomized trials. Not always, but often” (L. Kessler, personal communication). These devices are often expensive and sometimes controversial because of their costs.

Class II devices are perhaps the most interesting. They comprise an intermediate group, generally requiring only performance standards. Examples would be biopsy forceps, surgical lasers, and some hip prostheses. The performance standards focus on the engineering characteristics of the device: does it deliver an electrical stimulus if it claims to, and is it in a safe range? Is it made of noncorrosive materials? Most of these devices get approved by the “510(k)” mechanism. The 510(k) approval requires demonstrating “substantial equivalence” to a device marketed before 1976. “And,” says Kessler, “the products that have been pushed through 510(k) are astonishing” (L. Kessler, personal communication).

Kessler points out, “For the first 5 to 10 years after 1976, this approach made sense. But in 2001, 25 years after the Medical Device Amendment, does it make sense? There was a lot of stuff on the market that wasn’t necessarily great in 1975—why would you put it back on the market now?” (L. Kessler, personal communication). The new device need not prove superiority to the older product—just functional equivalence. If a company wants to tout a new device as a breakthrough, why would it claim substantial equivalence to something 25 years old?

The reason is that the 510(k) process is easier and cheaper than seeking a premarket approval. The 510(k) process usually does not require clinical research. In the mid-1990s, a 510(k) application on average required 3 months for approval, and about \$13 million. A premarket approval required, on average, about a year and \$36 million. Both are modest compared with new drug approvals. The process by which the agency decides if something is “equivalent enough” to be approved by the 501(k) mechanism is subjective.

Because pre-1976 devices were not subject to any rigorous tests of clinical effectiveness, a newly approved device may be equivalent to something that has little or no therapeutic value. Doctors, patients, and payers therefore often have little ability to judge the value of new devices. As an example, the FDA still receives 510(k) applications for intermittent positive pressure breathing machines.¹² Yet a thorough review by the federal Agency for Health Care Policy and Research found that these devices offer no important benefits.¹⁶

How much do manufacturers take advantage of the easier 510(k) approach? Since 1976, nearly 98% of new devices entering the market in class II or III have been approved through the 510(k) process.¹³ In 2002, the FDA reported 41 premarket approvals and 3708 approvals through the 510(k) process.¹⁷

Pressures for Approval

Perhaps the biggest challenge and source of friction for the FDA is the speed of approvals for drugs and devices. Protecting the public from ineffective or harmful products would dictate a deliberate, cautious, thorough process. On the other hand, getting valuable new technology to the public—to save lives or improve quality of life—would argue for a speedy process. Some consumer protection groups

claim the agency is far too hasty and lenient, bending to drug and device company pressure. On the other hand, manufacturers argue that the agency drags its feet and kills people waiting for new cures. Says Kessler: "That's been the biggest fight between the industry, the Congress, and the FDA over the past decade: getting products out fast" (L. Kessler, personal communication).

To speed up the review process, Congress passed a law in 1992 that allowed the FDA to collect "user fees" from drug companies. This was in part a response to AIDS advocates, who demanded quick approval of experimental drugs that might offer even a ray of hope. These fees, over \$300,000 for each new drug application, now account for about half the FDA's budget for drug evaluation, and 12% of the agency's overall \$1.3 billion budget.¹⁸

The extra funds have indeed accelerated the approval process. By 1999, average approval time had dropped by about 20 months, to an average of a year. In 1988, only 4% of new drugs introduced worldwide were approved first by the FDA. By 1998, FDA was first in approving two thirds of new drugs introduced worldwide. The percentage of applications ultimately approved had also increased substantially.¹⁸ Nonetheless, industry complained that approval times slipped to about 14 months in 2001.¹⁹ In 2002, device makers announced an agreement with the FDA for similar user fees to expedite approval of new devices, and Congressional approval followed with the Medical Device User Fee and Modernization Act.²⁰

Critics, such as 2 former editors of the *New England Journal of Medicine*, argue that the user fees create an obvious conflict of interest. So much of the FDA budget now comes from the industry it regulates that the agency must be careful not to alienate its corporate "sponsors."²¹ FDA officials believe they remain careful but concede that user fees have imposed pressures that make review more difficult, according to *The Wall Street Journal*.²²

An internal FDA report in 2002 indicated that a third of FDA employees felt uncomfortable expressing "contrary scientific opinions" to the conclusions reached in drug trials. Another third felt that negative actions against applications were "stigmatized." The report also said some drug reviewers stated "that decisions should be based more on science and less on corporate wishes."²² *The Los Angeles Times* reported that agency drug reviewers

felt if drugs were not approved, drug companies would complain to Congress, which might retaliate by failing to renew the users' fees¹⁸ (although they were just reapproved in summer, 2002). This in turn would hamstring FDA operations and probably cost jobs.

Another criticism is that the approval process has allowed many dangerous drugs to reach the market. A recent analysis showed that of all new drugs approved from 1975 to 1999, almost 3% were subsequently withdrawn for safety reasons, and 8% acquired "black box warnings" of potentially serious side effects. Projections based on the pace of these events suggested that 1 in 5 approved drugs would eventually receive a black box warning or be withdrawn. The authors of the analysis, from Harvard Medical School and Public Citizen Health Research Group, suggested that the FDA should raise the bar for new drug approval when safe and effective treatments are already available or when the drug is for a non-life-threatening condition.²

According to *The Los Angeles Times*, 7 drugs withdrawn between 1993 and 2000 had been approved while the FDA disregarded "danger signs or blunt warnings from its own specialists. Then, after receiving reports of significant harm to patients, the agency was slow to seek withdrawals." These drugs were suspected in 1002 deaths reported to FDA. None were life-saving drugs. They included, for example, one for heartburn (cisapride), a diet pill (dexfenfluramine), and a painkiller (bromfenac). The *Times* reported that the 7 drugs had US sales of \$5 billion before they were recalled.¹⁸

After analysis, FDA officials concluded that the accelerated drug approval process is unrelated to the drug withdrawals. They pointed out that the number of drugs on the market has risen dramatically, the number of applications has increased, and the population is using more medications.³ More withdrawals are not surprising, in their view. Dr. Janet Woodcock, director of the FDA's drug review center and one of the analysts, argued that "All drugs have risks; most of them have serious risks." She believes the withdrawn drugs were valuable and that their removal from the market was a loss, even if the removal was necessary, according to *The Los Angeles Times*.¹⁸

Nonetheless, many believe the pressures for approval are so strong that they contribute to employee burnout at FDA. In August 2002, *The Wall Street Journal* reported that 15% of the agency's

medical officer jobs were unfilled.²² Their attrition rate is higher than for medical officers at the National Institutes of Health or the Centers for Disease Control and Prevention. The *Journal* reported that the reasons, among others, included pressure to increase the pace of drug approvals and an atmosphere that discourages negative actions on drug applications. Attrition caused by employee “burn-out” is now judged to threaten the speed of the approval process. In 2000, even Dr. Woodcock acknowledged a “sweatshop environment that’s causing high staffing turnover.”¹⁸ FDA medical and statistical staff have echoed the need for speed and described insufficient time to master details.^{18,19}

An opposing view of FDA function is articulated in an editorial from *The Wall Street Journal*, by Robert Goldberg of the Manhattan Institute. He wrote that the agency “protects people from the drugs that can save their lives” and needs to shift its role to “speedily put into the market place. . . new miracle drugs and technologies. . . .” He argues that increasing approval times for new treatments are a result of “careless scientific reasoning” and “bureaucratic incompetence,” and that the FDA should monitor the impact of new treatments after marketing rather than wait for “needless clinical trials” that delay approvals.²³

Thus, the FDA faces a constant “damned if it does, damned if it doesn’t” environment. No one has undertaken a comprehensive study of the speed of drug or device approval to determine the appropriate metrics for this process, much less the optimal speed. It remains unclear how best to balance the benefits of making new products rapidly available with the risks of unanticipated complications and recalls.

Postmarketing Surveillance of New Products

Although user fees have facilitated preapproval evaluation of new drugs, the money cannot be used to evaluate the safety of drugs after they are marketed. Experts point out that approximately half of approved drugs have serious side effects not known before approval, and only post-marketing surveillance can detect them. But in the opinion of some, FDA lacks the mandate, the money, and the staff to provide effective and efficient surveillance of over 5000 drugs already in the marketplace.²⁴ Although reporting of adverse effects by manufacturers is mandatory, late or nonreporting of cases by drug

companies are major problems. Some companies have been prosecuted for failure to report, and the FDA has issued several warning letters as a result of late reporting. Spontaneous reporting by practitioners is estimated to capture only 1% to 13% of serious adverse events.²⁵

Widespread promotion of new drugs—before some of the serious effects are known—increases exposure of patients to the unknown risks. It is estimated that nearly 20 million patients (almost 10% of the US population) were exposed to the 5 drugs that were recalled in 1997 and 1998 alone.²⁶ The new law allowing user fees for device manufacturers does not have the same restriction on postmarketing surveillance that has hampered drug surveillance.

Conflicts of Interest in the Approval Process

Another problem that has recently come to light in the FDA approval process is conflict of interest on the part of some members of the agency’s 18 drug advisory committees. These committees include about 300 members, and are influential in recommending whether drugs should be approved, whether they should remain on the market, how drug studies should be designed, and what warning labels should say. The decisions of these committees have enormous financial implications for drug makers.

A report by *USA Today* indicated that roughly half the experts on these panels had a direct financial interest in the drug or topic they were asked to evaluate. The conflicts of interest included stock ownership, consulting fees, and research grants from the companies whose products they were evaluating. In some cases, committee members had helped to develop the drugs they were evaluating. Although federal law tries to restrict the use of experts with conflicts of interest, *USA Today* reported that FDA had waived the rule more than 800 times between 1998 and 2000. FDA does not reveal the magnitude of any financial interest or the drug companies involved.²⁷

Nonetheless, *USA Today* reported that in considering 159 Advisory Committee meetings from 1998 through the first half of 2000, at least one member had a financial conflict of interest 92% of the time. Half or more of the members had conflicts at more than half the meetings. At 102 meetings that dealt specifically with drug approval, 33%

of committee members had conflicts.²⁷ *The Los Angeles Times* reported that such conflicts were present at committee reviews of some recently withdrawn drugs.¹⁸

The FDA official responsible for waiving the conflict-of-interest rules pointed out that the same experts who consult with industry are often the best for consulting with the FDA, because of their knowledge of certain drugs and diseases. But according to a summary of the *USA Today* survey reported in the electronic *American Health Line*, “even consumer and patient representatives on the committees often receive drug company money.”²⁸ In 2001, Congressional staff from the House Government Reform Committee began examining the FDA advisory committees, to determine whether conflicts of interest were affecting the approval process.²⁹

Conclusion

Despite derogatory comments from some politicians and some in the industries it regulates, the FDA does a credible job of trying to protect the public and to quickly review new drugs and devices. However, pressures for speed, conflicts of interest in decision-making, constrained legislative mandates, inadequate budgets, and often limited surveillance after products enter the market mean that scientific considerations are only part of the regulatory equation. These limitations can lead to misleading advertising of new drugs; promotion of less effective over more effective treatments; delays in identifying treatment risks; and perhaps unnecessary exposure of patients to treatments whose risks outweigh their benefits.

Regulatory approval provides many critical functions. However, it does not in itself help clinicians to identify the best treatment strategies. Physicians should be aware that new drugs may not be as effective as old ones; that new drugs are likely to have undiscovered side effects at the time they are marketed; that direct-to-consumer ads are sometimes misleading; that new devices generally have less rigorous evidence of efficacy than new drugs; and that value for money is not considered in the approval process. If clinicians are to practice evidence-based and cost-effective medicine, they must use additional skills and resources to evaluate new treatments. Depending exclusively on the regulatory process may lead to suboptimal care.

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