32. Food and Drug Administration

Congress should

- allow drug companies an "opt-out" option from FDA efficacy testing or repeal the FDA's authority to review efficacy,
- eliminate user fees,
- phase out FDA review of drug safely to increase patient access to potential medical breakthroughs,
- curb FDA authority to regulate marketing practices, and
- eliminate FDA regulations that undermine competitiveness and investment.

Federal Pharmaceutical Policy

Research in and development of innovative medical technology is literally a matter of life and death. But at a time when the United States is on the verge of revolutionary improvements in health, medical progress is under attack by excessive regulation by the FDA.

The 104th Congress considered some minor though welcome changes in the tangled and time-consuming regulations that govern the development, testing, and marketing of Pharmaceuticals and medical devices. Unfortunately, no significant reforms were passed.

Currently, the federally mandated process for introducing a new drug to the retail market consists of three phases. Under Phase I, the FDA must be satisfied that the new drug is safe and will not harm patients. Under Phase n, the FDA must be satisfied that there is a correlation between the use of a product and the effect that the product is suppose to produce. Under Phase III, a company is required to run tests to demonstrate just how effective the product is.

That system has been built up over decades. Under the Food, Drug and Cosmetic Act of 1938, companies had to submit a new drug application (NDA) before selling a new medicine. The NDA was to contain evidence that the drug was safe to use. The FDA had 60 days in which to reject an application, otherwise it was automatically approved.

Today the FDA uses administrative means to prolong the time required to permit clinical use of medicines. According to Peter Barton Hutt, FDA's chief counsel during the 1970s, the FDA throws up several obstacles to access to drugs in the name of safety. The FDA

- requires unnecessary animal studies before permitting clinical investigation;
- requires a lengthy and complex investigation of new drugs before those drugs are allowed on the market;
- places "clinical holds" on human investigations to prevent immediate determinations of clinical value; and
- prohibits companies from charging for drugs used in clinical investigations, thus increasing the cost of development.

By a conservative estimate, FDA delays in allowing U.S. marketing of drugs used safely and effectively elsewhere around the world have cost the lives of at least 200,000 Americans over the past 30 years. That figure does not include deaths that might have been prevented by the use of drugs such as Prozac, which is associated with the decline in suicides of individuals suffering from depression. FDA regulations denying Americans timely access to new drugs have extracted a high cost in health and lives.

Five Cases of Tragic Delays

- Dr. Louis Lasagna, director of Tufts University's Center for the Study of Drug Development, estimates that the seven-year delay in the approval of beta blocker heart medicines cost the lives of 119,000 Americans.
- During the three and half years it took the FDA to approve the new drug Interleukin-2, 25,000 Americans died of kidney cancer even though the drug had already been approved for use in nine other countries. According to Eugene Schoenfeld, a cancer survivor and president of the National Kidney Cancer Association, "IL-2 is one of the worst examples of FDA regulation known to man."

- In 1985 the National Heart, Lung and Blood Institute of the National Institutes of Health stopped a study comparing a genetically engineered clot-busting drug called TPa because the study showed that TPa was so effective in reducing heart attack-related deaths that it would be unethical to withhold it from volunteer patients. Yet it took the FDA four years to approve the drug, despite the NIH decision. That delay cost 30,000 lives.
- Even though the generic Alzheimer's drug Tacrine was being safely used by humans here and around the world, it took the FDA seven years to approve the drug. The FDA claimed that because the drug caused temporary liver toxicity it was unsafe.
- The generic anti-cancer drug Flutamide was available in Europe for years and was proven safe, but the FDA failed to approve it. According to Dr. Bruce Chabner, director of the National Cancer Institute's Division of Cancer Treatment, "We're talking about delays of years." Subsequently the National Cancer Institute accused the FDA of being "mired in a 1960s philosophy of drug development, viewing all new agents as ... poisons."

As a result of the lobbying efforts of AIDS activists, the FDA has moved quickly to approve NDAs for AIDS drugs since the early 1990s. Three protease inhibitors, a class of drugs that block the replication of the HIV virus nearly to the point of stopping progression altogether, were approved in less than three months. Although AIDS drugs are being approved more quickly than in the past, approval times for breakthrough drugs that could give hope to patients with other life-threatening diseases, such as cancer and brain diseases, remain astonishingly slow. The FDA takes an average of 14 months to review the NDAs for cancer drugs and 32 months for drugs designed to treat brain diseases such as ALS, Alzheimer's, and depression.

In 1962 Congress gave the FDA the power to require companies to demonstrate that their drugs were effective as claimed. At the time, drugs were a relatively new form of therapy; surgery and palliatives were still first-line therapy for most illnesses. Today, drugs are the first therapy physicians use before having to resort to surgery or giving up hope. In turn, insurers, physicians, and patients expect increasingly improved results from new drugs. Manufacturers must be able to demonstrate that their new products are more clinically effective than existing products or be faced with a limited market. The market is essentially doing the job the FDA was chartered to do more than 30 years ago.

In 1969 the Department of Health, Education and Welfare (now the Department of Health and Human Services) recommended evaluation procedures such as self-certification by companies and delegation of the approval authority to advisory groups made up of patients, specialists, and researchers. Such organizations would act like Underwriters Laboratories, a private, nonprofit organization that sets safety standards for various products, mostly electrical. Private alternatives to the FDA would ensure the safety of drugs and provide companies and consumers with a forum for establishing a drug's effectiveness using criteria selected by consumers rather than *FDA* bureaucrats.

The benefits of FDA efficacy regulation are paltry at best; the costs, however, are substantial. Efficacy regulation makes drugs more expensive and less accessible. According to the Center for the Study of Drug Development at Tufts University, the time required to get a new drug through the FDA approval process has been increasing since 1962. Today it takes an average of 15 years to get a drug reviewed by the FDA.

As a result, the cost of drug development has skyrocketed, increasing by over 400 percent in less than two decades. The Office of Technology Assessment has determined that the cost of developing a new drug is, on average, $394 million. Drug manufacturers now conduct an average of 60 clinical trials of each new drug for which they seek marketing approval and dozens more to extend approval of existing drugs that are effective in treating diseases other than those for which they were originally approved. Since 85 percent of the cost of pharmaceutical development goes to complying with FDA regulations, those regulations amount to a tax on investment in basic biomedical research.

The effect of FDA regulation on the price of drugs is profound. Assuming a 14 percent return on drug development, excessive FDA regulation increases the required break-even return on a drug by about 200 percent. Not only do such regulatory costs raise the price of new drugs, they also reduce basic research at a time when the opportunities for medical progress are increasing.

In the name of consumer protection, the FDA is retarding biomedical research and development. Just as control of information in despotic counties destroys creativity and innovation, the FDA's monopoly on the research, development, and use of new medical knowledge is choking off the next medical revolution. In the process it is raising the cost of essential drugs and denying sick people access to lifesaving medicines.

The Solution

A five-step process could free pharmaceutical manufacturers and biotech firms from the federal approval process.

Allow Drug Companies to Opt Out of FDA Efficacy Testing

A simple way to accelerate the approval process would be to allow manufacturers to not subject their products to the Phase III field test of efficacy. Companies could be required to label their products "Determined to be safe by the FDA, but the FDA has not reviewed the efficacy data and cannot make any claims to the efficacy of the drug as set forth in this product's label."

That approach would allow consumers the option of using safety-tested products far earlier than otherwise would be the case. Producers, of course, would seek to demonstrate the efficacy of their products to consumers. By giving producers a choice of ways to do that, the opt-out option would foster the development of independent certification labs, which would perform the functions that Underwriters Laboratories performs for electronic and other consumer products.

After this step, or perhaps even in place of it, Congress should repeal the FDA's authority to review drug efficacy. That would result in a number of benefits. It would reduce the amount of time and money research-based companies must spend on drug development. And it would mean that companies could invest more money in basic research, the source of future medical breakthroughs. Without the FDA, companies would still be forced to demonstrate their products' effectiveness to patients and physicians.

Reductions in development costs and time would accelerate new discoveries and their commercialization. As a result, more products would enter the market, forcing lower costs and greater price competition. Lower development costs and prices would encourage investors and researchers to put more money into basic research and development of new drugs.

The FDA has already proven the value of repealing efficacy authority. Manufacturers of generic drugs—copies of drugs whose patents have expired—need only show that the performance of a generic drug is similar to that of the pioneer drug. Generic drugs have been widely accepted by physicians and patients.

Further, under pressure from AIDS activists, the FDA has suspended the efficacy standard for some AIDS drugs. Instead, companies must show simply that drugs are safe and have a reasonable chance of being effective in terms set by patients themselves. As a result, the number of AIDS

drugs in development has increased despite the fact that advances are hard to come by. In addition, the price of AIDS medicines, though high, has declined as a result of increased competition.

Eliminate User Fees

Much FDA regulation, particularly Phase III regulation and delays on new drug applications, is unnecessary. Supporters of the FDA claim that a lack of staff is forcing the agency to sit on approvals. In fact, the FDA has added nearly 1,000 staffers with $300 million raised by requiring companies to pay for the privilege of undergoing FDA scrutiny. Called "user fees," such charges are nothing more than a tax on innovation. Not only has the FDA failed to reduce approval times, it has actually expanded its regulatory sweep by proposing even more rules and regulations.

The FDA claims that user fees are allowing it to reduce the time it takes to approve new drugs. In fact, the FDA has manufactured an artificial reduction. It has transferred many aspects of review from one part of the approval process to another and counts as "approval time" only the reduced part of the process. Moving the goal posts makes the agency appear more efficient, but it does not reduce the 10 to 15 years a company must invest to move a drug onto the market.

User fees are an extraordinary burden on the hundreds of small biotechnology firms that are the source of many medical breakthroughs. Eliminating user fees would amount to eliminating an unfair tax on the most innovative and entrepreneurial high-tech firms. Supporters of the FDA might complain that the loss of user fee revenue would force the agency to slow down drug approvals. In fact, there is an alternative to feeding the FDA's regulatory addiction: allow less costly private certification of a product's efficacy.

Furthermore, the FDA has not yet been able to accomplish its main objective in creating user fees—to cut drug approval times in half in five years. The FDA testified before Congress in 1992 that the additional revenue from the user fees would enable the agency, by September 1997, to acquire the resources needed to approve breakthrough drugs in 6 months and all other drugs in 12 months. However, next year will mark the five-year anniversary, and reauthorization, of the User Fee Act. Perhaps that would be an opportune time to reexamine the, as yet, unmet goals of the legislation and begin, in earnest, the campaign to reform the FDA.

Phase Out FDA Review of Drug Safety

Even if the FDA's efficacy review authority were eliminated, the agency's control over pharmaceutical safety would still deny patients

access to many important drugs, which costs billions in health care dollars, causes unnecessary suffering, and results in an untold number of lost lives. Over the past 30 years the FDA has gained nearly complete control over drug testing. But the FDA takes little account of the harm done by delays in introducing new products into the market. To ensure that patients have quicker access to safe drugs, Congress should legislate the following changes:

- The FDA should be permitted to require only nonclinical studies to ensure safety if it determines that the risk from a drug outweighs the risk from disease. Standards should be liberalized when there is no effective alternative therapy.
- Clinical holds should be limited to instances in which they are essential to public health. Patients and groups such as the American Heart Association and others focusing on cures for various diseases should be empowered to challenge a clinical hold by petition.
- Companies should be able to use well-controlled foreign studies or a definitive study at any phase to demonstrate safety.
- The FDA should not delay approval because of manufacturing process review unless it can prove in writing that the safety risk of a manufacturing process outweighs the risk of the disease.
- The FDA must review an NDA within 180 days, or the application will be deemed approved.

Those steps should only be interim measures en route to a completely private system for ensuring product safety.

Curb *FDA Authority to Regulate Marketing Practices*

Thanks to the FDA, we now live in a country where patients can use unapproved drugs to commit suicide if terminally ill but are not allowed to use off-label drugs to stay alive.

The FDA has far exceeded the bounds of its statutory authority to monitor the marketing practices of companies; it now asserts a right to control the flow of all new medical information. The FDA has gone beyond ensuring that companies provide truthful and scientifically supportable information; it now characterizes any discussion of or reference to a product—whether in an advertisement, article, or conference—as marketing. The FDA assumes that neither doctors nor patients can make reasonable choices among drugs and that it must control those choices through strict regulation.

Even though unapproved uses are regularly reported in the medical literature, the FDA prohibits companies from engaging in or supporting any form of public education about or providing any information on those uses. As a result, doctors and patients are prevented from obtaining useful information about unapproved uses of drugs for treating disease.

The FDA's regulation of marketing practices should be limited to ensuring that a drug is safe for use. The FDA should be able to review and approve labeling to ensure that it is consistent with findings of safety studies. Disputes about the truthful advertising and promotion of drugs should be resolved by other regulatory bodies or through litigation.

Companies should be permitted to discuss unapproved uses of drugs without fearing an investigation. They should be allowed to include information about unapproved uses in advertising and labeling as long as the use has been evaluated in well-controlled studies published in peer-reviewed medical literature. At present, the FDA requires companies to conduct expensive studies to demonstrate the effectiveness of unapproved uses of approved products. That requirement should be eliminated as long as other studies indicating the effectiveness of an unapproved use are available.

Eliminate FDA Regulations That Undermine Competitiveness and Investment

The FDA's regulation of other aspects of biopharmaceutical research, development, and manufacturing imposes unnecessary costs on consumers and affects the competitiveness of the nation's biomedical enterprises.

No new product can be approved until the FDA certifies that the manufacturing process is acceptable. The FDA has a stranglehold on manufacturers at the preapproval stage because it can impose any manufacturing requirements it wishes without fear of being challenged. The FDA hinders the use of new manufacturing methods by insisting that it approve every single manufacturing change. That forces companies that wish to use the latest manufacturing technology to move overseas. The FDA should be prohibited from delaying approval because of manufacturing unless it can show in writing that the risk outweighs the risk of disease.

The FDA denies companies the ability to export drugs to other countries where those drugs are already approved for marketing by making it difficult for companies to obtain export licenses. As a result, companies cannot sell products abroad before they are approved for marketing here and therefore must export their technology, build manufacturing facilities abroad, and emphasize foreign marketing. Congress should eliminate the

export license requirement, and companies should be allowed to export if any of 21 developed countries has approved the drug.

Conclusion

FDA reform is truly a matter of life and death, not only for America's biotechnology industry, but for the billions of people around the world who wait and hope for cures and better treatments for major illnesses. Some of the FDA's critics suggest that while the agency needs fixing, its basic mission, protecting the public from unsafe and useless drugs, should be preserved. However, the FDA has not yet shown that it can achieve that goal without hindering consumers' access to much needed medicine. The solution to that problem is not to reinvent government regulations and agencies. Rather, it is to back the government out of the drug approval business, turning the task over to the private sector that has time and again proved its capacity to produce lifesaving and pain-reducing medicines.

Suggested Readings

Epstein, Ralph, et al. "The Future of Medical Innovation: Health, Safety, and the Role of Government in the 21st Century." Washington: Progress and Freedom Foundation, February 7, 1996. At www.pff.org/pff/mip/fdatac.html.

Gieringer, Dale H. "Compassion vs. Control: FDA Investigational Drug Regulations." Cato Institute Policy Analysis no. 72, May 20, 1986.

Goldberg, Robert M. "Breaking Up the FDA's Medical Information Monopoly." *Regulation,* no. 2 (1995).

Higgs, Robert. "FDA Regulation of Medical Devices." Cato Institute Policy Analysis no. 235, August 7, 1995.

Peltzman, Sam. *Regulation of Pharmaceutical Innovation: The 1962 Amendments.* Washington: American Enterprise Institute, 1974.

Siegel, Joanna E. "Reforming FDA Policy: Lessons from the AIDS Experience." *Regulation,* no. 4 (1991).

Ward, Michael R. "Drug Approval Overregulation." *Regulation,* no. 4 (1992).

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