Breaking Up the FDA's Medical Information Monopoly

Robert M. Goldberg

Two years ago FDA commissioner David Kessler stated what could be the credo for his agency: "If individual patients and doctors made medical decisions on their own behalf, then the rationale for the FDA would cease to exist." The ideas that freedom of medical choice should be strictly limited and that the authority to make life or death decisions should be concentrated in a federal agency are what doomed the Clinton health plan last year.

Yet Kessler's statement amounts to a brief for the FDA's authority to control not only the content of critical medical choices but the development, use, and dissemination of information that might be used to make medical decisions. Until recently such grabs for power have gone unchallenged. More to the point, the FDA is held in high regard by many Americans precisely because people believe that it does more good than harm. As a result, the FDA has been able to enlarge its charter and expand its control over medical information.

In fact, the FDA's control of the drug approval process and the development and dissemination of information has hindered the development of new products and of more effective uses of products. It has done this in a number of ways.

Controlling New Drug Approval. The kind of efficacy information that the FDA requires on new products creates significant delays in getting those products to market. As a result, many patients suffer needlessly or die while waiting for treatment.

Controlling New Medical Information. As more and more drugs are tested, approved, and used by patients, a huge data base is being built up concerning what kinds of substances have what kinds of effects. That information should reduce the costs of developing many future products. But the FDA's approval procedures have short-circuited the natural process of incorporating such information in the development of new products. The FDA in effect forces pharmaceutical companies to reinvent the wheel, thus driving up development costs.

Controlling the Use of New Drugs. Once the FDA allows a drug on the market, physicians discover ways to tailor its use to particular types of patients, as well as other benefits of the drug that were not known when it was introduced. The FDA now seeks to restrict or ban the dissemina-

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tion of information about such uses.

Controlling Cost-Effectiveness Claims. The FDA in recent years has been withholding products from the market—not because they are unsafe or because it needed to determine the efficacy of the products; rather, the agency has been making judgments concerning which products are most cost-effective. But such determinations are best worked out in the market, after products are introduced and have a chance to compete with other products. What is really needed to give pharmaceutical companies the opportunity to develop new and better products in a timely and cost-effective manner, to save lives, and relieve misery, is a market-based drug approval regime, rather than a command-and-control one.

Knowledge as Control

Currently, the federally mandated process for introducing a new drug in 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. The FDA's authority to certify safety was established in the Food, Drug and Cosmetic Act of 1938, which requires a company seeking to market a new drug to submit a New Drug Application (NDA) containing evidence that a drug is safe to use.

Under Phase II, the FDA must be satisfied that there is a correlation between the use of a product and the desired effect that the product is suppose to produce. Under Phase III, the company is required to demonstrate, through larger field tests, the exact efficacy of products. The latter requirements were established in 1962 by Sen. Estes Kefauver's amendments to the earlier act. 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 widely used and are the first therapy physicians use before having to resort to surgery or giving up hope.

Efforts to reform or do away with the FDA altogether are doomed to fail if people fail to understand what makes Kessler and the FDA run. The answer is not found in any of the countless studies or reports on how to improve the FDA. The answer is found in Kessler's aphorism concerning who makes decisions, the FDA or private individuals. The FDA is a monopoly. It controls the market for medical information, determining the price for knowledge production, that is, the approval of new pharmaceuticals, the terms under which the "product" will be available, who will deliver the product, and who can receive it. And like all monopolies, the FDA must limit the amount of information consumers have in order to perpetuate its control. A key to the FDA's power has been its ability to limit consumer information about the relative risks and benefits of drugs. The proof of efficacy requirements were added because critics of the pharmaceutical industry regarded much drug development as overly profitable. Further, they viewed drug marketing and advertising as a largely ineffective and wasteful means of selling drugs.

But the so-called Kefauver Amendments to the Food, Drug and Cosmetic Act of 1938 had nothing to do with safety, the banner under which many FDA forays into regulation fly. The FDA already had the authority to withhold unsafe drugs from the market before the 1962 Kefauver Amendments. Rather, as Samuel Peltzman notes, "The 1962 Drug Amendments sought to reduce the costs incurred by consumers for ineffective and unsafe drugs" by taking the power to produce information out of the hands of the private sector and centralizing its production through the agency. Writes Peltzman, "The amendments try to change the composition of consumer information as well as its amount. Specifically, the amendments regulate the amount of privately produced information which is tied to a new drug."

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The efficacy statute has been used to expand the FDA's control over the character and amount of privately produced information. The degree to which the FDA has been able to accomplish the centralization of medical knowledge is a result of its ability to hide the opportunity costs and benefits of its regulatory sweep. The public lacks information about the adverse effects of the FDA's medical monopoly on other values such as health, cost-effectiveness, and quality of life. Disastrous effects occur when the FDA keeps

useful products off the market for years more than necessary or deprives the public of information about a drug's most effective use. But consumers are unwilling to forgo the seeming safety the FDA's monopoly provides.

Because of its monopoly position, the FDA is able to raise substantially the cost of obtaining medical knowledge. Hence, the cost of subsidizing the purchase and production of FDA "safety" is borne by people who have imperfect information about the relative costs and benefits of consuming other types of medical knowledge.

In his seminal 1973 article "The Benefits and Costs of New Drug Regulation" in the book *Regulating New Drugs*, edited by Richard Landau, Peltzman noted that the FDA justifies its medical information monopoly by arguing that the monopoly raises the "true" value of a new drug, since the substitution would reduce the anticipated costs of learning from experience

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that a drug was ineffective. Yet we now know what Peltzman could only surmise. First, the benefits of withholding additional medical information from doctors and patients are nil. Second, the clinical judgment of the marketplace is more effective and quicker than the FDA regulatory scheme in making the comparisons required to determine what drugs work and for whom. And third, the medical marketplace is now able to determine the cost-effectiveness of certain classes of drugs relative to others; it can make such determinations on a patient level, taking into account the severity of an illness and the interaction between drugs and other therapies.

The FDA has sought to swat down the private production of medical information and has used the efficacy standards to maintain its monopoly position. The process has taken three different forms: controlling new drug approvals, controlling information, and controlling evaluations. Each phase of monopolization allows the FDA to maintain its position as the ultimate arbiter of clinical decisions.

The FDA is currently seeking to regulate information on the cost-effectiveness or relative value of drugs, carrying its power to practice medicine to its logical conclusions. It has moved from imposing its judgment on the relative efficacy of drugs to controlling the prescribing decisions of doctors, and finally to controlling the criteria by which patients, physicians, and payers can choose which drugs to use and for what reasons. For the most part, the elimination of patient freedom compromises the quality of medicine and places a tax on the development of patient-level information in real-life settings. If the FDA gets complete control of cost-effectiveness determinations, it could seriously compromise the ability of patients to obtain important new drugs in a timely fashion, if at all. Only by breaking up the FDA's monopoly will the proper balance between risks and benefits, patient health and patient safety, be restored.

Controlling New Drug Approvals

Much has been written about how the FDA delays the approval of new drugs. Such analysis has been valuable in helping policymakers assess the potential costs of FDA regulation compared to the benefits of avoiding unsafe and ineffective drugs. In response, the FDA has pledged to reduce the amount of time it takes to review an NDA and decide whether or not to approve it for marketing. (This article will not discuss the FDA's performance in that regard. However, it appears that much of the "progress" the FDA has made in reducing approval times has been by simply redefining what an NDA is, not by acting more expeditiously. For a more complete analysis, see the FDA chapter in *The Cato Handbook for Congress*, cited at the end of this article.)

A significant part of the delay in drug approval times occurs because pharmaceutical companies must obtain FDA approval of the way in which efficacy is evaluated and in which the efficacy data are reviewed. Consider that since 1977, 60 to 70 percent of new drug approvals received their first marketing approval outside the United States. That drug "lag" has persisted despite increased knowledge regarding the use of drugs in general and growing understanding of how they affect diseases. The lag persists even for biotechnology-based drugs that generate fewer side effects and are more specific in their mechanisms of action on diseases—attributes that reduce the uncertainties that are the subject of

safety and efficacy tests. The lag persists even though the kind of information that FDA efficacy tests sought to generate is now generated by the private market.

Further, it is apparent that the FDA's regulation of new drug approvals yields little in the way of additional safety. In fact, over the past 20 years the number of drugs that the FDA or manufacturers pulled from the market because of safety concerns has been insignificant both here and abroad. Worldwide only a handful of drugs has been discontinued for safety reasons, and little difference exists in the rate that unsafe drugs have been pulled from the market in the United States and the United Kingdom. While the number of safety discontinuations in the United Kingdom was larger than in the United States, more drugs were approved in the United Kingdom. As a result, safety discontinuations as a percentage of total new drug introductions in each country were similar, approximately 4 percent in Britain versus nearly 3 percent in America. In other words, the probability that a marketed drug will be removed for safety reasons was not appreciably greater in the United Kingdom than in the United States.

If we assume that the British are no more tolerant of deadly drugs than Americans, we must ask the next question: if we are not getting that much more safety out of efficacy-driven standards, what is the value of FDA-produced medical information relative to what would be available if private organizations, consumers, researchers, and clinicians produced their own information?

One way to measure the relative value of the FDA's medical monopoly is to approximate the costs and benefits associated with delay in obtaining new medical information about new drugs. Much more work needs to be done in developing measures of the medical and economic impact of delays in getting drugs onto the U.S. market. For now, to get a sense of the opportunity costs of the FDA monopoly, we can develop an "impressionistic" model of the impact of delays.

The Thalidomide Case. Perhaps the best place to start is the much-celebrated FDA interception of thalidomide in 1960, before it reached the U.S. market. The FDA's role in that episode has, over the years, attained mythical status. Thalidomide, a drug used to induce sleep, caused birth defects in several thousand pregnant women in Europe. Many policymakers assume that but for the diligence of the FDA, many American babies would have suffered the same horrible fate. In fact, according to a contemporary account, "Thalidomide had been blocked by FDA for non-relevant reasons, and was actually moving toward approval when the drug company itself reported the terrible news. At that time, approximately 2.5 million thalidomide tablets—potential cripplers—were in the hands of physicians as samples. It took the FDA more than four months to realize that many people were still at risk, but even that comprehension was provided from the outside by Dr. Helen Taussig of the Johns Hopkins University. More months passed before the FDA moved with dispatch, this time with the aid and insistence of President John F. Kennedy. The FDA had, in this episode, been at its bureaucratic worst. Months after the entire matter had been reported . . . Senator Estes Kefauver and his staff contrived to dramatize the catastrophe through the medium of the press as a means of securing passage of his bill. The world was at last shocked into action, the 1962 Amendments were passed, new heroes were manufactured." [See Joseph D. Cooper, "Purpose, Technique and Strategy" in *Regulating New Drugs*, edited by Richard L. Landau, University of Chicago Press, 1972.]

The FDA's control over the production of medical knowledge has not only failed to provide a marginal increase in safety, it has contributed to an increase in medical costs of an undetermined amount.

The thalidomide case is a classic example of how sophisticated our knowledge about the risks, benefits, and mechanisms of drugs has become. In the 1950s the science of teratogenicity—establishing the relationship between prescription drugs and birth defects—was rudimentary. Careful testing of such effects is now standard. Forty years ago the knowledge necessary to establish the relationship between a certain drug and the risk of birth defects was limited to a few experts. The FDA certainly had no particular expertise in the area. Moreover, the possibility of the relationship between thalidomide and birth defects was already in the medical literature nearly two years before the FDA sought to stop

thalidomide from being marketed in the United States.

The FDA's blanket ban on thalidomide had the effect of delaying research into its useful application. Scientists now know that thalidomide is a valuable tool for the treatment of certain HIV-related illnesses. Further, it reduces adverse host-versus-graft reactions in people with bone marrow transplants. Similarly, the FDA's 1962 ban on folic acid as an "unsafe" food additive delayed the discovery that folic acid is essential to reducing birth defects such as spina bifida. Today the U.S. Public Health Service urges all women who expect to be pregnant to take folic acid on a daily basis.

The FDA's control over the production of medical knowledge has not only failed to provide a marginal increase in safety, it has contributed to an increase in medical costs of an undetermined amount. Ideally, the FDA or some independent organization would undertake to do an audit on the costs and benefits of the agency's monopoly over medical information. However, one can select a handful of important drugs, and by examining the number of cases and morbidity before each drug's introduction, get some idea of the cost of FDA delay. Consider the following examples:

The FDA's control of medical information has costs—human costs—that flow from the agency's unwillingness to allow patients and physicians a greater role in medical decisionmaking.

Beta Blockers: Beta blockers regulate hypertension and heart problems. The FDA held up approval of beta blockers for eight years because it believed they caused cancer. In the meantime, according to Dr. Louis Lasagna of the Tufts University Center for the Study of Drug Development, 119,000 people died who might have been helped by that medication.

Clozaril: First approved and used in 1970 in Europe, Clozaril's ability to treat schizophrenics who did not respond to other medicines became known in 1979. Yet the drug was not approved in the United States until 1990 because companies believed the FDA would reject it on the grounds that 1 percent of all patients who take the drug contract a blood disease. As an article in the *New England Journal of Medicine* marveled last year: "What is remarkable is that [Clozaril] has a beneficial effect on a substantial proportion [30 to 50 percent] of patients who have an inadequate response to other . . . drugs." FDA delay therefore meant that nearly 250,000 people with schizophrenia suffered needlessly, when relief was at hand.

Mevacor: Mevacor is a cholesterol-lowering drug that has been linked to reduction in death due to heart attacks. It was available in Europe in 1989 but did not become available in the United States until 1992. Studies confirm what doctors saw to be the case: taking the drug reduced death due to heart disease by about 55 percent. During that three-year period as many as a thousand people a year died from heart disease because of the FDA delay.

Havrix: The first vaccine to prevent hepatitis A, a highly infectious and serious virus, Havrix was only approved this year. Yet the vaccine has been available in Europe and 40 other countries for three years. During the time Havrix was awaiting FDA approval, hepatitis A remained the most common form of the disease.

Interleukin-2: Interleukin-2 is a recombinant drug that treats kidney cancer. It was approved for use in Europe in 1989, but it failed to win approval for that use in the United States until 1992. In the interim, 3,500 people died of the disease that might have been saved if the drug had been available.

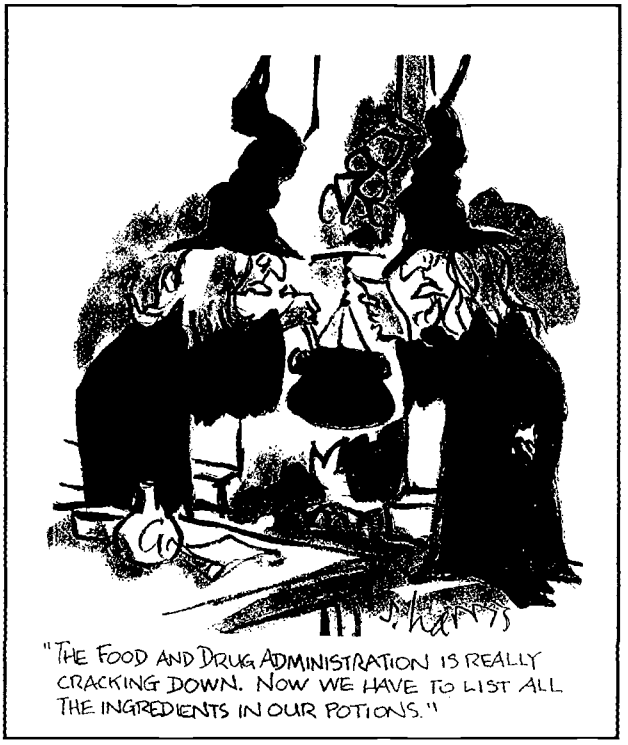
There are other examples, including drugs to treat mental illness, heart disease, and cancer. The point here is not to paint FDA officials as killers. Rather, it is to show that the FDA's control of medical information has costs—human costs—that flow from the agency's unwillingness to allow patients and physicians a greater role in medical decisionmaking.

Controlling New Medical Information

Beginning in the late 1970s the FDA began to extend its control over the character of new medical information by imposing its judgment about the relative therapeutic value of "follow-on" products—drugs similar in effect and chemical composition to other drugs. Again, the way in which the FDA controlled the production of follow-on knowledge was through the application of

the efficacy standard. One of the FDA's goals is to limit socially wasteful drug development. Thus, it follows that since companies engage in such development, the agency would have to go beyond simply determining to what degree drugs were effective to deciding which of similar drugs were most therapeutically useful. Thus, the FDA intensified its regulatory activity, increasing the cost of developing all new drugs and discouraging follow-on drug development by designating drugs as more or less significant relative to existing products.

In principle, the objective of the FDA is to help consumers and doctors avoid purchasing less efficacious drugs or buying drugs of similar efficacy at a higher price. In practice, the FDA has substituted its own clinical judgment for that of consumers and doctors. For the most part, the FDA's effort to form an opinion on efficacy data alone has resulted in many important newer therapies being arbitrarily withheld from the market at significant costs to both consumers and medical progress.



Increases in Cost and Risk

The cost of going through the drug development process has risen due to increasingly stringent and demanding application of the efficacy standard. The overall cost of drug development—production of medical knowledge as per the FDA's specifications—has risen, on average, 180 percent, from $125 million for drugs approved between 1963 and 1975 to $394 million for drugs approved between 1981 and 1990. While one would reasonably expect consumers and physicians to learn more about the value of drugs through research and the clinical experience of specialists, the FDA presumes no production of private knowledge. Indeed, it has raised the cost of privately producing medical knowledge by requiring innovators to spend more time and money proving efficacy. That requirement comes at the expense of other research investments and lower drug prices. In short, the efficacy regulations have delayed development and increased the cost of acquiring medical knowledge.

The imposition of the FDA's clinical judgment has increased the cost of health care and substantially increased human suffering. The total cost for developing each new drug has increased at 6.6 percent per year over and above the general rate of inflation. In particular, Phase I and Phase II costs doubled from 1970 to 1982. Average drug development costs rose, adjusted for inflation, about 13 percent between 1989 and 1993. However, the decline in the rate of increase was overwhelmed by the fact that the FDA began requiring more clinical information and more participants in clinical trials. Thus, total costs have been rising at a faster rate than in previous years.

The number of procedures per patient has, on average, nearly doubled in less than four years. That is, the amount of efficacy data demanded by the FDA increased in an era in which the market already had an existing base of information on the value and efficacy of drugs. Moreover, clinical complexity increased geometrically in the very areas in which research breakthroughs could be considered life saving or life enhancing. For example, drug studies for such diseases as Alzheimer's, Parkinson's, and depression more than doubled in complexity in terms of numbers of procedures and patients required in Phase II and III trials between 1989 and 1993.

The rapid increase in cost has contributed to a decline in certain forms of drug development. A study conducted by Joe DiMasi of the Center for the Study of Drug Development found that the mean total development times for drugs treating depression, schizophrenia, and other psychiatric diseases

are nearly twice as long as for all other types of drugs. In addition, the rate at which the FDA approves such drugs has declined over the last 30 years to the point that psychotropic drugs are nearly half as likely to get through the agency as all other new medicines. At the same time the capitalized cost of FDA approval to the pharmaceutical company developing such drugs is nearly 10 percent higher than for other new drugs. The added time delay means a company is tying up investment for a longer period before returns might be earned than with other classes of drugs. As a result, a significant amount of information generated by basic researchers and clinical observation—information that constitutes the knowledge base for future drug development—has been grossly underutilized.

Therapeutic Substitution. As more drugs enter the market, the opportunity for comparative evaluation grows. But rather than allow the market, that is, physicians, hospitals, research universities, and, of course, patients to produce information, the FDA has eliminated the "competition" by imposing its own judgment on the clinical value of drugs prior to their use in the marketplace.

The FDA has also extended its monopoly by limiting the ability of patients and physicians to apply findings and pursue hunches in an effort to develop the best therapeutic regimen possible.

Until 1990 the FDA used a drug classification system that ranked drugs according to what the agency regarded as their "therapeutic potential." The system included Class A, a drug that provides an important benefit; Class B, a drug that is a moderate therapeutic improvement; and Class C, a drug similar in importance and benefit to other drugs already on the market. While that classification system was scrapped in favor of one that ranked a drug by how fast it should be approved, the FDA has firmly established its authority to judge the relative efficacy of drugs—a power never explicitly provided for in its charter.

As it turns out, the FDA's judgment has been poor. Dr. Raymond Woosley and Sally Usdin Yasuda of the Georgetown University Medical Center reviewed drugs approved from 1981 to 1988 and classified by the FDA as Class C: those drugs that according to the FDA offer little therapeutic gain compared with already available products. The 42 drugs reviewed included medications for ulcers, infectious diseases, and hypertension. Woosley and Yasuda found that 72 percent of all the drugs classified by the FDA as marginally useful turned out to be the front-line therapy for the disease they treated. For example, one ulcer drug originally classified as 1-C wound up being regarded as a superior product because it worked for many patients who did not respond to other drugs, and with fewer side-effects.

How could the FDA have been so wrong in its clinical judgment? The answer is that the clinical value of a drug may not be obvious immediately after its introduction or even after only a few years of clinical use. Therefore, a system based on an assessment of years of clinical experience with a drug would be expected to yield results that are different from the early, static FDA classification system. The reason, as the authors point out, is that "individual responses to a particular drug may be unpredictable and variable for reasons that are still unknown. . . . The individualized approach to therapy makes maximum use of the unique characteristics each drug has to offer, improves the likelihood of benefit and reduces the risk of adverse drug reactions."

A classic example of the FDA's faulty clinical judgment is its evaluation of Prozac. The first of the serotonin uptake inhibitors, a new class of anti-depressants with fewer side effects, Prozac was introduced in Europe in 1986 and in the United States in 1989. The FDA failed to approve Prozac because it regarded it as a marginal improvement over existing medications. It classified Prozac as 1-C, an only marginally effective anti-depressive drug. The agency failed to take into account that many people who did not improve with older drugs responded well to Prozac. As is now well known, Prozac has become widely used in the treatment of all forms of depression and has been associated with a decline in the suicide rate in the United States.

Controlling the Use of New Drugs

The FDA has also extended its monopoly by limiting the ability of patients and physicians to apply findings and pursue hunches in an effort to develop the best therapeutic regimen possible. Years of clinical experience and the development

of biotechnology have reduced the cost and difficulty of individualizing treatment and created more opportunities for the development of novel drugs or novel uses for existing compounds.

A rational system of drug development would encourage the production of such medical knowledge precisely because it facilitates the best treatment of individuals. Yet the FDA has moved to limit patient-centered information. Initially, it did that by placing limits on off-label drug use. The FDA either restricted or prohibited drug companies from informing physicians, and physicians from informing patients, of observed benefits of drugs in addition to those certified by the FDA. Later the agency began making determinations of the relative efficacy and cost-effectiveness of individual drugs—yet a further distortion of the agency's original function. Now the FDA prohibits companies from making any claims about the relative effectiveness of drugs that do not use the FDA's methods of proving efficacy—namely random clinical trials. But such tests can fail to discover information on how a drug might be more or less effective for patients with certain characteristics of age, past medical history, and other relevant factors.

The FDA and the supporters of its medical monopoly, such as the Nader-run group Public Citizen, contend that such limits do not prohibit researchers and physicians from publishing articles on the safety and effectiveness of drugs outside the FDA's purview, nor do they restrict a doctor's prerogative to obtain and apply such information. As Dr. Robert Temple, director of the FDA's Office of Drug Evaluation asserts, "I remain puzzled by the idea that highly educated people like physicians can't get information unless it's provided for them by a drug company."

Dr. Temple's statement begs the main question of this article, namely, why can physicians and interested patients not obtain, apply, and evaluate therapeutic information unless it is produced and provided by the FDA? The answer is somewhat circular: the agency has a near-monopoly over determining the ultimate therapeutic value of a drug by making the preclinical analysis of drug efficacy the "gold standard" of what is scientifically and legally acceptable. Companies are finding it expensive and illegal to produce or disseminate information on the relative clinical value and cost-effectiveness of drugs. Yet the same sort of information is acceptable when produced by everyone else except drug companies or people who obtain support from pharmaceutical firms. In essence, the FDA is deciding what is approved speech and what is not.

The FDA has gone beyond ensuring that companies do not engage in misleading promotional activities. It now seeks to ensure that anything that is not developed in accordance with the FDA's determination of scientific certainty is inherently an unapproved use. At the same time, managed care organizations are beginning to limit reimbursement to those drug uses that the FDA has approved—and only those approved uses that are cost-effective.

Under nonmonopolistic conditions, companies would have had a larger base of information showing that drugs developed originally for one use may have many other beneficial applications. The foregone knowledge is an opportunity cost of the FDA's regulatory regime. It is not just that consumers must pay a higher cost and wait longer for maximum therapeutic benefit; the lack of knowledge leaves clinicians and patients without information needed to evaluate the value and quality of care under insurance or managed care situations in which access to health care is limited to what third parties decide is worthwhile or cost-effective. Absent a body of medical information on the relative value of different drugs and procedures, consumers and physicians have no scientific foundation for challenging bureaucratic decisions. The FDA's shrinkage of relative and cost-effective medical knowledge has been an important element in transferring control of medical resources and medical decisions from patients and physicians to large managed care organizations.

The FDA's insistence on supplemental approvals for off-label uses simply reinforces the agency's control over medical information.

Supplemental Uses for Existing Drugs. An analysis of FDA efforts to control the determination of relative therapeutic benefits again shows that those efforts take a significant toll on consumer welfare and health. The FDA's handling of supplemental approvals for new uses of drugs approved by the FDA is a case in point. As off-

label use has become an important means of producing therapeutic information for treating such diseases as AIDS, cancer, and mental illness, the FDA has begun to challenge the dissemination of off-label findings and has begun to call for firms to submit applications for approval of important off-label uses. In doing so, the FDA is arguing that when an individual doctor prescribes an unapproved use for an approved drug, he is engaging in an investigation that should be subject to the same regulatory review as is a pharmaceutical company developing a new drug.

The question is, what medical benefit is derived from submitting off-label applications to FDA review? At present, off-label drug use of an investigational sort is an important pathway for medical progress. According to Dr. Frederick Goodwin, professor of neuroscience and psychiatry at George Washington University Medical School and the former director of the National Institute of Mental Health, nearly all the breakthroughs in treating depression, manic depression, and schizophrenia came through unapproved uses. Dr. Larry Norton, head of breast oncology surgery at the Memorial Sloan-Kettering Cancer Center and one of the world's leading researchers in the treatment of breast cancer, commented, "If I had to use drugs for their approved uses only, half my patients would be dead." Nearly 90 percent of curative anti-cancer therapy involves experimental and off-label uses or combinations of drugs. In other words, subversion of the FDA's efficacy standard is important to advances in medical care.

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Indeed, the FDA's insistence on supplemental approvals for off-label uses simply reinforces the agency's control over medical information. As Dr. Joseph DiMasi of the Tufts University Center for the Study of Drug Development notes, in most cases the FDA's safety and toxicity concerns associated with new approvals have already been addressed in original reviews. Yet the mean review time for supplemental approvals submitted to the FDA between 1989 and 1993 was 32 months, while the mean review time for associated original indications was approximately 25 months.

In many cases the relative effectiveness and cost-effectiveness of off-label uses are already catalogued in medical compendia, discussed at conferences, and published in professional journals. Apart from the FDA's desire to regulate distribution of those materials by drug companies promoting their products, what other rationale exists for limiting the market's comparative evaluation of off-label drug uses? This question takes on even greater urgency because managed care organizations have begun to limit reimbursement to FDA-approved uses and at times actually penalize physicians who might otherwise be inclined to try an off-label approach to investigate a promising use.

The most absurd example of the FDA's adverse impact on health is its refusal to allow aspirin makers to promote or discuss the value of aspirin as a preventative for heart attacks. Despite the abundance of clinical literature about aspirin's role in reducing the rate of death due to heart disease, the FDA prohibits companies from providing any information about aspirin's value. The reason? The FDA has not approved the use of aspirin for preventing heart disease, and companies are prohibited from disseminating any information—including the studies that support such conclusions—about its life-saving properties. As Paul Rubin, a professor of economics at Emory University, notes, "The ban on aspirin advertising causes tens of thousands of needless deaths per year."

Picking Winners and Losers. By forcing producers to submit an increasing number of supplemental applications, the FDA has been able to establish itself as the ultimate arbiter of the therapeutic value of drugs. Increasingly, however, the FDA has based its approval of drugs on a product's relative efficacy or cost effectiveness. In fact, the FDA now as a matter of course substitutes its judgment for that of the doctors who actually care for patients—as well as the judgment of patients themselves.

The area of cancer treatment provides us with an excellent example of how the FDA has substituted its decisionmaking for that of the medical marketplace. The most effective usage of cancer drugs is routinely established after approval, not before, through experimentation and off-label use. For example, a cancer drug called Ethyol

was determined by the FDA to be "marginally efficacious" in fighting cancer. All nine members of the FDA's advisory panel voted against approval. Yet earlier last year the European Committee for Proprietary Medical Products voted nine to three in favor of the drug. U.K. drug regulators approved it as well. Both decisions were based on the same data submitted to the FDA.

It turns out that the FDA's decision to deny approval was based on the judgment that the drug was, given its efficacy, not cost-effective. Paul Bunn, director of the University of Colorado Cancer Center in Denver and a member of the cancer drug panel at the FDA, summed up the reason for rejecting the drug as follows: "It's likely the drug did act to lower kidney and bone marrow toxicity. But is the amount it did worth the effects and expense versus standard doses of chemotherapy? So the question is, how valuable is it to the community?" In other words, patient and doctor are denied their freedom to make treatment decisions.

Use of Taxotere, a chemotherapy drug for breast cancer treatment, was also rejected by the FDA for similar reasons. Even though Taxotere was shown to shrink breast tumors in patients who did not respond to any other treatment, the FDA's decision was based on the judgment that Taxotere did not, in its opinion, improve a patient's quality of life! Yet other clinicians argue that in real clinical settings, patients would not receive the dosage levels demanded by the FDA for its tests. In fact, as physicians gained more experience with the drug, the toxicity levels declined and the quality of life improved. Moreover, the FDA had already approved drugs with more risky side effects than Taxotere, including some AIDS drugs.

Indeed, the FDA's looser control over HIV drug development underscores the opportunity cost of the agency's regulatory regime. To be sure, AZT and other drugs are not the magic bullets people with AIDS desperately seek. They were found to be more toxic and less efficacious than had been hoped. But the rapid uptake of AZT stimulated price-reducing competition and led to the discovery that combinations of antiviral drugs slow HIV replication better than one drug alone.

Because the FDA waived the need for large-scale efficacy trials, companies could obtain approval and market drugs for HIV if there was a reasonable chance that the drug might be effective. And since open, community-based trials were used, more people were able to obtain the drug more quickly than under conventional FDA review. Finally, the potential for accelerated approval encouraged companies to invest in future generations of research and to work together to develop drug combinations to stop HIV's progression. And overall, while the risk of toxicity remains high, as it does with cancer drugs, wider access to AIDS drugs has not brought greater risk than the risk of dying from the disease itself.

Controlling Cost-Effectiveness Claims

The FDA claims that it must regulate cost-benefit research to protect consumers and companies from "dubious claims of cost-effectiveness." But there is nothing to suggest that the same marketplace that has successfully reviewed and evaluated claims of therapeutic benefits and cost-effectiveness in the past cannot continue to do so in the future. The methodological purity claimed by the FDA merely has the effect of limiting patient and physician discretion. More important, the FDA's attack on cost-effectiveness promotion preserves its medical information monopoly.

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Just as the practice of medicine would be severely compromised if doctors only prescribed on-label uses, so too will the practice of medicine be undermined if the FDA remains the ultimate arbiter of the comparative value of drugs. Nor is there any benefit from prohibiting companies from distributing the research of others on the relative value of drugs or particular approaches to drug availability.

As noted, the FDA often fails to approve a product or use that patients with full knowledge of the potential risks might find acceptable. Eliminating comparative drug evaluations in the market would likewise eliminate some parts of the population's access to products that are cost-effective. The additional cost and uncertainty

that random cost-effectiveness studies require would have a chilling effect on research and development. Moreover, the requirement would restrict the dissemination and development of studies that have had a profound effect on the quality of care. It is disingenuous for the FDA to suggest that research that focuses on the individual patient's response to medicine would be widely available under its regime. Why conduct such research if the venues for dissemination are closed off and reimbursement schemes of insurers recognize only FDA definitions of cost-effectiveness and quality of life?

Requiring cost-effectiveness and quality-of-life studies to adhere to efficacy standards amounts to suppressing the individualized data needed to insure that people are getting the best medicine possible. For example, according to Dr. Frederick Goodwin, 70 percent of all random trials of drugs treating mental illness could have missed 50 percent of the difference in response rates among patients.

More to the point, random clinical trial data yields no information about the relative importance of certain drugs in the real world. Nearly 20 years ago Dr. Lasagna asserted that he was "troubled by the undue emphasis on 'controlled trials' by experts and the denigration of more 'naturalistic' trials by 'ordinary' practitioners." His critique of the blanket use of controlled trials has a direct bearing on the FDA's effort to limit the production of cost-effectiveness knowledge and is quoted in its entirety: "A drug is now evaluated primarily by its performance in what is in some ways a very artificial setting—inpatients (usually), expert investigators, reasonably homogeneous populations, a minimum of other medications given concomitantly and supervised drug intake. Once marketed, the drug is used under circumstances almost totally different. There is every reason in the world for the performance to be different, yet we pay little attention to studying the drug as it will be used. Why not at least do such studies after the introduction on the market?" The answer is, such studies would be another blow to the FDA's insistence that all drugs, unless proved otherwise by random trials, be treated as therapeutically equivalent.

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That is, even if doctors know better from years of use on actual patients, they are supposed to assume that no drug is different from any other. Deviation from that dogma undermines the agency's medical monopoly. Comparative evaluations made independently by patients and physicians would be a direct hit on the FDA's power.

The FDA's effort to preserve the ideology of therapeutic equivalence is at best what Lasagna once termed "pharmacologic Lysenkoism." At worst, it is medical malpractice. For example, under TennCare, the state of Tennessee's health care program for the poor, nearly 90 percent of all doctors were told to switch their prescriptions to the cheapest therapeutic equivalent. As a result, a survey of physicians reveals that nearly two-thirds of those who did switch their patients' prescriptions reported that the switch made people sicker, causing heart attacks, strokes, congestive heart failure, and delayed healing of infections.

Similarly, Dr. Susan Horn, who conducts outcomes research for the Intermountain Health System in Utah, found that adjusting for a patient's severity of illness and using a more expensive and newer antibiotic after certain surgical procedures reduced overall length of stay, brought down total per-patient hospital costs, and improved patient quality of life. Overall treatment costs fell by $5,000 per patient. Yet such research could not be shared by pharmaceutical firms in any forum because it was not a random trial. Noted Dr. Horn, "The proof of the validity of the research is that the hospital saved money and patients felt better. It would have been unethical and more expensive to withhold better care simply to comply with clinical trial procedures."

Finally, the FDA's strictures on cost-effectiveness will delay access to important new drugs. Just as insurers deny reimbursement for drug uses not approved by the FDA, they will also begin to deny reimbursement for drugs if their cost-effectiveness has not been verified by the agency.

That is already happening with the latest wave of biotechnology products. At present, ReoPro, a biotech drug that reduces the reclogging of arteries, is being considered for use in hospitals. Because the drug adds to initial costs, while savings come later, hospitals are being asked to shoulder costs that will result in savings to others, including patients. If the FDA's controlled-trial edict becomes the standard for reimbursement, it will be difficult, if not impossible, for most drugs to receive the evaluation they need and still be widely available to patients.

Even if hospitals conduct their own research on the outcomes of using the drug, Centecor, the company that produces ReoPro, could be barred from disseminating its findings because they do not fit the FDA's guidelines. The Texas Heart Institute is tracking the relative benefit of the drug to patients in terms of quality of life and other areas. That important real-world clinical information is largely valueless in the eyes of the FDA. The ban on cost-effectiveness promotion could lead to avoidable morbidity and mortality, and could slow patient access to drugs of considerable value.

Conclusion: Deconstructing the FDA

This article has shown that society incurs significant costs due to the FDA's regulatory regime. To deconstruct the agency, it is not enough simply to haul Commissioner Kessler before various congressional committees and chastise him for the agency's arrogance and inefficiency. Real reform requires questioning the FDA's mandate and very existence. Real reform at least requires strict limits on the FDA's ability to impose its medical judgment and regulate the production of medical knowledge.

Politicians and policy analysts have offered a host of proposals to make the FDA more efficient. But few of the proposals would prohibit the FDA from suppressing medical information in order to maintain its medical monopoly. In the rare instances when the FDA has been challenged, as, for example, when the National Cancer Institute objected specifically to FDA actions against a drug company cancer newsletter, the protests have been ignored. Similarly, the companies regulated by the agency have little incentive to challenge the monopoly on legal grounds. As Kessler himself has observed, "Companies interested in maintaining positive relationships with the FDA usually agree to the FDA's remedy [in advertising matters]." The FDA has leveraged its power to such an extent that it bears almost no relationship to legislation or any other legal foundation.

Only explicit changes in the FDA's statute will weaken the agency's monopoly. The place to start is to curb the FDA's ability to deny access to drugs it regards as not efficacious. The FDA might be limited to affirming that a company has conducted safety and efficacy trials; assuring that companies have abided by protocols that have been agreed to and reviewed within 30 days of submission; and publicizing the findings of such trials. The agency should be precluded from making judgments about the relative value of drugs. To that end, the "compassionate use" provision that exempts some drugs from full FDA test requirements should be rendered obsolete by a provision allowing patients access to drugs after safety has been established. Patients and doctors, not the FDA, should make the determination of when the potential benefits of a drug outweigh any potential risks.

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Perhaps for a transition, pharmaceutical companies could be allowed to "opt out" from efficacy tests a new drug that the FDA certifies as safe, as long as the product is clearly labeled as not certified for efficacy by the FDA. Such an approach would foster the expansion of private labs that could test faster and more efficiently. Further, the FDA might be prohibited from regulating the off-label use or promotion of drugs. The agency should be explicitly barred from regulating the character and claims of cost-effectiveness. Clinicians, researchers, and managed care organizations have been doing a good job of separating out and developing effective treatments—and a much better job of practicing medicine than the FDA. They are also better equipped to determine the relative value of treatment regimens for patients.

No doubt those suggestions will generate tremendous controversy. It should be remem-

bered, however, that the cost the FDA imposes on society is part and parcel of its existing mission and regulatory regime. Altering it on the margins, as most reformers suggest, will not change the agency's fundamental character or orientation, or reduce the damage its medical judgment has done to patients over the years. Allowing the FDA to make such decisions faster does not weaken the FDA's monopoly on the production of medical information. Reformers should not congratulate themselves if such "reforms" sail through the legislative process. They will still leave the FDA's monopoly on medical information intact. Only allowing patients and physicians the freedom to make medical judgments on their own behalf will create real change. As the FDA knows only too well, knowledge—and the control over its production and placement—is truly power.

Selected Readings

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