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THE RIGHT TO A TRIAL

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Should dying patients have access to experimental drugs?

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In 2002, Kianna Karnes, a forty-one-year-old nurse and mother of four in Brownsburg, Indiana, was given a diagnosis of kidney cancer. She had surgery to remove the tumor, but a year later the cancer spread to her bones. Karnes's doctors treated her with interleukin-2, a protein that stimulates the immune system and, in its synthetic form, was the only medication approved by the Food and Drug Administration for use against kidney cancer. The drug causes high fevers and the accumulation of flu in the lungs, and it shrinks tumors in only fifteen per cent of cases. "High-dose interleukin-2 damn near killed her," Karnes's father, John Rowe, recalled recently. "It's a brutal treatment, but her husband pushed her pretty hard, because he didn't want to lose her."

Karnes did not improve on interleukin-2, and Rowe began to look into experimental therapies. Four years earlier, he, too, had received a diagnosis of a life-threatening cancer, chronic myelogenous leukemia, for which there were few effective treatments. He had found the Web site of a man from South Carolina with leukemia, who had enrolled in a clinical trial of an experimental drug, now called Gleevec, and had experienced a remarkable remission. Rowe learned about a trial comparing Gleevec with interferon, then the standard therapy for his illness, and asked his doctor to help him apply. He was the last patient to be admitted. "Luckily, I got the good stuff," he told me, referring to Gleevec. His cancer has been in remission for five years.

While Rowe was recovering, he worked on Capitol Hill, in the office of Dan Burton, a Republican congressman from Indiana, who chaired the House Government Reform Committee. He became friendly with Frank Burroughs, whose daughter Abigail had died of a head-and-neck cancer at the age of twenty-one, after being denied admission to a clinical trial for a drug that might have helped her. After her death, Burroughs founded the Abigail Alliance, an advocacy group that seeks to make experimental drugs—commonly defined as drugs that are being tested by a pharmaceutical company and have yet to be approved or rejected by the F.D.A.—available to people with terminal illnesses. In 2004, Rowe learned from the Abigail Alliance that Pfizer and Bayer had each developed a drug for kidney cancer and were conducting clinical trials. But, while he was trying to enroll Kianna in a trial, she learned that her cancer had spread to her brain. Surgeons removed the tumors, but a history of brain cancer almost always disqualifies a patient from participating in a trial. Such patients are prone to seizures, and it can be difficult to distinguish symptoms caused by an experimental therapy from those caused by the illness it is supposed to be treating. Rowe tried to obtain one of the drugs through a provision in F.D.A. regulations known as "compassionate use," which allows pharmaceutical companies, with the agency's permission, to release an experimental drug to a patient who is not enrolled in a clinical trial. With the help of the Abigail Alliance he contacted Pfizer and Bayer to discuss compassionate use, but he made little headway.

"By this time, we were way down the road, and Kianna was in dire straits," Rowe said. "So I finally asked Congressman Burton for help." Burton told a staff member to look into Karnes's case, and, in March, 2005, Rowe got a call from Robert Pollock, a journalist on the editorial board of the *Wall Street Journal*, who had been writing about the efforts of politicians in Congress to prevent the husband of

Terri Schiavo, the brain-dead Florida woman, from removing her feeding tube. “I think if the Congress can pass a law for Terri Schiavo, a single person, that’s O.K.,” Pollock told Rowe. “But there are a lot of people like your daughter. And I think Congress should pass a law to help all of them.” On March 24th, the *Journal* published an editorial titled “How About a ‘Kianna’s Law’?,” urging Congress to pass legislation requiring the F.D.A. to grant dying patients access to experimental drugs.

That morning, Burton’s office contacted Pfizer and Bayer, as well as the F.D.A. In the afternoon, an F.D.A. official called Rowe and told him that if either of the companies submitted an application for compassionate use on Karnes’s behalf the agency would approve it. A couple of hours later, Kianna’s doctor heard from representatives of Pfizer and Bayer, offering to prepare applications for Karnes. “At nine-forty-one that same night, Kianna died,” Rowe told me. “Just like Abigail. Too little, too late.”

By January, both experimental drugs had been approved by the F.D.A. for use against advanced kidney cancer. “Here is a case where her old man understood about clinical trials,” Rowe said. “I knew about compassionate use; I had a friendship with a powerful member of Congress; I’ve got the *Wall Street Journal* behind me. But I still couldn’t save her life. Now, what about the thousands of people out there who don’t have these kinds of resources available to them? I don’t know that either of these drugs would have saved Kianna’s life. But wouldn’t it have been nice to give her a chance?”

Families of seriously ill patients are understandably consumed by a desire to help, and stories about unexpected recoveries inspire hope that an experimental drug might prove to be lifesaving; it’s possible that Abigail Burroughs and Kianna Karnes would now be alive had they been able to take one. Yet a similar impulse—to protect patients’ lives—lies behind F.D.A. regulations restricting access to such drugs. Guaranteeing drug safety has been part of the agency’s mandate since 1938, when Congress passed the Federal Food, Drug, and Cosmetic Act after more than a hundred people died from taking a medicine for strep throat which contained diethylene glycol, an active ingredient in antifreeze. Today, the vast majority of patients with life-threatening diseases are treated with drugs that have been approved by the F.D.A. after a stringent evaluation process designed to insure that they are safe and effective. It typically takes a pharmaceutical company six and a half years from the time it discovers a promising molecule to gather enough data to apply to the F.D.A. for permission to test a drug on patients. Completing the clinical trials requires, on average, another seven years: an initial set (Phase I), usually involving fewer than a hundred patients, to determine the maximum tolerated dose and likely side effects; a second set (Phase II), involving several hundred patients, to identify the diseases—or stages of a disease—that are affected by the experimental therapy; and a final set (Phase III), in which the drug is given to several thousand patients and compared with another drug that has already been approved by the F.D.A., or with a placebo. After the trials, the F.D.A. reviews the results and, usually in consultation with an advisory panel of experts, decides whether to approve an experimental drug. Drug companies pay most of the costs for clinical trials, and by the time a drug reaches the market the manufacturer will have spent nearly a billion dollars on its development.

Nearly ninety per cent of drugs that enter Phase I trials are eventually abandoned because they are shown to be unsafe or ineffective. (Last week, Pfizer announced that it was cancelling its Phase III trial of torcetrapib, an experimental drug for heart disease, after eighty-two patients in the study died. Pfizer had spent almost a billion dollars on torcetrapib, which had shown exceptional promise in earlier trials. “This drug, if it worked, would probably have been the largest-selling pharmaceutical in history,” Steven E. Nissen, the chairman of cardiovascular medicine at the

Cleveland Clinic, told the *Times*.) In the past decade, the number of new drugs approved by the F.D.A. has fallen sharply. According to a recent article in the *Journal of the American Medical Association*, between 1994 and 1997 the agency approved an average of nearly thirty-six new drugs a year, but between 2001 and 2004 the approval rate averaged just twenty-three a year.

The Bush Administration, seeking to reverse this trend, has appointed new leaders to the F.D.A., including Andrew von Eschenbach, the recently confirmed commissioner, who is a cancer specialist from Houston and a close friend of the Bush family; and Scott Gottlieb, the deputy commissioner for medical and scientific affairs, who, as a fellow at the American Enterprise Institute, published frequent editorials arguing for a more flexible approach to drug approval, particularly for cancer drugs. “The FDA is trying to save patients from the harmful effects of new medicines that haven’t fully proved their mettle,” Gottlieb wrote in an Op-Ed piece in the *Oklahoman*, in May, 2005. “In the process, many more patients will die waiting for the good medicines than from using bad ones.”

At the same time, the Abigail Alliance, which shares this view, has gained political influence. In November, 2005, Senator Sam Brownback, a Republican from Kansas, who survived melanoma and is the co-chair of the Senate Cancer Caucus, introduced a bill that would compel the F.D.A. to make experimental drugs available to seriously ill patients who have exhausted standard treatments. Brownback, who had met with Frank Burroughs and read about Kianna Karnes in the *Wall Street Journal*, called the bill “Kianna’s Law.” Six months later, the Abigail Alliance won its first victory in court against the F.D.A., when the United States Court of Appeals for the District of Columbia upheld, in a two-to-one decision, the group’s argument, in *Abigail Alliance v. Andrew von Eschenbach*, that access to experimental drugs is a constitutional right.

The opinion—by Judge Judith Rogers, a Clinton appointee, and Chief Justice Douglas Ginsburg, a Reagan appointee—shocked legal scholars and officials at the F.D.A., which had begun drafting proposals aimed at increasing patients’ access to experimental drugs. The agency, determined not to cede control of drug regulation to Congress or the courts, intends to release some of the proposals for public comment this week. According to senior F.D.A. officials, the agency is also developing plans for a program that would encourage drug companies to distribute experimental drugs to thousands of cancer patients through their personal physicians. If adopted, the program would constitute the most ambitious initiative by the agency in two decades.

The F.D.A.’s reforms, the D.C. circuit-court decision, and the Brownback bill present different guidelines for providing access to experimental drugs, and it’s not clear which, if any, of the proposed changes will ultimately take effect. Nevertheless, the efforts reflect an unlikely convergence of interests between patient-advocacy groups and the deregulation-minded Bush Administration, and they underscore the F.D.A.’s vulnerability to political pressure. Some critics worry that the current regulations aren’t strict enough to protect patients. (In September, the Institute of Medicine, a branch of the National Academy of Sciences, released a report that was sharply critical of the F.D.A., and, in particular, of a rule passed by Congress in 1992 that allows pharmaceutical companies to pay the agency substantial fees to expedite reviews of their drugs. The report castigated Congress for failing to provide the F.D.A. with sufficient funds to monitor drugs after they have been approved. It cited Vioxx, the arthritis drug that was withdrawn in 2004 after it was found to double the risk of heart attack.) The challenge will be to insure that deregulation does not occur at the expense of science and safety. “The common perception is that safety and efficiency in drug development are not compatible,” Scott Gottlieb told me. “I don’t think that’s true.”

During the first four decades of the twentieth century, drug companies often tested experimental medications by sending them to doctors to give to their patients. The F.D.A. required little

information from drug-makers about side effects and had no standard criteria for determining safety or efficacy. In 1960, Frances Kelsey, a doctor and pharmacologist, joined the F.D.A. as one of seven full-time physician drug reviewers. Assigned to evaluate thalidomide, which had been approved in forty-two countries, including much of Europe, as a sedative and an anti-nausea drug, Kelsey was shocked at how little data the agency had about the drug's safety, and she was concerned about its side effects. Richardson-Merrell, which wanted to market thalidomide in the United States, had already distributed it to twenty thousand patients in this country, but Kelsey refused to approve the drug and ordered the company to conduct additional clinical studies. Later, it was discovered that thousands of mothers—most of them outside the United States—who took thalidomide during pregnancy to combat nausea had delivered babies with severely deformed arms and legs, segmented intestines, and closed ear canals. In 1962, Congress passed the Kefauver-Harris Amendments, which required pharmaceutical companies to show the F.D.A. that their drugs were effective and gave the agency greater control over clinical trials.

However, with the advent of the AIDS epidemic, in the nineteen-eighties, regulations that had been praised for protecting the public's health were attacked as too restrictive. AIDS activists demanded what they called "expanded access," arguing that AIDS patients who were not enrolled in a clinical trial should be allowed to take experimental drugs under the supervision of their personal physicians. (They also requested that the F.D.A. do away with clinical trials of AIDS drugs in which some patients received a placebo.) In 1987, the F.D.A. agreed to allow patients who could not participate in clinical trials—because they were too sick or lived too far from a university hospital, where trials are typically conducted—to obtain experimental drugs from their doctors on a compassionate basis, or as part of a national expanded-access program. In both cases, only experimental drugs that had completed at least Phase II of clinical trials were eligible for distribution.

AIDS activists persuaded the F.D.A. to relax its policy on experimental drugs in part by relying on dramatic protest tactics and sympathetic media coverage; members of ACT-UP and other groups covered themselves with fake blood and staged "die-ins" in front of the White House and the National Institutes of Health. Pharmaceutical companies, under political pressure to provide promising therapies for AIDS patients, who at the time faced certain death, agreed to distribute the drugs, despite considerable legal and financial risks. (Drug companies are typically reluctant to supply experimental drugs outside a clinical trial, fearing that patients who suffer adverse reactions will sue the company or that the F.D.A. will demand more extensive safety testing. Moreover, manufacturing an experimental drug for thousands of patients in an expanded-access program is hugely expensive, and there is no guarantee that the F.D.A. will ultimately approve the drug for sale.)

Doctors, too, got swept up in the campaign to distribute experimental drugs. I began treating patients with AIDS in 1981, and for more than a decade I watched helplessly as they grew sicker and died. In 1994, saquinavir, the first anti-H.I.V. protease inhibitor, was tested in clinical trials. In test-tube experiments, the compounds were remarkably potent in preventing the virus from multiplying, and studies on rodents suggested that they were relatively safe; the only known side effect was liver damage, and then only at very high doses. Word of the inhibitors' promise spread rapidly through the AIDS community, and, like many doctors, I was eager to get the drugs to my patients as quickly as possible, by enrolling them in clinical trials. Hoffman-LaRoche, the company that made saquinavir, invited several physicians at my hospital to run one of the trials, and four slots in the study were reserved for patients from my practice. I agonized about which names to submit. Some of my patients were expected to die within weeks, and yet I thought it was possible that the drug would help them. Others, who appeared healthier, had abnormal blood-test results—including elevated levels of liver enzymes—which were likely to disqualify them, so

I repeated the tests in a vain effort to obtain values in the normal range. Heartsick, I eventually submitted the names of twenty patients to the nurse in charge of administering the trial, believing that they were the most likely to be accepted. Most of the rest had no chance of being admitted, because they had serious infections, such as cytomegalovirus and systemic cryptococcus (a fungus).

Tom (a pseudonym), a physician living near Boston, belonged to this group. He had developed a cytomegalovirus infection in his retina and was slowly going blind, but each time he visited the clinic he pressed me for information about saquinavir and asked me to tell him when the clinical trial would begin. His father begged me to persuade Hoffman-LaRoche to bend its rules and admit Tom. I said that I would try but had little hope of succeeding, explaining that the trial was designed to assess the drug's safety, and if Tom's vision got worse while he was taking the protease inhibitor we would have to report it to the drug company as an "adverse event." Although we might suspect the infection of his retina to be the cause, Hoffman-LaRoche would have to list "declining vision"—and the F.D.A. would have to consider it—as a possible side effect of the drug.

Saquinavir proved to be strikingly effective against H.I.V. Within a few months, the immune systems of most patients who had taken the drug improved and the amount of H.I.V. in their bodies decreased. They gained weight, and had fewer infections. Tom, who had been denied admission to the trial, soon lost his sight and, not surprisingly, became clinically depressed. I assured him that I would make every effort to see that he did not suffer. He developed seizures, and a brain scan revealed a large mass with the characteristics of a lymphoma. He refused further treatment, was placed on a morphine drip at home, and died with his family at his bedside.

At the time, newspapers were filled with stories of AIDS patients whose lives had been saved by the protease inhibitors. It was later discovered that the drugs caused significant side effects in some patients, including an increased risk of diabetes and elevated cholesterol, but, when used with other anti-viral drugs, protease inhibitors helped reduce the death rate from AIDS in the United States by at least seventy per cent. It is possible that Tom would still be alive if he had been able to take saquinavir.

In the case of other experimental AIDS drugs, however, doctors' expectations were tragically misplaced. In 1980, I spent ten months on a fellowship at U.C.L.A., collaborating with other researchers on a project to purify gamma interferon, a naturally occurring protein made by immune cells. Many scientists had a near-mystical regard for gamma interferon, believing that it could help the immune system defeat infections, as well as cancer. Our laboratory succeeded in purifying a small amount of gamma interferon—the first step toward developing a drug—and we published our results in *Nature* in 1982. Not long afterward, Genentech, a biotechnology company, announced that it had created a synthetic version of the protein and was planning to conduct clinical trials. In 1984, after I had returned to Boston, I helped run a trial of gamma interferon for AIDS patients who had Kaposi's sarcoma, a cancer that causes large lesions on the skin and, in many cases, respiratory failure and internal bleeding. Gamma interferon appeared to be the ideal treatment for these patients. It had been shown to have powerful anti-viral effects in test-tube studies and to reduce the size of tumors in rodents.

I enthusiastically told my AIDS patients about the trial, including George (also a pseudonym), who had recently moved to Boston to be with his partner. George was in reasonably good health; he had not developed any serious infections, and his Kaposi's-sarcoma lesions were mostly on his chest and arms. The goal of the trial was to test the effects of different doses of gamma interferon, and George belonged to the group that received the largest dose. Like many participants, he experienced unpleasant side effects—fevers, muscle pain, and headaches—but he was determined to finish the trial. After six weeks, however, new lesions appeared on his skin and in his mouth,

and a chest X-ray suggested that the cancer had spread to his lungs. George was not the only patient who grew sicker on gamma interferon. None of the patients improved, and in at least four cases we believed that the therapy had hastened the tumors' growth. Ultimately, the trial was judged a failure. (Gamma interferon has since proved effective in treating children with a rare immune-system disorder called chronic granulomatous disease.) George reluctantly agreed to undergo chemotherapy, which had little effect. He returned to California, where his family lived, and died five months later. (Although I continue to conduct basic research, I currently have no consulting relationships with pharmaceutical companies whose drugs are under review for approval by the F.D.A.)

If Congress passes Brownback's bill, or the D.C. circuit court's opinion in Abigail Alliance is upheld, there will doubtless be more cases like George's. Brownback told me that the goal of his bill is to "get more testing of treatments and options available in the system for cancer patients, much as we did during the AIDS crisis." However, AIDS is caused by a virus whose presence in the body can be measured by a simple blood test, and is thus much easier to monitor than cancer. Lung cancer, one of the most common forms of the disease, encompasses a dozen different kinds of tumors; a given drug is likely to help only a small sub-set of patients, and it is often impossible to predict which ones. Nevertheless, Brownback's bill would grant conditional approval of experimental drugs that have completed Phase I or Phase II testing, based on preliminary evidence—from test-tube experiments, animal studies, computer simulations, and individual patients—that they might be beneficial and safe. "If the potential risk to a patient of the condition or disease outweighs the potential risk of the product, and the product may possibly provide benefit to the patient," the bill asserts, then the F.D.A. is obligated to approve the drug if a physician and a patient request it. (The new law would coexist with the current system: if an experimental drug approved under the scheme did not win F.D.A. approval at the end of Phase III trials, it would no longer be distributed.)

Brownback's bill would grant access to experimental drugs to patients with "serious or life-threatening" illnesses; the decision in Abigail Alliance limits such access to patients who have terminal diseases. In both instances, patients would be taking drugs whose risks and benefits are largely unknown. "We all know that Phase I testing doesn't prove that a drug is safe enough," Sonia Suter, a professor of law at George Washington University and an expert in medical ethics, told me. "There are very small numbers of participants in Phase I, and they are treated for a very limited period of time. So if you believe that there is this constitutional right, that there are risks you are willing to take and not have the government interfere, why have a cutoff at Phase I? Why not just say, 'Any drug I'm willing to take,' because of some anecdotal experience, or some animal study, or the molecular structure, is reason to think the drug might work?"

In June, F.D.A. lawyers, in an attempt to have the decision in Abigail Alliance reversed, asked that the entire panel of judges on the D.C. circuit court hear the case en banc. The request was granted last month; the full court will hear the case next year. Many constitutional-law scholars believe that the opinion is flawed and that the case could eventually go before the Supreme Court. In the opinion, the circuit-court judges cite the case of Nancy Cruzan, a young woman who had suffered brain death after a car accident and whose parents were seeking legal permission to disconnect her from life support. In 1989, the case went before the Supreme Court, which ruled that patients have a right to decline medical treatment. (With regard to Cruzan, however, the Court said that her parents had not demonstrated "clear and convincing evidence" that she would prefer to die than to be sustained on life support. Several of Cruzan's friends later testified about her wishes in a lower court, and Cruzan's feeding tube was eventually removed.) The judges in Abigail Alliance reasoned that the same right of self-determination that allows someone to refuse treatment allows him to "choose to use potentially life-saving investigational new drugs." They

pointed out that for “over half of our Nation’s history”—until the passage, in 1906, of the Pure Food and Drug Act, which made it a crime to sell mislabelled or adulterated medicines—“a person could obtain access to any new drug without any government interference whatsoever.”

“This is the kind of case that you see tugging at people’s heartstrings,” Ira Lupu, a professor of constitutional law at George Washington University, said. “Everyone has a friend or a sibling or, especially, a child who has a fatal illness. You think they’re going to die in three to six months anyway, so giving them a drug is their only hope. You can see that the sympathies attached to this could push a judge who is otherwise quite disciplined over the edge.” By relying on the Cruzan decision, Lupu said, the D.C. circuit court “walks away from a long-standing aspect of common law: touching somebody without his consent is a battery. The Supreme Court assumes, in Cruzan, that the right to refuse continued treatment is a constitutional right, because it is based on the long-standing right to be protected from battery. As a matter of philosophy, it may seem to make sense that if you can refuse treatment you can also have access to treatment. But, from the perspective of constitutional law, it is very hard to see what platform this court is standing on.”

Even if the D.C. circuit-court decision survives legal challenges or Brownback’s bill passes, neither gives pharmaceutical companies any incentive to make experimental drugs widely available. Under the existing regulations, only once a drug is approved does the Center for Medicare and Medicaid Services decide whether it will be covered by Medicare, and private insurance companies usually follow the government’s lead in determining which drugs to cover. Brownback’s bill could be amended to require the government to reimburse companies for the costs of experimental drugs, but they would still face daunting practical and financial obstacles. Richard Merrill, a professor at the University of Virginia Law School and a prominent expert on drug regulation, said that Brownback’s legislation “would require a major investment to scale up production of an experimental drug”—after treating only a few hundred patients in Phase I and Phase II trials—“and it would not be at all clear that the drug had a good chance of ultimately being widely marketed, because its safety and efficacy could prove problematic in more extensive human testing.”

Brownback’s bill stipulates that drug companies cannot be held liable for a patient’s adverse reactions to an experimental medication. But this may not be enough to reassure pharmaceutical companies, and it could inadvertently encourage retailers of alternative therapies that have little or no basis in science. “The bill opens the space for products that are sold by charlatans,” said David Parkinson, an oncologist who worked at the National Cancer Institute for many years and is now a senior vice-president at the biotech company Biogen Idec. One of Parkinson’s tasks at the N.C.I. was to evaluate herbal remedies and animal extracts, such as shark cartilage, that are sold in health-food stores and on the Internet, accompanied by testimonials from patients about their anti-cancer benefits. Some of these products could pass Phase I trials, Parkinson said, and, under Brownback’s bill, the F.D.A. would be compelled to approve them.

In March, the F.D.A. approved the use of a drug called Gemzar, in combination with a standard chemotherapy medicine, as a treatment for recurrent ovarian cancer. The agency’s Oncologic Drugs Advisory Committee, a group of cancer doctors and statisticians, had voted, nine to two, against approving the treatment, on the ground that it didn’t significantly improve the survival rate of patients. In July, Richard Pazdur, the director of the F.D.A.’s Office of Oncology Drug Products, issued a statement defending the agency’s decision to overrule the committee. He cited data from Gemzar’s manufacturer, Eli Lilly, showing that patients who were given the drug as part of their chemotherapy regimens had longer periods of remission than patients who did not take the drug. “Although improvement in overall survival remains the gold standard,” Pazdur wrote, “delay in disease progression” has been advocated as a “surrogate” for clinical benefit in

cancer patients.

Many cancer doctors saw the F.D.A.'s decision as evidence that the agency is willing to adapt to patients' needs. When I spoke to Pazdur, he mentioned this—and the agency's recent approval of similar drugs for kidney cancer (Nexavar), multiple myeloma (Revlimid), and a rare gastrointestinal tumor (Sutent). "We need to be more flexible in how we evaluate drugs for patients like this," Pazdur said. "The provision is that the drug's benefits have to be clinically meaningful—and it doesn't mean delaying the progression of the tumor by two days—so you're not approving iffy drugs."

Pazdur said that the F.D.A. has rarely denied a patient's request to obtain an experimental drug under the compassionate-use provision. (He recalled only one instance in which the agency has done so: in the case of a boy with a brain tumor whose parents had refused to give him radiation therapy, the standard treatment for his condition. "That's not a regulatory issue; that was bad medicine," Pazdur said.) He also cited a recent program—modelled on the expanded-access programs for AIDS patients in the eighties—in which the drug Iressa was given to more than twenty-four thousand lung-cancer patients after a Phase II trial yielded promising results. (Ultimately, Iressa was not approved; few patients in Phase III trials improved on the drug, and its use is now restricted to those patients.) Nevertheless, Pazdur acknowledged that pharmaceutical companies currently have little motivation to comply with requests for experimental drugs. "There are some companies that flat out refuse to even get involved in expanded access," he said. "We are told over and over by the industry that the F.D.A. will find some toxicity in the expanded-access program, and the evil Dr. Pazdur will take out his ruler and slap your hand, and the drug will be killed."

Pazdur is overseeing the F.D.A.'s plans for a new program that will enable pharmaceutical companies to distribute experimental drugs to thousands of cancer patients through large networks of community-based oncologists. To be eligible for the program, drugs would have to be at the end of Phase II trials or partway through Phase III, depending on the kind of drug and cancer involved. The oncologists who administer the drugs would be required to report their patients' progress and any side effects to the F.D.A. and to the pharmaceutical companies. The doctors would also have to answer simple questions about the drug—whether patients did better on a high dose twice a day or on a lower dose three times a day, say, or whether it helped patients with an advanced stage of cancer.

To encourage drug companies to participate, the F.D.A. would allow them to recover some of the program's costs, including a portion of the doctors' fees, from patients or insurance companies. But the data generated by doctors and patients could prove equally lucrative. The knowledge that a drug works just as well taken twice rather than three times a day—information that might not be obtained in a Phase III trial—could make it easier to market. Similarly, knowing that a drug helps patients with advanced cancer—the kind of severely ill patients who are generally excluded from clinical trials—could enable a company to obtain broader approval for the drug from the F.D.A. and increase revenues by hundreds of millions of dollars.

The program could also save pharmaceutical companies equally large sums in marketing costs. It is against the law to promote a drug to physicians before it has been approved by the F.D.A., but it is perfectly legal for pharmaceutical companies to provide information about such a drug to a doctor in an agency-approved expanded-access program. Many oncologists tend to be wary of prescribing new medications, because anti-cancer drugs usually cause serious side effects. The more rapidly a doctor can be educated about a drug's toxicity and proper dosing, the less money the pharmaceutical company will need to spend to promote the therapy and the greater the likelihood that the doctors will continue to use it.

The F.D.A. is also proposing to make clinical trials more efficient by adapting them while they

are in progress. In a traditional trial, an experimental cancer drug would be tested in a group of lung-cancer patients with different types of the disease, in the expectation that perhaps fifteen to twenty per cent might benefit. An “adaptive trial” might begin with a heterogeneous group and then add patients with a particular type of the disease, as data from outside the trial emerged suggesting that they would be most likely to benefit. “Whenever it comes to discussions about the F.D.A. using adaptive clinical trials to be more efficient, critics say, ‘Oh, the F.D.A. is cutting corners,’ ” Scott Gottlieb, the deputy commissioner, told me. “But it is really about the F.D.A. using better science and better technology.” Moreover, he added, “there’s a real difference between assessing the safety of drugs like Vioxx, for arthritis, and drugs for patients with life-threatening diseases. What might be considered too risky for an arthritis patient could be an acceptable risk for a cancer patient.”

In early November, Frank Burroughs, of the Abigail Alliance, met with Andrew von Eschenbach and seventeen other senior officials at the F.D.A. The officials did not mention the new initiatives, but after the meeting Burroughs told me, “For the first time in five years, I felt we were heard, that Dr. von Eschenbach is forward-thinking about our position.” Under the program for cancer patients being developed by the F.D.A., both Abigail Burroughs and Kianna Karnes would have been able to obtain the experimental drugs they sought. Still, the program is unlikely to satisfy those who believe that people with a terminal illness have a right to take any drug under development without government interference. “The Abigail Alliance holds to the position that the decisions about experimental drugs should rest with the patient and his physician,” Burroughs said.

At the same time, critics who believe that the F.D.A. needs stricter drug regulations are likely to consider the program too radical, and it may not altogether please pharmaceutical companies, either. If many patients with different kinds of tumors started taking experimental drugs outside controlled clinical trials, doctors could have a hard time discerning which of the drugs were working and for which cancers. “The signal-to-noise ratio would be very low if we allowed experimental drugs to be widely distributed,” David Parkinson, of Biogen Idec, said. As a result, he speculated, some drug companies might be inclined to abandon cancer research. “Many people think cancer is a lucrative market, but it really isn’t when you factor in the risks, since so many experimental agents fail at the stage of Phase III testing,” Parkinson said. “There are only a few real blockbuster drugs in cancer treatment, and a businessman can take a conservative approach and reap considerable revenues from developing another statin for high cholesterol, or another anti-hypertensive for elevated blood pressure. When I go to upper management, I have to convince them that it’s worth investing hundreds of millions of dollars in an experimental cancer agent that may well fail. With a new approval system that would make it difficult to identify effective drugs, the risk rises considerably, and this will shift investment from oncology to other areas where the developmental process is well defined and much less risky.”

Moreover, the F.D.A.’s initiatives could make it more difficult to recruit patients for clinical trials. Only three per cent of cancer patients in the United States are enrolled in such trials, which are typically conducted at academic medical centers. (Many American drug companies, unable to recruit sufficient numbers of patients, have begun to conduct Phase III trials in Eastern Europe and Southeast Asia, where such studies may be the only way to receive treatment.) If patients can obtain experimental drugs from physicians in their communities, they would have little reason to leave home to participate in a trial. Enrollments are particularly likely to suffer in the case of trials comparing an experimental drug with a standard therapy: what patient would want to risk receiving the standard treatment in a trial when he could get the experimental drug directly from his doctor? “Trying to make progress in cancer should be done by professionals, not by hoping that through this process somehow wonderful drugs should emerge,” Parkinson said of the

agency's plan to give experimental drugs to patients through community oncologists. "I would venture to say that responsible pharmaceutical and biotechnology companies will react to this as a terrible idea."

Ultimately, the F.D.A. is proposing a national experiment. The goal—to deliver experimental drugs to seriously ill patients who otherwise would probably not be able to obtain them—is a worthy one, but, as in a clinical trial, it entails considerable risks. If some version of the Brownback bill, the D.C. circuit-court decision, or, more likely, the F.D.A.'s plan is eventually adopted, the agency will need to be more involved in the oversight of drugs early in the approval process. It will have to develop new techniques for evaluating data from Phase I and Phase II trials in order to predict with greater accuracy which medications are likely to benefit which patients and when they should be distributed. In short, deregulation of experimental drugs will require new forms of regulation in order to insure that patients like Abigail Burroughs and Kianna Karnes are helped, not harmed. As Richard Merrill, the University of Virginia law professor, put it, "The agency won't just be calling balls and strikes but will be taking some initiative. It's not necessarily a mistake to go in this direction, but it will require a commitment to intervene that is unprecedented." ♦