



Access before Approval — A Right to Take Experimental Drugs?

Susan Okie, M.D.

A surprising court decision this past May has advanced an effort to allow terminally ill people to purchase experimental drugs after initial safety testing but before they have been shown to work.

A three-judge panel of the U.S. Court of Appeals for the D.C. Circuit was considering a lawsuit by the Abigail Alliance, a patient-advocacy group, against the Food and Drug Administration (FDA). Two members of the panel ruled that patients with life-threatening and otherwise untreatable diseases have a constitutional right to seek experimental treatments for which efficacy is not yet established and that the government cannot interfere unless it proves it has a “compelling interest.” The suit was sent back to a lower court, which had dismissed it. The dissenting judge, Thomas Griffith, wrote that “there is no evidence in this Nation’s history

and traditions of a right to access experimental drugs.”

Accepting the existence of such a right would fundamentally challenge the government’s system for evaluating drugs. In mid-June, federal officials filed an appeal seeking to have the case reheard by the full nine-judge panel of the appeals court. If the ruling is upheld, “it’s a huge, huge, devastating decision,” says William Schultz, a former deputy commissioner for policy at the FDA. “The more you offer early access, the harder it is to get the data” on safety and efficacy, because many patients will seek treatments directly rather than enrolling in trials in which they might be ran-

domly assigned to receive placebo or another treatment. “It would be very hard to figure out which drugs work,” says Schultz; the incentive for conducting clinical trials “would seriously diminish”; and permitting companies to market drugs without evidence of efficacy would create “massive opportunity for fraud, involving people who are very sick and very desperate.”

But some observers applaud the Abigail Alliance for highlighting the struggle to balance the desire of sick people for cutting-edge treatments with society’s need for scientific evidence of safety and efficacy. Many people with life-threatening diseases cannot find appropriate clinical trials, live far from research centers, or do not meet eligibility criteria, and many cannot obtain experimental drugs from manufacturers through “compassionate-use”

History of Regulation of, and Rights to Access to, Drugs in the United States.*	
1906	Federal Food and Drugs Act is enacted, regulating labeling and prohibiting adulteration of food and drugs entering interstate commerce.
1914	Harrison Narcotic Act is passed, regulating products containing opiates and cocaine.
1938	Federal Food, Drug, and Cosmetic Act is enacted after more than 100 people die from taking elixir sulfanilamide that contained the solvent ethylene glycol. The law requires that a new drug can be marketed only after it has been shown to be safe.
1951	Durham–Humphrey Amendment is passed, creating the category of prescription drugs.
1962	The Kefauver–Harris Amendments are enacted after birth defects occur in babies whose mothers have taken thalidomide as a sleeping pill or to treat morning sickness during pregnancy. Manufacturers must now demonstrate the effectiveness of their products to the FDA. The FDA is also given greater authority over clinical trials and regulation of drug advertising.
1980	In <i>Rutherford v. United States</i> , the Supreme Court rules that patients do not have a right to obtain unapproved drugs.
1983	Orphan Drug Act is passed to promote research on and marketing of drugs for rare diseases.
1987	The FDA changes investigational drug regulations to give patients who have serious diseases and no other therapeutic options access to experimental drugs.
1990	In <i>Cruzan v. Director, Missouri Department of Health</i> , the Supreme Court rules that patients have a right to refuse medical treatment.
1991	The FDA publishes regulations to accelerate reviews of drugs for life-threatening diseases.
1992	The FDA Modernization Act mandates the most wide-ranging reforms in agency practices since 1938. Provisions include a measure to accelerate review of devices.
2005	In <i>Gonzales v. Raich</i> , the Supreme Court rules that “the dispensing of new drugs, even when doctors approve their use, must await federal approval.”

* Adapted from the majority opinion issued by the U.S. Court of Appeals for the District of Columbia Circuit on *Abigail Alliance v. Von Eschenbach* and from the “Chronology of Drug Evaluation in the United States,” published by the Center for Drug Evaluation and Research.

programs. Dale O’Brien, medical director of the California-based Lorenzen Cancer Foundation, one of several patient-advocacy groups that have expressed qualified support for the Abigail Alliance’s efforts, argues that “dying people ought to have special latitude to work with the growing edge of science.”

The Abigail Alliance was founded in 2001 by Frank Burroughs, a former engineer whose 21-year-old daughter, Abigail, died that year of squamous-cell carcinoma of the head and neck. Burroughs had tried unsuccessfully to obtain cetuximab (Erbix) or gefitinib (Iressa), which were undergoing clinical trials and were recommended by Abigail’s oncologist at Johns Hopkins because her tumor

was rich in epidermal growth factor receptors, which the drugs inhibit. Neither drug was being tested for head and neck cancer, although Erbix has since been approved for that indication. “She had the right cells in the wrong place, and she didn’t qualify for any of the clinical trials,” Burroughs recalls. After his daughter’s death, he vowed to lobby for expanded access to experimental drugs, and he was joined by others who had lost family members to cancer or other diseases. The alliance has an annual budget of only about \$50,000, but it has attracted attention from legislators and members of the media who favor reducing government regulation.

Under the current system, drugs

undergo three phases of clinical testing before the FDA approves them for marketing. Phase 1 trials usually enroll small numbers of subjects (often fewer than 100) and are designed to study the metabolism and toxicity of a drug and the effects of different doses; they provide preliminary information about safety but little or no information about efficacy. Phase 2 trials usually involve up to several hundred subjects, address efficacy, and yield additional information about risks and side effects. Phase 3 trials are usually larger, including up to several thousand subjects. They are designed to provide more conclusive evidence of efficacy and additional safety data; they help regulators and physicians assess

the risks and benefits of a drug in treating a specific condition. Sometimes drugs for life-threatening diseases receive “accelerated approval” after phase 2 testing if they favorably affect a surrogate end point — causing tumor shrinkage, for example — but then the manufacturer must conduct further studies with a more definitive end point, such as prolonged survival. Some patients

keted for seriously ill patients who had exhausted other treatment options, if they waived the right to sue the manufacturer and permitted collection of their clinical data. Tier 2 approval would correspond to today’s accelerated approval, and tier 3 approval to full approval.

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patients who have run out of options,” warns Begg, “it’s not at all clear that things would stop there.”

Cancer-related clinical trials cannot accommodate all the patients who want experimental medications, but instead of permitting access after phase 1 testing, a better solution would be to expand treatment IND programs for later-phase drugs, says Bruce Chabner, clinical director of the Cancer Center at Massachusetts General Hospital, Boston. “Even safety is not resolved” by the end of phase 1, Chabner says. “I don’t have a right to fly somebody’s experimental airplane, so why should I have the right to some drug that a company has dreamed up?”

Rather than allowing untested medications to be marketed, “we should be promoting and making

The prerogative asserted by the FDA — to prevent a terminally ill patient from using potentially life-saving medication to which those in Phase II clinical trials have access . . . impinges upon an individual liberty deeply rooted in our Nation’s history and tradition of self-preservation.

— D.C. Circuit Judge Judith Rogers

with life-threatening diseases who cannot participate in a clinical trial can get an experimental drug — usually one in phase 3 trials — through a compassionate-use program or treatment protocol such as a treatment IND (an application for an investigational new drug), depending on the manufacturer’s willingness to supply it and the physician’s willingness to apply for it.

The Abigail Alliance’s lawsuit is one component of its campaign to radically change this system. The organization’s legislative proposal can be found in the ACCESS Act, a bill introduced this past November by Senator Sam Brownback (R-Kans.). Under the proposal, a drug could obtain tier 1 approval on the basis of phase 1 testing and preclinical evidence — from testing in animals, case histories, pharmacologic studies, or computer modeling — that it “may be effective against a life-threatening condition.” A drug with tier 1 approval could be mar-

I have serious doubt about how a court can know, as a matter of constitutional law, that the lesser of two evils will be achieved by providing all terminally ill patients access to all Phase I experimental drugs, given the risks these drugs present.

— D.C. Circuit Judge Thomas Griffith

keted for seriously ill patients who had exhausted other treatment options, if they waived the right to sue the manufacturer and permitted collection of their clinical data. Tier 2 approval would correspond to today’s accelerated approval, and tier 3 approval to full approval. The bill has alarmed the clinical research community and large health-advocacy groups. Only 11 patients who have run out of options,” warns Begg, “it’s not at all clear that things would stop there.” Cancer-related clinical trials cannot accommodate all the patients who want experimental medications, but instead of permitting access after phase 1 testing, a better solution would be to expand treatment IND programs for later-phase drugs, says Bruce Chabner, clinical director of the Cancer Center at Massachusetts General Hospital, Boston. “Even safety is not resolved” by the end of phase 1, Chabner says. “I don’t have a right to fly somebody’s experimental airplane, so why should I have the right to some drug that a company has dreamed up?” Rather than allowing untested medications to be marketed, “we should be promoting and making

clinical cancer research normative and part of how we treat cancer,” suggests Ellen Stovall, president of the National Coalition for Cancer Survivorship. Only about 5 percent of adults with cancer enroll in clinical trials, Stovall notes, partly because many community oncologists do not encourage participation and because databases of trials are confusing and incomplete. Yet stories like that of Abigail Burroughs resonate with the public. And “public opinion could pass a bad bill,” notes Stovall.

Both the bill and the lawsuit

suggest that the FDA alone controls access to experimental drugs, but major barriers to access lie beyond the agency's jurisdiction. Manufacturers, for instance, worry about liability, and physicians may not seek such drugs for fear of the FDA paperwork. In addition, Medicare, Medicaid, and private insurers generally will not pay for experimental drugs.

Pharmaceutical-industry representatives also express other reservations. "One of the biggest limitations is manufacturing capacity," says Scott Lassman of the Pharmaceutical Research and Manufacturers of America. "Especially in very early phases, the company may still be working out how to manufacture the product." Although the bill proposes allowing companies to charge for tier 1 drugs, says Lassman, they certainly couldn't charge full price. More important, "the whole purpose of large clinical trials is to fully evaluate benefits and risks," argues Frank Rockhold, an executive at GlaxoSmithKline, "and short-changing that is not in patients' best interests."

Nonetheless, the recent actions have apparently stimulated efforts

to broaden access to experimental drugs within the current system, especially in light of increased demand from patients. "We've seen a significant increase in the treatment INDs that are requested," says Scott Gottlieb, the FDA's deputy commissioner for medical and scientific affairs. "The agency has generally been aggressive in granting those," usually acting within 24 to 48 hours on physicians' IND requests and encouraging companies to establish broader treatment IND programs if there is considerable demand for a drug. According to Gottlieb, the agency is working to clarify the process of requesting access to experimental drugs, in part by providing standardized application forms and an interface on the FDA's Web site.

This spring, the National Coalition for Cancer Survivorship and the American Society for Clinical Oncology petitioned the FDA to issue guidance to the pharmaceutical industry on standards for expanded-access programs; they suggested criteria for deciding when such programs are appropriate, ways to ensure equitability, and approaches to data

collection and informed consent. Gottlieb says that the FDA has created a task force to respond to the petition and is clarifying its rules regarding what companies may charge. The FDA is permitted to approve compassionate use only for diseases in which evidence suggests that a given medication may have efficacy. However, the agency hopes to persuade companies to sponsor "simple, large, nonrandomized, open-access trials" for certain drugs that are in phase 3 trials, or possibly late in phase 2 trials, to make them available to more patients while providing additional data. "We think that you can have an approval process that is rigorous . . . even though you have parallel mechanisms to allow broader access to a drug that has shown activity and promise," Gottlieb says.

An interview with Mr. William Schultz, a partner at the law firm Zuckerman Spaeder and a former deputy commissioner for policy at the FDA, can be heard at www.nejm.org.

Dr. Okie is a contributing editor of the *Journal*.

1. Society for Clinical Trials Board of Directors. The Society for Clinical Trials opposes US legislation to permit marketing of unproven medical therapies for seriously ill patients. *Clin Trials* 2006;3:154-7.

Measles in the United States, 2006

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The control and virtual elimination of measles in the United States is a public health success that has provided a model for immunization programs in other parts of the developed world. Before measles vaccination was introduced in the United States in the mid-1960s, more than half a million cases of measles were re-

ported each year. Once a vaccine was developed, public health officials set out to use it to control the disease, envisioning eventual global eradication. By the mid-1970s, fewer than 50,000 cases were being reported annually in the United States, but a severe outbreak in Los Angeles in 1977 reminded authorities how tenuous

the control of measles was. Compulsory immunization of schoolchildren followed — the first in a series of steps that led to the interruption of the transmission of measles in the United States. The most effective of these steps was probably the introduction of a second dose of measles vaccine in 1989, again in response to a