Investigational Drugs and the Constitution

by Rebecca Dresser

In May 2006, a federal court of appeals issued a decision with radical implications for U.S. drug regulation. The ruling in *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach* expands the terminally ill person's ability to gain access to drugs early in the testing process.[1] If the decision stands, it will restrict significantly the Food and Drug Administration's control over investigational drugs.

The decision was surprising in several respects. The decision itself was a surprise, for the case had previously attracted little national attention. Also, the decision adopted a much broader concept of constitutional rights than did the precedents it relied on, and it reflected a naive impression of drug development.

In these and other respects, the decision departs from the mainstream scientific and ethical understanding of clinical research policy. Indeed, the decision is interesting in that it embraces popular ideas about the miracles that can occur when terminally ill patients gain access to novel agents. It emphasizes the benefits available from early-phase investigational drugs and shows little awareness of the harms early access could produce.

The Abigail Alliance Case

Grass-roots patient advocacy lies at the heart of the case. The events leading to the lawsuit occurred in 2000, when drug companies were testing two new cancer drugs. Many patients not in the trials sought early access to the drugs. The drug companies voluntarily operated a small early access program, but they were unwilling to expand the program to satisfy patient demand.

Abigail Burroughs, a twenty-one-year-old college student, was one of the patients denied admission to the early access program.[2] After she died, her father founded the Abigail Alliance for Better Access to Developmental Drugs to promote speedier approval of new drugs. With the assistance of the Washington Legal Foundation, a libertarian law and policy center, the Alliance petitioned the FDA to liberalize its early access policies. The FDA denied the request. The Alliance then went to the federal district court, which dismissed the case on grounds that there were no constitutional claims that would justify overturning the FDA denial.

The appellate court was more sympathetic to the Alliance's point of view, however. Two judges on the three-judge panel agreed that terminally ill patients have a constitutional right "to decide, without FDA interference, whether to assume the risks of using potentially life-saving investigational drugs that the FDA has yet to approve for commercial marketing, but that the FDA has determined, after phase I clinical human trials, are safe enough for further testing."

Existing FDA Policies

Current FDA regulations require three phases of human testing before a drug may be marketed for clinical use. Phase I tests are conducted on twenty to eighty subjects and are designed to measure adverse effects associated with increasing doses of a new agent. The regulations also establish a secondary objective for phase I trials: "if possible, to gain early evidence on effectiveness."

Drugs that appear to produce an acceptable safety profile may then enter phase II testing, which may involve up to several hundred subjects. Here, the goal is "to evaluate the effectiveness of the [new agent] and to determine the common short-term side effects and risks associated with the drug." If there is evidence that the agent produces an acceptable range of potential harms and benefits, the drug sponsor may conduct larger phase III trials. If these trials give acceptable evidence of effectiveness and safety, the sponsor may seek FDA approval for marketing to patients.

Current FDA regulations permit early access in certain situations. The FDA has a "compassionate use" program that allows companies to distribute drugs in voluntary programs, including one that governed access to the drugs Abigail Burroughs tried to obtain. The Accelerated Approval and Fast Track programs represent additional FDA efforts to hasten and expand seriously ill patients' access to new drugs.[3] For the Abigail Alliance supporters, however, these programs are insufficient to meet patients' interests.

According to FDA critics, a major problem is the agency's prohibition on commercial marketing of drugs before they are approved for clinical use. The Abigail Alliance wants the FDA to abandon the prohibition on drug marketing because it reduces the financial incentive for companies to offer early-phase drugs to patients outside clinical trials. The Alliance wants to substitute a rule allowing companies to market post-phase I drugs to "mentally competent, terminally ill adult patients who have no alternative government-approved treatment options." [See John Robertson's essay in this issue for further discussion of the case's implications.]

Constitutional Analysis

The *Abigail Alliance* judges cited two U.S. Supreme Court decisions as support for the constitutional right. The judges relied most heavily on the Court's physician-assisted suicide case, *Washington v. Glucksberg*.[4] In *Glucksberg*, the Court held that terminally ill patients have no constitutional right to obtain physician-assisted suicide. Because there was no traditional recognition of such a right, states were free to prohibit physician-assisted suicide.

Despite the Court's negative holding, the majority's *Abigail Alliance* opinion said that *Glucksberg* supported a constitutional right to obtain investigational drugs. Two parts of *Glucksberg* justified this view. First, the Supreme Court said that constitutional rights must be narrowly described. Noting that the Alliance "claims neither an unfettered right of access to all new or investigational new drugs nor a right to receive treatment at government expense," the judges thought that the Alliance's claim easily met *Glucksberg*'s demand for a narrow due process right.

The *Abigail Alliance* majority also thought that the plaintiffs satisfied a second *Glucksberg* requirement. This was the Supreme Court's demand claiming that substantive due process rights demonstrate a long-standing tradition of protection. According to the majority judges, traditionally protected rights associated with bodily integrity and self-preservation encompassed the right to obtain investigational new drugs. Federal drug regulation is a fairly recent phenomenon, which demonstrated to the Court's satisfaction that tradition recognized the freedom of people seeking life-saving medications.

The *Abigail Alliance* judges also looked to the *Cruzan* case as a source of support.[5] The Supreme Court's recognition of a right to refuse life-sustaining treatment had as a "logical corollary . . . that an individual must also be free to decide for herself whether to assume any known or unknown risks of taking a medication that might prolong her life." According to the *Abigail Alliance* judges, *Cruzan* demonstrated the Supreme Court's support for a liberty interest in obtaining drugs that had cleared phase I trials.

The dissenting judge in *Abigail Alliance* found much to criticize in the majority's analysis. The majority, he said, wrongly interpreted *Glucksberg* and *Cruzan*. First, the majority failed to supply evidence that the claimed right was part of the nation's traditions; instead, it created a new right based on several general principles, such as the right to self-preservation. But *Glucksberg* itself said that courts should not infer constitutionally protected liberty interests from broad concepts like those the majority described. Second, *Cruzan* recognized only the individual's right to be free of forced treatment, not to affirmative access to experimental agents. Third, "the history of drug regulation in this country does not evidence a tradition of protecting a right of access to drugs; instead, it evidences government responding to new risks as they are presented." Indeed, he said, Supreme Court precedents suggest that experimental drugs present scientific questions that should be resolved by Congress and regulatory agencies, not judges.

Uncertain Consequences

The majority's understanding of investigational drug testing is deficient in several ways. The majority seems to assume that most drugs that get through phase I testing will eventually be approved because their expected benefits will outweigh harms. The judges also seem to assume that phase I testing, which primarily examines safety, yields high-quality data on effectiveness. They seem to assume, too, that data from twenty to eighty people can supply sufficient evidence for patients and doctors to make informed decisions about new agents.

These assumptions led the majority to overlook the downsides of early access. The majority implied that terminally ill patients have little to lose in taking post-phase I drugs. In fact, an investigational drug may hasten death and significantly reduce quality of life. The majority ruling also raises slippery slope questions. For example, the majority's analysis would support a right to obtain "futile" treatments rejected by most of the medical community.

The majority's ruling could also impose serious social harm. Drug testing for safety and effectiveness primarily helps future patients. To advance knowledge, some subjects participating in clinical trials must be assigned to standard therapy. Trial participation also involves special examinations and other inconveniences. Obtaining early-phase drugs through a physician would be a more attractive option for many people. Thus subject recruitment will be more difficult if the majority's expanded access ruling goes into effect.

It is unclear whether the *Abigail Alliance* ruling will stand. Although the majority found that patients had a constitutional claim, it sent the case back to the lower court to determine whether the FDA's current policies are narrowly tailored to serve a compelling government interest. The FDA may indeed meet this standard. The FDA has also petitioned for a rehearing by the full court of appeals, which could overturn the ruling.

The FDA is now engaged in an effort to redesign the drug testing process, which could lead to a more varied and flexible approach and would speed drug approval when appropriate.[6] The revisions are likely to incorporate the views of many experts and consumers. As the *Abigail Alliance* dissent asserted, drug testing policy should be developed by regulatory agencies and Congress, not by federal judges.

Acknowledgments

Thanks to Nancy King for reviewing a draft of this column.

1. 445 F.3d 470 (D.C. Cir. 2006).

2. M. Kaufman, "Court Backs Experimental Drugs for Dying Patients," *Washington Post*, May 3, 2006; C. Leonnig, "Group Sues for Access to Experimental Drugs," *Washington Post*, July 29, 2003.

3. See 21 C.F.R. Parts 312, 314 (2006).

4. 521 U.S. 702 (1997).

5. 497 U.S. 261 (1990).

6. S. Okie, "Access before Approval: A Right to Take Experimental Drugs?" *New England Journal of Medicine* 355 (2006): 437-40.

Contributors

Priscilla Alderson is professor of childhood studies at the Social Science Research Unit, Institute of Education, University of London. She recently published, with Virginia Morrow, *Ethics, Social Research and Consulting with Children and Young People*, (Barnardo's, 2004). Her research interests include children's views and experiences of their education and health care, and equity between generations in terms of global justice, economies, and ecologies.

Adrienne Asch is the Edward and Robin Milstein Professor of Bioethics at the Wurzweiler School of Social Work and professor of epidemiology and population health at the Albert Einstein College of Medicine, both at Yeshiva University. She was recently appointed as director of YU's newly created Center for Ethics. In addition to her scholarship on issues of reproduction, genetics, and quality of life, she has been involved in clinical ethics consultation and the public policy process at the state and federal levels.

Alex Bond is an actress, comedienne, and writer who decided at the age of seven to live her life in a way that would make a good book. Middle-aged now and thoroughly exhausted, she's writing it down and will soon complete a novel about her time as a chanteuse in the gay leather bars of Dallas, Texas.

Katherine Curtis is a PhD student and, previously, a research fellow at the Child Health Research and Policy Unit, Institute of Health Sciences, City University, London. Her PhD aims to identify levers and barriers to patient-centred care with children using type 1 diabetes as a case study.

Rebecca Dresser is a professor in the law and medical schools of Washington University in St. Louis, where she teaches courses on policy issues in medicine and research. Since 2002, she has been a member of the President's Council on Bioethics.

Elizabeth Fenton is working towards a doctorate in philosophy at the University of Virginia. Her research interests are in ethics and political philosophy, particularly justice and human rights. She is currently studying the foundations of human rights, as well as the role of human rights, dignity, and nature in the biotechnology debate.

John Lantos is professor of pediatrics at the University of Chicago. His latest book (with William Meadow), *Neonatal Bioethics*, explores the ways in which our attitudes and practices toward imperiled newborns have changed over the last three decades.

Richard L. O'Brien is university professor at the Center for Health Policy & Ethics of Creighton University. He is particularly concerned about health care teams' delivery of patient-centered care and diminishing health disparities in underserved communities.

Christy A. Rentmeester is assistant professor at the Center for Health Policy & Ethics of Creighton University Medical Center. Her recent work considers how practitioners' patterns of moral perception can change over time and how young practitioners are taught to negotiate moral ambiguity as they become professionalized.

John A. Robertson holds the Vinson & Elkins Chair at the University of Texas Law School. He chairs the ethics committee of the American Society of Reproductive Medicine.

Katy Sutcliffe is a research student at the Social Science Research Unit of the Institute of Education and the Centre for Paediatric Pharmacy Research at the School of Pharmacy, University of London. She recently contributed a chapter to *Childhood Obesity: Contemporary Issues* (Taylor & Francis, 2005).

Submission Guidelines

The *Hastings Center Report* welcomes manuscript submissions. Prospective contributions may take many forms: **articles** that explore philosophical and ethical issues in medicine, health care, technology, medical research, the use of human subjects, and the environment; **reports or reviews** of empirical studies that implicate relevant philosophical and ethical questions; short, provocative **essays; case studies** (which may be accompanied by commentary on the case); **personal narratives** about receiving or providing health care; and **brief commentary** on relevant events in the news.

Most articles and empirical reviews accepted for publication are no longer than 6,000 words, and short essays no longer than 2,400 words. Shorter work is encouraged. For case studies, descriptions should be about 400 words, and commentaries should be no more than 650 words. Brief commentary should be no more than 800 words.

All feature articles, all reports and reviews of empirical work, and many short essays are reviewed blind. Authors' names and identifying information should appear only on a separate cover page. In matters of grammar and usage, the *Report* refers to the *Chicago Manual of Style*, although for purposes of review, submissions need not conform to *Chicago*. Authors' instructions for formatting endnotes are available at www.thehastingscenter.org/publications/hcr/hcr_author_instructions.asp.

The *Report* requires authors to disclose all financial relationships that might have biased their judgment, including:

- sources of funding for the item submitted
- financial or other significant relationships (including, for example, consulting, speakers' fees, membership on corporate advisory committees, and expert legal testimony) of the author and the author's immediate family in the last five years with companies, trade associations, unions, litigants, or groups that may gain or lose financially from the conclusions the author presents

Please complete a Conflict of Interest form for each author when submitting. This form is available at www.thehastingscenter.org/pdf/publications/hcr_conflict_of_interest.pdf.

To facilitate review, please submit electronic copies in *.rtf or *.doc format to editorial@thehastingscenter.org. Review averages ten to twelve weeks.