A New Era of Unapproved Drugs
The Case of Abigail Alliance v Von Eschenbach

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MORE THAN 100 YEARS AGO, INEFFECTIVE AND OFTEN DANGEROUS MEDICINES WERE WIDELY SOLD. THEN, IN 1906, THE US CONGRESS ENACTED THE PURE FOOD AND DRUG ACT,\(^1\) PROHIBITING THE SALE OF MISBRANDED, MISLABELED, OR ADULTERATED FOODS AND DRUGS IN INTERSTATE COMMERCE. OVER THE NEXT 60 YEARS, CONGRESS TIGHTENED DRUG INDUSTRY REGULATION, REQUIRING MANUFACTURERS TO DEMONSTRATE TO THE FOOD AND DRUG ADMINISTRATION (FDA) THAT THEIR PRODUCTS ARE BOTH SAFE AND EFFECTIVE.

In recent years, the FDA drug approval process has been heavily criticized. An Institute of Medicine report cites safety problems with approved drugs, such as rofecoxib,\(^2\) as evidence that FDA regulation has become too lax.\(^2\) By contrast, libertarians and some patients’ rights groups have castigated the FDA for blocking access to new and, they claim, potentially lifesaving drugs.\(^3\)

In May 2006, the battle took a new turn when a 3-judge panel on the US Court of Appeals for the District of Columbia decided in Abigail Alliance for Better Access to Developmental Drugs v Von Eschenbach\(^4\) (panel opinion) that terminal ill patients have a constitutional right to purchase unapproved drugs that have successfully completed phase I testing. Recognizing the serious ramifications at stake, the FDA requested a rehearing before the full DC Circuit Court of Appeals. Recently, the court granted the FDA’s petition to rehear the case and vacated the panel opinion.\(^5\) If the full court approves the panel’s decision, the case may reshape the regulation and sale of pharmaceuticals and, perhaps, encourage increased use of unregulated drugs. Such a ruling would open the door to “the romance of the latest new untested treatment,”\(^6\) threatening the ability of the FDA to protect public health.

The Case
Troubling cases often arise from unfortunate events. In 1999, Abigail Burroughs, aged 19 years, was diagnosed with squamous cell carcinoma of the head and neck. Despite chemotherapy and radiation therapy, the tumor was not eradicated. Cytogenetic analysis of the tumor revealed increased expression of the cell surface membrane receptor EGFR (epidermal growth factor receptor). At the time, 2 targeted EGFR treatments, genfitinib and cetuximab, were undergoing clinical trials. But Abigail did not meet inclusion criteria for the genfitinib trials, and the cetuximab trial was restricted to patients with colon cancer. Shortly before her death on June 9, 2001, she enrolled in a clinical trial of erlotinib (OSI774).

In November 2001, Abigail’s father, Frank Burroughs, founded The Abigail Alliance for Better Access to Developmental Drugs to advocate for greater patient access to pharmaceuticals in early stages of development and testing.\(^7\) Ordinarily, investigational drugs may be used only within a controlled trial. Under the compassionate-use policy instituted by the FDA in the 1990s, the FDA may approve the use of an investigational drug outside of clinical trials for life-threatening diseases when there is no comparable treatment alternative, clinical trials of the drug are under way, and formal FDA approval for the drug is being sought.\(^8\) The FDA may deny compassionate use if the scientific evidence does not provide a reasonable basis to conclude that the drug may be effective for its intended use or if it would add an unreasonable and significant risk of illness.

The alliance criticized the FDA for unduly restricting the scope of the compassionate-use policy, hence imposing marketing limits on drugs still in development. The alliance contended that this leads to an inadequate supply of compassionate-use drugs.\(^9\) At least in part because demand exceeded supply, the Burroughs family, despite working “very hard to acquire the drugs on a compassionate basis, got nowhere.”\(^10\)

In 2003, the alliance and the Washington Legal Foundation submitted a citizen’s petition to the FDA requesting broader availability of investigational drugs for terminally ill patients.\(^9\) Before the FDA acted formally on the petition, the alliance sued in federal district court, alleging that the failure of the FDA to permit the sale of investigational drugs to terminally ill patients violated patients’ rights to privacy and due process under the Fifth Amendment. (On December 11, 2006, the FDA announced proposed regulations designed to expand access to experimental drugs.\(^11\) Even if promulgated, the regulations are unlikely to meet the alliance’s demands.)

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On August 30, 2004, the district court granted the FDA’s motion to dismiss, ruling that there is no fundamental right of access to investigational drugs. On appeal, the panel overruled the lower court in a 2-to-1 decision on May 2, 2006. Writing for the majority, Judge Rogers analyzed the constitutional claims by asking whether the government’s regulation infringes upon a constitutionally protected “fundamental right.” If so, the government must show that its regulation is narrowly tailored to serve a compelling state interest. Absent a fundamental right, the government need only show a rational relationship between its regulation and a legitimate state goal.

To decide whether the right claimed is fundamental, the panel majority relied heavily on the Supreme Court’s analysis in Washington v Glucksberg, which held that there is no fundamental right to physician-assisted suicide. In Washington, the Court articulated a relatively restrictive test requiring courts to consider the right claimed as narrowly as possible and look to the nation’s history and legal traditions for evidence of whether that right has been treated as fundamental.

The panel ruled that on a physician’s recommendation, mentally competent terminally ill patients with no alternatives have a constitutional right to obtain potentially life-saving drugs that are eligible for post-phase 1 testing. Finding that the nation’s history and traditions support recognizing such a right, the panel majority reasoned that federal regulation of pharmaceuticals is only 100 years old and that not until 1962 did the government require premarket review of their safety and effectiveness.

The panel majority further relied on the Supreme Court’s decision in Cruzan v Director, Missouri Department of Health that competent individuals have a constitutionally protected right to reject life-sustaining medical treatment. Cruzan’s recognition of a constitutionally protected liberty interest in ending life-sustaining treatment implies “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.”

In dissent, Judge Griffith argued that courts should be wary of recognizing new constitutional rights and that the constitutional right plaintiffs claimed could not be found in the nation’s history or legal traditions. The absence of drug regulation until 1906 did not show a protected right prohibiting such regulation, merely that the government initially opted not to act. The dissent also criticized the majority’s understanding of the drug approval process, arguing against the majority’s inference that drugs showing success in phase 1 trials would “probably have a medical benefit with sufficiently minimal risk.”

Importantly, the dissent cited Supreme Court opinions upholding the FDA’s ban on lan cetri14 and Congress’s prohibition of medical marijuana as illustrating that the political branches should determine the “balances between the uncertain risks and benefits of medical technology.”

The Implications
As a microcosm of contemporary health policy tensions, this case raises challenging issues regarding drug safety at the limits of scientific knowledge, the role of markets vs regulators, medical care of terminally ill patients, individual rights vs protection of public health, and the allocation of scarce resources. The panel opinions offer dramatically divergent views of how to balance individual patient needs with broader public health considerations. Although the troublesome legal issues are beyond the scope of this commentary, the decision ultimately reached by the full court of appeals will have broad public policy and clinical implications. Whatever the decision, the case could well reach the Supreme Court.

Drug Safety
Despite the enthusiasm often accompanying new pharmaceuticals, premature diffusion of untested drugs can increase morbidity from adverse events and hasten death. Absent assessment in phase 2 or phase 3 clinical trials, pharmaceuticals cannot be assumed safe and effective. Since phase 1 trials involve only small numbers of patients, these studies reveal little about a drug’s true safety and efficacy profile. As an example, further testing of amonifide for treating advanced breast cancer was discontinued after safety concerns emerged in a phase 2 trial. The trial demonstrated that use of amonifide resulted in serious hematologic toxicity (severe and life-threatening leukopenia and thrombocytopenia) and systemic allergic reactions.

The amonifide example is not unusual. Only 5% of all cancer drugs that enter clinical testing are approved for patient use; among cancer drugs assessed in phase 2 trials, only 30% proceed to phase 3 assessment. During clinical trials for all drugs from 1981-1992, attrition (ie, abandonment) occurred for 3 reasons: safety concerns (including toxicity) averaged 20.5%; lack of efficacy averaged 35.3%; and economics averaged 31.8%. These data almost certainly underestimate the safety concerns.

In particular, data reflecting safety issues might not be publicly available. To protect proprietary interests, data on unapproved drugs or reasons for discontinuing trials are not always disclosed. Despite recent pressure for study results to be posted on publicly available Web sites, concerns remain that not all results will be included in new drug applications. Furthermore, safety concerns may not be apparent until the postmarketing phase (eg, as was the case for rofecoxib). For these reasons, the consequences of early diffusion are not as benign as the panel majority suggested, even for patients with no other treatment alternatives.

Equally unfortunate, the panel’s approach, if adopted, could reduce patients’ willingness to enroll in randomized clinical trials, the gold standard for determining safety and efficacy of investigational drugs. Without random assignment of patients to receive either the new...
drug or a placebo or comparator drug, the true efficacy and adverse-event profile of an investigational drug will be unknown.

**Regulatory Authority**

In subordinating patient safety to the misperception that there are miracle cures that the government is concealing from the public, the panel’s opinion usurped the FDA’s responsibility to balance the risks and benefits of new drugs and strikes at the core of the FDA’s raison d’etre. If access to experimental drugs is considered a fundamental right, the FDA’s regulatory authority is inevitably diminished, as is its ability to conduct premarket review of new pharmaceuticals for safety and effectiveness.

Thus, this case starkly juxtaposes the tensions between free market and regulatory approaches to pharmaceutical evaluation. In its legal briefs, the alliance unmistakably considers the litigation as part of a major assault on the government’s authority to regulate pharmaceuticals. As the alliance stated, “denying a terminally ill patient with no approved treatment options the right to purchase a promising experimental drug, simply because that drug has not yet been proven effective in the estimation of government regulators, goes against the grain of historical American practice.” The alliance couples this argument with support for legislation that would abolish regulatory requirements for placebo trials, provide access to investigational treatments that have shown promise, and allow pharmaceutical manufacturers greater opportunity to market unapproved medications.

The panel’s opinion, if followed, would facilitate the alliance’s objectives, leaving the FDA’s regulatory authority vulnerable to further erosion. For instance, the fundamental rights analysis, rooted in patient autonomy, could easily apply to medications expected to prevent pain or disability. As the dissent noted, why would the majority’s reasoning not apply to pharmaceuticals for patients with serious but not terminal medical conditions? Suppose, for example, a new pharmaceutical for irritable bowel syndrome successfully completes phase 1 testing. To alleviate their symptoms, patients with this syndrome are no less likely to demand the drug prior to additional trials than are terminally ill patients. Likewise, other FDA actions, such as bans on reimporting drugs from Canada, may be susceptible to similar challenges. Put more starkly, why not return to a deregulated world in which patients can obtain access to any drug they believe will be lifesaving or lifenhancing?

While a market-oriented, deregulated environment for pharmaceuticals is an entirely plausible policy, it would raise important public health concerns. Past experience with the use of unapproved drugs (e.g., laetrile) has not been auspicious. What is especially dangerous about the panel’s decision is that it would simultaneously permit drug companies to stimulate demand via advertising while removing the regulatory safety net designed to protect patients from untested therapies.

**Clinical Implications**

Ostensibly, the panel’s opinion respected physicians, ceding to them, rather than to the FDA, the authority to determine which medications may be available for prescribing to terminally ill patients. In reality, that approach might prove problematic for physicians, leaving them caught between patient demands for ineffective or dangerous pharmaceuticals and physicians’ ethical obligation to do no harm. Perhaps even more troublesome, it would encourage the antithesis of evidence-based medicine.

The essence of the alliance’s clinical argument is that terminally ill patients should have the choice of using experimental drugs in consultation with physicians. “All [the plaintiffs] ask is that the government get out of their way, so that they can use their own private resources to fight for their own lives at the inherently uncertain frontiers of modern science.” Consistent with current market theory, the panel’s opinion shifted the risks to the patient but also to the physician.

Physicians already face considerable pressure from patients who demand medications that are heavily marketed through direct-to-consumer advertising. As contentious as such advertising has been, allowing access to unapproved pharmaceuticals places physicians in the uncomfortable position of prescribing drugs with unknown risk profiles that may be more harmful than beneficial, explaining to patients why simply calling something lifesaving does not make it so, or being candid that medicine has nothing more to offer. While this is precisely the risk-benefit discussion that physicians should be having with patients, there is a substantial added burden when discussing drugs that have not completed appropriate clinical trials, especially when no data or published reports exist to support the physician’s professional opinion of safety and efficacy. As the government argued to the panel, terminally ill patients are particularly vulnerable to promises that unproven treatments will be effective.

Consequently, the authority that the panel’s opinion would have given physicians may increase their risk of liability. If physicians prescribe an unapproved drug, they will be required to inform patients about what is known and not known about the drug. If, however, an unapproved drug proves ineffective, dangerous, or both, informed consent may not be sufficient to shield physicians from a medical liability claim for prescribing a treatment outside the standard of care. Conversely, patients who do not respond to standard therapies may bring claims if they were not informed about alternative, unapproved treatments.

**Conclusion**

As the full court considers the case, it should reexamine the panel’s aggressively individualistic view, one that breath-
Takingly slights the public’s interest in drug safety. The court should reject a constitutional right to unapproved drugs and give more weight to the important public health interests served by the FDA’s regulatory process. Despite the appealing rhetoric of choice and the belief that there is a medical cure for every illness—even at the end of life—public policy must balance the harms and benefits of pharmaceuticals and determine the optimal level of regulation. No one wants to deprive dying patients of access to drugs that may extend their lives. But no one should understate the potential scientific and clinical consequences of removing the FDA’s role in monitoring drug safety and effectiveness.

There are serious concerns about the FDA’s drug approval process, particularly the speed of new drug approval and postmarketing scrutiny, which deserve rigorous policy attention. Nonetheless, neither the court’s adoption of the panel’s opinion nor legislation codifying that approach would provide a sound solution.21 The idea that the way to save lives is through unapproved drugs offers the illusion of choice and the reality of false hope—not an acceptable basis for public policy.

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REFERENCES
5. 2006 US App LEXIS 28974 (DC Cir November 21, 2006).
8. 21 CFR 312.34 et seq.
21. ACCESS Act (Access, Compassion, Care, and Ethics for Seriously Ill Patients), S 1956, 109th Cong (2005).