

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Mary Beth Hamel, M.D., M.P.H., *Editor***Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs**Jonathan J. Darrow, S.J.D., J.D., M.B.A., Ameet Sarpatwari, J.D., Ph.D., Jerry Avorn, M.D.,
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The Food and Drug Administration (FDA) reviews clinical-trial data for new drugs and determines whether the benefits of these drugs outweigh the risks.¹ This requirement, legislated in 1962,² raised the bar to approval and reduced the likelihood that new drugs would be ineffective or cause major health problems. Developing such data about investigational drugs takes time for the assessment of products that ultimately prove to be safe and effective. Such a time lag can be a problem if alternative treatments for the condition are not available. The FDA therefore developed a system of expanded access to permit patients with serious conditions to receive investigational drugs before formal product approval.

The expanded-access system has become increasingly controversial. Recently, the family of Josh Hardy, a 7-year-old with a life-threatening infection, sought an experimental antiviral drug — brincidofovir — that was recommended by his doctors. After the media drew attention to his plight,³ the drug's manufacturer offered to include him in a newly created open-label study.⁴ The question of making untested drugs or vaccines available has also entered public debate in the context of the treatment or prevention of Ebola virus disease, which is often fatal and for which no clearly effective medications or vaccines exist. Each year, thousands of patients wanting to expand their treatment options seek access to incompletely evaluated treatments, but not all obtain them.⁵ We discuss the practical, legal, and ethical issues associated with expanded access and use of investigational drugs.

REGULATION OF EXPANDED ACCESS

After Congress mandated that the FDA validate substantial evidence of safety and effectiveness

for new drug products based on adequately controlled clinical trials, the average development time for a new drug predictably rose from 2.5 to 8 years.^{6,7} Although Congress stipulated that the FDA must act on new-drug applications within 180 days, staff shortages in that era caused the agency to often miss its deadlines in the years after this codification, a problem that has been largely addressed since then.⁸ To address the lengthened development cycle, the FDA permitted patients or physicians to petition to receive access to unapproved drugs.

These informal pathways were institutionalized in 1987 in the context of the growing AIDS epidemic and were substantially revised in 2009 (Tables 1 and 2).^{9,10} Three categories of expanded access now exist. The most common request is for individual use, a subset of which involves emergency circumstances leading to treatment even before a formal written request has been submitted to the FDA. The second situation relates to requests by intermediate-size patient populations (tens to hundreds) who are eligible to receive a drug early in its development. The final situation is widespread use under a treatment protocol, such as might occur after a successful trial of an experimental agent has been concluded but before it has received FDA approval. The 2009 revisions sought to increase access to investigational therapies but also included eligibility requirements and other safeguards that the FDA considered to be necessary to protect vulnerable patients. The regulations aim to reconcile the protection of patients (who are often seriously ill and desperate) from the use of products that may be useless or worsen their condition with the desire to provide more rapid access to treatments that may ultimately prove to have merit but for which approval comes too late for those who die during the lengthy evalu-

Table 1. Criteria for Making an Investigational Drug Available through an Expanded-Access Program, According to Type of Use.

Key Criterion	Required for All Categories	Additional Requirements for Individual Use	Additional Requirements for Intermediate-Size Use	Additional Requirements for Widespread Use
Risk-benefit assessment	The FDA must determine that the disease or condition is serious or immediately life-threatening, that there is no similar or satisfactory alternative therapy, and that the potential patient benefit justifies the potential risks.	A physician must determine that the risk from the drug is not greater than the risk from the disease or condition.	The FDA must determine that there is sufficient evidence that the drug is safe to justify a clinical trial for the number of patients expected to receive the drug under expanded access and that there is preliminary clinical evidence of effectiveness or of a plausible therapeutic effect.	In the case of serious disease, the FDA must determine that there is sufficient clinical evidence (ordinarily, from phase 3 trials or compelling data from completed phase 2 trials) of safety and effectiveness. In the case of life-threatening disease, the FDA must determine that available evidence (ordinarily, from phase 2 or 3 trials or more preliminary evidence if appropriate) suggests that the drug may be effective and would not expose patients to an unreasonable risk.
Trial progress	The FDA must determine that providing the drug will not interfere with the initiation, conduct, or completion of clinical investigations.	The FDA must determine that the patient cannot obtain the drug in a clinical trial or other expanded-access protocol.	The manufacturer must explain why patients cannot be enrolled in a clinical trial. If no trials are under way, the FDA will consider whether a clinical study is possible, and the manufacturer must explain why the drug cannot currently be developed.	The FDA must determine that the drug is being investigated in a controlled clinical trial (or all clinical trials have been completed) and the sponsor is actively pursuing marketing approval.
Other requirements	NA	Treatment generally must be limited to a specified duration.	NA	NA

* NA denotes not applicable.

ation process — all without compromising the completion of preapproval clinical trials.

For all expanded-access categories, the FDA must determine that the condition is serious or immediately life-threatening, that there are no similar or satisfactory alternative therapies, and that access will not interfere with pivotal clinical trials.¹¹ These caveats appropriately place primacy on the traditional FDA approval process. In addition, the FDA must determine that the potential benefits of expanded access justify the potential harms. The evidentiary threshold for this criterion increases with the number of patients who are involved and is higher for less serious conditions.¹²⁻¹⁴ For example, the FDA must find sufficient evidence of safety and effectiveness before it permits an expanded-access protocol involving large numbers of patients with serious disease. However, for individual patients, a physician only needs to conclude that the experimental drug does not pose a greater risk than the disease itself.¹²

The FDA has permitted almost all expanded-access requests regardless of category.^{15,16} The FDA estimated that by 2006, approximately 100,000 patients had obtained expanded access to experimental drugs.¹⁷ Between 2010 and 2013, the FDA imposed clinical holds on only 2 of the 2472 individual, nonemergency protocols, on 1 of 66 intermediate-size requests, and on none of the 41 widespread expanded-access protocols it received.¹⁸

CONSIDERATIONS LIMITING EXPANDED-ACCESS USE

Numerous practical considerations have nonetheless presented a challenge to more widespread implementation of expanded-access programs. In April 2014, only 86 of the 32,304 studies listed at ClinicalTrials.gov as enrolling new participants were available for expanded access.¹⁹

INDUSTRY PARTICIPATION

Manufacturers must agree to make the product available, and a combination of business and regulatory factors make this an important rate-limiting step. One factor is the administrative burden for the drug maker. The FDA has estimated that 120 hours of human effort are required for a company to prepare a protocol for an intermediate-size patient population, with the

Table 2. Obligations of the Investigator and Manufacturer in an Expanded-Access Program.*

All Categories	Individual Use	Intermediate-Size Use	Widespread Use
Investigator			
Report adverse drug events to the sponsor	The investigator or manufacturer must provide the FDA with a treatment summary, including adverse events, at the conclusion of treatment.	NA	NA
Ensure that informed-consent requirements are met			
Ensure that approval is obtained from an institutional review board			
Maintain accurate case histories and drug-disposition records			
Manufacturer			
Submit safety reports to the FDA	The manufacturer may be required by the FDA to monitor the patient, if the use is for an extended duration.	The manufacturer must submit an annual report to the FDA and ensure physician compliance with the protocol and applicable regulations.	Same requirement as for intermediate-size use
Submit annual reports to the FDA (if expanded access continues for longer than 1 yr)			
Ensure that investigators are appropriately qualified			
Provide investigators with information to minimize drug risks and maximize drug benefits (e.g., an investigator's brochure), if available			
Maintain and retain drug-disposition records			

* NA denotes not applicable.

task divided among a director of clinical research (60 hours), a regulatory affairs director (24 hours), and a clinical research associate (36 hours).¹⁰ These burdens may weigh particularly heavily on smaller manufacturers.²⁰ Even if manufacturers are willing and able to devote the necessary time, production capacity may not be sufficient to meet demand for both expanded use and ongoing clinical trials.¹⁰

Because of these factors and the substantial manufacturing costs of some prescription drugs (particularly biologic agents), expanded-access programs may also be seen as financially problematic. The FDA allows companies to charge patients or their insurers the direct costs of the expanded-access program, including manufacturing and shipping costs. For intermediate-size and widespread-use programs, companies can also charge the costs of monitoring and reporting.²¹ Charging direct costs, however, could lead to adverse publicity because these costs will be far less than the price of a drug when it is ultimately approved by the FDA, a price that sometimes exceeds \$1,000 per pill or \$200,000 per patient per year.^{22,23} Some manufacturers, therefore, guard cost information carefully, even if it means forgoing the modest revenue that might be obtained through this pathway.²⁴ If a manufacturer does seek to impose charges, it may be under pressure from patients to waive costs because they may not be covered by insurance.²⁵ The FDA accordingly reports that most manufacturers do not charge for their products.²⁶

Manufacturers must additionally consider the effect of expanded-access programs on ongoing development and regulatory approval efforts. Generally, limited data are collected during expanded-access protocols (particularly as compared with clinical trials), and the FDA has recognized that such data may not be collected in a systematized fashion and therefore may not be useful.¹⁰ However, all adverse events that occur in any patient receiving a drug during its pre-approval period must be reported to the FDA,¹¹ and patients receiving treatment under expanded-access protocols are often sicker than trial participants.¹⁰ Companies may worry that this obligation could reduce the chance of approval, lead to additional label warnings, or create negative publicity.^{24,27}

Expanded-access programs can also deter enrollment in clinical trials, thereby increasing the amount of time and effort necessary to accrue requisite statistical power, especially in studies involving patients with rare conditions. At the extreme, such programs may encourage gaming of clinical trials in ways that ensure access to a potentially effective medication.²⁸ Although many phase 3 trials of investigational agents are blinded, it can be possible for patients to determine whether they have been randomly assigned to receive placebo, particularly if expected side effects do not occur,²⁹ and then withdraw from the trial.³⁰ In one case, a woman withdrew from a cancer trial after being assigned to the

Table 3. Features of Existing “Right-to-Try” Laws in Three States.

State	Patient Eligibility	Drug Requirements	Informed-Consent Requirements	Protections for Physicians	Protections for Manufacturers
Colorado	Must have a terminal illness Must lack viable approved treatment alternatives Must be unable to enter a clinical trial within 100 mi of home or not be accepted within 1 wk after applying Cannot be an inpatient	Phase 1 testing must be completed Must be recommended by a physician	Explains approved treatment alternatives Details best- and worst-case outcomes and specifies patient’s responsibility for outcomes Cautions that payers or providers may not pay for treatment, that hospice care may be terminated, and that in-home health care may be denied	Provides limited civil immunity Prohibits professional disciplinary action for good-faith recommendations	Provides limited civil immunity
Missouri	Must have a terminal illness Must consider treatment alternatives	Must be recommended by a physician Must be in testing in ongoing clinical trial	None	Provides limited civil immunity Prohibits professional disciplinary action for recommending experimental therapy	Provides limited civil immunity
Louisiana	Must have a terminal illness Must lack viable approved treatment alternatives	Phase 1 testing must be completed Must be recommended by a physician Physician must attest that the probable risk of treatment is not greater than the risk of illness	None	Provides full civil immunity Prohibits professional disciplinary action for good-faith recommendations	None

control group and sought expanded access to the active treatment.³¹ The company denied her request.

Finally, expanded-access programs could bring liability exposure.³² Litigation in this arena, however, has been limited to obtaining access rather than seeking redress of treatment-related harm. The lack of adverse-event lawsuits may reflect the willingness of such patients to assume risks³³ as well as the adequacy of existing regulatory and manufacturer safeguards.

PHYSICIAN KNOWLEDGE AND COOPERATION

Effective expanded-access programs require the active participation of treating physicians. Some may be unaware of particular investigational drugs or unfamiliar with the process of obtaining them.³⁴ Physician-directed expanded-access requests are infrequent.¹⁰ One explanation may be the difficult situation facing a physician who is considering an expanded-access request: regulations require that the physician determine that the risks of the disease outweigh the risks of the drug, but there is usually little published literature relating to the drugs at issue. The clinical information that manufacturers submit to the FDA is proprietary and, thus, available only to the extent that manufacturers permit.¹⁰

Physicians may also be reluctant to shoulder the administrative burden, since it takes approximately 8 hours for a physician to prepare an individual patient request.¹⁰ Federal regulations require obtaining appropriate informed consent and approval from institutional review boards, maintaining accurate case histories and drug-disposition records, and reporting adverse events.¹¹ The FDA considers the use of expedited procedures with respect to institutional review boards inappropriate for expanded access,¹⁰ and full reviews can be costly. Many academic centers charge \$2,000 to \$3,500 for a protocol review, although fee-waiver requests in these settings may be available.^{35,36} For clinicians outside academic medical centers, locating and obtaining review by an institutional review board can be even more challenging.²⁷

LEGAL CHALLENGES

The difficulties in accessing investigational drugs have led to three primary kinds of legal challenges. First, some patients have argued that

the FDA regulatory apparatus itself violates their constitutional rights if it limits their ability to access drugs at any stage of testing. However, courts have generally ruled that no constitutional right of access exists in these circumstances. In the landmark 1979 case *United States v. Rutherford*, the Supreme Court found no right of terminally ill cancer patients to access amygdalin (Laetrile), a now discredited treatment, for which an application for clinical testing was pending before the FDA.³⁷ More recently, in *Abigail Alliance v. von Eschenbach*, a federal court of appeals explicitly held that “there is no fundamental right . . . to experimental drugs for the terminally ill.”³⁸ In 2008, the Supreme Court declined to review the case.

Second, some patients have asserted contractual rights to expanded access. These claims have sometimes prevailed when a patient received a drug during the course of a clinical trial and then requested continued access after the trial ended but before the drug was approved.³⁹ However, this contractual right may be unavailable if post-trial access was not promised,^{40,41} and some courts have ruled that investigators’ promises do not bind manufacturers.⁴²

Third, some state legislatures have sought to override the restrictions imposed by the FDA regulatory system. In 2013 and 2014, for example, Colorado, Missouri, and Louisiana passed so-called “right-to-try” laws that permit manufacturers to provide experimental medicines to terminally ill patients without FDA authorization, purportedly eliminating certain obstacles to expanded access.⁴³ These three laws require that the treating physician recommend the experimental therapy, and the Colorado and Louisiana statutes further mandate that the treating physician attest to the inadequacy of FDA-approved treatment alternatives (Table 3).⁴⁴⁻⁴⁶ The laws shelter physicians from professional discipline and negligence actions for making good-faith recommendations; Colorado and Missouri also extend limited civil immunity to manufacturers related to harms that experimental drugs may cause.⁴⁴⁻⁴⁶

Right-to-try laws, which have also been adopted in Michigan and Arizona, will have limited effect. They do not compel manufacturers and insurers to supply and pay for experimental therapies. They also cannot prevent the federal government from rescinding Drug Enforcement Administration registration of physicians who

prescribe experimental drugs independent of the FDA,^{47,48} though such action is very unlikely if no controlled substances are involved. Only Colorado requires eligible patients to have been unable to participate in a clinical trial “within one hundred miles of the patient’s home address” or not to have been “accepted to the clinical trial within one week of completion of the clinical trial application process.”⁴⁴ Without addressing the structural limitations to making experimental treatments available outside pivotal clinical trials, such strategies will not improve access and could instead exacerbate existing tension over the fair distribution of available supplies.

In addition, right-to-try laws are unlikely to withstand a constitutionality challenge that is based on conflict with the FDA’s enabling legislation and existing expanded-access regulations. Under the Supreme Court’s long-standing preemption doctrine, state laws that conflict with federal statutes or regulations are “without effect.”⁴⁹ Limiting the reach of these state laws to patients with terminal illnesses cannot avoid the conflict. As Justice Thurgood Marshall noted in *Rutherford*, “Nothing in the history of the [Food, Drug, and Cosmetic Act] suggests that Congress intended protections only for persons suffering from curable diseases.”³⁷ The frustration that these laws reflect may nonetheless mount pressure on Congress and the FDA to reassess the expanded-access system.

ETHICAL ISSUES

The primary ethical argument for expanded access is that patients should have a right to mitigate extreme suffering and to enhance self-preservation. This logic holds that as rational actors, patients are presumed to be capable of making well-informed treatment decisions in consultation with their physicians. According to this argument, not only can patients with serious or life-threatening conditions accurately identify promising experimental drugs, but they should also be entitled to utilize their own risk-benefit thresholds in deciding whether to consume such products. Advocates of expanded access argue that deference to the assumed capacity of patients to thereby make appropriate treatment decisions should be greatest when the stakes are highest (i.e., when death is likely or certain).

By contrast, those who seek to limit access to unapproved medications argue that the odds of an experimental therapy working in many expanded-access settings are extremely small — the probability of clinically meaningful benefit from early-stage experimental trials may be less than 10%^{50,51} — and informational asymmetries can lead to patient vulnerability. By definition, data on experimental drugs are very limited, and patients generally do not have access to all the information that does exist, because some of it is proprietary. Moreover, most patients do not have the training or experience to evaluate the combined pharmacologic, clinical, and statistical information on experimental therapies that is available to them. Risk comprehension among the general public is low,⁵² is not strongly correlated with self-perceived ability to understand risk,⁵³ and may be more impaired in sicker patients.⁵⁴ Skeptics of expanded access caution that the risk of treatment-selection decisions that could exacerbate suffering or hasten death justifies greater — not reduced — paternalism for patients with serious or life-threatening conditions.

The clash between autonomy and informed consent in decision making by vulnerable patients mirrors the discussion of the appropriateness of physician-assisted suicide in the context of a serious illness. In both scenarios, patients are seeking to avoid a “hard death.”⁵⁵ The two issues differ, however, in that expanded-access programs have broader public health implications by prolonging the process of drug development and delaying drug availability to the general population by potentially diverting resources and patients from preapproval clinical trials.

Expanded-access programs can also raise concerns about equity. Most but not all manufacturers shoulder the cost of expanded access,²⁶ and when they fail to do so, insurers may refuse to step in. Medicare, for example, covers only treatments that are “reasonable and necessary,”⁵⁶ and many private insurers have similar policies.⁵⁷ Some observers have accordingly argued that expanded access generally favors the rich or well-connected over the poor.^{5,58}

POLICY RECOMMENDATIONS

As frequently recognized by the courts, the best pathway to widespread access to experimental drugs is found by showing their efficacy and safety sufficiently to earn prompt FDA approval.

Even an augmented system of expanded access can never match the access that occurs once the FDA grants approval. Thus, one of the most straightforward means of addressing the issue of expanded access is to shorten the time between the determination that a new substance may be clinically useful and the point at which it becomes widely available.

Review times for U.S. drugs have decreased considerably and are now similar to or better than those in most industrialized countries.⁵⁹ The FDA has created several kinds of fast-track approval mechanisms, and a priority-review designation ensures review within 6 months or less.⁶⁰ It may be possible to shorten this interval further for truly important new treatments by innovative means of drug evaluation, such as adaptive trial design.⁶¹ Plans for bridging the gap between early promise and market availability could also be addressed when a drug first enters clinical trials so that more manufacturers are prepared for expanded-access demands on products that prove to be successful. For devices, the Medicare program has introduced the concept of “coverage with evidence development,” in which it will pay for a new medical device despite poorly documented effectiveness and safety, as long as such use comes with collection of additional data about how the product performs. A modification of this approach for medications could harvest useful clinical information about drugs that are provided through expanded-access programs.

Although right-to-try laws are misguided, a more pragmatic — and lawful — approach is for states to work collaboratively with the FDA to make expanded access more practical when it is appropriate. For example, since the FDA has acknowledged that gaining approval from an institutional review board can pose a barrier,⁶² states could partner with the FDA to fund multicenter institutional review boards that focus specifically on expanded-access requests. Such multicenter panels would conduct full reviews, but their subject-matter expertise and limited dockets would translate into faster review times. Through subsidies, states and the FDA could eliminate the need for patients or clinicians to incur fees for proposal review, which would facilitate expanded-access requests outside of academic medical centers.

Practical obstacles to enhancing expanded-access programs, including administrative bur-

dens and industry costs, would also be best tackled by the states in partnership with, instead of in opposition to, the FDA. For example, a manufacturer's reluctance to provide product because of financial concerns could be addressed by permitting companies to charge amounts closer to the likely postapproval cost of drugs. Falit and Gross propose that manufacturers place any profits in interest-bearing escrow accounts until experimental-drug approval.³⁴ This requirement would enable manufacturers to recoup development and distribution expenses without revealing proprietary financial information. Such a policy would provide incentives to expanded-access programs while precluding financial gain from products that ultimately prove to be unsafe or ineffective, with escrowed profits then reallocated to other health-related government use. But this approach could also increase patients' financial burdens and disparities in access.

The ethical and policy debate on the appropriate balance between access to and protection from potentially useful but also possibly harmful or ineffective medicines began with the passage of the Pure Food and Drug Act in 1906. The escalation of the battle over expanded access has rekindled this debate a century later. In the ensuing years, Congress has unambiguously delegated authority over striking this balance to the FDA, but growing antiregulatory sentiment has begun to threaten this assumption, with the most persuasive arguments being made concerning patients with terminal illnesses who appear to have much to gain and little to lose by accessing unapproved drugs. However, this debate will need to take into account the simple concept that led to the regulatory authority of the FDA in the first place: that it may well not be in the interest of patients, however sick they may be, to have easier access to products that are ineffective and may actually worsen their clinical status.

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