

THE IMPLICATIONS OF EXPANDING ACCESS TO UNAPPROVED DRUGS

FOR EDUCATIONAL USE ONLY
35 J.L. Med. & Ethics 316

Journal of Law, Medicine and Ethics
Summer, 2007

Meghan K. Talbott [FN2]

Copyright © 2007 by American Society of Law, Medicine & Ethics,
Inc.; Meghan K. Talbott

Federal regulations limit access to investigational drugs to approved clinical trials, but they also provide “expanded access” for patients with serious or life-threatening diseases. [FN1] Patients are permitted pre-approval access to drugs from manufacturers, but compliance with applicable regulations for investigational new drugs is still required. [FN2] On December 11, 2006, the Food and Drug Administration (FDA) published proposed regulations aimed at expanding access to unapproved drugs. [FN3] The proposed regulations would expand access to experimental drugs by allowing qualifying patients to receive unapproved drugs earlier in the clinical trial process in certain circumstances. [FN4] This proposal comes after years of patient advocacy, including multiple lawsuits, seeking broader access to new drugs. [FN5]

In a recent decision, *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, [FN6] the D.C. Circuit held that terminally ill patients have a constitutional right of access to unapproved drugs that have successfully completed Phase I testing. The case is now pending rehearing by the full court, [FN7] but even if the panel decision of the D.C. Circuit is reversed, the Abigail Alliance organization has succeeded in spurring a change in FDA policy and has also opened a new age of patients' access rights. Regardless of whether the debate ends with a final FDA rule or a judicial determination of a constitutional right to unapproved drugs, access will be expanded. This article addresses some of the implications of expanded availability of unapproved drugs and

therapies, which focus on increased physician and sponsor liability, as well as changes to informed consent.

Existing Regulations

The FDA traditionally restricted access to investigational drugs because of the potential hazards involved [FN8] and because easy access would make it difficult to enroll adequate numbers of patients in clinical trials, thereby hindering drug development. [FN9] Nevertheless, the FDA has permitted treatment use for investigational drugs for many years, even before its formal recognition in the investigational new drug (IND) regulations. [FN10] In the late 1980s, IND regulations were revised to allow for use of investigational drugs outside of clinical trials by patients with serious diseases. [FN11] Today, a drug that is not approved for marketing may be used as treatment by patients with serious or immediately life-threatening diseases for whom no comparable or satisfactory alternative drug or other therapy is available. [FN12] Under current regulations, there are several options for obtaining a drug outside of a clinical trial. [FN13] The best known, or the treatment use of IND, requires that the drug sponsor be actively pursuing marketing approval of the investigational drug with due diligence within a clinical trial. [FN14] Availability for treatment depends in part on the phase of the trial the drug has reached and the medical condition with which the patient is afflicted. [FN15] In appropriate circumstances, drugs are made available during Phase 2 for patients with “serious diseases,” but ordinarily, drugs are only available for treatment use during Phase 3 or after all clinical trials have been completed. [FN16] A drug to treat an “immediately life-threatening disease” may be made available for treatment use earlier than Phase 3, but rarely earlier than Phase 2. [FN17] In order to receive approval from the Commissioner to use a drug intended to treat an immediately life-threatening disease, it must be determined from scientific evidence as a whole that there is a reasonable basis for concluding that the drug may be effective for its intended use in its intended patient population, or that the drug would not expose the patients to an unreasonable and significant additional risk of illness or injury. [FN18] For a drug intended to treat a serious disease, there must be sufficient evidence of safety and efficacy. [FN19]

Expanding Access through the Courts

Although current FDA regulations allow some access to unapproved drugs, patients have expressed dissatisfaction with their limitations. [FN20] Patient advocates want to increase the number of seriously ill patients with access to unapproved drugs and hasten their availability earlier in the lengthy FDA approval process of drugs that exhibit potential benefit. [FN21] In 2003, the Abigail Alliance for Better Access to Developmental Drugs filed a citizens' petition with the FDA that challenged the FDA's policy restricting the sale of unapproved drugs that have successfully completed Phase I trials to terminally ill patients. [FN22] When it did not receive a response, the organization, along with the Washington Legal Foundation, filed a lawsuit against the FDA Commissioner and the Secretary of Health and Human Services. [FN23] In *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, the plaintiffs sought to enjoin the FDA from preventing access to Phase 1 drugs for terminally ill patients not eligible for clinical trials. [FN24] The district court dismissed the complaint for failure to state a claim, finding that no court had previously recognized a patient's right to receive medical care under the Due Process clause of the Fifth Amendment. [FN25] The organization appealed, and the D.C. Circuit held that the Due Process clause protected the right of terminally ill patients to make decisions to prolong life, specifically through the use of investigational drugs not yet approved for marketing by the FDA. [FN26] Defining the right narrowly, the court neither recognized a broad right to access all investigational drugs nor a right to receive treatment from the government or at the government's expense. [FN27] The court based its decision on a long-standing tradition of protecting one's right to control his or her own body compared to the relatively new powers of the FDA. [FN28] The court held that the liberty interest in self-determination included the right to access life-sustaining medication. [FN29] This panel decision was subsequently vacated by the D.C. Circuit and is pending en banc review. [FN30]

Proposed Regulations

The FDA's proposed rules attempt to reconcile the interests of the FDA in protecting public health and safety with those of patient advocates who seek greater access to promising drugs for treatment. [FN31] Under the proposed regulations, access to experimental drugs is based on a three-tiered approach: single

patients, small groups of patients, and larger groups of patients under a treatment IND. [FN32] Generally, to obtain authorization for these expanded access treatment uses, the FDA must be assured that (1) the patient's serious or immediately life-threatening disease or condition has no satisfactory approved therapy; (2) the potential benefit for the patient justifies the potential risks; and (3) the therapy will not interfere with the drug's development. [FN33] The regulations also attempt to make experimental drugs more widely available, which includes allowing the use of post-Phase 1 drugs in appropriate situations, by establishing criteria that link the level of evidence needed to support the use of an experimental drug to the seriousness of the disease and the number of patients to be treated with the drugs. [FN34] More "clinical experience" is required as the population of the study group increases. [FN35]

Implications of Expanding Access

Physician Liability

Under the Abigail decision, physicians are given the authority to decide whether unapproved medications are appropriate for patients, [FN36] and physicians play an important role in the FDA's expanded access provisions. [FN37] In considering whether to prescribe an unapproved drug, the physician must determine whether the probable risk to the patient from the investigational drug is greater than the probable risk from the disease or condition. [FN38] Under the proposed rules, a physician who administers or dispenses an investigational drug for expanded access use is considered an investigator and, in some cases, the investigator and the sponsor. [FN39] Investigators have several responsibilities, such as the following: (1) reporting adverse drug events to the sponsor; (2) ensuring that the informed consent requirements are met; (3) ensuring that the Institutional Review Board (IRB) review of the expanded use is obtained in a manner consistent with the regulations; (4) maintaining accurate case histories and drug disposition records; and (5) retaining records. [FN40]

Although physicians have substantial responsibilities, they do not have special protections against lawsuits for their participation in clinical trials or expanded access. [FN41] IRBs provide oversight and guidance in order to protect the safety of patients, which may

reduce the risk of liability. [FN42] The informed consent document can also provide some protection, but these documents do not immunize physicians from all liability. [FN43] Access outside of clinical trials is restricted by the FDA to certain patients based on their severity of illness precisely because of an increased risk of adverse events with unapproved treatments. [FN44] Earlier access increases the risk of adverse events for patients, [FN45] which could lead to increased risks of lawsuits for physicians involved. Not only will physicians be subject to theories of liability common in lawsuits stemming from clinical trials, such as common law fraud, intentional misrepresentation, battery, lack of informed consent, and violation of the FDA “Common Rule,” [FN46] but other potential theories of liability could be based on the additional duties of a physician in expanded access programs. Physicians could face liability for such omissions as the failure to inform the patient about the availability of an IND, failure to monitor dosing, failure to identify adverse events, and failure to adjust other medications appropriately.

Physicians who participate in expanded access protocols are often already at a disadvantage. Normally in a clinical trial, the clinical investigators are skilled researchers relied upon by the sponsor to provide a high level of medical care. [FN47] Investigators usually have access to sophisticated technology, not available to most physicians, to monitor patients and to assist in recognition of the onset of adverse reactions. [FN48] Physicians who participate in expanded access protocols may not even have research experience. [FN49] Also, these physicians may oversee only a few patients taking a particular drug, and therefore, they may have more difficulty identifying the side effects of an investigational drug than an investigator who has a large number of patients on the same drug, as is more likely in a clinical trial. [FN50] Although physicians will be responsible for informing patients about unapproved options, [FN51] the fear of liability may make them less willing to administer therapies under expanded access.

Sponsor Liability and Future Regulation

Pharmaceutical manufacturers may also have increased liability due to expanded access. More patients will be seeking and using investigational drugs. [FN52] Pharmaceutical companies may be liable for adverse events under such theories as strict products liability, failure to warn, negligence, and fraud. [FN53] At the same

time, they may also be confronted with litigation for denying access. Allowing access to investigational drugs is potentially costly to pharmaceutical manufacturers, especially when many patients are involved, and a company might not have a sufficient quantity of the drug, particularly early in development. [FN54]

Informed Consent

Expanded access is a distinct process from the clinical trial, yet the FDA's proposed rules require the same basic informed consent information for the new expanded access as for the typical clinical trial. [FN55] Unlike clinical trials, treatment use does not ordinarily benefit the pharmaceutical company, as it is not intended to support the goal of market approval. [FN56] Expanded access involves, and is primarily intended to benefit, very sick patients by permitting them to receive investigational drugs to treat their diseases and conditions when they have no other viable alternative. [FN57] For that reason, a new model of informed consent should include some assumption of the risks involved. If patients truly desire expanded access and increased availability of unapproved drugs, they must be willing to accept the risk of using drugs with little clinical experience.

The protection of vulnerable patients should continue to be a priority for the FDA. The duty of physicians and manufacturers to meet a reasonable standard of care should likewise remain unchanged. Nevertheless, if physicians and manufacturers are subject to numerous lawsuits for adverse events caused by unapproved drugs, it will have a chilling effect on drug discovery and compassionate use.

Expanding informed consent is one way to balance these interests. Informed consent for expanded access should involve a thorough discussion of the level of risk a patient is accepting and should require an acknowledgement of this risk by the patient before he or she is allowed to receive the drug. In many instances, it may be advisable to have a third party, such as an unaffiliated physician to help explain the risk involved. In addition, the manufacturer and physician should be required to reveal to the patient what is known about the drug from both pre-clinical and clinical studies up to that point, and a document acknowledging this information should be signed by the patient. Requiring that this information be shared in the informed consent will better educate patients and, while not depriving patients of their rights, could provide increased

protection in the event of a lawsuit for those physicians willing to dispense unapproved drugs. Also, such an acknowledgement could lessen manufacturers' fears of liability from use of unapproved drugs. Without efforts to reduce liability and concerns about liability, a right to access unapproved drugs may become illusory.

Conclusion

The United States is on the verge of a new era of expanded access to unapproved drugs, as a result of either FDA or court action. Expanding available treatments to patients with serious or life-threatening diseases will present challenges to patients, physicians, manufacturers, and the drug development process. Expanded access could mean increased liability for both manufacturers and physicians. It is also likely that patients may still face difficulty accessing unapproved drugs if the fear of liability drives physicians and manufacturers into protective mode. Both the courts and regulators need to be mindful of the implications of expanding access as they decide how access to unapproved drugs is expanded in advancing the dual goals of drug development and timely availability of potential treatments to patients.

Acknowledgement

I would like to thank Mark Rothstein for his helpful comments and suggestions.

[FNa1]

. About this Column

Mark A. Rothstein serves as the section editor for "Currents in Contemporary Ethics." Professor Rothstein is the Herbert F. Boehl Chair of Law and Medicine and the Director of the Institute for Bioethics, Health Policy and Law at the University of Louisville School of Medicine in Kentucky. (mark.rothstein @louisville.edu)

[FNa2]. Meghan K. Talbott, J.D., is a Research Associate at the Institute for Bioethics, Health Policy and Law at the University of Louisville School of Medicine.

[FN1]. 21 C.F.R. § 312.34 (2006).

[FN2]. Id. § 312.34(c).

[FN3]. FDA News Release, “FDA Proposes Rules Overhaul to Expand Availability of Experimental Drugs,” available at <<http://www.fda.gov/bbs/topics/NEWS/2006/NEW01520.html?>> (last visited March 6, 2007).

[FN4]. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75147–75168 (December 14, 2006) (to be codified at 21 C.F.R. pt. 312).

[FN5]. Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 445 F.3d 470, 473 (D.C. Circuit 2006) (vacated for rehearing en banc) [hereinafter cited as Abigail Alliance]; S. Okie, “Access before Approval -- A Right to Take Experimental Drugs,” *New England Journal of Medicine* 355, no. 5 (2006): 437–440; Marti Nelson Cancer Foundation/CancerActionNow.org, “Expanded Access: Our Efforts,” available at <<http://www.canceractionnow.org/advocacy/expandedaccess.php>> (last visited March 5, 2007).

[FN6]. Abigail Alliance, 445 F.3d 470.

[FN7]. Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, No. 04–5350, 2006 U.S. App. LEXIS 28974 (D.C. Circuit November 21, 2006).

[FN8]. See Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. at 75,150.

[FN9]. Id.

[FN10]. Id., at 75,148.

[FN11]. Id.

[FN12]. 21 C.F.R. § 312.34(a).

[FN13]. T. Class, “Expanded Access to Unapproved Medical Products: Compassionate Use,” *Regulatory Affairs Focus* magazine, May 2006, available at <

http://www.raps.org/s_raps/rafocus_article.asp?TRACKID=&CID=61&DID=2720> (last visited March 8, 2007).

[FN14]. 21 C.F.R. § 312.34(b)(1)(iv).

[FN15]. *Id.* § 312.34(b)(2)–(3).

[FN16]. *Id.* § 312.34(a).

[FN17]. *Id.*

[FN18]. *Id.* § 312.34(b)(3).

[FN19]. *Id.* § 312.34(b)(2).

[FN20]. See Okie, *supra* note 5.

[FN21]. *Id.*

[FN22]. Abigail Alliance, 445 F.3d at 473.

[FN23]. *Id.*

[FN24]. *Id.*, at 473–474.

[FN25]. *Id.*, at 475.

[FN26]. *Id.*, at 475–487.

[FN27]. *Id.*, at 484, 486.

[FN28]. *Id.*, at 480–483.

[FN29]. *Id.*, at 484–485.

[FN30]. Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, No. 04–5350, 2006 U.S. App. LEXIS 28974 (D.C. Circuit November 21, 2006).

[FN31]. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,150 (December 14, 2006) (to be codified at 21 C.F.R. pt. 312).

[FN32]. *Id.*

[FN33]. *Id.*, at 75,166.

[FN34]. *Id.*, at 75,151.

[FN35]. *Id.*, at 75,151.

[FN36]. *Abigail Alliance*, 445 F.3d at 473.

[FN37]. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. at 75,166–75,167.

[FN38]. *Id.*, at 75,167.

[FN39]. *Id.*, at 75,166.

[FN40]. *Id.*

[FN41]. R. Milligan and B. Bailey, “Physician Participation in Clinical Trials: The Rewards Are Obvious, but Risks Are Real,” April 1, 2005, available at <http://www.hg.org/articles/article_1080.html> (last visited March 6, 2007).

[FN42]. 21 C.F.R §§ 56.109, 56.111.

[FN43]. *Abney v. Amgen, Inc.*, 443 F.3d 540 (6th Circuit 2006); see Milligan, *supra* note 40.

[FN44]. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. at 75,150.

[FN45]. *Id.*

[FN46]. See Milligan and Bailey, *supra* note 41.

[FN47]. E. Nichols and the Institute of Medicine, *Expanding Access to Investigational Therapies for HIV Infection and AIDS*, March 12–13, 1990 Conference Summary (Washington, D.C.: National Academy Press, 1991): at 50.

[FN48]. Id.

[FN49]. Id.

[FN50]. Id.

[FN51]. Id.

[FN52]. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,158 (Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).

[FN53]. M. Mello, D. Studdert, and T. Brennan, "The Rise of Litigation in Human Subjects Research," *Annals of Internal Medicine* 139 (2003): 40–45, at 41.

[FN54]. See Class, *supra* note 13.

[FN55]. See Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. at 75,166.

[FN56]. Charging for Investigational Drugs, 71 Fed. Reg. 75,168, 75,170 (Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).

[FN57]. Id., at 75,170.

35 JLMEDETH 316

END OF DOCUMENT