

Determining Patient Access to Investigational Drugs in the US

Philip Katz examines the reasons for and against treating terminally ill patients with investigational drugs, focusing on efforts to change the FDA's regulations.

Terminally ill patients do not have a constitutional right to obtain early-stage investigational drugs in the US. In 2003, the Washington Legal Foundation (WLF) and the Abigail Alliance for Better Access to Developmental Drugs challenged the refusal of the Food and Drug Administration (FDA) to allow such patients access to all available treatment¹. The suit failed but was reversed by an appeals court panel in May 2006². However, on 7 August 2007, the US Court of Appeals for the District of Columbia Circuit issued an opinion in *Abigail Alliance for Better Access to Developmental Drugs v von Eschenbach*, upholding the original 2003 decision³.

Although important, this opinion does not bring the public policy debate to a close. The US Court of Appeal's decision, a review of an earlier decision by a three-judge panel (the usual contingent for appellate cases), may be itself reviewed by the Supreme Court⁴. On 28 September, the WLF filed a petition urging the Supreme Court to reinstate the ruling of the appeals court panel⁵. The matter is further complicated by the fact that the FDA has pending two proposed rules that would amend current regulations to expand the circumstances under which a patient who is not part of a clinical trial can nonetheless be given an investigational drug^{6,7}. Even when these judicial and administrative undertakings are made final, their impact will be limited because they will be applied in the context of competing legal, economic and ethical principles. These "real world" factors conspire to restrict the supply of early-stage investigational drugs to patients and are likely to determine the outcome.

The Abigail Alliance case has served as a catalyst for greater discussion about the difficult issues involved in determining which patients, and under what circumstances, should be allowed to take drugs with unproven safety and efficacy. Arguably, the case has also spurred the FDA on to propose changes to the regulations governing access to drugs under investigation. What has not changed, and will not, is the fact that the pharmaceutical companies developing these new drugs are in the position of control. Even if the court had ruled that patients did possess a constitutional right that precluded the government denying access to early-stage investigational drugs, and even if the FDA revises its regulations to permit greater access to experimental drugs, a company will not be *required* to grant such access. For that reason, the drug company will continue to have ultimate authority in decision making. In addition to the impossible ethical questions a company may face, it must consider the risks of legal liability, the impact on data gathering and the possible financial implications.

Current FDA regulations

Generally in the US, a "new drug" (most often, a drug that has not been approved) may not be distributed in interstate commerce⁸. Exceptions are provided for drugs that are being studied in clinical trials that are the subject of investigational new drug exemptions (INDs)⁹. Clinical trials are typically pursued after development of safety and other data in *in vitro* and animal studies, and usually take place in three phases of increasing complexity and size. (Phase I trials normally involve a relatively small number of healthy volunteers, Phase II trials are usually controlled studies in patients with the disease or condition to be treated and Phase III trials, which are even larger, are well-controlled trials intended to provide effectiveness and safety data sufficient to support approval and provide a basis for labelling¹⁰⁻¹².)

There are circumstances outside the standard clinical trial setting in which it may be appropriate for an unapproved drug to be distributed to humans. If a drug is the subject of clinical trials and is being studied to treat a serious or immediately life-threatening disease or condition, the FDA may approve a "treatment IND" or "treatment protocol", under which the sponsor may, separate from the standard clinical investigation (which must continue), distribute the medication to patients for whom no comparable or satisfactory treatment is available. A request for a treatment protocol or treatment IND is preferably submitted by the sponsor, but may be submitted by an investigator¹³. If the drug is intended to treat a serious disease, treatment use generally will be approved if the drug is in Phase III trials, and during Phase II trials in "appropriate circumstances"¹⁴. In any event, the FDA may refuse a request for a treatment IND or treatment protocol if there is "insufficient

The Supreme Court may review a decision denying terminally ill patients a right to early-stage drugs

The FDA is proposing changes to the regulations concerning access to investigational drugs but pharmaceutical companies have the upper hand

Currently, the FDA may approve a treatment IND or protocol, allowing unapproved drugs to be given to humans in "appropriate circumstances"

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evidence of safety and effectiveness to support such use¹⁵. If the drug is being investigated to treat an immediately life-threatening disease, a drug may be made available before Phase III, "but ordinarily not earlier than Phase II"¹⁶. The FDA may deny a request for treatment use if the available scientific evidence does not provide a reasonable basis for concluding that the drug may be effective and would not expose patients to an unreasonable and significant additional risk¹⁷.

In emergency situations, the FDA may authorise distribution of a drug for a specified use even before an IND or treatment IND is submitted¹⁸. Such authorisation is almost always conditional upon the sponsor's submitting an IND or treatment IND as soon as is practicable, except in "extraordinary circumstances"¹⁹.

Treatment or emergency use of an investigational drug is subject to the regulations governing investigational drugs generally, including the requirements for informed consent and approval and oversight by an institutional review board²⁰. Additionally, a company may not charge for an investigational drug without FDA approval²¹. A sponsor seeking to charge for a drug that is the subject of a treatment IND must submit an IND amendment, showing that: there is adequate enrolment in the ongoing standard IND; the charging does not constitute commercial marketing of the drug; the drug is not being commercially promoted or advertised; and the sponsor is actively pursuing approval²². If charging is approved, the price cannot exceed the amount "necessary to recover costs of manufacture, research, development, and handling" of the drug²³.

A company may not charge for an investigational drug without FDA approval and then the price cannot exceed costs

The Abigail Alliance case

The plaintiffs in *Abigail Alliance* sought an exception to the restrictions on the distribution of investigational drugs described above. Their aim was to enjoin the FDA from prohibiting the commercial sale of potentially life-saving investigational drugs to certain competent, terminally ill adult patients²⁴. Recognising a narrow exception to the general regulatory scheme, a three-judge panel of the District of Columbia Circuit Court of Appeals held that "where there are no alternative government-approved treatment options, a terminally ill, mentally competent adult patient's informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials warrants protection under the Due Process Clause"²⁵. By holding that there was a constitutional right to access, and that it extended to drugs for which Phase II trials had not yet been started, this decision would have significantly expanded patient access to early-stage investigational drugs, albeit only where the patient is terminally ill and there is no approved treatment. However, the decision was overturned on 7 August 2007, in an en banc opinion of the full federal Court of Appeals for the District of Columbia Circuit²⁶.

The decision to allow terminally ill patients a constitutional right to early-stage drugs was overturned on 7 August

Proposed changes to FDA regulations

On 14 December 2006, after the issuance of the three-judge panel's opinion but before the decision of the full court to overturn it, the FDA published two proposed rules intended to broaden the avenues of expanded access to investigational drugs.

The first proposed rule

The first proposal involves consolidating and revising the regulations governing treatment INDs and their emergency use²⁷. The major proposed change is the creation of three types of situations in which access outside of a standard clinical trial could be appropriate: for individual patients; for intermediate-size patient populations (typically between 10 and 100 patients); and for a treatment IND or treatment protocol (generally over 100 patients)²⁸. Additionally, the proposed rule would permit expanded access earlier in the clinical trial process by requiring less information regarding safety or effectiveness in certain circumstances than is called for by the current regulations.

Consistent with the requirements of the statute, the general criteria for expanded access would remain; before any expanded access would be approved, the FDA would have to determine that:

- the patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
- the potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
- providing the investigational drug for the requested use will not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use²⁹.

An FDA proposed rule would create three situations in which earlier access to a drug could be given

In addition to the general criteria, further conditions would relate specifically to use by individual patients, use with intermediate-size patient populations and treatment INDs/protocols.

Individual patients

Should an individual patient want an investigational drug, the patient's doctor would have to conclude that the risks associated with the drug do not exceed the risks from the disease or condition to be treated, and the FDA would have to determine that the patient cannot obtain the drug under another IND or protocol. Additionally, the FDA would limit individual patient access to a single course of therapy for a specified duration³⁰. In applying the general requirement that the potential benefits justify the risks and the risks are not unreasonable, the FDA anticipates that "little if any clinical evidence to suggest a potential benefit or perhaps only animal data to support safety of the use" would be sufficient with regard to an immediately life-threatening disease or condition³¹.

Intermediate-size patient populations

Before small groups of patients could be granted access to investigational drugs beyond a standard clinical trial, the FDA would first have to determine that the evidence of the drug's safety for the proposed use is sufficient to justify a trial of the intended size, and that there is at least preliminary clinical evidence of effectiveness or a plausible pharmacologic effect to make the proposed use a "reasonable therapeutic option"³².

Treatment IND/protocol

With regard to treatment INDs/protocols, the FDA would have to determine that:

- the drug is being investigated under an IND designed to support an application for the proposed use (or that all clinical trials have been completed);
- the sponsor is actively pursuing approval with due diligence;
- if the treatment use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness (usually data from Phase III trials, but compelling data from Phase II may be adequate) to support the use; and
- if the treatment is for a life-threatening disease or condition, there is evidence (usually Phase II or Phase III data, but more preliminary clinical data may suffice in some circumstances) providing a reasonable basis on which to conclude that the drug may be effective and would not pose an "unreasonable and significant risk" to patients³³.

Additional conditions would relate to individual patients, intermediate-sized patient populations and treatment INDs/protocols

The FDA would have to determine that the IND is covering a drug with sufficient clinical evidence of safety and effectiveness

The second proposed rule

The second proposed rule is intended to broaden the circumstances under which a company is permitted to charge for an investigational drug, by establishing in regulation the criteria that must be met and by clarifying the costs that may be recovered³⁴. The FDA's goal of making charging more available is especially clear with regard to the expanded use of investigational drugs. As a general rule, the FDA believes the cost of investigational drugs should be borne by the sponsor, which derives benefit from the data generated by clinical trials; allowing sponsors to charge for investigational drugs is not only unnecessary, the agency argues, it can also create a disincentive for the sponsor to actively pursue approval. However, the FDA is less concerned about treatment use of investigational drugs; such use "is not a necessary part of the drug development process and does not benefit the pharmaceutical companies by leading to systematic accumulation of data intended to support marketing authorization"³⁵.

The proposed regulation for treatment use in individuals or intermediate-size patient populations accordingly would only require that the sponsors seeking to charge for the investigational drug "provide reasonable assurance that charging won't interfere with developing the drug for marketing approval"³⁶. Reflecting the agency's concern that a larger treatment study could divert patients from standard clinical trials, the regulations would permit charging for treatment INDs or treatment protocols only if the sponsor: showed sufficient enrolment in other clinical trials to assure the FDA that the trials would be completed; demonstrated adequate progress in developing the product for approval; and submitted information regarding the drug development milestones to be met over the coming year³⁷.

As an additional incentive, the proposed rule would allow sponsors of treatment INDs, treatment protocols and treatment programmes for intermediate-size patient populations to charge not only for the direct costs of drugs (which is available for sponsors of standard clinical trials that qualify for charging), but also for the administrative costs associated with the expanded access, such as monitoring the programme and complying with IND reporting requirements³⁸.

A second proposed rule would broaden the circumstances under which a company may charge for an investigational drug

The sponsor would have to prove that this access would not divert patients from standard clinical trials

Practical barriers to patient access

Should the *Abigail Alliance* plaintiffs ultimately prevail, the FDA may be forced to revise significantly its regulations governing patient access to investigational drugs. In fact, issuance of the pending proposals may well have been influenced by the first appellate decision. Even if the most recent court decision is upheld and there is no constitutional right, the FDA is clearly interested in expanding the opportunities for patient access to treatment with investigational drugs.

An FDA adoption of regulations providing expanded access or a court decision establishing a constitutional right to access would be significant, but it would only create the opportunity for greater patient access to early-stage investigational drugs. It would not require a drug company to provide investigational drugs to patients. The FDA, as it recognised in issuing the proposed expanded access regulations, "cannot compel a drug manufacturer to provide access to investigational drugs for treatment use"³⁹. It is decisions made by drug companies, institutional review boards (IRBs) and doctors that ultimately will determine whether a given patient (or population of patients) has the opportunity to be treated with an investigational drug. Although the decision not to provide investigational drugs can be heartrending, everyone involved in making the decision has incentives not to provide investigational drugs to patients outside the realm of clinical trials, which are intended to yield data for submission to the FDA.

Drug companies, IRBs and doctors must each agree that treatment use is appropriate in any given circumstance. It is unavoidable that this decision will include a consideration of the potential legal liability, especially the risk of liability for the patient's injury or death. Even under the proposed regulations, treatment use of an investigational drug would require written evidence of the patient's informed consent, consistent with current regulations, which prohibit "any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agent from liability for negligence"⁴⁰. Although a patient, in order to obtain a drug he or she hopes will save his or her life, may be willing to waive his or her right to sue any of the involved parties in the case of an injury or death caused by negligence, such a waiver is simply not permitted by the regulations and protection from liability cannot be given. Given that expanded access involves administering drugs with unproven safety and effectiveness to patients who are seriously or terminally ill, the risk of injury or death is significant, as is the concomitant risk of a lawsuit. Such liability exposure may dissuade a pharmaceutical manufacturer, IRB or physician from agreeing to provide an early-stage investigational drug for treatment use.

Furthermore, the management of a company developing a drug must consider the potential impact on the development and approval process of having the drug administered to seriously ill patients outside the clinical trial process. Treatment use would be subject to IND regulations and so adverse events resulting from treatment use must be reported to the FDA. This means they could have an impact on the conduct of ongoing clinical trials, which could be suspended while investigation of the adverse event is conducted, or even permanently halted. Although treatment use is not primarily intended to gather data in support of an application for marketing approval, information is gathered and much of that information will need to be reported to the FDA and may well influence the agency's evaluation of the drug's safety and effectiveness.

The risks associated with negative results from treatment use are not limited to the FDA approval process. Early undesirable outcomes may discourage doctors from participating in the standard clinical trials that are necessary to support a marketing application, or may influence IRB decisions about whether such trials appropriately balance potential risks and benefits.

Moreover, particularly for smaller companies, if early-stage treatment use produces negative results, it can influence stock prices or the availability of funding. Earlier this year, the *Wall Street Journal* reported on the dilemma faced by Neotropix, a small biotech company developing a virus that, in early test-tube and mouse experiments, appeared to attack certain cancer cells⁴¹. The drug had been tested in only six humans when the company was approached by a father seeking treatment for his four-year-old daughter's neuroblastoma, which had resisted all known treatments. To treat the girl with a dose that mirrored that seen to be effective in mice would have required a dose that was 100,000 times greater than what had been used in humans to date. The company board met several times to consider the request, consulted a medical ethicist, and ultimately decided not to provide the drug to the girl. Among the factors that swayed the board members was their fiduciary duty to act in the company's best interests, and the risk that this one use might undermine the development process for a promising therapy was seen as too great.

Conclusion

Actions by the courts or the FDA certainly may make it easier for patients to obtain access to early-stage investigational drugs. But they cannot mandate that a doctor agree to administer such a drug

Whatever the outcome of the appeal, drug companies, doctors and IRBs will determine whether a patient receives the drug

Manufacturers, doctors and IRBs may be deterred by the increased risk of litigation should a patient die from taking an unproven drug

There is a risk that early-stage treatment may influence or even halt standard clinical trials, undermining the development of a promising therapy

to a particular patient, force an IRB to conclude that the potential benefits of such use justify the potential risks, or require a company to accept the risk of being sued or of having to report negative results to the FDA and the financial community. For that reason, the impact of the proposed regulatory changes, or the sought judicial ruling, will necessarily be limited.

The impact of the proposed regulatory changes, or the appeal, will be limited

References

1. Legal complaint, Abigail Alliance/Washington Legal Foundation v FDA/HHS, 28 July 2003, www.wlf.org/upload/Abigail%20Alliance%20complaint.pdf
2. WLF press release, 3 May 2006, www.wlf.org/upload/050306RS.pdf
3. US Court of Appeals for the District of Columbia Circuit opinion, No 04-5350, 7 August 2007, www.wlf.org/upload/-8-06-07AbigailEnBancOpinion.pdf
4. Food and Drug Law Institute audio conference, Abigail Alliance Will Appeal DC Circuit Court Decision, 22 August 2007
5. WLF website, accessed 11 October 2007, www.wlf.org/Litigating/casedetail.asp?detail=266
6. *Federal Register*, 14 December 2006, 71(240), 75147
7. *Federal Register*, 14 December 2006, 71(240), 75168
8. 21 USC § 355(a)
9. 21 USC § 355(i)
10. 21 CFR § 312.21(a)(1)
11. 21 CFR § 312.21(b)
12. 21 CFR § 312.21(c)
13. 21 USC § 360bbb(c); 21 CFR § 312.34(a); 21 CFR § 312.35
14. 21 CFR § 312.34(a)
15. 21 USC § 360bbb(c)(6); 21 CFR § 312.34(b)(2)
16. 21 CFR § 312.34(a)
17. 21 USC § 360bbb(c)(7); 21 CFR § 312.34(b)(3)
18. 21 CFR § 312.36
19. Ibid
20. 21 USC § 360bbb; 21 CFR § 312.34(c)
21. 21 CFR § 312.7
22. 21 CFR § 312.7(d)(2)
23. 21 CFR § 312.7(d)(3)
24. Abigail Alliance, 445 F.3d at 472
25. Id at 486
26. See Reference 3
27. See Reference 6
28. Id at 75166-68 (proposed 21 CFR Subpart I)
29. Id at 75166 (proposed 21 CFR § 312.305(a))
30. Id at 75167 (proposed 21 CFR § 312.310(a), (c))
31. Id at 75153
32. Id at 75167 (proposed 21 CFR § 312.315(b))
33. Id at 75168 (proposed 21 CFR § 312.320(a))
34. See Reference 7
35. Id at 75170
36. Id at 75181 (proposed 21 CFR § 312.8(c)(1))
37. Id (proposed 21 CFR § 312.8(c)(2))
38. Id (proposed 21 CFR § 312.8(d)(2))
39. *Federal Register*, 14 December 2006, 71(240), 75150
40. 21 CFR § 50.20; 45 CFR § 46.116
41. *Wall Street Journal*, 1 May 2007, A1

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