nature medicine

Dying to live

A 2 May court ruling in the US may place experimental drugs in the hands of terminally ill individuals. Attempting to save the lives of these individuals is certainly an admirable goal. But providing investigational compounds to people who are dying before the medicines have been adequately tested may endanger the entire drug approval process. Even worse, it may hasten the death of the people these same medicines are intended to save.

The Abigail Alliance, launched by the father of a woman who died of cancer when drugs that may have extended her life were in clinical development, brought the case against the US Food and Drug Administration (FDA). The Alliance challenged the agency's policy of providing access to a new drug only after a series of clinical trails have proven its safety and efficacy. A US Court of Appeals sided with the Alliance, arguing that dying patients have the constitutional right to obtain investigational medicines that may extend their lives (see page 596). The ruling gives pharmaceutical companies the option to provide experimental drugs that pass phase 1 trials to dying patients, but does not compel the companies to do so.

Although phase 1 trials are intended to evaluate drug safety, much information about drug toxicity comes from subsequent clinical trial phases. This is because phase 1 trials contain fewer participants and test fewer doses of the investigational drug. Also, most phase 1 trial participants are healthy volunteers. Sick participants who have the disease that the drug is intended to treat generally only begin to receive the medicine in later trials. But those who are already suffering from a disease may show much more severe toxic responses to a drug than would healthy individuals. This could be one reason why 70% of drugs clear initial safety trials, but only 8% of drugs that enter clinical trials are eventually approved.

Because so little is known about how sick individuals will respond to medicines after phase 1 trials, people who are dying must realize that they are exposing themselves to substantial risks when they take untested drugs. The compound may itself be lethal, or may exacerbate illness and ruin what little time the individual has left. It may be wrong to deny people medicines that will save their lives, but neither is it right to allow access to a drug that may be toxic or fatal, with the small hope that it may do some good. Dying individuals should be allowed to try promising experimental therapies when all other treatment options have been exhausted. But medicines should be tested in people who have the best chance of responding before giving the drugs to people who are dying.

Consider what could happen if a terminally ill individual received an experimental drug that was ineffective or even toxic. Would that compound then be ruled out as a potential therapy for people at an earlier stage of the same disease, potentially halting the further testing of that drug? If so, providing experimental medicines to dying individuals could have drastic consequences for the entire drug development process.

In part because of this issue, it is unclear whether pharmaceutical companies would ever want to take on the substantial risks associated with providing investigational medicines to the dying. Not only may drug failure in dying patients halt further clinical trials, but it would also expose the pharmaceutical industry to enormous liability. Big Pharma spends considerable time and money fighting lawsuits on FDA-approved drugs, and can ill afford to take on additional liabilities by administering unproven drugs to terminally ill individuals. If drug makers do not agree to provide these medicines to people who are dying, then the court ruling will have no practical effect on how these patients are treated.

At the heart of this issue is a push to hasten drug discovery and approval, so that those who need experimental medicines can get them as quickly as possible. The FDA is in fact already allowing preapproval access to investigational medicines for individuals with life-threatening illnesses who do not qualify for clinical trials. However, the earliest the FDA extends this access is during phase 2 trials, and only when there is some evidence of the drugs' safety and efficacy. This willingness of the FDA to provide experimental medicines to individuals not enrolled in clinical trials illustrates the FDA's flexibility when there is a clear and immediate need for a novel drug. For example, after September 11th, 2001, doctors treating burn victims took advantage of the FDA's "emergency investigational new drug" designation to speed patient access to sulfadiazine cream by Solvay Pharmaceuticals.

The FDA is already under fire for approving medicines quickly only to discover significant side effects later on, as was the case with Vioxx and Tysabri (*Nat. Med.* **10**, 1143; 2004; *Nat. Med.* **12**, 373; 2006). In this case, the FDA's insistence on some measure of patient safety and efficacy before providing investigational drugs to dying individuals could save lives.