A delicate balancing act

Timely access to novel therapies for life-threatening diseases is in the spotlight in the wake of a US court ruling that patients do not have a constitutional right to investigational drugs. How might the desire for early access to therapies and the need to demonstrate efficacy and safety be more effectively balanced?

On 7 August, the US Court of Appeals for the District of Columbia Circuit voted 8–2 that the US constitution does not provide terminally ill patients with a right of access to experimental drugs that have passed limited safety trials but have not been proven to be safe and effective (see page 691). This overturns a ruling last year by a three-member panel of the same court that had the opposite conclusion — which, had it been upheld, would have had major implications for drug development.

The lawsuit against the US FDA and US Department of Health and Human Services was brought by the Abigail Alliance for Better Access to Developmental Drugs, a patient-advocacy group, and the Washington Legal Foundation. The Abigail Alliance contend that patients with terminal illness should be able to opt for a new treatment that has met a lower evidentiary hurdle with respect to safety and efficacy, and argued that the US constitution provides terminally ill patients with a fundamental right to experimental drugs that have passed Phase I trials.

The assessment rejecting this argument draws on the history of US drug regulation, concluding that there is no fundamental right "deeply rooted in this Nation's history and tradition" of access to experimental drugs for the terminally ill[1]. Writing for the majority, Judge Thomas Griffith notes[1] that "although terminally ill patients desperately need curative treatments…deaths can certainly be hastened by the use of a potentially toxic drug with no proven therapeutic benefit." Indeed, given the historical failure rates for potential anticancer drugs (~90% for those that are successful in Phase I trials[2]), it seems very probable that most patients would not benefit from receiving such agents at such an early stage in their development.

Creating the type of access to investigational drugs sought by the Abigail Alliance also raises several issues that could have a detrimental effect on drug development. For instance, an obvious potential pitfall is that the incentive for patients to enrol in clinical trials could be dramatically reduced, which could slow the approval of those few drugs that do ultimately demonstrate a favourable benefit–risk profile.

Furthermore, making access a right could pose thorny challenges for the companies involved. First, the potential for liability claims against companies and physicians providing investigational drugs outside clinical trials could be a strong discouragement for doing so. Second, for investigational drugs, production capacity may be limited to providing enough drug for clinical trials, especially for smaller companies or for drugs with complex manufacturing procedures such as biologics. So, the willingness or ability of a company to provide an investigational drug outside clinical trials might also be an important factor in its availability. Indeed, the case of two inhibitors of the epidermal growth factor receptor (EGFR) — cetuximab and gefitinib — seems to support this possibility. During its development, few patients were able to access cetuximab, a monoclonal antibody, outside trials. By contrast, gefitinib, a small molecule that is relatively easy to manufacture, was made available to more than 20,000 patients outside trials in an expanded access programme under existing regulations.

So, how might the growing demand for earlier access to potential cancer drugs be reconciled with the need to demonstrate that a drug has an appropriate benefit–risk profile? The answer here could lie in part in accelerating the integration of advances in research on biomarkers of efficacy and toxicity and innovative trial designs into clinical trials and regulatory decision-making. Regrettably, however, current efforts to achieve such goals, such as the FDA's Critical Path Initiative, are severely underfunded.

If the potential of such efforts were to attract the attention of patient-advocacy groups too, perhaps this situation could improve. A key question highlighted by the Abigail Alliance case, as well as an upcoming lawsuit related to the delay in approval of the cancer vaccine Provenge (see page 691) — whether the recent emphasis on drug safety has tipped the balance too far in the direction of demanding certainty about the benefit–risk profile of cancer drugs before approval — also merits consideration. As Judge Griffith notes[1] in his summary: "Although in the Alliance's view the FDA has unjustly erred on the side of safety in balancing the risks and benefits of experimental drugs, this is not to say that the FDA's balance can never be changed."

1. United States Court of Appeals for the District of Columbia Circuit. Abigail Alliance *et al*. vs Andrew von Eschenbach *et al*., 7 August. *PACER web site* [online], < http://pacer.cadc.uscourts.gov/docs/common/opinions/200708/04-5350c.pdf > (2007).
2. Kola, I. & Landis, J. *Nature Rev. Drug Discov.* **3**, 711–715 (2004).