The drought continues

Last year, the number of novel drugs approved by the US FDA was again close to an all-time low. Collaborative efforts to enhance the application of emerging science in drug development and regulation deserve particular attention, and, most importantly, resources if the drought in drug approvals is to be brought to an end soon.

Each year for the past 5 years, *Nature Reviews Drug Discovery* has featured an article discussing drug approvals over the previous year, and 2008 is no different (see the news story on page 107). Regrettably, the 'scorecard' of novel drug approvals this year also tells a familiar story; indeed, the total of 17 new molecular entities (NMEs) and 2 biologic license applications approved by the US FDA makes 2007 the worst year for novel drugs assessed in these terms for a quarter of a century.

Unsurprisingly, several familiar questions have emerged this year in commentaries considering the factors underlying the continuing drought of novel drugs. Is over-cautious regulation to blame? Is there a shortfall in the number or quality of submissions being made to the regulators? And are the scientific challenges inherent in the novel therapeutic strategies now being pursued greater than those in the past?

In some cases, the answer might be all of the above. A potential example could be provided by one of 2007's high-profile investigational therapies not to be approved: the prostate cancer vaccine Provenge (Sipuleucel-T; Dendreon). Certainly, the science behind Provenge is novel: if it had been granted approval by the FDA, it would have been the first cancer vaccine of any kind to be introduced in the US.

However, perhaps owing in part to uncertainty over the most appropriate way to evaluate such a novel therapy, Provenge failed to meet its primary end point of increasing time to disease progression in the pivotal clinical trials. Nevertheless, although the trials had not been designed to show this, subsequent analyses indicated that Provenge extended median overall survival. On the basis of these results, an FDA advisory committee voted in favour of its safety and efficacy.

The subsequent — and unusual — decision by the FDA to overrule the advisory committee's decision and delay approval, asking for further data, has generated considerable controversy, in part because of alleged irregularities in the decision-making process. Even putting aside such potential irregularities though, the decision might be taken to indicate growing regulatory caution. This caution could be even stronger for highly novel therapies, such as cancer vaccines, that the regulators are unfamiliar with.

With the benefit of hindsight, it is possible to suggest how the outcome of future cases like that of Provenge could be more positive for companies, regulators and, most importantly, patients. First, investigating and applying the latest science and strategies to clinical trial design and drug regulation could help in finding more effective approaches to evaluating novel therapies. Second, fostering good communication between regulatory agencies and companies during development could help ensure that deficiencies are identified and resolved before trials are started. This would require more FDA staff for conducting meetings at critical points in the process[1].

At present, however, the pursuit of such goals in the US is being seriously hampered by a lack of resources. Not only is the FDA overall chronically under-funded — to such an extent that a recent expert report concluded that it is not positioned to meet current or emerging regulatory responsibilities[2] — but so are focused efforts to address its deficiencies. The FDA's Critical Path Initiative has a budget of just US$5 million for the next fiscal year and the Reagan–Udall Foundation, established at the end of last year specifically to help the FDA deal with increasingly complex science, spur innovation and improve safety, has had government funding blocked owing to concerns over conflicts of interest.

Although it is to be strongly hoped that such initiatives in the US can obtain the funding they need in the near future, there is also new hope on the horizon in Europe in the form of the Innovative Medicines Initiative[3]. This public–private project, which was formally adopted by the European Union in December 2007 with the aim of removing major bottlenecks in drug development, has a total budget of a much more impressive 2 billion euros, with 125 million euros in 2008 alone. Wherever such initiatives are based, their success could do much to ensure that a reflection on drug approvals in 5-years time is much more positive than this one.

1. *Independent evaluation of the FDA's first cycle review performance — retrospective analysis final report*. [online], < http://www.fda.gov/OHRMS/DOCKETS/98fr/oc05257-rpt0001.pdf > (2006).
2. *FDA Science and Mission at Risk*. [online], < http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf > (2007).
3. *Overview of IMI*. [online], < http://imi.europa.eu/docs/overview-presentation-of-imi_en.pdf > (2007).