Editorial: Yin, yang and the biopharmaceutical industry

The historic decline of technology stocks over the past three years has seen the biopharmaceutical sector ravaged more than most. Investors are realising that there are too many companies chasing too few products that are hugely expensive to bring to market. During 2002, a series of Food and Drug Administration (FDA)-mandated delays in clinical trials and failures and regulators' rejections of marketing approvals probably contributed to the deterioration of the value of the NASDAQ Biotechnology Index, which dropped 16 per cent in 2001, and a further 46 per cent during 2002.

But all is not gloom and doom. As we acknowledge the 20th anniversary late last year of the FDA's approval of human insulin the first gene-spliced drug, or biopharmaceutical, the sector shows a kind of yin and yang.

On the positive side, more than a hundred recombinant DNA-derived drugs and vaccines are on the market and have benefited some 250 million people worldwide.[1] These include life-saving therapies for anaemia, cystic fibrosis, haemophilia, hepatitis, transplant rejection and leukaemia and other cancers. The approximately 1,400 biotechnology companies in the USA boast a market capitalisation over US$200bn and spend more than US$15bn annually on research and development.[1]

There is less auspicious news, however, on several fronts. The American drug development system is hugely expensive, and the time and costs of drug development are spiralling out of control. Discriminatory taxes on drug development in the guise of user fees paid to federal regulators continue to increase.[2]

According to the Tufts University Center for the Study of Drug Development, since the 1960s the total time required for drug development – from synthesis or discovery in the laboratory to the patient's bedside – has almost doubled, from 8.1 years to 15.2 years.[3] The average number of clinical trials performed on an average drug before marketing approval is granted increased from 30 in the early 1980s to 68 during 1994–95, while the average number of patients in clinical trials for each drug more than tripled.[4,5]

Bringing a new drug to market now costs upwards of US$800m, by far the highest price tag in the world.[6] An important reason is that the highly risk-averse FDA keeps raising the bar for approval, especially for innovative, high-tech products. In a letter to the journal *Clinical Infectious Diseases* last year, Wyeth Ayerst vice-president David M. Shlaes and co-authors publicly criticised an FDA rule change that made it harder to prove efficacy in trials of new antibiotics. They charged that the rule has drastically raised clinical trial costs for many antibiotics and has prompted companies to suspend work on several drugs, concluding that the new policy has 'wreaked irreparable damage to [the industry's] ability to provide a reliable pipeline of new antibiotics for treatment of serious infections.'[7]

In 2002, the FDA approved only 18 new chemical entities, compared with a five-year average of 31.[8] The FDA has increased the regulatory burden for biotechnology products, in particular with human gene therapy; in response to two cases of leukaemia in (highly successful) clinical trials for children with potentially lethal X-SCID immunodeficiency, the agency placed on hold and withheld approvals for a wide spectrum of trials.[9]

To many observers, the FDA s behaviour is puzzling. Isn't the job of regulators not only to be gatekeepers but also to actively facilitate the availability of new therapies?

The short answer is that regulators are the victims of a distorted system that encourages them to overreact to the potential harms from new activities or products, while leaving them free to discount the lost benefits of unused or under-used ones. The result is a lopsided decision-making process that is inherently biased against innovation.

The FDA's demands for unnecessarily comprehensive clinical trials have delayed the approval of the first recombinant DNA-derived vaccine intended to prevent hepatitis B. The new vaccine was clearly superior to an existing but unpopular one whose source was pooled plasma from patients with chronic active hepatitis. But the FDA characteristically adopted the most risk-averse course: large clinical trials that had to be performed in Asia (where the disease was epidemic), involving thousands of patients and the expenditure of additional scores of millions of dollars. This decision meant a delay of several years in getting the product to market. During that hiatus, only the inferior, first-generation vaccine was commercially available. Significantly, during the decade following the approval of the recombinant vaccine in 1986, the incidence of hepatitis B fell by 65 per cent.[10]

Regulation aside, there is arguably too much competition for too small a commercial pie. Nationally, approximately 1,400 biopharmaceutical companies are developing, by the industry's own count, perhaps 375 drugs.[1] Not all of these products will be successful, and even among the small fraction that do gain marketing approval from federal regulators, historical precedent suggests that fewer than one in three will garner sufficient revenues to recoup the costs of development.

Biopharmaceutical companies are more in the red than in the pink. According to a survey of California biopharmaceutical companies, which constitute about a third of those in the nation, 35 per cent had no revenue in 2000, while 40 per cent had no products.[11] These data are hardly reassuring, and the traditional financial rescues from large-cap pharmaceutical companies are likely to become more rare.

The big pharma companies are themselves experiencing financial problems and slumping productivity and are inclined to support only the most promising, big-ticket, low-risk products. According to data from the venture capital firm Recombinant Capital, the number of announced alliances between biotechnology and pharmaceutical companies fell from 524 in the year 2000 to 442 in 2001.[12] Moreover, many such arrangements have not fared well: a 2001 poll of biotechnology and pharmaceutical executives by PricewaterhouseCoopers found that 59 per cent of alliances, whether full-fledged joint ventures or simply cooperative development, co-marketing or co-promotion of individual products, failed fully to meet original expectations.[13] This does not bode well in the short term for the highly innovative, niche-conscious strategy of many biopharmaceutical companies.

Perhaps even more alarming than the current woes of biopharmaceutical companies themselves are the implications for the future as the effects of straightened circumstances trickle down from the corporate world to academia. Biopharmaceutical companies are becoming less willing and able to fund research collaborations with academics, and it appears that the threshold for investors to fund start-ups has changed. In recent years, a company that merely sold information or made research tools for drug discovery was attractive to investors, but now they want good prospects for getting a product to market. In the long term, this shift seems certain to reduce the scientific substrate on which biotechnology innovation (to say nothing of the creation of the next generation of start-ups) is based.

Biotechnology applied to pharmaceuticals has made signal contributions to preventive and therapeutic medicine during the past 20 years but languishes far behind its potential. Important and often life-saving products will continue to emerge, benefiting patients

and perhaps lowering medical costs. However, with so much competition to make so few products, products that are over-regulated and very expensive to test and bring to market, biopharmaceutical companies (and investors) will need to be especially perspicacious about plotting their strategies.

Henry I. Miller, MD
The Hoover Institution,
Stanford University, USA

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