community performs the vast majority of the research conducted in academic institutions—‘this magic moment of discovery, this eureka moment smiles mostly on our younger scientists’, stated Gottfried Schatz, President of the Swiss Science and Technology Council. The demise of this valuable resource thus represents a far greater loss of scientific potential, creativity and progress and it is going to hit Europe the hardest. Not only is the whole of the Pacific Rim a massive human resource for US universities, but many European postdocs are also lured across the Atlantic by better research resources and better career prospects—the so-called brain drain. Furthermore, the US government recently doubled the budget of the US National Institutes, which will eventually result in higher salaries for postdocs working in the USA and may thus contribute further to the steady migration of scientists from Europe.

As a result of studies, such as the Sir Gareth Roberts Review, ‘there is now a broad recognition that we will not get people into the profession if we do not pay reasonable salaries’, said Niall Dillon, a group leader from the MRC Clinical Sciences Centre in London, UK. But while ‘the situation in Britain has improved in the last couple of years as the MRC and the Wellcome Trust have both increased salaries’, he warns that the problem in the rest of Europe ‘is much greater’. Indeed, there is still a long way to go and there are no easy answers. Coutinho considers that it ‘is unacceptable that people with 10 to 15 years of education end up with these levels of salaries’. Although salaries in the UK and the USA are beginning to rise, there are many other issues, particularly the problem of inflexible pension schemes, that urgently need to be addressed. ‘The solution for this, like for most things, is political’, said Coutinho and thinks that these basic problems have

to be solved first to attract more students to the natural sciences. Yaniv agrees: ‘Instead of spending money on futile programmes, [the EC] should find a way to pay postdocs and for a longer time’. He does, however, admit that it is not easy for governments to raise budgets at the drop of a hat and that merely calling for more government funding is not the answer.

One fact, however, is clear. The postdoc system has proven immensely successful over the last few years at producing scientific results and well-trained scientists and replacing it is out of the question. Changes are needed but, as Niall Dillon said, ‘the system works and is a successful model for research. It created a revolution in the biosciences and we should do what we can to improve it’.

Jack Parker

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When will the bear move on?

The current problems of the biotechnology industry are not solely a reflection of the whole market but are also caused by some specific problems

The year 2002 has not been kind to biotechnology: the industry has lost nearly half its value since January. In the USA alone, the Nasdaq Biotechnology Index is down by 49% after a 2 year rally that ended in April 2001, when the Nasdaq Biotech Index had gained 60% in comparison with Nasdaq losses of 24%. But, in general, 2002 has been one of the worst years ever on Wall Street, not just for biotechnology. On September 24, the Nasdaq slipped to its lowest point in 6 years and, on the same day, the Dow Jones hit its lowest low in 4 years. And there are still no signs of recovery. Recently, the *New York Times* noted that ‘there are more signs [than a few months ago] that recovery is weaker than expected and that [as] optimistic earnings expectations for the third quarter are fading, the list of concerns is growing’. Besides not knowing when the bear will make way for the bull once more, some

wonder if biotechnology’s current slide is just one aspect of a general economic downturn or if the industry has some specific problems.

Clearly, various corporate scandals such as Enron and, closer to home, ImClone Systems (New York, NY) are playing a role in biotechnology’s current

Stock slides can be contagious: many companies with drugs in the same areas have hit snags and their stocks have also slid downwards

travails, but the cumulative effects of a weak economy pummelled by the events of September 11 2001, an increasing chance of war with Iraq, unsteady oil prices and falling interest rates are exerting their toll on the biotechnology market.

In addition, recent rejections of new drug applications (NDAs) from various biotechnology companies by the US Food and Drug Administration have led to a general downturn of the stocks of companies with similar drugs in the pipeline.

Furthermore, bad news from clinical trials and new FDA regulations for drugs in development have also meant plunges in stock prices. Failures of phase III trials to meet endpoints are more numerous than ever, including Dendreon’s (Seattle, WA) Provenge for prostate cancer, Pharmacia’s (Peapack, NJ) SU-5416 to treat colon cancer and Cubist Pharmaceuticals’ (Lexington, MA) new antibiotic Cidecin; but this is balanced by the fact that there currently are a record number of biotechnology drugs in late-stage development. Unfortunately, stock slides can be contagious: many companies with drugs in the same areas have hit snags and their stocks have also slid downwards—guilt by association.

Finance has also been hard to come by for both new and early-stage firms. Initial Public Offerings declined sharply this year, compared with the boom days of 1999 and 2000. In times like these, investors are more hesitant to become involved with early-stage companies, which can also drag stock prices down, explained Geraldine O'Keefe, an Amsterdam-based equity analyst at Fortisbank. Stock prices have seen intermittent rallies over the past year, but the gains have been fleeting, according to G. Steven Burrill, CEO of Burrill & Company (San Francisco, CA), a private merchant bank devoted exclusively to the life sciences.

Whatever the reasons for the bad performance of biotechnology stocks, some analysts do not see the current situation in dire terms. 'The biotechnology industry has done worse than it has this year', said Bennett Weintraub, Vice President of Research at Btech Investor Inc. in Beverly Hills, CA. 'The tech world actually did worse this year than biotech.' Funding generally has been tight for biotechnology, with the timetable for drug development still in the range of one or two decades whereas, for computer companies, it might take 6 months to develop a product, Weintraub observed. The boom of 2000, when money was plentiful, is actually more of an aberration, he said, pointing to the wild optimism on Wall Street generated by the Human Genome Project and by Celera Genomics (Rockville, MD). Soon after, however, it

even though the US government has not been forthcoming with guidance on the development of these products, one critic said.

More drug rejections will follow as the number of new drug applications has increased

became clear that it would take much longer to translate those discoveries into drugs, and stock prices of genomics companies started to fall. Some companies, such as Incyte Genomics (Palo Alto, CA) and Celera, are thus redefining their strategy and establishing their own drug discovery programmes or investing in companies devoted to drug development. Indeed, this seems to be more pleasing to investors—biotechnology companies developing vaccines or diagnostics to fight bioterrorism rallied in the fall 2001

Some put the blame for the current financial problems in the biotechnology sector on the FDA and criticize the agency for its slow approval process, various drug recalls in recent years and a lack of leadership. Consequently, the FDA announced in September that it would move biotechnology drugs into the main oversight unit in order to speed up the approval process. Also, President George W. Bush recently nominated Mark McClellan to head the FDA, since the post had been vacant since early 2001. Carl Feldbaum, President of the Biotechnology Industry Organization, praised the reorganization, noting that it took the biologics division a few months longer than the drug division to review applications. But some analysts doubt that the move will hasten drug approval times. In any event, the number of drug applications has increased over the past few years, making it certain that more drug rejections will follow, as only one in 10 drugs in development are eventually approved.

Others note that increased approval times may be due to more caution by the FDA. This may have been escalated by the Jesse Gelsinger gene therapy trial debacle as well as an increasing number of drug recalls within the past 2 years, and has led some companies to believe that the FDA is dragging its feet with many NDAs, said O'Keefe. She cited the case of Genzyme's and Transkaryotic's (both Cambridge, MA) therapies for Fabry's disease, who filed their respective NDAs 2 years ago. The drugs were to have an expedited 6-month review, but both are still waiting to be reviewed.

The year got off to a bumpy start for other companies as well. Last winter, in the course of a few months, the FDA rejected NDAs from ImClone, Corixa (Seattle, WA), Celgene (Warren, NJ) and Sepracor (Marlborough, MA), but each case has different reasons as to why approval was not given. ImClone's NDA of its anti-cancer Erbitux based on phase II trials was incomplete, with key information missing, and a new trial will most probably be necessary, according to the FDA. The subsequent scandal put the New York-based company in a league of its own, with its ex-CEO Sam Waksal later indicted for fraud and insider trading, charged with selling stocks before the FDA decision not to accept the company's NDA was made public.

Celgene had also wanted to file on phase II data for Thalomid to treat multi-

The mood swings of the market are based largely on news of approvals and delays

ple myeloma, but the FDA ruled that phase III trials would significantly strengthen and broaden its application. Although Celgene had delayed its NDA by 2 years to get approval for early-stage treatment, this decision ultimately will open up a larger market for the drug when it is approved. Regarding Sepracor's allergy drug Soltara, the agency stated that Sepracor had not addressed adequately three issues of concern that had been present in earlier versions of this and other antihistamines. Elsewhere, Elan

in Dublin, Ireland, suffered a double blow when development of its vaccine for Alzheimer's disease was halted after a number of patients experienced suspicious brain inflammation. Prior to that, Elan's financial records were found to have questionable book-keeping techniques.

Nevertheless, Weintraub does not consider the number of NDA rejections this year to be high. 'From a venture capitalist vantage point, I have to know that 60% of drugs in phase III will be approved and 40% will not', he said. The mood swings of the market are, however, based largely on news of approvals and delays. But this is a short-term view, and Weintraub expects the market to rebound as soon as new products are approved. 'The industry is close—within 2 years—to the approvals of some really great medicines', he predicts. Weintraub compares the current situation, which he calls a buyer's market for banks, with the 1980s, when there were many companies vying for limited funds. 'That's what makes the US biotechnology market different from Europe's. The US has bigger companies and more sophistication in its organisation of funding', he said. 'The US has historically been more conservative in funding little companies than has Europe.'

In addition, 'Enronitis'—illegal accounting practices and other corporate misbehaviour—is also playing its role in investors' reluctance, and for good reason. When biotechnology companies such as ImClone and Elan display ethical lapses, they can take down the entire sector with them. One biotechnology industry commentator thus believes that the current problems cannot be blamed on investors, nor on the FDA, but on the industry itself. 'A far more insidious problem [than the FDA] is the pressure to push experimental drugs into clinical trials and quickly off to the FDA for regulatory approval at any cost', Stephan Herrera commented in the business magazine,

RedHerring. He blames the failure of drugs such as Corixa's Bexxar, Elan's Betabloc and ImClone's Erbitux on company pressure to produce positive trial

results with Erbitux that were based on much lower response rates.

Herrera thus believes that the problem is not the FDA, but that the number of drugs that are effective enough to withstand clinical trials is on the decline. He puts the blame on 'greedy management and investors'. 'One might think that in a down-bound market, investors would value a careful approach to clinical trials on the theory that it's better to be safe than sorry', Herrera notes. 'Quite the opposite is true.' He points to Curagen (New Haven, CT), whose CEO stated in April that its colitis drug would not enter the clinic by year's end as projected, and that he would

rather delay the drug now than see it flop years and millions of dollars later. Curagen saw a big sell off of its stocks. 'What's the point of cutting short-term costs and shaving years off development if it compromises the approvability of the finished product?' Herrera commented. Indeed, some CEOs seem to believe that the end justifies the means as long as investors can make money along the way, he noted.

Submitting phase II results for expedited review instead of waiting for strong phase III data is a risk that few companies can take, Weintraub said. However, there are

'Enronitis' is also playing its role in investors' reluctance, and for good reason

exceptions where it makes sense to submit early results, as was the case with Novartis's (Basel, Switzerland) Glivec, a drug that blocks the proliferation of white blood cells in patients with chronic myelogenous leukaemia. Firstly, this is a relatively rare disease and no good treatment currently exists, therefore waiting for large patient accrual would truly be futile and a waste of precious time. But more importantly, the company's phase II data were stellar: a 90% response rate was observed with the gene-targeting treatment in contrast to ImClone's patchy

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Strong leadership of a biotechnology company cannot counteract an overall bear market, but it can help companies avoid unnecessary pitfalls that, when they come in multiples, can drive the whole market down. Thus, cutting corners on clinical research by fast-tracking a compound through to the FDA on weak phase II data, poor documentation and exaggerated promises to investors does hurt the entire sector. The loss of confidence in corporate business culture, which runs companies not just like Enron but also all those involved in the business of biomedical research, will hurt all, but none more than patients waiting for treatments and cures.

Vicki Brower

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