SPECIAL REPORT

When there's no room to grow

To maintain profits in the face of rising development costs and slow drug pipelines, big pharmaceutical firms are trying to cut back. **Heidi Ledford** examines how GlaxoSmithKline has tried to adapt.

When Stephen Frye was made redundant from the world's second biggest pharmaceutical company last year it marked the end of his 20-year relationship with the firm — and perhaps the end of an era for researchers enjoying long careers in big pharma. "I grew up in that company," he says. "I had put my life and soul into it."

Frye was hired, fresh from completing his PhD in chemistry in 1987, as one of the first scientists to work at the new US headquarters of a pharmaceutical company called Glaxo. By the time he picked up his redundancy payout, he had survived two major mergers, helped discover some of the company's most prized drugs including Avodart (dutasteride), and, as vice-president of discovery medicinal chemistry, managed a group of more than 200 chemists.

Glaxo had also grown up, becoming GlaxoSmithKline (GSK), and by 2007 Frye was ready to part company. The spate of mergers was interrupting the flow of research at the firm, he says. "It was a futile cycle of constant restructuring," he claims. "A successful project takes 15 to 20 years. If you change your bets on science and people every three to four years, you will fail."

And the recurrent lay-offs — the most recent cycle of which were announced this June — drove morale to a new low. Frye decided to seek the shelter of academia, and now heads a centre for chemical biology and drug discovery at the University of North Carolina at Chapel Hill, minutes down the road from GSK's outpost in Research Triangle Park.

In many ways, the situation at GSK is emblematic of the troubled pharmaceutical

Stephen Frye spent 20 years working at GSK.

industry. The many mergers produced a drug-making behemoth with more than 100,000 employees worldwide, 17,000 of whom work in research and development (R&D). The company, like many others, faces a dilemma. To please the shareholders, GSK must continue to grow profits. But how can the company do this when it is already so large, in a regulatory environment that is reacting to a chain of drug-safety scandals, and in an industry with a high failure rate and a product cycle that lasts well beyond the attention span of the average shareholder? Some of GSK's biggest blockbuster are about to go off-patent, adding the threat of competition from generics.

Frye is quick to acknowledge that GSK is coping with these challenges to the best of its ability. But "they're struggling", he says. "Everybody's struggling. It's a tough business."

For GSK, 2007 was a tough year. In June,

Steven Nissen, a cardiovascular expert at the Cleveland Clinic in Ohio, released a meta-analysis of clinical-trial data that suggested that one of the company's biggest money-makers, the diabetes drug Avandia (rosiglitazone), could be increasing the risk of heart attack (S. E. Nissen & K. Wolski *N. Engl. J. Med.* 356, 2457–2471; 2007). Although GSK has disputed the validity of the results, the effect on sales was clear. GSK estimates that 'the Nissen paper' and the ensuing media coverage cost the company US\$2 billion.

"This [2007] is not a pretty year for us," Chris Viehbacher, president of North American pharmaceuticals at GSK, told investors at a conference last month. Viehbacher went on to assure investors that GSK was cutting costs. "There are no sacred cows," he said. "Do we have to spend \$5 billion a year on R&D? Can we do that with less?" One day earlier, news had broken that the company had laid off 350 R&D staff.

Industry-wide cuts

The lay-offs are small compared with AstraZeneca's 2007 cuts, which reduced its R&D staff by 700. Pfizer, meanwhile, laid off 10,000 employees, mostly in sales and marketing, and announced the closure of three R&D facilities in Michigan. Blogs are buzzing with rumours that additional cuts at Pfizer are on the way. Although GSK has declined to comment on specifically where the cuts were made, employees are reporting that some programmes have been hit particularly hard. More than half of the metabolic disease research group in Research Triangle Park has reportedly been let go, as have an estimated 70% of the

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The biotech model

It is no secret that large pharmaceutical companies have developed a voracious appetite for biotechnology firms, and GlaxoSmithKline (GSK) is no different. "I spend personally about 20% of my time shopping," Chris Viehbacher, president of North American pharmaceuticals for GSK told shareholders. The entrepreneurial spirit and nimbleness of young biotechnology companies has become the envy of the established

giants, which must cope with the inflexibility and communication woes of a large bureaucracy.

"They look longingly at these small biotech and say 'How do they do it?'" says Kenneth Kaitin, director of the Tufts University Center for the Study of Drug Development in Boston, Massachusetts. Kaitin's group has compared the cost of drug development in pharmaceutical companies and biotechnology companies and found little

difference (J. A. DiMasi & H. G. Grabowski *Manage. Decis. Econ.* 28, 469–479; 2007). "There are still people within pharma who view biotech as faster, cheaper, and more successful," says Kaitin. "But there's no evidence to support that whatsoever."

Companies often regard the 'Genentech model' as the ideal of how an arrangement between biotechnology and pharmaceutical companies should work. In 1990, Swiss pharmaceutical company

Roche bought Genentech, the flagship of the biotechnology industry, a company based in South San Francisco, California, and then essentially left the firm to function autonomously. Genentech flourished and Roche benefited, but most acquisitions have not been as rewarding. And the resignation by chief executive David Mott of MedImmune in Gaithersburg, Maryland, which was recently acquired by AstraZeneca, does not bode well. **H.L.**

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Suggestions that Avandia (inset) could increase the risk of heart disease did not make 2007 easy for GlaxoSmithKline.

GLAXOSMITHKLINE

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cardiovascular-disease team in Pennsylvania. The GSK lay-offs are part of a three-year 'operational excellence' plan, and the company aims to institute additional cost-cutting measures in R&D over the next two years.

Some speculate that recent acquisitions may have influenced the decision (see 'The biotech model'). In April, GSK announced that it had paid \$720 million to acquire Sirtris Pharmaceuticals, a biotech company based in Cambridge, Massachusetts, that, according to Viehbacher, appealed to GSK because its drug candidates target metabolic disorders such as diabetes. In November of last year, GSK also purchased Reliant Pharmaceuticals of Liberty Corner, New Jersey, for \$1.65 billion. Reliant develops cardiovascular drugs.

When not out shopping for biotech companies, many pharmaceutical executives have been restructuring internal research programmes in an attempt to achieve the biotech firms' secret formula. In 2000, GSK research chairman Tadataka Yamada reorganized research teams into several centres of excellence for drug discovery. The teams were hived together according to the disease they were tackling, and no team was to exceed 300 people. "When you get more than that, you can't remember everybody's name," says Yamada, who now works for the Bill & Melinda Gates Foundation. In effect, the model attempts to cope with GSK's swelling size by breaking the research teams into

more manageable, biotech-like bits.

Some suggest that the recent spate of lay-offs at GSK is an indictment of the 'centres of excellence' model. Most, however, agree that it is too early to tell whether the model is a success. Robert Huckman of Harvard Business School, who has studied the model, says that several years after it was implemented GSK saw an upturn in the number of early drug candidates from the centres.

Worst of both worlds

Yamada says the 33 molecules that have emerged from the programme and already reached phase III trials are signs of success. "The model seems to be producing exactly what it was meant to do," he says. Others argue that although centre leaders held some autonomy over their research programmes, the bureaucracy remained thick. There are rumours that GSK has proposed giving its centres a three-year budget that will be renewed contingent on performance of the team, a situation much like that faced by young biotech firms. Frye worries that this creates an unstable research environment. "You get all the bureaucracy of GSK and all the risk of biotech," he says. "Three years from now, they could throw out your idea and decide to do something else."

Several other companies, including Pfizer and Abbott, have also grouped their researchers into teams organized by therapeutic class. Not everyone, however, believes that the solution to the big pharmaceutical companies'

problems is to become more like biotech companies. Two former GSK centre leaders, Frank Walsh and Robert Ruffalo, who left to join Wyeth Pharmaceuticals in Madison, New Jersey, are re-centralizing the R&D programmes there.

And researchers who have worked through several restructurings are sometimes left wondering what was so wrong with the original model. "My friends are burned out," says Paul Domanico, a former vice-president at GSK who now runs his own consulting firm. "They've been doing this kind of dance for a decade now. They truly believe if they had been allowed to focus and continue doing what they did, they would have been successful."

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Regardless of which model is taken, it is clear that the future will hold more lay-offs. In addition to the growing role of biotechnology acquisitions

in pharmaceutical R&D, the industry is increasingly relying on contract research organizations to provide many functions that were once performed in-house. "There's a massive shift of the R&D into the smaller companies and there is going to be a massive reduction of internal R&D in big companies," says Daniel Webster of Webster Consulting Group in New York, who predicts that the waves of pharmaceutical lay-offs will continue for the next five years. The damage to morale is already palpable. "You talk to any R&D scientist at a big company and you feel like you're talking to someone in Dante's Inferno," he says. "I've never seen the morale in pharma R&D lower."