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Bigger isn't always better

The pharmaceutical industry's merger mania has done little to spur the innovation on which its future health will depend. Is it time to rethink the role of research within 'big pharma'?

In his heyday in the 1960s and 1970s, James Black demonstrated a Midas touch that turned base chemicals into pharmaceutical gold. An old-fashioned British pharmacologist who would think through his experiments for weeks before picking up a pipette, Black passionately believed in his duty to help cure disease — and in the capability of drug companies to help him do so. After leaving academia for ICI, he developed beta-blockers to treat hypertension. Later, working for Smith, Kline & French, his work on histamine H2-receptor blockers revolutionized the treatment of stomach ulcers. Black's contribution to medicine was honoured with a Nobel Prize in 1988, and these two classes of drug are still bestsellers.

What wouldn't the world's pharmaceutical giants give for a return to the days when the steady arrival of new blockbuster drugs saw the industry riding high? Today it's a different story. The patents are running out on established earners and, despite the billions of dollars that the firms are pouring into research and development, the number of new drugs launched each year is falling. At the same time, the average cost of bringing a drug to market is rising, having doubled over the past 15 years; it now stands at as much as US$800 million, according to the Tufts Center for the Study of Drug Development in Boston. Put these two trends together, and it is easy to see why analysts are warning that historical patterns of profit growth are unlikely to continue. Factor in the threat of a big earner being blown away by a successful patent challenge — as happened to GlaxoSmithKline's antibiotic Augmentin earlier this year — and things look bleak indeed.

There is no single explanation for what is going wrong. In part, the answer is that the 'easy' diseases have already been tackled with drugs that work well and are very cost-effective. A gastric ulcer, for instance, is caused by the oversecretion of stomach acids, mediated by unique biochemical pathways that are easy to hit selectively. Drug companies are now facing complex conditions with multiple causes, both environmental and genetic, such as asthma and Alzheimer's disease. And while the firms' publicity departments talk glibly about the prospect of 'personalized medicine', it's hard to find a pharmaceutical executive who has a clear idea of how to maintain profit margins in the pharmacogenomic era.

Getting together

Advances in both biological and chemical technologies are still yielding a multitude of drug targets and candidate compounds, but the pipeline from intriguing lead to finished product is leaky in the extreme. The vast majority of drugs — more than 99.9% — fall by the wayside in preclinical testing or in clinical trials. The latter failures are a particular problem, given the huge and rising cost of providing the clinical data to meet the stringent requirements of the US Food and Drug Administration and other regulators.

In recent years, the industry's answer to this pipeline problem has been an orgy of mergers. Pfizer, already the world's biggest-selling drugs company, last week unveiled plans to purchase Pharmacia for some $60 billion in stock. GlaxoSmithKline, the product of a series of mergers including the mega-deal in 2000 between Glaxo Wellcome and SmithKline Beecham, is also reportedly also seeking another partner. Put two giants with complementary late-stage pipelines together, cut costs by shedding staff with overlapping functions, add the mysterious ingredient of 'synergy', and everything is back on course — or at least, that's the theory.

The problem is that the merger medicine isn't working — as witnessed by the cool stockmarket reaction to these latest developments, and the steady decline in GlaxoSmithKline's share price since the 2000 amalgamation. Merged companies are still facing the same problems, such as how to work out when to fail a drug candidate to avoid throwing good money after bad. Worse, some industry insiders claim that the mergers are stifling innovation, rather than promoting it.

Speak to researchers at the bench and their immediate managers, and they will tell you that a merger is extremely disruptive. Projects are stalled and collaborations with start-up companies are put on ice until new research priorities are sorted out. Uncertainty reigns for months, if not years. And many feel that the resulting corporate hierarchies become too big and aggressive for a research group leader, or even a research director, to champion his or her projects successfully. It is hardly the sort of environment to entice an ambitious young researcher who wants to emulate Black's achievements.

New start

If disruption were temporary, the complaints could be put down to natural human discomfort with change. But the malaise seems deeper. Many of big pharma's best researchers are defecting for small biotech companies, where they soon feel revitalized and inspired. GlaxoSmithKline appeared to recognize the problem when it divided its research effort into six smaller drug-discovery centres modelled on biotech firms. But the recent departure of senior staff (see page 360) suggests that the experiment has not been an unqualified success.

If Black were entering his prime today, it seems highly likely that he would gravitate to an energetic start-up drug-discovery firm — even in the 1970s, his scientific individualism sat uncomfortably with the prevailing culture of the larger drug companies. So it's no surprise that, in search of the elixir of innovation, the drugs giants are increasingly turning to collaborations with start-ups (see *Nature* **414,** 482–483; 2001).

Many start-ups are engaging in highly speculative science that will never turn a profit, but others are quietly nurturing tomorrow's pharmaceutical money-spinners. Picking winners is notoriously difficult, which helps explain why big pharma is happy to let smaller partners take the risks. But perhaps it's time to start pushing this trend to its logical conclusion. The pharmaceutical industry's leaders could stop thinking about mergers, and instead turn over the early stages of drug discovery to nascent companies experimenting with new chemical, biological, genomic and computational technologies.

Big pharma's muscle will still be needed to push drugs through clinical trials and to supply them to global markets. But in future, its role in the early stages of the drugs pipeline might well be restricted to coordinating, facilitating and funding the work of the real innovators. If so, what we are currently witnessing may not be the start of the pharmaceutical industry's slow demise, but rather the first stirrings of its reorganization into a new and more viable form. ■