In the light of continuing job cuts in recent years, one might easily overlook the fact that the pharmaceutical industry has also created thousands of new jobs. However, those new jobs are often not for scientists but in administration, sales and marketing.

For example, Pfizer shut six research centres, including its UK research hub (and largest European lab) in Sandwich, Kent, in February 2011. In April 2012, Merck shut its Serrano research facility in Geneva cutting 580 research jobs. In June 2012, Swiss-based Roche cut 1,100 jobs from its US research centre in New Jersey (where valium was discovered). In July 2012, French-based Sanofi outlined further details of job cuts affecting up to 3,000 staff, including those at its research centres in Montpellier and Toulouse. It is expected to completely shut its Toulouse laboratory, currently employing 610 staff.

According to the Tufts Center for the Study of Drug Development, job cuts from 2006 to spring 2012 totalled around 263,000. Up to 10 percent of these cuts was direct R&D (Nature 2012, 486:281-2). In 2008 Tufts estimated that 50,750 workers were employed worldwide in pharmaceutical and biotechnology R&D. By 2010, this total had fallen to 41,275.

Is a loss of profitability the reason?

Worries about loss of profitability have dominated Big Pharma’s actions over the last decade. Even though these worries were unfounded, investors have tended to expect higher returns on their company shares. Since reaching a peak in its stock market valuation around 2000, the whole pharmaceutical industry has been in a state of relative decline and crisis. Shares in Pfizer, the biggest of Big Pharma, lost more than half their value between 2000 and 2010, equivalent to a loss in market capitalisation of $115 billion (The Pharma Letter; 5th Jan 2012).

During the 1990s, profits at the top ten drug companies worldwide made up over 20% of their sales (easily outperforming other sectors). But by 2003 this profit margin had fallen to 14.3% and there were questions about whether this was a long-term trend and how it could be reversed. Investors had come to expect bigger returns from drug companies.

To maintain profitability, the pharmaceutical industry has a choice: either it increases drug sales or it cuts operating costs. There are four main strategies to push up sales and profit.

Higher drug prices and the ‘patent cliff’.

One of analysts’ key obsessions has been the so-called ‘patent cliff’. The reason is that Big Pharma has been so highly profitable during this time of turmoil is that it can set its own price for patented drugs and prevent anyone else from selling cheaper versions. But when a drug falls off the ‘patent cliff’, its price can plummet. Generic versions of drugs have been sold at less than a fifth of the patent-protected price (healthcare.blogs.ihs.com/2012/01/06/generic-drug-price-trends-france-germany-italy-spain-uk/). Losing patent protection means lost profits.

Sell more drugs through ‘better’ marketing.

The pharmaceutical industry has been regularly found guilty of immoral and downright illegal practices. Unfortunately, these commercial activities have also had a negative effects on Big Pharma’s own R&D.

“How the drug industry abandoned science for salesmanship” shows ways, in which research has been used as a marketing tool to maintain patent protection and boost drug sales (Forbes.com; 5th August 2006). Take, for example, the development of ‘me-too’ drugs like Prilosec, AstraZeneca’s bestselling acid reflux drug. Before Prilosec fell off its patent cliff, AstraZeneca ‘tweaked’ the
drug to create a very similar molecule called Nexium that it could patent again. In order to prove that Nexium was a better drug than Prilosec, high doses of Nexium were studied in five clinical trials totalling 12,000 patients. Nexium apparently helped the oesophagus heal in an extra 1 in 20 patients, but three of the trials only compared it to half the dose of Prilosec. Nevertheless, thanks to aggressive marketing and sales promotion, Nexium soon displaced Prilosec in the market. In 2005, with sales of €4.6 billion, it became the world’s third best-selling drug.

Fortunately, Nexium has no lethal side-effects. Big Pharma’s marketing departments sometimes seem to forget that drugs are not the same as chewing gum and Coca-Cola. Maintaining sales appears to be more important than safety. Consider, for example, Merck’s behaviour with Vioxx, an over-priced, overpromoted pain-killer that incidentally caused thousands of lethal heart attacks before it was finally withdrawn (see Marcia Angell’s “Your dangerous drugstore”, NY Review of Books, 8th June 2006).

Creating new markets

Drug companies have also ‘created’ new markets for their drugs by illegally convincing doctors and patients that they can cure diseases and conditions, for which they have not received official approval (see Marcia Angell’s “Drug companies and doctors: a story of corruption”, NY Review of Books, 15th January 2009).

In 2009, Pfizer was found guilty of illegally marketing four drugs: Bextra, Geodon, Zyvox and Lyrica, “with the intent to defraud or mislead” by promoting the drugs for non-approved uses. It received a record-breaking fine of €1.8 billion. In July 2012, GlaxoSmithKline beat this record with a fine of €2.4 billion for the off-label marketing of its anti-depressants, Paxil and Wellbutrin, and diabetes drug Avandia (“Breaking down GSK’s billion dollar wrongdoing”, Time, 5th July 2012). Both court cases revealed evidence of the extensive bribery and corruption of medical staff, including academics responsible for medical research and health officials.

A further twist to this undermining of scientific truth in the search for higher drug sales and bigger profits has been the ‘discovery’ of new medical diseases. Quite literally, drug companies have discovered previously unknown diseases that their patented drugs can treat. For example, in 1999 SmithKlineBeecham (before it became GSK) renamed shyness ‘social anxiety disorder’ or ‘social phobia’ and marketed its Paxil anti-depressant as a cure.

Acquire other bestsellers through mergers.

Another way to increase drug sales and (hopefully) profit is to buy into someone else’s bestselling drugs. Company mergers and acquisitions have resulted in the creation of some very large Big Pharma corporations. Some 261 firms produced all of the 1,222 new drugs approved in the US between 1950 and 2008. In 2009, only 105 still existed; 137 had disappeared in mergers and acquisitions (Nature Rev Drug Discov 2009, 8:959).

Make new drugs, especially blockbusters.

A blockbuster drug has sales of more than $1 (€0.8) billion a year. This is the kind of drug that Big Pharma needs to keep profits up. Unfortunately, they aren’t so interested in developing drugs that earn less. Many R&D decisions depend on predicted marketing and sales volumes, not on the need to cure diseases with new and better drugs.

“Lessons from 60 years of pharmaceutical innovation” notes that 1,222 new drugs were approved in the US between 1950 and 2008 at a rate of around 20 drugs per year (Nature Rev Drug Discov 2009, 8:959). The author, Bernard Munos, then claimed that the corresponding cost of drug discovery had risen “exponentially”. He took a widely-cited (and heavily disputed) estimate that it cost $802 (€640) million to discover and bring a new drug onto the market in 2000, then estimated that costs had risen to €3.1 billion per drug for 2008. That’s pretty exponential!

Let’s cut R&D costs!

However, investors have looked at such huge sums and accepted that Pharma R&D costs far too much, while producing too little. To improve profit margins, they insist research costs must be drastically cut (“World pharma: Leaner labs?”, The Economist, 13th February 2012).

But are investors pushing Big Pharma too hard? “Pharma’s forced to put squeeze on R&D” notes that current stock market valuations for the pharmaceutical industry are, “almost entirely based on future revenues from currently marketed medicines, placing no value on products in development but yet to be launched” (Financial Times, 16th October 2011).

Big Pharma CEOs are now complaining that their companies are undervalued and that investor ‘scepticism’ is threatening their capacity to find new drugs. According to the head of Roche, Severin Schwan, “The current valuations assume we have ten more years and it’s all over.” This ignores their past successes, efforts to boost innovation, and drug development ‘pipelines’ that are “far fuller of experimental drugs than a few years ago”.

Let’s cut R&D costs!
But industry consultants are equally sceptical of claims made by drug company executives who “consistently overestimate not only the chance of their experimental drugs being approved, but the income they will generate at a time of growing scrutiny by healthcare systems and reluctance to pay high prices or purchase in large volumes.”

Perhaps “the market is right. A whole reset in R&D is required”.

How much does Pharma R&D cost?

Ironically, the ‘idea’ of high R&D costs has previously been of service to the pharmaceutical industry – after all, they used it to justify their high drug prices. An influential study from the industry-funded Tufts centre estimated R&D costs in the year 2000 of $802 (€640) million per drug approval (DiMasi ‘The price of innovation: new estimates of drug development costs’, J Health Econ 2003, 22:151–185). Others have questioned how such high costs were calculated (‘Drug development costs estimate hard to swallow’, CMAJ 2009, 180:279).

Recalculating from the original data, Light and Warburton found numerous flaws in the Tufts study (‘Demythologizing the high costs of pharmaceutical research’, BioSocieties 2011, 6:34–50). Instead of €640 million, they arrived at a far lower estimate of €47 million per drug (see also Lab Times 2/2011, page 53: ‘Dismantling an Urban Legend’).

The Tufts study started with limited confidential data, provided by just ten US Pharma firms. No attempt was made to analyse how costs were calculated. No figures were provided for early-stage drug discovery. To fill this gap, the Tufts team simply made a guess – they estimated costs of €97 million per drug and that the process of discovery (‘the average time from synthesis of a compound to initial human testing for self-originated drugs’) took an average of 52 months.

Doubling the initial estimate

They then introduced a calculation for capital costs. In effect, they imagined what Big Pharma might have done with all that money if they hadn’t used it for R&D. Their answer: a high-earning stock market investment! This allowed them to further inflate costs by 11% a year. Allowing 52 months for basic research and an estimated 90.3 months covering clinical trials and government approval, this effectively doubled the initial R&D cost estimate from €322 million to €640 million.

Furthermore, Tufts seems to have taken no account of public contributions to Pharma’s R&D costs. Much of the fundamental research underlying drug discovery is made using public finances. Industry also benefits from all sorts of tax incentives that allow it to deduct the costs of R&D.

Other studies have also questioned what Big Pharma includes in its R&D claims. Gagnon and Lexchin found that companies spend almost twice as much on drug promotion as they do on R&D, but that many promotional expenses are included under research and development (‘The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States’, PLoS Med 2008, 5:29-33).

Sailing under false colours

For example, the term ‘education’ often appears. This covers all sorts of product promotions for the medical profession, designed to increase their awareness of new drugs and disease treatments. The industry argues that this is part of R&D because it involves the diffusion of new research results and studies. Furthermore, they claim it’s a public service since they’re helping medical doctors to keep up-to-date in their knowledge and training. Overall, in 2004 the US pharmaceutical industry spent €46 billion to promote their drugs to around 700,000 US medical doctors. This comes to around €68,700 per doctor! The number of promotional meetings for doctors has also increased, for example, from 121,000 in 1998 to 371,000 in 2004. In 2000, Big Pharma’s top ten companies openly spent €1.5 billion on such events.

There are also considerable doubts about some of the research results presented at such ‘educational’ meetings. Much of them concern Phase IV clinical trials. These are postmarketing studies of a drug’s effects on patients that are meant to provide additional information about the treatment’s risks, benefits, and optimal use. But it has been revealed that many Phase IV clinical trials are not generating any new scientific data. Instead, ‘seeding’ trials are designed to promote the prescription of new drugs. In 2004, some 13.3% of R&D expenditure by US pharma (€3.9 billion) was spent on phase IV trials, “Almost 75% of these trials are managed solely by the commercial, as opposed to the clinical, division of biopharmaceutical companies, strongly suggesting that the vast majority of these trials are done just for their promotional value!”

When such promotional activities are removed from R&D costs and instead accounted for under marketing, the whole perception of expenditure changes. In 2004, the US pharmaceutical industry spent 24.4% of its sales revenues on advertising and sales promotion versus 13.4% for R&D. A 2006 survey of European pharmaceutical firms found even higher marketing costs of 31-50% of sales revenue (Consumers International).

Why isn’t Pharma R&D more productive?

Some industry researchers have explained how hard it is to do good research when decisions are dominated by management and marketing. In Drug Discovery in Jeopardy, Pedro Cuatrecasas describes the rise of a management culture in the pharmaceutical industry that has effectively hampered real progress in drug development (J Clinical Investigation 2006, 116:2837). Cuatrecasas talks from long experience. After academic research at Washington University, NIH, and Johns Hopkins, he moved his lab to Boughroughs Wellcome. Subsequently, he became head of R&D and director of Glaxo (1985–1989), then president of R&D and corpo-

He argues that reduced productivity in the drug industry is caused mainly by corporate policies that discourage innovation. This is, “compounded by various consequences of mega-mergers, the obsession for blockbuster drugs, the shift of control of research from scientists to marketers, the need for fast sales growth and the discontinuation of development compounds for non-technical reasons.”

He also claims that inefficiencies in drug discovery and development have actually encouraged Big Pharma’s immoral and illegal practices. Unable to produce enough innovative drugs, the pharmaceutical industry, “resorted to practices that have drawn public criticism, including markedly increasing drug prices, increasing spending on advertising and promotion, direct-to-consumer advertising, ineffectively conducting postmarketing surveillance, and limiting comparative efficacy/safety studies with alternative drugs.”

The problems of “modern” management

In fact, Cuatrecasas dates R&D problems back to the 1970s when ‘modern management’ arrived. The managers had legal or business school training or came from non-drug industries that, “functioned with greater organizational discipline”. They had little or no technical experience and did not understand the “complexities of science, its mode of conduct or objectives”. He says that such managers were so “uncomfortable with seemingly ‘unfocussed’ research organizations” that they perceived to operate in a freewheeling, independent style. They imposed order on their researchers through the introduction of management techniques, often recommended by outside management consulting firms used to advising non-technology-based corporations. They were not familiar with, “complex professional-based matrix organizations”, such as scientific research labs.

Managers were often over-focused and employed top-down decision-making to direct R&D. This resulted in “more mediocre, not novel, products and there was no evidence of improved long-term profitability. Ironically, great-sounding slogans were used to achieve conformity while proclaiming the importance of innovation, empowerment, diversity and compassion. Freedom, spontaneity, flexibility, nimbleness, tolerance, compassion, humor, and diversity were replaced by bulky and inflexible organizational structures characterized by regimentation, control, conformity, and excessive bureaucracy.”

Most solutions for improving R&D still involve cuts within Big Pharma research labs. On the one hand, ‘merger mania’ brought companies together and shed excess research capacity. Then outsourcing found it cheaper to sack in-house researchers and pay other people to do the work instead.

Merger mania

The negative impact of mergers on pharmaceutical R&D was described by John LaMattina, former President of Pfizer Global R&D (Nature Rev Drug Discov, 2011 10:559), “Before 1999, Pfizer had never made a major acquisition. Over the next decade, it acquired three large companies – Warner-Lambert (in 2000), Pharmacia (in 2003) and Wyeth (in 2009) – and multiple smaller companies.” It is now the world’s largest pharmaceutical company.

The business rationale behind such mergers is to improve profits through the purchase of successful products marketed by other companies. This also provides an opportunity to reduce costs by eliminating duplication. For example, sales and marketing have the capacity to sell extra products with fewer people and offices.

But how do you merge R&D teams? LaMattina says R&D is the last part of the companies to begin merger discussions because of the commercial sensitivity of the drug ‘pipeline’ and the intellectual property of the company. When the discussions about integrating R&D organisations do finally occur, the initial focus is on Phase III programmes (drugs in clinical tests), followed by mid-stage candidates, with the early-stage discovery programmes handled last. This process takes at least nine months, during which early-stage R&D will be slowed. No new programmes

John LaMattina, Pfizer’s former R&D president, is aware of the negative impact of major acquisitions.
will be started. Nobody is recruited. Mergers have a substantial, negative impact on the momentum of research programmes. And Cuatrecasas remarks that, despite outward appearances, decisions about staff and programmes are often made arbitrarily by people far removed from the science and labs, “Good programmes are eliminated in attempts to consolidate, and knowledge, training, and expertise, often cultivated over years, are lost.”

**Popular “solution”: Let’s outsource!**

Outsourcing R&D has become popular because it’s considered cheaper. Full-time staff in pharmaceutical companies cost more than contractual workers employed for specific projects by smaller companies. Contract research organisations (CROs) provide services such as pre-clinical research, clinical research, clinical trials management and pharmacovigilance. In 2007, more than 1,000 CROs received over €12 billion from the pharmaceutical industry. There has also been a tendency to do such work in developing countries where salaries are lower and regulations less restrictive. For example, clinical trials can be faster and cheaper to conduct outside the US or Western Europe.

**Questions about academic research**

Outsourcing research to publicly-funded labs also reduces industry costs. However, Big Pharma researchers have questioned the quality of outsourced research. It may be cheaper in the short-term but is it good enough to produce new drugs? Industry researchers have been looking for promising leads in academic labs. In the last year, however, R&D teams from Bayer and Amgan have revealed that the majority of the published academic results that they carefully retested were not reproducible (see ‘Academic truth or biotech bullshit’, *Lab Times* 3/2012, page 40-44). They suggested that much of this academic research, often published in prominent scientific journals, was poorly executed rather than fraudulent. Industry scientists fear this tendency is growing, driven by increasing competition among academic researchers for limited job and funding opportunities that are frequently dependent on publication records.

But could Big Pharma itself have influenced this degradation of publicly-funded research? The recent prosecution of Pfizer and GlaxoSmithKline provided ample evidence that Big Pharma’s promotional activities have been corrupting medical research; undermining scientific truth in favour of commercial gain. Prominent medical researchers received large sums of money in return for their endorsement of patented drugs, irrespective of the scientific evidence.

Cuts in public research budgets have also encouraged academic researchers to accept funds from the pharmaceutical industry to work on projects that may be of little personal or scientific interest to them. Such funds can help maintain the lab’s real research activities but do researchers spend as much time and effort on such outsourced commercial research?

**Shut down all in-house R&D!**

Given the way that Big Pharma operates, it should come as no surprise to learn that the latest R&D ‘guru’ is a salesman. Bernard Munos spent 30 years in sales at Eli Lilly then began research into, “disruptive innovation and the radical redesign of the pharmaceutical business model”.

As *Forbes Magazine* put it, “Munos has a radical idea to save the drug industry: Take bigger risks and cut R&D” (22nd August 2011). He says that Big Pharma should stop doing research that simply tweaks blockbuster drugs that they can patent. Instead, they should focus on true breakthroughs that really do help to treat diseases and that can help patients. This doesn’t sound particularly shocking, but Munos has decided that Big Pharma’s own in-house organisations are no longer good enough to do this kind of research. He says that Big Pharma should simply close its labs and outsource the research work to “tiny, nimble startups that can explore bigger, crazier ideas”. Looking at drug discovery patterns over the last 60 years, he has concluded that more progress took place when there were more, smaller companies doing research. In this respect, company mergers certainly haven’t improved productivity. His solution involves reversing the process.

“Why keep researchers in house? Why not force them to form tiny companies of their own and outsource work to them?” To survive, smaller companies are obliged to try new things and, “risk breeds results”.

**Reducing internal research**

In an interview, Munos analysed the current R&D situation for Big Pharma (fiercebiotech.com, 7th February 2012). He was optimistic about Novartis, GSK and Sanofi, recognising “They have worked hard to retool themselves and recreate an innovation culture in their R&D divisions.” But he was less enthusiastic about AstraZeneca, Lilly, Merck, Pfizer and Amgen, who have, “embraced a strong process culture and insist on running regimented R&D divisions. It’s a bankrupt model and has never delivered (for good reason).”

Sanofi has certainly listened to Munos’ ideas. The company’s CEO, Chris Viehbacher, began to restructure Europe’s 3rd largest drug company in 2009. His aim was to reduce internal research in favour of small biotech companies and academic research. R&D jobs have been cut and research centres in Toulouse and Montpellier are set to close. But Viehbacher isn’t finished yet. Indeed, his answers in a February 2012 interview suggest that little in-house R&D will survive, “Sanofi CEO: Who Needs Big Pharma Scientists?” (*PharmaIot*, 1st Febr 2012).

Viehbacher said, “The days when we locked all of our scientists up in a building and put them on a nice tree-lined campus are done. We will do less of our own research. We’re not going to get out of research. We believe we do certain things well in research but we want to work with more outside companies, start-up biotechs, with universities.” He then asserted, “The reality is, the best people who have great ideas in science don’t want to work for a big company. They want to create their own company. So, in other words, if you want to work with the best people, you’re going to have go outside your own company and work with those people…”

Will any in-house R&D remain after all this outsourcing? Viehbacher replied, “Big Pharma has competencies in validation.” So it appears that Sanofi will still need a few researchers, if only to validate the quality of the drugs they sell.

Jeremy Garwood