



A computer screen is seen reflected in the glasses of Dr Nick Brooks as he works in a laboratory at Imperial College in London, May 28, 2010. Photos REUTERS/Paul Hackett

BIG PHARMA, SMALL R&D

Are big western pharmaceutical companies turning into distributors rather than inventors? By Ben Hirschler and Kate Kelland, London

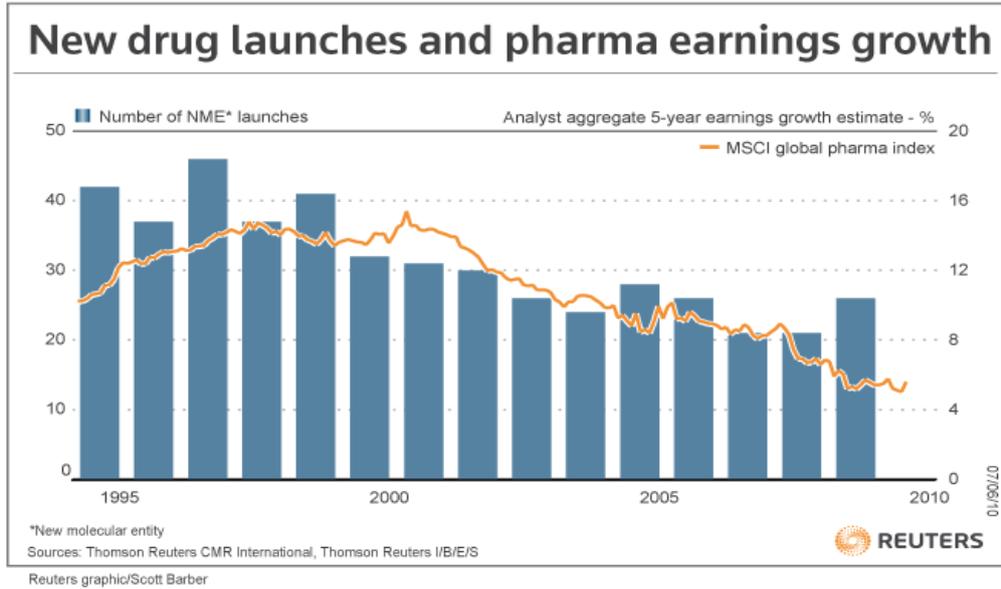


At just 28, Duncan Casey has already been from the university science bench to the world of Big Pharma research and back again. Now working in an Imperial College lab tucked behind London's famous Science Museum, he has no illusions about the prospects for researchers in the pharmaceutical industry.

"The unit I used to work in -- GlaxoSmithKline's place in Harlow -- has been closed down now," says Casey, dressed in signature protective goggles and white coat as he works on synthetic chemistry. "It used to be a job for life. Now it's a job until the next restructuring."

Across the western world, Big Pharma is cutting back on the number of scientists it employs in its labs and the money it spends on research and development. The hunt for new drugs continues, but the men and women in white coats -- traditionally viewed as the lifeblood of the industry -- are not as untouchable as they once were.

It's a similar story at GlaxoSmithKline's research laboratories in Verona, where lunchtime conversations can be decidedly gloomy. Glaxo is axing the Italian facility, shedding 500 jobs as part of a programme of cuts designed to improve returns on R&D. Many scientists feel stranded or wonder why they entered the profession at all.



"It's a sad but true fact that science really doesn't pay any more," says one young researcher who would not give her name for fear of jeopardising her future prospects in the industry. "The lunchtime discussion today was about what we'd go back and study if we were 18 again and choosing university courses. There were only a few of us who said they'd still go for a science degree."

Across the Atlantic in Cambridge, Mass., Adrian Ivinson, director of Harvard's NeuroDiscovery Center, is reminded of the shifts underway in the industry every time he looks out of his window. Over the road, the "gorgeous, state of the art labs" no longer house Merck & Co Inc's neuroscience team. "They only built it a few years ago and had this wonderful neuro group in there," Ivinson says. "Now they're gone."

The magnitude of the changes is hard to ignore.

U.S. drug giants Pfizer Inc and Merck have slashed thousands of jobs since acquiring smaller rival firms last year. British-Swedish firm AstraZeneca has plans to close its research labs at Charnwood in central England by the end of 2011, with the loss of up to 1,200 jobs; its Swedish research unit in Lund will also shut. In Japan, Astellas Pharma Inc has announced plans to limit its research expenditure.

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DUNCAN CASEY

Sam Isaly, managing partner at OrbiMed Advisors -- with some \$5 billion under management it is one of the world's largest healthcare investment firms -- expects employment in the 14 Big Pharma companies across the United States, Europe and Japan to fall around 20 percent between 2009 and 2015. That means some 200,000 jobs will disappear across the drugs business -- not only in research but also in sales and back office functions. "The management of these companies have to deliver to their shareholders, so they are downsizing or making acquisitions or diversifying," says Isaly.

NEW PRODUCTS, NEW MARKETS

One factor forcing Big Pharma to rethink its business model is the huge number of patents that are set to expire over the next five years. As patents run out on blockbuster prescription tablets like Pfizer's \$12 billion-a-year cholesterol medicine Lipitor and AstraZeneca's \$5 billion heartburn pill Nexium, cut-price generics are sure to rush in and slash margins. Between now and 2015 products with sales of more than \$142 billion will face copycat competition, according to IMS Health, the leading global supplier of prescription drug data.

Add in tougher regulatory hurdles and a brutal squeeze on healthcare budgets as cash-strapped governments push austerity programmes and it's little wonder that drug companies are cutting back and shifting focus.

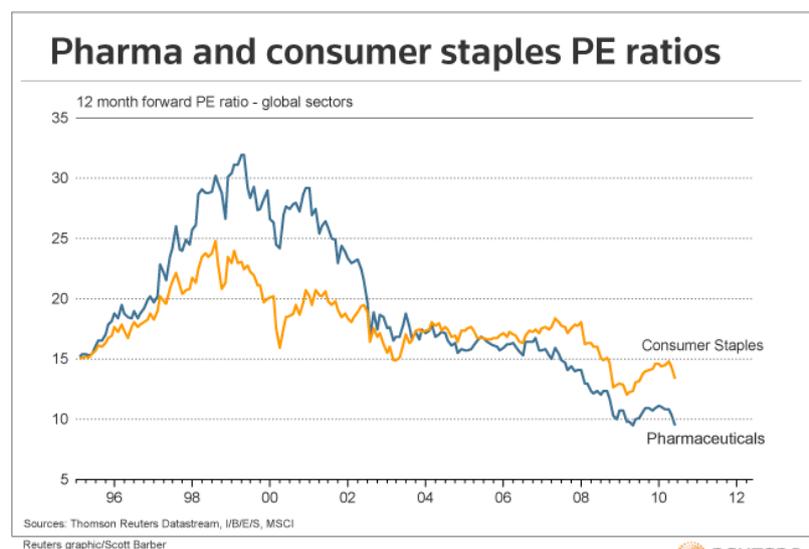
The strategy so far has been to buy promising new drugs from outside developers and boost investment in the relative safety of non-prescription consumer products. Big drugmakers are also moving into new markets -- with Asia at the top of everybody's list. It all adds up to a redesign of the multinational pharmaceutical company. In the 21st century, says Isaly, Big Pharma will primarily be a distribution business.

In the 21st century, says Sam Isaly, Big Pharma will primarily be a distribution business

HORLICKS HELPS CEO SLEEP AT NIGHT

A peek inside the bag of free goodies handed out to shareholders at Glaxo's annual meeting in London gives an idea of one direction the industry is headed. Aquafresh toothpaste, Corsodyl mouthwash, Breathe Right nasal strips and Lucozade energy drink are not exactly at the cutting edge of bioscience, yet they are all products that now enjoy top billing under Glaxo's youthful Chief Executive Andrew Witty.

Under Witty, who has been in the top job for two years, over-the-counter remedies, oral care and health drinks have become a key pillar of Glaxo's drive to reduce reliance on traditional prescription pharmaceuticals. As if to emphasise that fact, the one new hire highlighted by the CEO in his address to the meeting was Emma Walmsley -- an executive



poached from French cosmetics group L'Oreal SA and heir apparent to run Glaxo's reinvigorated consumer healthcare business.

Glaxo may be working on groundbreaking treatments for cancer, but one of Witty's favourite products is Horlicks, a malted milk powder best known in Britain as a bedtime drink for the elderly. Horlicks is a huge seller in the key emerging market of India. The brand clocked up 146 million pounds (\$214 million) in Indian sales in 2009, bagging an enormous 48 percent of the hot drinks market there.

For industry veterans like Andy Smith, who worked at what was then SmithKline Beecham in the 1990s and is now a healthcare fund manager at Axa Framlington, the change is profound. "When I worked for consumer healthcare we were always the poor relation, which is actually why I moved to the pharmaceuticals division," he says. "Senior management always used to complain about the mixed P/E (price-to-earnings) multiple of having a consumer healthcare business and a pharmaceutical business and the fact that the analysts didn't understand it -- but now they are really appreciating it."

It's not hard to see why. Ten years ago, the pharmaceutical sector was trading at 30 times expected earnings. Today, most Big Pharma shares have a forward P/E of under 10, while consumer products companies like Procter & Gamble Co fetch around 15 times forecast earnings.

But diversity doesn't just mean selling a wider range of products. Big western drugmakers are also expanding into emerging markets such as China, which is set to overtake Germany as the world's third biggest drugs market next year, according to IMS. The fast-expanding middle classes in China and elsewhere are demanding drugs that they couldn't afford a few years ago. Overall sales growth in emerging markets is expected to be three times that of developed markets in the next five years.

In China, western companies have linked up with local players and research institutes. Some firms are even cosying up to old enemies in the Indian generics sector, following new legislation that has improved patent protection in that country.

But multinational drugmakers know they have to do more than sell toothpaste and expand into Asia. They need more and better drugs to sell -- and they need them fast.

Horlicks is a huge seller in India, bagging 48 percent of the hot drinks market.



People leave a building at Imperial College in London, May 28, 2010.

REVERSE ALCHEMY

The problem is, Big Pharma doesn't have nearly enough new drugs in the pipeline to replace all those it is about to lose. Since 1950 -- virtually the dawn of the modern era of medicine -- a total of 1,256 new drugs have been approved by the U.S. Food and Drug Administration (FDA). But the industry today produces roughly the same number of new medicines that it did 60 years ago.

Ten years ago there was a lot of hope that process-led research systems would industrialise the hunt for new drugs. But that optimism may have been misplaced. A spike in drug approvals in the mid-1990s, it turns out, was not the result of any fundamental improvement in productivity but largely down to the FDA clearing a backlog of applications after the introduction of a new system under which companies paid "user fees" to help speed the process.

Despite pouring billions into research -- more than \$65 billion last year in the U.S. alone -- the number of new drugs launched annually has fallen 44 percent since 1997, according to CMR International, a Thomson Reuters subsidiary.

Big Pharma has also struggled over the past decade to produce the kind of big new hits that make the bulk of its money. As with other industries dominated by

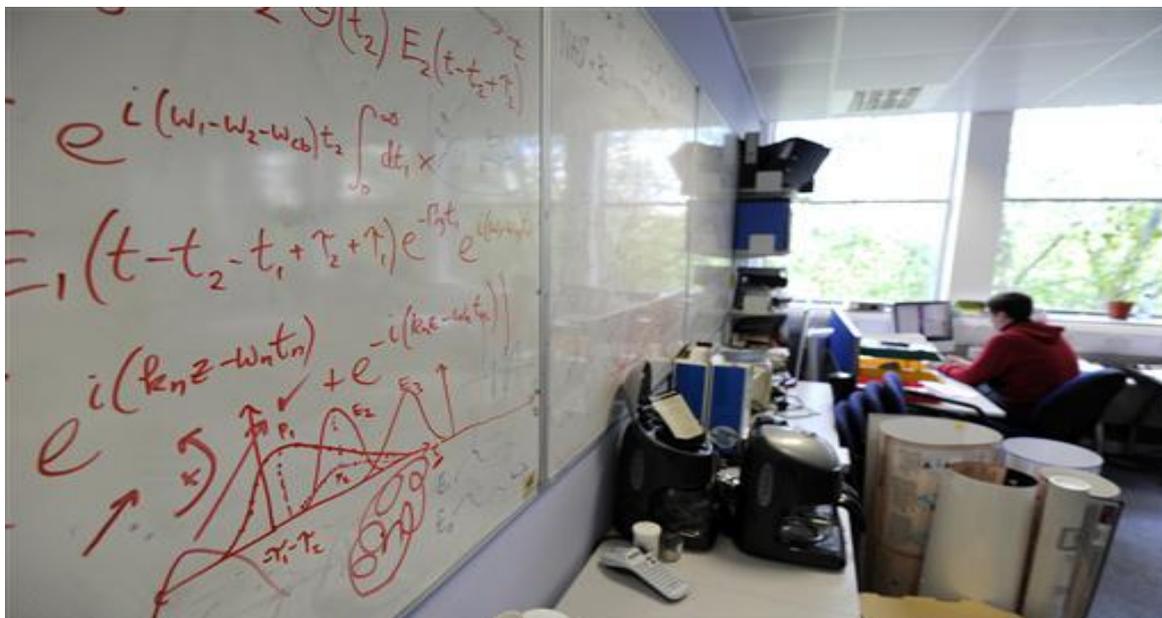
The number of new drugs launched annually has fallen 44 percent since 1997

blockbusters -- think Hollywood movies or oil and gas exploration -- it's not easy to pick winners years in advance. Even after a drug gets approval, commercial success can be a hit-and-miss affair, as evidenced by lacklustre sales of recent arrivals such as the keenly anticipated blood-thinner Effient from Eli Lilly and Co and Daiichi Sankyo Inc.

"Once you take into account all the drugs that have fallen by the wayside, the returns have been pretty bad," says Peter Fellner, a veteran with three decades experience in both pharmaceuticals and biotechnology. "It is a reverse alchemy calculation where you are taking a very large amount of gold and quite rapidly transmuting it into lead."

Few people understand the current change better than Fellner. After working for Swiss drugs giant Roche Holding AG in the 1980s, he headed up Britain's flagship biotech company Celltech. Now the quietly spoken management veteran chairs a clutch of small drug development and medical technology companies.

The move to cut R&D, he says, is one of the most profound changes in the industry in decades. Some firms are pulling back from problematic areas like depression, where proving the value of new medicines in clinical trials is fiendishly difficult. Lack of progress in this field is a prime reason behind Glaxo's decision to cut research in Verona. Other firms are cutting back in areas that used to be their bread and butter. Pfizer, for instance, is trimming research into cardiovascular drugs and AstraZeneca is ending discovery in psychiatric medicine.



Calculations are seen on a white board in a laboratory at Imperial College in London, May 28, 2010.

Instead of pouring money into R&D themselves, drugmakers are turning to smaller firms, outsourcing routine research functions and even buying in smart blue-sky discovery work.

Some scientists fear that shift will strip drug companies of the creative talent that has driven the industry for decades.

But it is good news for contract research organisations (CROs) like U.S.-based firms Covance Inc and Charles River Laboratories International Inc, which saw their shares soar -- at least until late 2008, when the recession and the scale of the structural problems facing the pharmaceuticals industry forced many smaller drugmakers to abandon certain areas of research altogether. Despite the setback, big CROs expect to expand in the long-term and are investing heavily in drug discovery services.

BRAIN SHIFT

They're also happy to pick up Big Pharma's leftovers. Glaxo, for example, is negotiating to sell its Verona site to a U.S.-based CRO called Aptuit. Parexel International Corp, which is based in Boston and conducts clinical trials for drugmakers around the world, is busy hiring hundreds of new staff -- many of them refugees from Big Pharma. "It's a brain shift," says Parexel's chief executive and founder Josef von Rickenbach. "The rate of outsourcing has continued to tick up pretty much every year across all clinical trial activities."

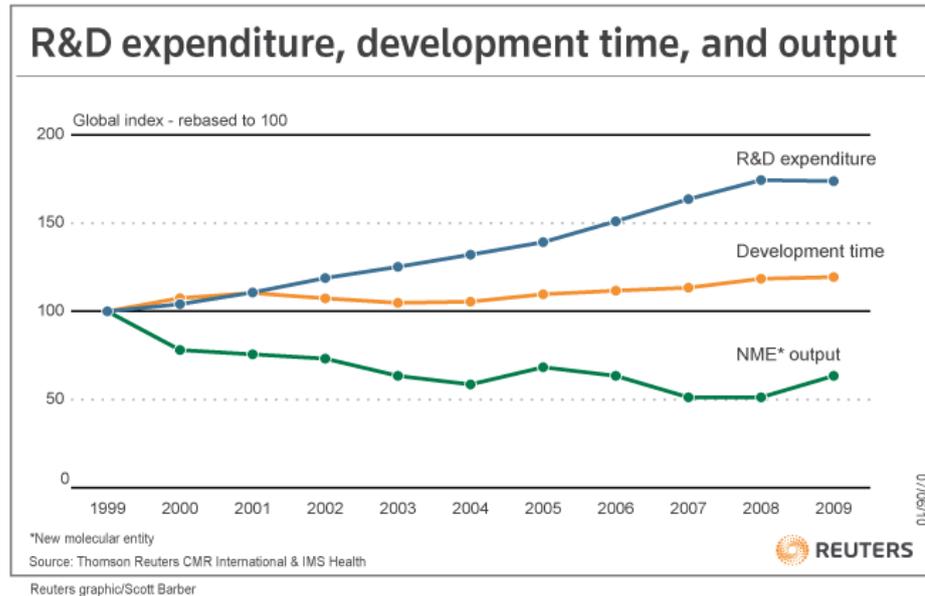
It's good news for contract research organisations

How far can it go? Does it make sense for big drugmakers to simply throw in the towel on early-stage research and instead buy in promising products from smaller operators in the biotech sector? "In the current phase of the cycle, I think you will see companies come close to it," says Fellner.

The short-term commercial case is compelling. Morgan Stanley analysts calculate that \$1 invested by a big drugmaker in a product licensed from outside researchers will, on average, deliver three times as much value as the same dollar invested in in-house research. Some of today's top drugs started life in outside labs, including AstraZeneca's cholesterol fighter Crestor and Bristol-Myers Squibb Co's schizophrenia drug Abilify.

While the immediate reasons for exiting some areas of R&D may be clear, though, the long-term implications are harder to know. There are obvious practical considerations. For one thing, pharmaceutical companies will need to make sure they retain enough internal know-how that they can continue to properly assess new drug prospects pitched to them by outside firms.

There are also significant reputational issues. Drug companies have long promoted the idea that they pursue new drugs for the good of humanity; it's an argument Big Pharma regularly uses to justify the huge profits it makes. High returns, the industry argues,



can be ploughed back into research on the next medical breakthrough. If Big Pharma is not doing the research itself, will the big margins be harder to defend?

Glaxo's Witty says it's all about balance. "We'd like to have a decent western, white pill business but I don't want any part of the group to be overwhelmingly important. I want a balanced organisation," he told Reuters. "I'd feel very comfortable if in a few years' time ... we had a quarter of the business in that traditional pharmaceutical space, a big chunk of business in vaccines, a big chunk in consumer products and a big chunk in emerging markets, with new large molecules (biotech drugs) also coming through."

A BIOTECH FUTURE -- PERHAPS

There's also a question of control. One hunting ground in the new-look world of Big Pharma is biotechnology. Biotech start-ups contribute an increasing share of the experimental compounds entering the development pipeline. Biotech's "large molecule" protein drugs, made using genetic engineering, have proven superior at fighting complex diseases like cancer to many conventional "small molecule" chemical drugs.

By 2014, the world's two top-selling prescription drugs won't be tablets sold in blister packs but needle-based biotech treatments -- Avastin for cancer, sold by Roche, and Humira for rheumatoid arthritis, from Abbott Laboratories -- according to consensus forecasts compiled by Thomson Reuters.

But while biotech is attracting increased interest from large pharmaceutical firms, the sector is struggling with its own problems. Early funding is hard to come by and there's growing scepticism from investors because of the huge risks involved in researching something that might never pay off. "Theoretically, this should all be good news for biotech because it means that Big Pharma is looking round more intensively for good pipeline opportunities," says Sijmen de Vries, chief executive of Dutch biotech firm Pharming Group NV. "The reality is different. Financially, much of biotech is in a bad state of health because of the extremely unhealthy situation that

exists at the moment with regards to investing in things that have even remotely the word 'risk' associated with them."

De Vries, a straight-talking Dutchman who trained as a doctor before working at Novartis AG and SmithKline Beecham, knows all about risk. His company lies at one of the extreme edges of biotechnology and is pinning its hopes on a drug derived from the milk of genetically modified rabbits. The company hopes the milk can help a small group of patients with a rare genetic disorder, hereditary angioedema, which causes acute and painful swelling of the body's soft tissues. European regulators could announce their verdict on the drug this month. If the drug is approved, the company should thrive. If it's rejected, Pharming will struggle. Such binary events are typical in biotech.

All that puts biotech firms into something of a financial Catch-22. As Big Pharma cuts its R&D, it is looking to small independent companies such as biotech start-ups to fill the gap. But without financial backers to help develop new drugs through those early stages, those smaller firms struggle to survive. "Pharma companies are very good at certain things but the thinking-outside-the-box, early-stage stuff is generally better done in biotech than in pharmaceutical companies because pharmaceutical companies tend to be more conservative," says Steve Jackson, professor of biology at the University of Cambridge. "The problem with that model is that venture capital funding is becoming more difficult to come by for biotech companies ... so that is another threat to the pharmaceutical companies' pipelines. I'm not sure how many new biotech companies are going to be springing up over the next five years or so."

Jackson has first-hand experience at how tough it is to shepherd a drug through those first few years. In the 1990s, he developed a cancer drug that prevents certain DNA repair proteins from working. That led to the creation of biotech company KuDOS in 1997.

Finance was tough, but persistence and a winning idea eventually secured him three rounds of venture capital funding and, in 2005, the company's sale to AstraZeneca. Today, he is looking to start another biotech business but finding times much harder. Ironically, while his original cancer drug is

\$1 invested by a big drugmaker in a product licensed from outside researchers will deliver three times as much value as the same dollar invested in in-house research.

MORGAN STANLEY



continuing to show promise in clinical trials, the KuDOS facility in Cambridge is now one of those facing closure as a result of the AstraZeneca cuts.

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ONE LAST REFUGE

Back at Imperial College, Nick Brooks, a scientist working on membrane biophysics, scrutinises a computer screen showing the results of X-ray diffraction. For now, academia remains a refuge from change.

"Certainly, at the moment, the prospect of getting your job taken away is a lot less severe here than it is in the pharmaceutical industry," he says.

He wonders how far the drug industry can change before it loses its science core -- and its way. "I can't help but feel that the idea of a pharmaceutical company having good researchers in-house to be able to take part in the whole process from conception of a drug through to marketing must be a benefit," he says, before turning back to his work.

(Additional reporting by Julie Steenhuisen in Chicago and Bill Berkrot in New York; Editing by Simon Robinson and Sara Ledwith)

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