Prescription for change

Jun 16th 2005
From The Economist print edition

The pharmaceutical industry is ailing. Shereen El Feki (interviewed here) takes its pulse and predicts a partial recovery

AS A boy in the 1930s, your correspondent's father lived in fear of pneumococcal pneumonia. With good reason: one of his young friends had died of it. It caused coughing, chills and fever, leading to a crisis in which the patient either suddenly expired or miraculously recovered. Today, there are drugs to tip the balance in favour of survival, and a vaccine to prevent the disease altogether. But the pharmaceutical industry, which has been responsible for bringing such drugs to the market, is passing through its own crisis. Research and development (R&D) is spluttering, earnings have weakened, its public image is tarnished.

Pharma's giants 1

"Big Pharma" firms, by sales

Company	Pharma sales, $bn 2004	Market capitalisation, $bn end 2000	Market capitalisation, $bn end May 2005
Pfizer	51.1	290	207
GlaxoSmithKline	32.8	178	145
sanofi-aventis	27.4	49	128
Johnson & Johnson	24.7	146	200
Merck	23.9	216	71
Novartis	22.9	128	131
AstraZeneca	21.7	89	69
Roche	17.8	91	112
Bristol-Myers Squibb	15.6	146	50
Wyeth	14.3	83	58
Abbott Laboratories	14.3	75	75
Eli Lilly	12.7	105	66
Schering-Plough	6.9	83	29
Bayer	6.4	39	25

Sources: IMS Health; Thomson Datastream

This survey will examine the global drug industry, probe some of the patient's sorer spots and offer a diagnosis. Treatment is far trickier, but the following articles will suggest ways in which all those with an interest in its success—pill-makers and pill-takers—can hasten the recovery.

The global pharmaceutical industry consists of thousands of companies, including biotech firms, generic drugmakers, contract research organisations, wholesalers and retailers. On top of them all sits "Big Pharma"—a dozen or so multinational firms with headquarters in Europe or America (see table 1). Their sales account for roughly half of the world's $550 billion retail drug market. But the pharmaceutical industry is relatively fragmented, with the biggest company, Pfizer, holding less than 10% of the global market.

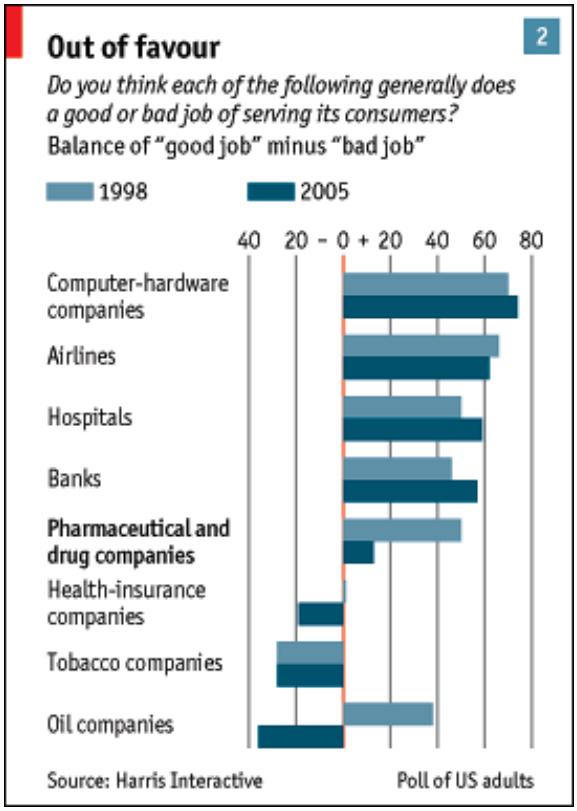
On the face of it, Big Pharma firms are in a business to die for. Populations in rich countries—and increasingly developing ones too—are getting older, and many people suffer from chronic conditions. Global drug sales have almost doubled since 1997, and will rise to more than $700 billion by 2008. By the standards of other industries, most big pharmaceutical companies are hugely profitable: operating margins are more than 25%, against 15% or so for consumer goods.

Tales of woe

But behind the healthy glow, a more worrying picture emerges. In the past few years large drug companies have had trouble getting new drugs out of their pipelines and into the market. At the same time, several high-profile medicines have been withdrawn because of safety concerns. Recently a whole group of drugs, anti-inflammatory medicines both old and new, have run into trouble. And several firms have suffered manufacturing problems.

Moreover, many so-called "blockbuster" drugs—those with more than $1 billion in global annual sales—have had their patents, and their market share, challenged by cheaper generic rivals. Over the next five years, a record $70 billion-worth of drugs will face generic competition in America alone. Drug-company sales, which increased by 10-15% a year for most of the 1990s, have slowed to single-digit growth. As a result, investors have shifted their attentions away from pharmaceutical firms, particularly in America, where drugmakers are currently in a worse

state than their European peers.



The internal travails of the world's leading drugmakers have been compounded by a broader social debate about the purpose and practices of the industry, again mostly in America. This is the world's largest drug market, accounting for over 40% of global sales. American drug prices are largely set by the market, which has prompted pharma firms to invest there on a large scale. As a result, they have become a highly visible target for criticism. Europeans are far less exercised about the industry, in part because their drug bills are paid for mainly by their governments, and in part because they are shielded from pharmaceutical marketing.

Last year, health-care spending in America reached an estimated $1.8 trillion, more than 15% of GDP. Some $200 billion of that went on prescription drugs. Despite this enormous expenditure, large numbers of Americans are becoming increasingly frustrated about the state of health care in their country. Many elderly people struggle to pay for their drugs (although from next year they will get a helping hand from the government), big companies complain about their medical bills, and 45m people lack health insurance. Over the years, this frustration has in turn been vented on doctors, managed-care companies and hospitals; now it is the drug companies' turn, their public standing having fallen as precipitously (see chart 2) as their share price.

The drugmakers' dilemma

Why this anger at companies in the business of making life-enhancing medicines? The following excerpts from a report on congressional hearings in America neatly summarise the case against and for Big Pharma in turn:

> It has been argued that the drug industry derived a higher rate of return on its investment than other American industries. It has been argued that the pharmaceutical companies have at times exaggerated in their claims for the therapeutic value of certain drugs. It has been argued that the drug companies have spent an unreasonable portion of their budgets in order to indoctrinate doctors so that they would prescribe high-priced trade-marked products.
>
> The drug industry is a success story. But success cannot be accomplished through miracles. Unless the drug industry was given an opportunity to reap the harvests of its successes and to invest large portions of it in the development of its facilities and its research, this phenomenal success would not

> have been possible. Without the profit motive, and without the profits being reinvested in the industry, the state of the American pharmaceutical industry today would not be what it is.

How true. Pharma profits are both a blessing and a curse. Many people feel uncomfortable with the idea of money being made from medicine, even when it is the price to be paid for innovation and better health. Pharmaceutical firms are not the only ones to make a handsome living out of health care, but they do so more conspicuously than others. Few patients know how much their doctor earns, or what a hospital is charging. But Americans blame high drug prices on Big Pharma's appetite for profits. Senator Edward Kennedy, a long-time critic of the industry, has a simple formula for categorising drug firms: he reckons that a third of them have the public interest at heart, a third are motivated by greed, and a third are somewhere in-between.

This is nothing new. Indeed, the congressional hearings quoted above took place back in 1960. The debate over pharma profits and practices has waxed and waned ever since. In the 1960s and 1970s, the first wave of blockbuster drugs for ulcers and high blood pressure came to market, drugs that treat—or even prevent—chronic conditions and are therefore taken for years. This was a fundamental change from an earlier generation of drugs that tackled acute ailments such as bacterial infections. The 1980s brought more new pharmaceuticals, for depression, cancer and nasty viruses, such as HIV.

By the early 1990s, the prospect of health-care reform and price controls in America brought gloomy predictions for the industry, but they turned out to be spectacularly wrong. Drugs that had been seen as modest earners, such as the cholesterol-lowering statins, became multi-billion-dollar blockbusters. Massive marketing campaigns lifted sales, and investors piled in as share prices rose ever higher. Firms flirted with all sorts of businesses before homing in on patented pharmaceuticals as the model for modern big drugmakers. The launch of a few high-profile drugs, such as Viagra and Lipitor, created the sense of an industry always on the verge of great scientific breakthroughs. And the growth of employer-sponsored health insurance provided a lot more money to pay for it all.

At the same time, white coats started to give way to dark suits in the boardroom as a new generation of CEOs from the commercial side of the business took over from scientists and doctors. Firms started to concentrate on hitting quarterly earnings forecasts, and mergers became a popular way to cut costs. Drugmakers began to spin out patents to stretch their sales, and became staunch advocates of strong intellectual-property rights at home and abroad. Existing drugs were tried out on different diseases, and more drugs of the same feather—so-called “me-too” medicines—poured out of the pipelines.

Much of the mess some of the big pharmaceutical companies have found themselves in over the past few years is a consequence of those heady days. The fruits of new science, such as bioinformatics and genomics, are only now starting to appear, later, as usual, than scientists had hoped for, and size has not helped the big pharmaceutical firms to excel at discovering new drugs.

Marketing practices are now under scrutiny, and drug companies stand accused of rushing drugs to market on the back of inadequate studies and withholding information about their drawbacks from patients and physicians. Drug companies have been slow to recognise that the traditional relationship between experts and the public has changed. Much of the public trust drugmakers enjoyed derived from the doctor-patient relationship, which is central to medicine. Yet that relationship too has changed over the past decade. If patients are prepared to question their doctors—sometimes prompted by pharmaceutical advertising—they are bound to start questioning the suppliers of their medicines too.

The cycle will in all likelihood turn again, and the bad press and gloomy investor sentiment will improve for a while. But drugmakers' essential dilemma will remain. As businesses, they are expected to innovate, take risks, compete vigorously and reap the rewards. But when they try to maximise shareholder returns, they run into trouble. If Kellogg wants to flood the airwaves with commercials to promote cornflakes for dinner, best of luck; but when Pfizer was trying Viagra for female sexual dysfunction, it was accused of inventing diseases to match its drugs.

A different kind of market

This illustrates the essential difficulty of bringing market forces into medicine. Health care does not work like a normal market, although there are ways of making it more market-like, such as shifting more purchasing power to patients and providing them with more information. But buying health care will never be like buying, say, a sports

car, because a sick consumer is more constrained in his choice than a healthy one.

Some critics of the drug industry argue that drugmaking should be taken out of private hands and put in the public domain; after all, many of the basic discoveries that drug companies develop and profit from came from universities and government institutes in the first place. But there is little evidence that governments or universities are any better than the private sector at bringing new drugs to market. The public may not like the way drug firms choose to spend their R&D dollars, or how they go about promoting their wares, but at least they have a record of bringing them to market in the first place.

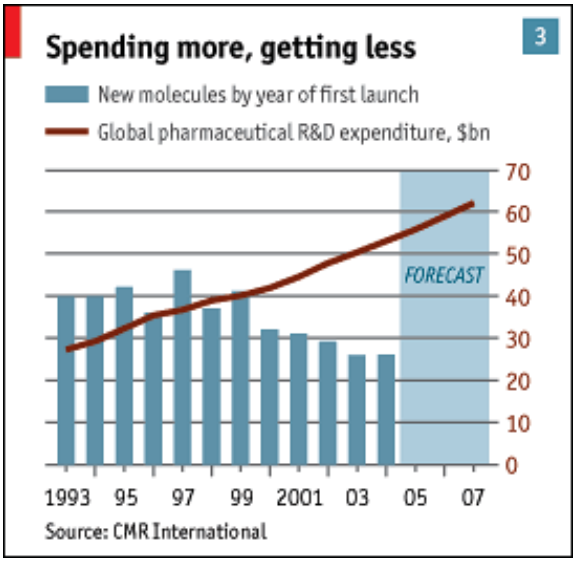
Pressure from investors, buyers, regulators, doctors and patients is already forcing the world's leading drugmakers to question the way they do business. “The industry was living a little fat and happy,” says Sidney Taurel, Eli Lilly's boss. Many firms are now busy cutting costs. Some are diversifying away from primary care to specialist drugs, vaccines, generics or diagnostics. Some smaller companies may find themselves in mergers over the next few years. Some of the biggest firms might get smaller as they spin off some of their operations, perhaps even their core R&D. It will become harder to tar the whole industry with a Big Pharma brush.

Whatever the individual prospects of today's big drugmakers, there is no doubt that their products as a whole have a bright future. The next decade will see the emergence of many more drugs of many more kinds to treat many more ailments. Some of these drugs will come from unexpected sources. Most of them will offer small but steady improvements over what went before, and will enhance the quality of life for some but not all patients. But there will also be a few breakthrough products that will tackle disease in fundamentally different ways. For all this to happen, though, better ways will have to be found of valuing these medicines, not only in terms of what they cost but also of the savings they bring elsewhere.

Testing times

Jun 16th 2005
From The Economist print edition

Getting more out of pharmaceutical R&D



R&D is the lifeblood of the pharmaceutical industry, but in the past few years many of the world's large pharmaceutical firms have been looking a little anaemic. The 1990s were a productive period, but more recently the number of new drugs launched on the global market has fallen dramatically (see chart 3).

The problem lies not just in the numbers of new drugs, but in how truly novel and useful they are. A few new drugs fighting disease in new ways have come to market since 2000, particularly cancer treatments. However, critics point out that only a third of the drugs launched on the market in the past few years were first or second “in class”. The rest were “me-too” medicines, tackling the same problem in much the same way as existing drugs.

Some drug-company bosses staunchly defend such drugs. They argue that the first product on the market is rarely the best, and that new entrants not only bring greater patient choice but also lower prices. “If everybody worked only on the high-risk, long-term projects, our investors would probably give up on us,” says Fred Hassan, boss of Schering-Plough.

Although output has been falling, drug companies have been increasing their R&D spending by about 6% a year since 1995, according to the Centre for Medicines Research International (CMR), to a forecast total of $55 billion by the end of this year, three-fifths of which came from big drugmakers. Given that it takes an average of 12 years to develop a drug from start to finish—depending on the nature of the molecule and the disease it tackles—the drugs coming to market today reflect the investments, and the science, of a decade ago. The big question is whether today's investments will yield better returns in the future. To answer that, it is necessary to understand why the output of drug companies has been declining, and what can be done about it.

Striking it rich in drug R&D is a chancy business. Drugs fall by the wayside at every stage: for every 10,000 molecules screened, an average of 250 enter pre-clinical testing, ten make it through to clinical trials and only one

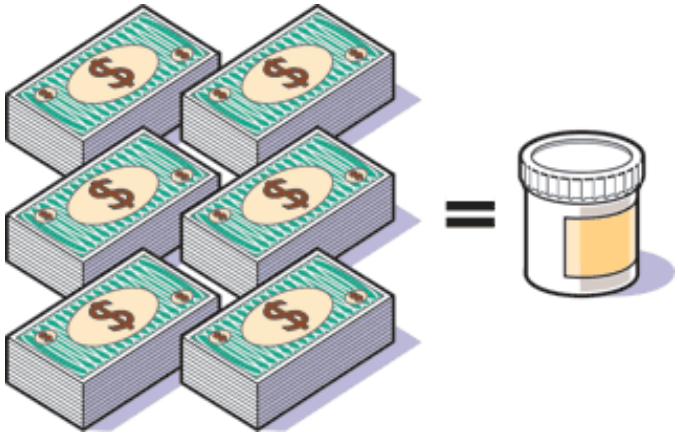
is approved by the regulator. Since the mid-1990s, average success rates have declined, most worryingly (because most expensively) at the later stages of clinical testing.

Stuart Walker, head of CMR, points to several reasons for the drop. Some of them are scientific: drugs that looked promising in preclinical development turn out either not to work or have unacceptable side-effects in clinical trials. Some of the problem, says Steven Paul, head of science and technology at Eli Lilly, stems from companies putting compounds into late-stage clinical development prematurely to gain a higher profile with investors.

Some of the reasons are structural. A wave of mergers over the past decade caused upheaval in R&D operations. Other contributing factors are commercial. One-third of all molecules fail to make it through clinical trials because it becomes clear that they will not justify further investment. But one drugmaker's reject is another company's opportunity—and more big drugmakers are licensing out their molecules to smaller drugmakers or not-for-profit groups, or spinning out whole research teams into new companies. Iceland's deCODE genetics, for example, picked up a discontinued asthma drug from Bayer and has taken it through mid-stage clinical trials for heart attack.

The time it takes to bring a drug to market has increased, with the biggest rise in the clinical-trials phase. Drugmakers often argue that because of increasing demands for data by regulators, the size and duration of clinical trials has risen steeply, delaying the entry of drugs to the market and bumping up their R&D spending. Critics say that drugmakers bring these problems upon themselves by running lots of trials simply to collect more data for marketing later on. Both sides have a point.

The cost of drugmaking is also going up. A much-quoted figure for bringing a drug to market is $802m, calculated by Joseph DiMasi, an economist at the Tufts Centre for the Study of Drug Development. Mr DiMasi used confidential industry data from 1983 to 2000 for a selection of new drugs discovered and developed within big companies. The average out-of-pocket cost for these drugs was just over $400m; the rest represents the discounted opportunity cost of capital. Dr Paul at Eli Lilly says the cost of bringing a new drug to market has now risen to $1.5 billion; others put it even higher.



In most industries such figures on the cost of product development are of purely internal interest. In the pharmaceuticals business, however, they have become the subject of public debate because they are (incorrectly) linked to drug prices. A recent analysis by Christopher Adams and Van Brantner at America's Federal Trade Commission, using the same methodology as Mr DiMasi, came up with an even higher average, but found wide variations across companies and products: for example, the average HIV drug cost $479m to bring to market, but the average figure for rheumatoid arthritis was $936m.

Shot in the arm

Some drugmakers have been restructuring their R&D operations to boost their productivity, most dramatically GlaxoSmithKline (GSK), which says it has doubled its early-stage clinical pipeline as a result. But investors are still sceptical about the ability of the world's biggest drug companies to discover new medicines. Many think that they should concentrate instead on what they do best: late-stage development and marketing.

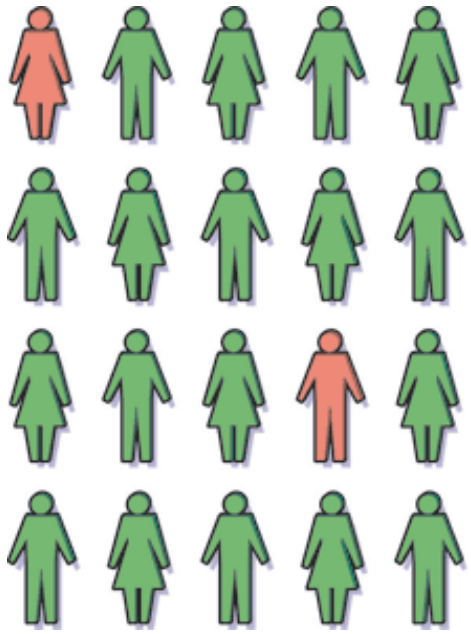
Certainly big drugmakers are looking to external sources of innovation. One-third of the molecules now in development originated in biotech companies. In-licensed molecules have had a higher chance of success in development in recent years because big drug companies tend to scrutinise these offerings more closely before bringing them in at a later stage of development.

But getting good bets is becoming harder and more costly as competition for molecules heats up, so big drugmakers are considering ever riskier projects. And a growing number of biotech firms are doing their own later-stage clinical development, regulatory submissions and sales.

Another route to more and better drugs lies in improving success rates. Until the 1990s, drug development focused on about 400 “druggable” molecules in the body that were known to be involved in diseases. The recent sequencing of the human genome has yielded thousands of potential new targets for researchers to try their molecules against; the problem is that it is proving much harder to “validate” these targets than researchers had hoped.

Drugmakers are looking for new technologies to help them predict a molecule's efficacy and toxicity as early as possible. One emerging tool among many is computer simulation, using software to model drug behaviour in a cell, tissue, organ or even population of patients in a much more sophisticated way than before, to improve the design of the real tests.

Novartis is trying another interesting tack: getting more information out of its early-stage clinical trials by using particular types of patients, rather than just healthy volunteers. For example, the firm has a new antibody drug to tackle IL-1, a protein involved in rheumatoid arthritis. To find out whether this drug affected the target, it turned to a patient with a rare disease called Muckle-Wells syndrome, in which too much IL-1 causes fevers, pain and migraines. The drug relieved her symptoms, showing that it affects IL-1 in the body, and at what dose.



Drugmakers are also pinning great hopes on biomarkers—biochemical or biological features that correlate with diseases and can therefore be used as a surrogate measure of efficacy or safety. For example, a widely used biomarker in the development of anti-retroviral medicines is viral load—the amount of HIV in the blood—because it is known to correlate with clinical outcomes, but is much faster and easier to measure than actual symptoms. Drugmakers would love to have reliable biomarkers for many more diseases.

To that end, companies are starting to talk about pitching in together. One new consortium is the Alzheimer's Disease Neuroimaging Initiative, which aims to test whether magnetic resonance imaging, blood markers, genetic profiling and neuropsychological testing can do a better job than existing methods of predicting the effect of drugs on early Alzheimer's disease.

Governments are keen to help clear the bottlenecks in drug development. The European Commission, having seen much of the continent's drug industry move its research money across the Atlantic, wants to help boost drug R&D at home. In America the National Institutes of Health and the Food and Drug Administration (FDA) have set up initiatives to push along drug discovery and development.

The personal touch

The sequencing of the human genome opened a new world of biomarkers. What if it were possible to tell by a person's genetic signature how they would respond to a particular drug? At the moment as many as half of all drugs do not work for the people who take them. Such pharmacogenomics could reduce the size and cost of clinical trials by allowing pharma firms to select the most suitable patients. In clinical practice, pharmacogenomic tests could lead to better use of drugs by matching subjects and treatment—the dream of “personalised medicine”.

But the reality is rather different. There are plenty of interesting genetic markers for scientists to look at; the

difficulty lies in proving that they reliably correlate with clinical outcome. Jörg Reinhardt, head of pharmaceutical development at Novartis, says his company was testing one new drug in 20 different countries, using a genetic marker that had been shown to give a 60% response rate. But when the researchers tried to subdivide their patient populations by country, they found response rates ranged from 25% to 90%. Something more than genetics was at work.

All the same, pharmacogenomics is slowly making an impact. The latest addition to the pharmacogenomic toolkit is the AmpliChip from Roche, which screens people for mutations in genes known to affect drug metabolism to determine the best dosage. Steven Burrill, who heads an eponymous merchant bank specialising in life sciences, reckons that diagnostics will be transformed from the poor cousin of pharmaceuticals into the main moneyspinner, leaving conventional drugs as the “commodity chemicals of the future”.

A world of personalised medicine would mean changes for drugmakers as well as for patients. At present, all roads lead to Big Pharma because of the size and complexity of clinical trials and the muscle required for marketing a blockbuster primary-care drug. But if personalised medicine allowed smaller trials, and marketing to more targeted populations, drug companies may not have to be so big.

Before and after

Getting a drug to market is one thing; a growing problem is keeping it there. High-profile withdrawals, such as that of Vioxx, a pain-relief drug, and Tysabri, a treatment for multiple sclerosis, have highlighted the problem of drug safety. This has created difficulties for both the drug companies and drug regulators. America's FDA has been accused of soft-pedalling on pharmaceutical safety, drug labelling and advertising, and being in thrall to an industry that pays many of its bills to maintain the drug-approval process; but it staunchly denies accusations of regulatory capture, and is setting up its own drug-safety oversight board within the agency.

Some members of Congress are pushing for a new, independent agency responsible for monitoring and acting on drug-safety issues. Senator Charles Grassley, who is heading the move, thinks the FDA lacks the right culture for the task. But others fear that a separate agency will be so concerned with the risks of drugs that it will neglect their benefits.

The present system of clinical trials is designed to demonstrate the safety and efficacy of drugs before they come to market. To pick up side-effects that are rare or occur only after long-term use before a drug is approved, clinical trials would have to become even bigger and more expensive. Moreover, clinical trials take place in highly controlled conditions that are quite different from the rough-and-tumble of routine clinical practice.

The remedy is to collect better data about the safety of drugs already on the market from doctors, patients and drugmakers. Systematic trawling of massive databases held by government payers and private health insurers might also show up problems that individual doctors and patients might not necessarily associate with a particular drug.

Such signals would still need to be followed by structured trials in the marketplace. The world's leading drug regulators already ask drug companies to follow their medicines in the market with so-called “phase IV” studies to look at various aspects of safety and efficacy; agencies in Europe and Japan have greater powers than the FDA to enforce this.

Another option, says Thomas Lönngren, head of the European Medicines Agency, is “conditional approval”—allowing drugmakers to bring their products to market earlier but obliging them to do more intensive follow-up in a much smaller population until they have proven their safety and efficacy. This already happens with drugs for certain conditions, such as cancer, but could be applied more widely. Such a tool may come in useful, because there are signs that the R&D pipelines are starting to fill up again.

Looking west

Jun 16th 2005
From The Economist print edition

Japan's drug industry is running hard to catch up

JAPAN is the world's second-largest pharmaceutical market, worth $58 billion last year, according to IMS Health, a research firm. A greying population means growing demand for medicines to treat chronic diseases. Generic-drug use is low, so drugs losing patent protection should be fairly safe from competition.

With their home markets straggling, western drugmakers are giving the Japanese market increased attention and now account for more than a third of pharmaceutical sales in Japan. But the place is not exactly a goldmine. First, Japan is one of those countries where drug prices fall rather than rise. Last year alone, the government cut prices by an average of 4%. Second, Japan's drug regulator still requires a lot of clinical testing in Japan of drugs already marketed in the West, which is time-consuming and expensive.

Japanese firms have so far largely relied on licensing western drugs, which is becoming harder because foreign firms like to sell them on their own. Japanese drugmakers have invested less in R&D than their western peers, and Hirotaka Yabuki, at the Boston Consulting Group, reckons that R&D productivity of top Japanese firms is a third lower than that of their western peers. Nor do Japan's drugmakers have much of a local biotech industry to turn to for innovation. Sales and marketing is not a strong point either: Japanese salesmen have to push many more types of drugs in a single call than do western ones.

Over the past two years, Japan's pharmaceutical industry has seen a wave of mergers that has created three new pharma firms. Toichi Takenaka, chief executive of one of them, Astellas, says it was growing international competition that pushed him to merge and redeploy his R&D and sales force. Linking up with a foreign firm through acquisition or alliance can have a similar effect. The part-acquisition by Roche of Chugai, one of Japan's most innovative drug companies, has boosted the company's R&D activity and allowed some western techniques to be introduced. For example, Chugai is now starting to create specialist sales forces to sell its cancer drugs, and is even reaching out to patients.

Mergers and alliances also help Japanese firms expand abroad. Roughly 10% of the world's top 50 drugs already come from Japan, but they tend to be co-developed and sold by western firms. Takeda, Japan's largest drug firm, already derives over 40% of its revenues from outside its home country. Astellas now has enough money to conduct clinical trials abroad, which are critical for early entry to western markets. Japanese firms are still a long way from giving western giants a run for their money; but remember that people also laughed at the thought of Japanese cars on American streets.

Devil in the detail

Jun 16th 2005
From The Economist print edition

The art of pushing pills

The blockbusters 5
Top ten brands, global sales, 2004, $bn

Lipitor (cholesterol-lowering)	12.0
Zocor (cholesterol-lowering)	5.9
Plavix (anti-clotting)	5.0
Nexium (anti-ulcerant)	4.8
Zyprexa (anti-psychotic)	4.8
Norvasc (anti-hypertensive)	4.8
Seretide/Advair (anti-asthma)	4.7
Erypo (blood-cell booster)	4.0
Prevacid (anti-ulcerant)	3.8
Effexor (anti-depressant)	3.7

Source: IMS Health

A PRETTY blonde sales rep sits opposite a doctor, ready to promote her company's best-selling drug. “So does Zestran work?” the doctor asks. “About as well as the others,” she shrugs. “We're more expensive; actually we're almost double the cost.” As for Zestran's side-effects, “Patients won't shit for a week.” The flabbergasted physician wonders why he should let this drug anywhere near his patients. “Because I'm going to be perfectly straight with you,” the rep replies. “You're going to know exactly what your patients are getting with this drug, the good, the bad, the ugly—not some sugar-coated version.”

If this scene sounds improbable, that is because it comes from a film. “Side Effects” is the story of a perky young political-science graduate who joins a drug company to promote medicines to physicians, but finds the hard sell too much. Before quitting her job, she decides to give doctors a dose of reality by telling them the complete truth about the products. Remarkably, her sales rocket, her bonuses swell and she finds it ever harder to leave.

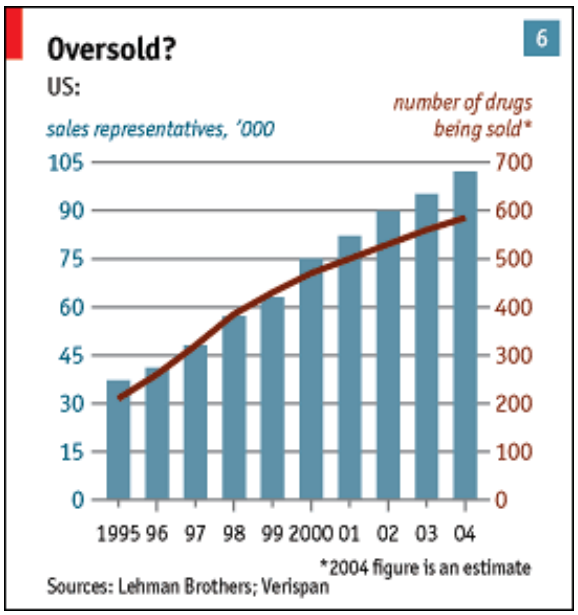
The film's writer-director, Kathleen Slattery-Moschkau, was a sales rep in the American mid-west until 2002. Much of “Side Effects” is fictional, she says, but many of its observations are true to life. When she was selling drugs, Ms Slattery-Moschkau's greatest fear was getting out of her depth when physicians started asking questions. Reps—who are invariably good-looking—were told never to let a doctor discuss the price of a drug. “It was not about getting a doctor to write a prescription for the best drug,” Ms Slattery-Moschkau recalls, “but your drug”.

Many of the promotional techniques used by drug companies are similar to those for selling cars. But drug reps do not actually sell drugs; they explain, or “detail” their products to physicians, and hope to persuade them to prescribe the drugs. Pharma firms back up this effort with ads and articles in medical journals, sponsored conferences and continuing medical education, plus direct-to-consumer advertising in some countries. The past decade has seen a massive rise in pharmaceutical marketing, to the point where a firm such as Novartis is spending around 33% of sales on promotion, compared with about 19% on R&D.

There has been a public outcry, especially in America, over the cosy relationship between doctors and drug companies. Some practices are illegal, others are simply part of the customary trio of food, flattery and friendship. But the days of wining, dining and free trips are slowly fading, at least in rich countries.

There has been a similar outcry about the industry's secrecy over clinical trials. Last year, GSK settled a lawsuit brought by Eliot Spitzer, New York's state attorney-general, which alleged that the firm had suppressed data showing a link between use of one of its antidepressants and suicidal tendencies in young people. Since then, a number of companies have volunteered to register their trials and report their results after a medicine is approved. But companies are still wrangling over how much information they are prepared to share, for fear that they might be giving away a competitive advantage.

As for “detailing”, drug-company bosses defend it as a means of technology transfer. A greater emphasis on blockbuster drugs, together with several mega-mergers over the past decade, has caused the number of reps in rich countries—and particularly America—to rocket, along with the numbers of drugs they are selling (see chart 6). Doctors known to be heavy prescribers are bombarded by up to half a dozen salesmen from the same company selling the same product because the drug companies know that more reps mean more sales. The average rep detailing to primary-care doctors generates $1.9m in sales each year, according to an analysis by Lehman Brothers. An additional 1,000 reps—at a cost of $150,000 a head—can bring in an extra $1.9 billion.



Drug companies have a powerful incentive to drive sales as hard as they can. Their patents are filed early in development and are being squeezed at both ends. Precious time is eaten up in clinical trials before the drugs come to market, and afterwards generic companies pile in. Meanwhile, other big drugmakers snap at their heels with rival products.

Even so, some firms are now starting to question their sales strategy. “Society doesn't want us to spend more money on marketing, and I agree,” says Jean-Pierre Garnier, head of GSK. But drug firms are caught in a classic dilemma: the first one to reduce its sales force will lose market share unless its rivals do likewise, and they are not allowed to co-operate: “We'd go to jail, that's anti-competitive behaviour,” notes Tom McKillop, head of AstraZeneca.

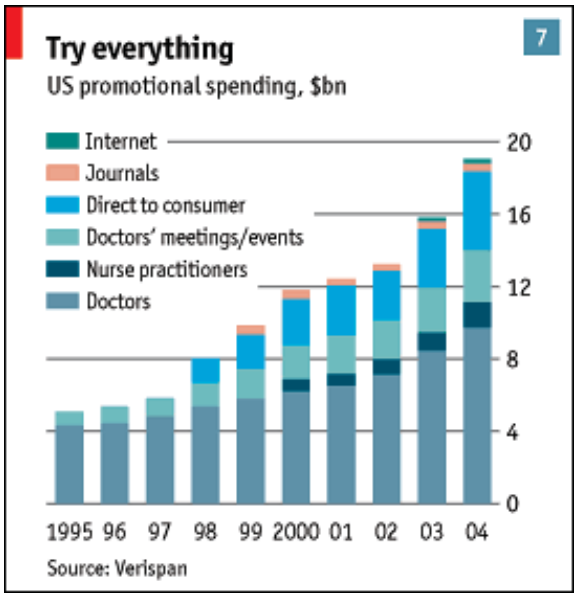
Pfizer, the world's biggest drug firm, is famous for its marketing prowess (it makes Viagra), but in April it announced a $4 billion cost-cutting programme, some of which will fall on its 38,000-strong international sales and marketing machine. In America, the firm is cutting the number of reps detailing a product to the same doctor.

Sales depend not just on how many reps you have but what you do with them, so Pfizer is also reorganising its reps the better to match Medicare's new prescription-drug coverage for the elderly. In America, drug firms already have access to a great deal of information about how each doctor behaves. New technology helps: Pfizer has tested issuing reps with tablet PCs so they can answer doctors' questions in greater depth.

Bristol-Myers Squibb has moved to using contract salespeople, who are easier to hire and fire as the pipeline fills and empties. The firm is also considering the use of tiered sales forces—better-qualified and better-paid reps to do the hard detailing, less high-powered and less expensive staff to deliver samples.

Perfect pitch

Another sore point for the industry is direct-to-consumer advertising. Only America and New Zealand allow makers of prescription drugs to promote their wares directly to the public. In most other countries the practice is prohibited. The proponents of consumer advertising argue that it helps make patients aware of medical conditions they may not have known about and gives them more information for discussing their condition with their doctor. Critics counter that such promotion encourages consumers to badger their doctors, compromising the quality of care and the doctor-patient relationship.



Drug companies have trebled their spending on direct-to-consumer advertising since it was legalised in America in 1997 (see chart 7), and the investment seems to have paid off. A study by IMS Health, looking at 49 brands advertised between 1998 and 2003, shows that the average return on $1 spent on advertising a blockbuster drug was more than $3.50.

But Vioxx may change that. The money that Merck and Pfizer poured into promoting COX-2 inhibitors undoubtedly drove many patients who might have done just as well on older drugs to ask their doctors for the latest thing. The perverse effect of this mass marketing is that drugs which would have been truly beneficial for a small proportion of patients are now out of reach for everyone.

Many drug-company CEOs admit they need to think again about direct-to-consumer advertising. AstraZeneca's Mr McKillop says he was never a great fan, but last year AstraZeneca spent $240m promoting Nexium, a controversial successor to its best-selling anti-ulcer drug which went off-patent, according to Verispan, a market-research firm.

A ban on such advertising in America is unlikely, given the country's constitutional protection of commercial free speech, but companies are beginning to accept that they need to change the way they advertise drugs to the public. Johnson & Johnson, for example, is now running ads that offer a more balanced presentation of risks and benefits. Pfizer is launching disease-awareness commercials, with its logo tucked in a corner. And Eli Lilly consults with payers and physicians before consumer campaigns.

But at a time when consumers are increasingly encouraged to take control of their own health, and expected to foot more of their own drugs bill, pharma firms need to do better than flood the airwaves. Other complicated businesses, such as retail banking, arguably do a better job of putting their message over to the public. To be fair,

drugmakers are trying to reach out to consumers in other ways, through websites, e-mail and call-centres. Roche is looking at sending SMS texts to patients to remind them to take their medicine. But such things are only a beginning. The pharmaceutical industry must do more to show that it is not the cause of today's health-care troubles but part of the cure.

The cost of living

Jun 16th 2005
From The Economist print edition

Drug prices need fresh thought

IN CHELMSFORD, Massachusetts, Tom and Linda Fall go through their ledger of medical expenses. The middle-aged couple have spectacularly unlucky medical histories, including diabetes, heart attacks, bypass surgery and a heart transplant. Between them, they take more than 30 drugs at a monthly cost of over $700, a quarter of their income. They have had trouble getting and keeping private health insurance, and have sold their house to help pay their medical bills. To their relief (mixed with embarrassment), they have just qualified for Medicaid, a state-funded insurance programme for the poor. Next year, Mr and Mrs Fall will get help from the federal government's new Medicare Prescription Drug Benefit for America's elderly, but still worry about the remaining cost. Mr Fall, although full of praise for the drugs, wonders why the prices have to be so high.

The price of pills is arguably the biggest bone of contention between drug companies and the outside world. Drug companies say that theirs is an increasingly costly and risky business; without prices that allow an adequate return on investment, pharmacological innovation will grind to a halt. This has fostered the belief that there is a connection between the price charged for a particular drug and the cost of the R&D that was needed to produce it. Not so. “The conventional fallacy is that the cost of R&D drives prices,” says Frederic Scherer, an economist at Harvard University. “In reality, it's the other way round: prices drive costs.” The more a company can charge for a drug, the more it will spend on developing and marketing it.

Unlike the science that goes into developing a drug, pricing is a bit of a black art that takes account of a number of factors, including how much better the drug performs than other treatments, the price of rival drugs already available, and what the market will bear. In rich countries, where governments generally foot their citizens' medical bills, a wide variety of tools are used to control drug spending. This infuriates drugmakers and does not necessarily make consumers happy either, because lower prices in a market tend to delay the arrival of new drugs.

Drug companies have been able to make up the money in America, where up to now the market has been willing to pay more for the latest products. But as employers shift more of their health costs on to employees, Americans are starting to ask why their drugs are more expensive than elsewhere. “People here are rightly very frustrated and angry that they are paying more for what looks like the same medication as many people get at a lower price in other parts of the world,” says Mark McClellan, head of the Centres for Medicare & Medicaid Services, the agency that administers the programmes.

So is the rest of the rich world free-riding on America? The answer depends on the type of drug and the particular supplier. Different Americans pay vastly different prices for their drugs. Some of the least well-off consumers, like the Falls, pay some of the highest prices because they do not come under the umbrella of a big employer or government agency that can negotiate discounts.

On the whole, generic drugs are actually cheaper in America than in many parts of Europe, according to Panos Kanavos, an economist at the London School of Economics. (A floor price, along with higher distribution costs, make generics in Europe relatively pricey.) The price differentials that really agitate Americans are those on blockbuster patented medicines, for which they pay much more. But a recent survey conducted by Mr Kanavos of the top 50 branded drugs in ten industrial countries shows that the differentials between prices in America and other rich countries are narrowing. The ten oldest drugs, launched before 1988, are up to four times more expensive in America than elsewhere; the ten newest drugs, launched after 1997, are only twice the price.

Narrowing the gap

America is keen to narrow the gap further. John Baldacci, governor of the state of Maine, is leading an attempt to persuade the federal government to allow cheaper prescription drugs to be brought in from Canada. Several bills are before Congress to permit so-called “reimportation” of pharmaceuticals from abroad; at the moment, the practice is technically illegal, but the authorities turn a blind eye to individuals bringing medicines for personal use across the border. Many American officials, and drugmakers, object to reimportation on the ground of safety, saying it exposes America to counterfeit drugs. Canadian politicians, for their part, are worried that pharmaceutical companies will stop supplying their country and drug supplies will run low.

Reimportation is just one of a range of tactics that the Americans are trying in order to control their drug bill. These aim at two targets: reducing the volume of new patented drugs consumed, and ratcheting down the prices paid for them. These measures are beginning to work: growth in retail drug sales last year slowed to 8%, the lowest in a decade.

Many of America's drugmakers take heart from the impending Medicare Prescription Drug Benefit, which will provide an estimated 29m elderly and poor people with at least partial coverage for their drug costs, and could boost the industry's sales by 2%, according to some estimates. The programme will be administered by private health-plan providers which will negotiate discounts with drugmakers. Dr McClellan reckons that competition for participants, combined with more price transparency thanks to the internet, will cause providers to drive hard bargains. Others are not so sure. “Medicare could have sent a strong signal to drugmakers. But because the law says there shall be no government negotiation over prices or formularies, we put a large lead shield over the beacon,” says Jerry Avorn, a professor of medicine at Harvard.

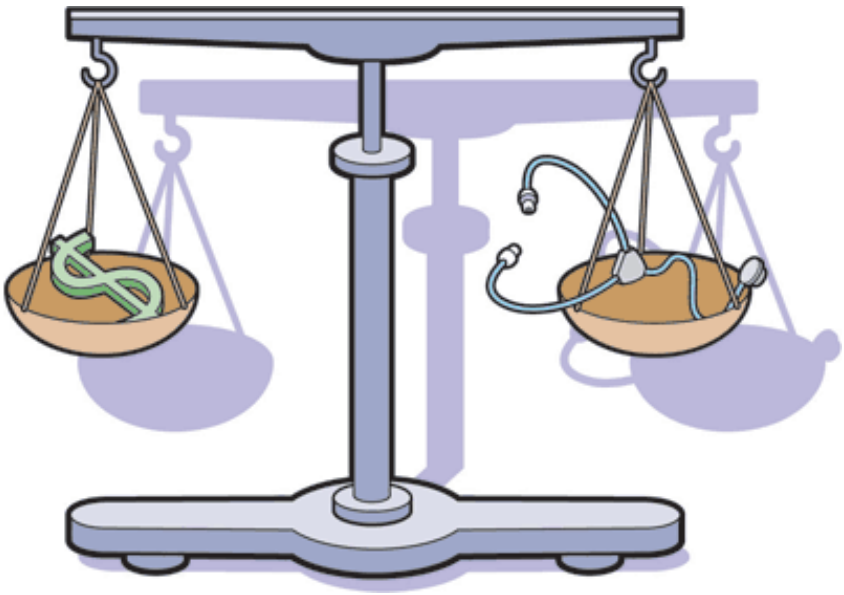
Spending more on drugs is not necessarily a bad thing. There is plenty of evidence to show that greater use of certain blood-pressure medications, for example, yields large overall savings through fewer hospitalisations and higher productivity when the patient is at work. What payers in America want to know when they decide whether to cover a drug is how its performance for a given condition compares with that of other drugs, says William Fleming, head of pharmacy at Humana, a big American managed-care company.

America's standards for regulatory approval require only that the drug in question be tested against a placebo to demonstrate safety and efficacy. In Europe, governments often ask drugmakers to test their drug against another of the same class to compare effectiveness before deciding whether to reimburse them. Britain, Australia and a number of other countries have also created special bodies to evaluate the cost-effectiveness of medicines and advise government on whether it is worth paying for them.

There are growing demands among American health insurers, big employers and state governments for something similar so that they can make better decisions on drug reimbursement. If more payers knew whether the drugs they pay for represent value for money, they might encourage drug firms to concentrate on developing the most cost-effective ones.

Heal thyself

Jun 16th 2005
From The Economist print edition



What the industry should do to get better

FOUR years ago, Novo Nordisk, a Danish drugmaker, was embroiled in a court case in South Africa. Together with 40 other drug companies, it was suing the South African government over its patent laws. For the pharmaceutical industry, this became a public-relations nightmare. Drugmakers stressed the importance of intellectual-property rights to encourage innovation, but non-governmental organisations argued that patents and high prices were condemning millions of poor AIDS patients to death.

Novo Nordisk does not actually make anti-retroviral medicines—the drugs at the heart of the South African debacle—but it is one of the world's leading producers of insulin and other diabetes drugs. Its boss, Lars Rebien Sorensen, realised that the problems the AIDS drugmakers had encountered could well be repeated over medicines for diabetes, a widespread disease in the developing world as well as in rich countries. So Novo Nordisk set up the World Diabetes Foundation, pledging $100m over ten years. The foundation works in 40 developing countries to raise awareness of diabetes and improve care in places where it is seriously underdiagnosed, such as India and China. There is no pressure on the foundation's beneficiaries to buy Novo's products; in fact, says Mr Sorensen, he prefers them to get their drugs from domestic generic suppliers. Where they do use Novo's products, the firm offers an 80% discount on prices charged in America and Europe.

Novo's local offices also teach doctors and patients how to prevent diabetes through diet and lifestyle, as well as setting up ancillary services such as foot-care clinics for diabetic ulcers. It might seem odd for a drug company to promote practices that could possibly reduce its sales, but Mr Sorensen reckons it is worth it for the long term. “Only by offering and advocating the right solutions for diabetes care will we be seen as a responsible company. If we just say, ‘drugs, drugs, drugs’, they will say, ‘give us a break’.”

Novo's example suggests that drugmakers might actually further their fortunes by teaching people when, and when not, to use their products. People who feel they are getting their money's worth tend to complain less about

the bill. Other pharmaceutical companies have been working along similar lines. Pfizer struck a deal with the state of Florida in 2001, helping 150,000 Medicaid patients to monitor and manage such chronic conditions as asthma and diabetes. In exchange, the state waived its demand for additional rebates on Pfizer drugs. The experiment cut Florida's costs by more than $40m over two years. The firm is now testing other health-management programmes in Britain and Italy.

The industry can certainly help improve the way its products are consumed. Sometimes drugs are overused: one study in Britain showed that two-thirds of prescriptions for so-called SSRI antidepressants, such as Prozac, were for “mild” depression, even though there is no good evidence that the drugs work in these cases. At the other extreme, many drugs, for example those for heart failure, are seriously underprescribed. And patients often fail to take their pills the way they are meant to.

Better use of pharmaceuticals depends on two main factors: a clearer understanding of why and how drugs should be used; and getting people to act on it. Technology can help: e-prescribing, for example, uses computer systems that steer doctors to the most appropriate drug for their patients. Another is setting up the right incentives, such as performance-based payments that reward doctors for achieving certain clinical outcomes in their patients and lower overall medical spending.

Where things have gone wrong, rebuilding reputations takes years. This is easiest for companies that do not have to pander to investors' demands for quick returns. Novo Nordisk, for example, can afford to invest in its programmes because the majority of its voting shares are controlled by a foundation. Roche has been able to make big bets on diagnostics and partnering with outsiders because the company's founding family still controls the voting shares. “The firm long-term commitment of this family which has seen up-and-down cycles of industry over 100 years makes it easier not to fall into the trap of short-term fixes,” says Franz Humer, the company's boss.

Signal failure

But most of the world's big drugmakers have to live with the whims of their investors, who over the past few years have been taking an increasingly short-term view of the industry. This is particularly true of hedge funds, which dip in and out of companies at will. The problem, claims Jeremy Levin, head of strategic alliances at Novartis, is that the respective cycles of the pharma industry and of investors are out of sync: stocks are bought and sold in an instant, whereas industry leaders stay in their jobs for five to ten years, and drug development takes even longer.

But some investors are hoping to encourage drugmakers to take an even longer-term view. Britain's Universities Superannuation Scheme, a £20 billion ($36 billion) pension fund, is concerned about executive pay packages that encourage short-term boosting of earnings per share. The group would like such pay to be based on more meaningful measures, such as the number of drugs moving through clinical development, or return on investment.

“It's very rare that an industry can see a train coming and also has the financial wherewithal to fix it,” says David Blumberg, a consultant with Accenture. Pharma companies still have enough money, and latitude, to make serious changes. They should start at the top. As the current generation of leaders retires, executive boards would do well to look beyond the usual suspects. Some of the drugmakers that have weathered the current storm best have bosses who have moved up from the clinic or the lab. But it is also worth thinking about talent from other industries, such as high technology; just look at the influence that Microsoft's Bill Gates has had on public health worldwide. The trouble is that many drugmakers suffer from a condition best described as “pharmaceutical exceptionalism”—a conviction that their industry is so complex that no one from the outside world can possibly grasp its intricacies.

One company that is looking outward is Wyeth. “We talk to companies in [the] airline, automotive, computer and low-tech [industries], trying to distill in R&D things that other industries do better than us,” says Bob Ruffalo, the company's head of R&D. “I think the last place you will find solutions is in the pharma industry.”

There are plenty of companies outside the industry from whose example drugmakers could learn. BP has managed to sail through rough seas, whereas Monsanto was sunk by genetically modified crops. That example is particularly close to home for the pharmaceutical industry, which saw that Monsanto could not win public approval by simply arguing the merits of its science. “Trust me, I'm a drugmaker,” is no longer enough.

Much of the criticism directed at the big drugmakers is richly deserved, but they do not work in a vacuum. If they are to serve the public better, many other changes are needed in the way health care is paid for and practised. Big pharmaceutical firms are full of clever, creative people who should be able to identify—and act on—big issues without being prodded by outsiders. Big firms, and not just drugmakers, have a tendency to react to events rather than anticipate them, though a few pharmaceutical companies have started trying to look ahead to the next storm.

With both science and social attitudes changing, the days of Big Pharma domination are numbered. Some of today's firms—those that can tap into the best science, streamline their operations and communicate more openly with the wider world—will still do well, although they may be less profitable. But those that cannot reinvent themselves will face decline.

The experience of Big Pharma holds a lesson for biotech firms and other rising stars of health care. Pricing, productivity, patents and safety are as critical to them as they are to the current giants. The next generation of drugmakers needs to deal with these issues more effectively. With the right medicine, the industry's current condition need not be chronic.