The Economist

Prescription for change

A survey of pharmaceuticals

June 18th 2005

Prescription for change

Also in this section

The pharmaceutical industry is ailing. Shereen El Feki 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.

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 pages 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, next page). 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 At the same time, several high-profile medicines have been withdrawn because of safety concerns.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 ▸▸

Acknowledgments
The author is grateful to the many people who so generously shared their expertise. Particular thanks go to Tarun Shah and colleagues at Mehta Partners; Stewart Adkins; Alastair Flanagan; Bill Haddad; and John Schaetzl.

A list of sources can be found online
www.economist.com/surveys

An audio interview with the author is at
www.economist.com/audio

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.

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

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.

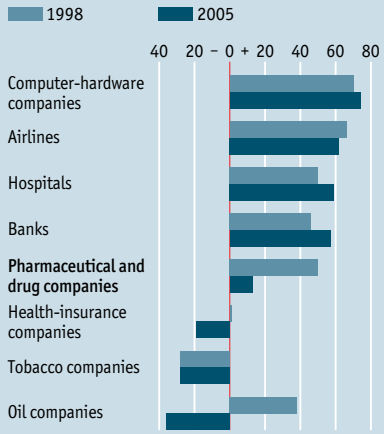
How true. Pharma profits are both a blessing and a curse. Many people feel uncomfortable with the idea of money being made from medicine, even when it is the price to be paid for innovation and better health. Pharmaceutical firms are not the only ones to make a handsome living out of health care, but 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—

Out of favour 2

Do you think each of the following generally does a good or bad job of serving its consumers?

Balance of "good job" minus "bad job"



Source: Harris Interactive Poll of US adults

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. Exist-

ing 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

Getting more out of pharmaceutical R&D

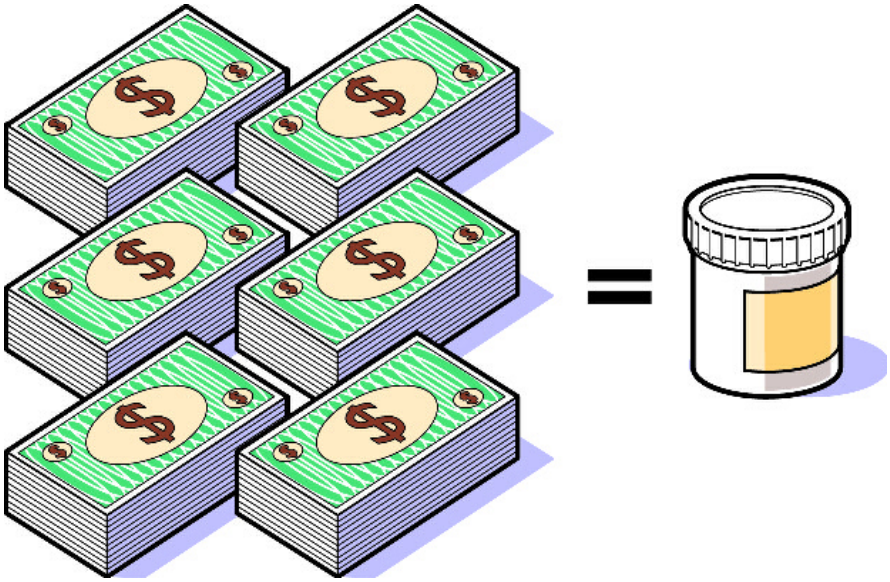
R&D is the lifeblood of the pharmaceutical industry, but in the past few years many of the world's large pharmaceutical firms have been looking a little anaemic. The 1990s were a productive period, but more recently the number of new drugs launched on the global market has fallen dramatically (see chart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

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-



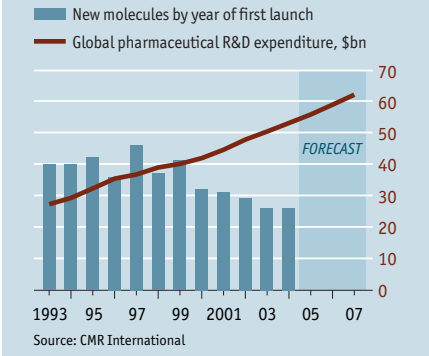
clinical testing, ten make it through to clinical trials and only one is approved by the regulator. Since the mid-1990s, average success rates have declined, most worryingly (because most expensively) at the later stages of clinical testing.

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.

Spending more, getting less 3



Source: CMR International

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

Looking west

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.

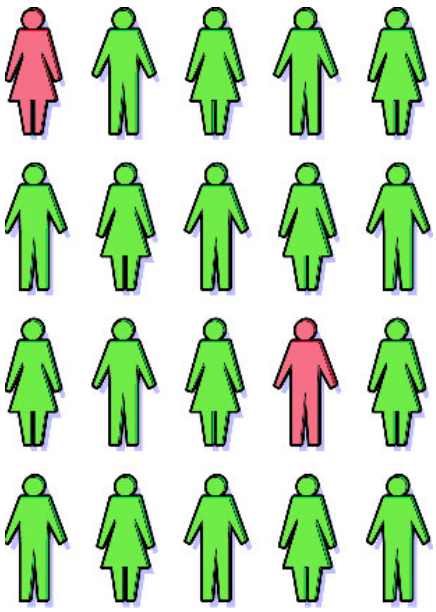
Mergers and alliances also help Japanese firms expand abroad. Roughly 10% of the world's top 50 drugs already come from Japan, but they tend to be co-developed and sold by western firms. Takeda, Japan's largest drug firm, already derives over 40% of its revenues from outside its home country. Astellas 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.

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 money-spinner, 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. ■

Alternative medicine

Neglected diseases are fighting for attention

ASK a big drug-company boss why he is in the business of making pharmaceuticals, and he will say he wants to "address unmet medical needs". But not all medical needs are equally attractive. Most of the 7,500-plus medicines currently in development by biotech and pharmaceutical companies are for chronic diseases of the rich world. At the same time, some of humanity's nastiest afflictions get little attention. Tropical diseases, such as sleeping sickness or leishmaniasis, are a turn-off for drugmakers because they strike mainly in poor countries and offer little hope of an attractive return on investment. Of the 1,500 or so drugs launched over the past 30 years, fewer than 20 deal specifically with tropical disease.

However, it is not just poor countries that are missing out. For example, there is an urgent need for new antibiotics in industrialised countries as drug-resistant bacteria emerge. Yet antibiotic development—once the cornerstone of the drug industry—has fallen out of favour with Big Pharma firms because of scientific hurdles and regulatory requirements.

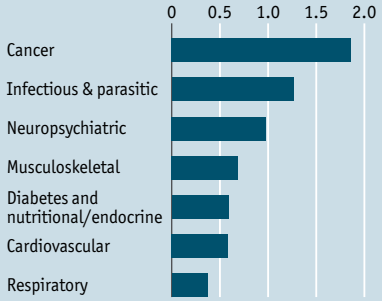
One way of getting attention for neglected diseases is for patients to take action. For example, the ALS Therapy Development Foundation, started by James Heywood, whose brother was struck down by this neurodegenerative disease, is using its modest budget to test hundreds of compounds in mice and men in the hope of finding a treatment for ALS.

Another route is to launch public-private partnerships. Drug companies contribute molecules, manpower and machines to not-for-profit groups that co-ordinate product development, funded mainly by private sources such as the Gates Foundation, with some government money. There are now about 20 such partnerships, focused on developing new drugs, vaccines or diagnostics for particular diseases of the developing world that will make them accessible to poor populations.

A few big drugmakers, such as GSK and Novartis, which inherited an interest in tropical disease from their parent firms, have chosen to invest in at least early-stage R&D in malaria, tuberculosis and dengue, with a view to partnering later on. They

Whose priorities? 4

Number of drugs in development
latest data, '000



Source: Pharmaprojects, PJB Publications

are motivated mainly by philanthropy, but also want to polish their image and hope to sell to travellers and to a rising middle class in developing countries.

Many of the partnerships act as virtual pharmaceutical companies, bringing together expertise from far afield. The Drugs for Neglected Diseases initiative, for example, has drawn together basic research from academics in Venezuela, molecules from Japanese and French drugmakers, clinical trials in Ethiopia and manufacturing by Brazilian firms.

The question is how to get the products out of the pipeline and to the people who need them. Development costs can be lower than in Big Pharma, in part because clinical trials for diseases such as malaria can be smaller, faster and therefore cheaper to run than for, say, Alzheimer's disease. Even so, Christopher Hentschel, head of the Medicines for Malaria Venture, reckons it will cost at least $100m to bring just one of its products to market, so much more money is needed.

All together now

One idea under discussion is "advance purchase commitments"—meaning that governments promise to buy products that meet certain standards at a pre-arranged price, thereby providing big drug firms with the promise of a certain return. But critics say that governments may well end up overpaying for the goods.

Another possibility is paying pharmaceutical firms in kind. For instance, they could be given longer intellectual-property protection, or faster regulatory approval, on a product of their choice, in exchange for developing one for a neglected disease. But generic drugmakers and consumer groups say this will dent competition and prop up prices.

A more radical proposal is for governments to sign on to an international treaty to devote a certain proportion of their GDP to R&D for drugs and vaccines, particularly for neglected diseases. Part of the plan is to create a prize system, paying a lump sum for an innovation which will then be placed in the public domain. But governments are notoriously bad at valuing innovation properly, and implementing this plan might be tricky.

Yet another tack is the Tropical Disease Initiative, which is trying to harness "open source", an idea pioneered in computer software. The aim is to bring together scientists through the web to trawl through databases and do computer experiments to find promising new molecules to feed into the public-private partnerships—all patent-free.

None of these strategies is perfect, admits Stephen Maurer, a backer of the initiative at the University of California at Berkeley. The important thing, he says, is to move beyond "dreamy first-world arguments" about which approach is more ideologically sound, and start looking at the real costs of what might be done. ■

Devil in the detail

The art of pushing pills

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 pharma-

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

Counter culture

Many prescription drugs are moving to over-the-counter

REACHING out to consumers comes naturally to the cheaper and, these days, more cheerful side of the business: over-the-counter (OTC) medicines. For example, Xenical, Roche's anti-obesity drug, was launched with great fanfare in 1998, but sales failed to take off, in part because of the way the drug works: it blocks the absorption of fat in the gut, so greasy foods come out at the other end as oily stools. Earlier this year Roche teamed up with GSK to turn Xenical into a lower-dose over-the-counter medicine. Instead of getting a bottle of pills, customers will buy a weight-loss kit with information and advice on how to change their diet and behaviour. So the drug becomes a tool to help customers identify and avoid hidden fats in food. Provided it meets all the FDA standards for safety, efficacy and customer comprehension, the drug could be on the market next year. Such consumer marketing—where a pill becomes part of a broader health-care solution—is just the sort of thing prescription drugmakers need to do more of.

The OTC market used to consist of drugs to treat acute conditions that were easy to self-diagnose, with little potential for harm from abuse by the patient. The new generation of OTC drugs, switched from prescription status, break that mould. They include Zocor, a cholesterol-lowering statin, which was switched last year in Britain, and Prilosec, an anti-ulcerant now available over the counter in America. Others that might make the leap in the next few years are drugs for asthma, osteoporosis and migraine. OTC drugs are sold much more cheaply than branded prescription pills, but big drug firms welcome them as a way of managing their product lifecycle, especially when a drug is about to go off-patent.

Private payers and governments like OTC because it offers the potential of reducing their drugs bills and saves on the cost of doctors' prescriptions. Such switches also fit well with the movement towards empowering patients. In Britain, taking Zocor OTC is part of a government strategy to help people at moderate risk of a heart attack to control their cholesterol levels.

America's FDA is also keen on selling more drugs over the counter. But America lacks the sort of "behind-the-counter" system found in many European pharmacies, where pharmacists hand out advice together with the medicine. Until something similar is introduced there, many potential OTCs will have to wait.

ceutical 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.

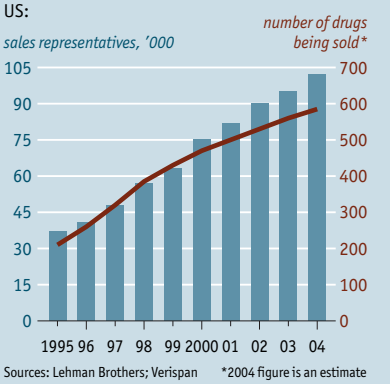
There has been a public outcry, especially in America, over the cosy relationship between doctors and drug companies. Some practices are illegal, others are simply part of the customary trio of food, flattery and friendship. But the days of wining, dining and free trips are slowly fading, at least in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

Oversold? 6

US:



Sources: Lehman Brothers; Verispan *2004 figure is an estimate

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.

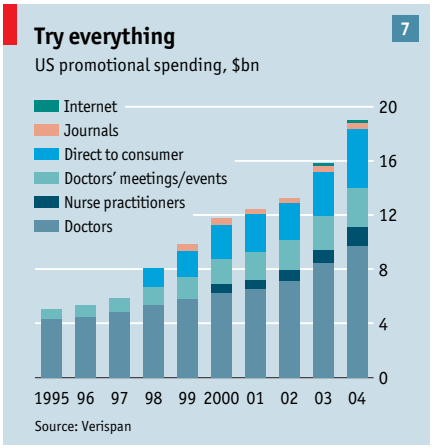
Bristol-Myers Squibb has moved to using contract salespeople, who are easier to hire and fire as the pipeline fills and empties. The firm is also considering the use of tiered sales forces—better-qualified and better-paid reps to do the hard detailing, less high-powered and less expensive staff to deliver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

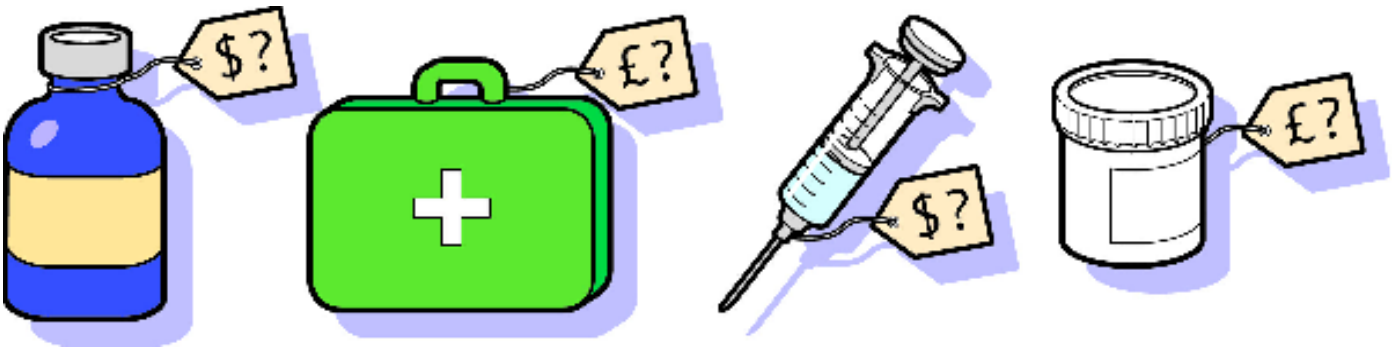
But at a time when consumers are increasingly encouraged to take control of their own health, and expected to foot more of their own drugs bill, pharma firms need to do better than flood the airwaves. Other complicated businesses, such as retail banking, arguably do a better job of putting their message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

The cost of living

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. ■

The next big thing

India and China hold great pharmaceutical promise

TO APPRECIATE the promise, and the problems, of globalisation for today's giant drugmakers, take a trip to Mumbai. Drive past the slums of the city and the lush villas of Malabar Hill to the R&D headquarters of Nicholas Piramal, one of India's leading drug companies. With their extensive labs and state-of-the-art equipment, they are a far cry from the western stereotype of India as the land of cheap copycats. Nicholas Piramal's ambition is to bring a new anti-cancer medicine to market for less than $100m.

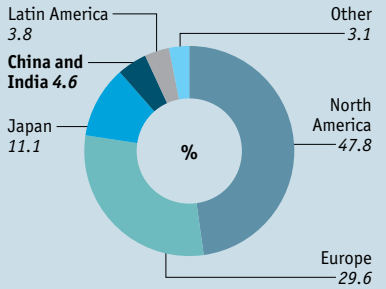
Western drugmakers have their eye on the rising urban middle classes of India, China, Brazil and other emerging economies, with their increasing incidence of diabetes, cardiovascular disease and other rich-country afflictions. In such countries, most spending on medicine comes out of customers' own pockets, not from some health-insurance scheme. As a result, the drug markets in these places are still small, and dominated by local generics. But the growth rates are astounding: IMS Health predicts that India's market will grow by 10% this year and China's by 19%.

But how to make sure the poor get a look-in too? In the late 1990s, western drugmakers were publicly taken to task over high drug prices in some of the world's poorest places by groups such as Médecins Sans Frontières and Oxfam. Most big drugmakers now have donation schemes for drugs to treat diseases such as leprosy and HIV. Firms are also voluntarily licensing some of their drugs to makers of generics in Africa, and putting up with the fact that generic companies in rich countries such as Canada are making drugs for poor ones that lack a home-grown industry. On the whole, though, big drugmakers tend to think of poor consumers in terms of philanthropy rather than good business. "I think it's wonderful as a concept, but I need practical applications," says Daniel Vasella, head of Novartis.

Poor people in stronger economies such as China and India are a trickier proposition, with drugmakers worrying that cheap or free drugs might cannibalise sales among the better-off. The biggest attraction of emerging economies, however, is not as markets to sell more drugs but as places for doing R&D and manufacturing. The post-war order in which pharmaceuticals were developed solely in Europe and America is changing. Singapore, for example, is investing billions to turn itself into a global centre of biomedical research and pharmaceutical development; South Korea is a rising star in biotechnology; and Brazil is trying to position itself as a leading supplier of generics to the developing world. Western drugmakers welcome the prospect of low-cost, high-yield partnerships with these newcomers, but worry about the competition they may generate. As in other fields, the most important contenders are India and China.

Ripe for development 8

Global drug market by region, 2004, % of total



Source: IMS Health

Crouching tiger

India is one of the few countries where people sound enthusiastic about the future of the drug industry. The excitement has been over 30 years in the making. In 1970, India introduced "process" patents which, unlike patents in America, allowed innovators to protect the way they made drugs, rather than the molecules themselves. This spawned thousands of small drug companies that copied drugs by inventing new processes—a perfect breeding ground for creative chemists.

About a dozen of these firms have turned into profitable businesses, publicly listed but essentially owned and run by the founder and his family. Indian companies' biggest competitive advantage is that they are cheap: they can develop, test, manufacture and market a generic medicine in India for 20-40% of what it costs in the West. But they are also able to develop better versions of old mouse traps, such as combination pills. This mixture of low costs and ingenuity has helped Indian firms expand their sales and acquire companies far beyond their borders. Both Ranbaxy and Dr Reddy's, India's two largest drug firms, have daring patent strategies, challenging big drugmakers on some of their core patents in key western markets.

Such bets can pay off handsomely in America, where the first generic company to succeed in challenging a patent wins a six-month head start in the market. But they can prove expensive: Satish Reddy, managing director of Dr Reddy's, reckons his firm spent $12m on legal bills last year, an amount equivalent to a quarter of its R&D budget. The mother of all patent battles is Ranbaxy's challenge to Pfizer's patent on Lipitor, a cholesterol-lowering treatment that is the world's best-selling drug. If Ranbaxy wins in America, the consequences will be enormous not just for the Indian firm, but for Pfizer too.

Other Indian firms, such as Wockhardt and Biocon, are making "biosimilars"—copies of such biotech drugs as insulin and human growth hormone. An estimated $13 billion-worth of biological drugs are due to lose patent protection by 2008. But biosimilars are more difficult to make, test and market than conventional generic medicines.

Earlier this year, India took another step into intellectual-property protection by recognising full product patents on pharmaceuticals, thereby fulfilling its commitment as a member of the World Trade Organisation. The law caused an outcry by public-health activists, who worry about its effect on drug affordability not just in India, but in even poorer countries that rely on Indian drugmakers for their medicine.

Multinational drugmakers have been slower than financial-services firms or carmakers to take advantage of offshoring. With the new patent law, foreign drug firms can now feel a little more comfortable about shifting more of their operations to India, which is churning out over 120,000 chemists and chemical engineers ▸▸

a year. Indian chemists are well trained and cheap to employ, at an average of $60,000 a year, all costs included, compared with $250,000 in America. Many foreign drugmakers are also turning to India for manufacturing their active pharmaceutical ingredients.

Clinical trials are another point of contact between east and west. At the moment, only a quarter of clinical trials for western drugmakers take place outside America, according to A.T. Kearney, a consultancy. India has a large pool of doctors, many of whom are western-educated and speak good English, and a plentiful supply of so-called "treatment-naive" patients who are not in the habit of consuming pharmaceuticals, making clinical trials faster and cheaper.

But some companies have discovered snags. The number of hospitals with the infrastructure to undertake clinical trials is still limited, and patients need to be followed closely so they do not drift away. Some Indian firms—among them Ranbaxy and Cipla—have had problems with Indian contract research organisations in the past that caused some of their drugs temporarily to be taken off the World Health Organisation's approved list. But with experience, quality is improving.

Given India's success in software—a model for many Indian drugmakers—it is no surprise that foreign pharma firms are turning to the country for IT skills. Novartis has set up an informatics centre in Mumbai. Wyeth has contracted its clinical-trials data management to Accenture, with operations in Bangalore. Vast rooms with hundreds of cubicles are filled with young Indians who transfer data from doctors' clinical-trial reports into databases, check for discrepancies and errors, and provide feedback to doctors within days.

Some Indian drug companies saw the new patent change coming years ago and realised that future growth would come from innovation, not imitation. Today, the country's top ten drug firms collectively spend $170m on R&D. But most of the new molecules they are looking at are directed against disease targets already tried and tested in the West.

The emergence of a research-based industry is also a strong recruiting tool for India Inc. In the past, many of the country's chemists ended up abroad because there were few opportunities at home; an estimated 15% of scientists working in the American drug industry are of Indian origin. Now a burgeoning Indian drug sector, combined with tougher times in America, is luring many of them back.

Indian firms may be competing with western drugmakers on generics, but they are keen to collaborate with them on new molecules. Ranbaxy, for example, has a deal with GSK to share discovery work. Biocon has taken a different tack, pairing with the Cuban Centre for Molecular Immunology to help it develop antibody treatments and cancer vaccines. And Glenmark Pharmaceuticals signed a $190m deal, the biggest in India, with Forest Laboratories in America to develop its new anti-asthma drug. But Indian firms are finding there is no leapfrogging the West's painful experience that drug-making ends in failure more often than in success.

Some firms are trying to load the dice by turning to traditional medicine. Lupin has joined with the Indian government to develop a drug for psoriasis based on a traditional plant remedy. R.A. Mashelkar, director of the Council of Scientific and Industrial Research, believes the drug, which is about to enter mid-stage clinical trials, could reduce the cost of treatment to a small fraction of the $20,000 that western medicines cost.

But whether India's pharma firms will continue to take an interest in poor patients' needs remains to be seen. A recent survey of Indian firms by Jean Lanjouw of the University of California at Berkeley shows that at most 10% of R&D spending by Indian drug firms is on products specifically suited to developing countries. As Kiran Mazumdar-Shaw, head of Biocon, puts it: "In India, we are in a quandary about being mercenary and missionary."

For all its promise, India still poses problems for domestic and foreign drugmakers alike. Some early drug testing remains tricky, and there is far too much red tape. A patent law on paper does not necessarily mean intellectual-property protection in practice. And Indian firms and investors will have to get over their revenues-at-any-price mentality and take a longer-term view of drugmaking, says Viren Mehta of Mehta Partners, an investment firm.

Bidden dragon

China has leapt ahead of India in many industries, but in pharmaceuticals it lags behind. Like India, it has a massive pool of well-trained chemists and a low cost base; but whereas India has produced a number of sizeable market-oriented drug companies, the Chinese industry has been dominated by sluggish, state-owned enterprises that are not internationally competitive. The sector is now in upheaval as the government is selling off assets and introducing minimum manufacturing standards. But as yet China lacks firms like Ranbaxy that can take on western markets.

Many foreign drugmakers now expect China to catch up with India quite quickly, but it will be some time before "Made in China" will be found in every western medicine cabinet. In the meantime, China already offers foreign firms opportunities for outsourcing because it is a world leader in basic pharmaceutical manufacturing. Even Indian firms have set up shop in China to produce raw materials more cheaply than at home. With an ample supply of suitable doctors and patients, China is also emerging as a centre for clinical trials. AstraZeneca works with some 20 hospitals on clinical trials for cardiovascular and respiratory drugs—not just to get their drugs on to the Chinese market, but as part of their global testing programme.

Traditional Chinese medicine, which accounts for 30% of the Chinese drug market, offers another opportunity. Bigger drugmakers are taking another look at traditional medicine as a way of finding new molecules to test against their disease targets. Novartis, for example, hopes its alliance with the Shanghai Institute of Materia Medica will deliver 1,500 new molecules from botanical and microbial sources in the next three years. One of the company's most important medicines—Coartem, a malaria treatment—has its origins in traditional Chinese medicine.

Although China lacks India's array of corporate partners, a few foreign firms are now taking the plunge and trying to do some of their early research in China. Eli Lilly has partnered with Shanghai Chem-

Explorer, a contract chemistry group. Roche has set up its own chemistry centre in Shanghai, and Novo Nordisk, which produces biotech products, has established a research centre in Beijing. But as John Wong, of Boston Consulting Group, points out, investing in research in China at this stage is as much of a commercial as a scientific decision. The Chinese government is keen on foreign pharmaceutical investment as a route to technology transfer. Drugmakers' investment in R&D may well pay off when they negotiate to get their drugs on to official reimbursement lists.

Like India, China has its drawbacks. The government regulator is slow in approving applications for clinical trials and marketing. And although the country strengthened pharmaceutical patents in 2001, companies still worry about enforcement. China has a thriving counterfeit-medicine industry—a big headache for western drugmakers and public health authorities around the world. Last year, the Chinese government overturned Pfizer's patent on Viagra, sending chills down the spines of western drugmakers.

China still lacks the tight links between academia, government research and industry that have been such a boon to America's drug industry, and there are cultural differences too that can get in the way. Generally speaking, Chinese scientists are more reluctant than western ones to question authority. "There are a lot of pearls here on the table," says Andreas Tschirky, managing director of the Roche centre."Now we need to link them in a chain."

Jonathan Wang of Burrill and Company reckons that although China lags behind in conventional drugmaking, it may well leap in front in biotechnology. Whereas western researchers are going slow on gene therapy because of safety concerns, China already has a product on the market for head and neck cancer, and is pushing ahead with stem-cell research too.

Emerging firms in countries like India and China are more of an opportunity than a threat for established drugmakers. "The most efficient way of making a computer is in cross-border transactions, making the design in one place, the chip in another, the keyboard somewhere else and then assembling the whole thing. The same will happen in drugs as well," says Swati Piramal, of Nicholas Piramal. With the right support from western industry, that could be good for drugmakers—and their customers—everywhere. ■

Heal thyself

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.

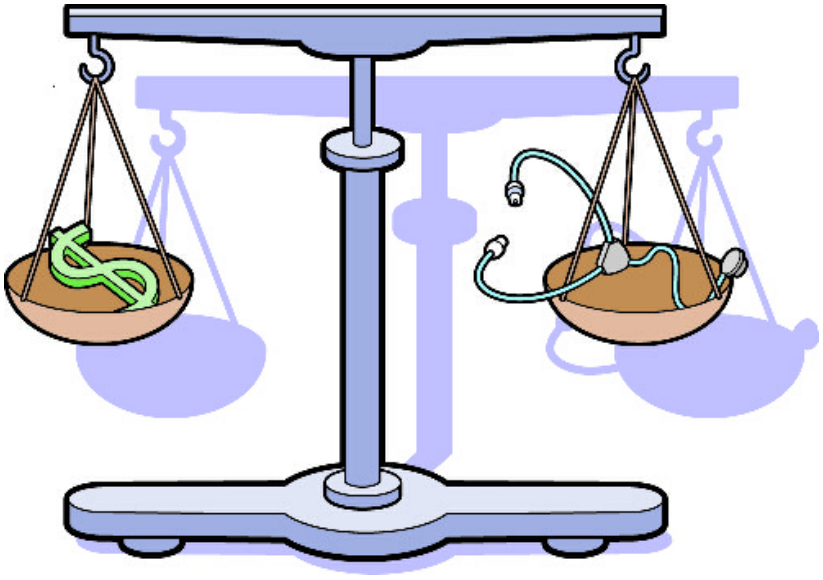
Novo's local offices also teach doctors and patients how to prevent diabetes through diet and lifestyle, as well as setting up ancillary services such as foot-care clinics for diabetic ulcers. It might seem odd for a drug company to promote practices that could possibly reduce its sales, but Mr Sorensen 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. ■

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