THE LIFE SCIENCES INDUSTRY

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Genetically modified crops continue their march but so far they have benefited farmers rather than consumers, says **Clive Cookson**
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Focus shifts to the emerging economies

Iconic image: President Obama's healthcare reforms have already generated much noise in the sector Getty

Andrew Jack notes unprecedented diversification in product ranges and markets in face of economic pressures

President Barack Obama's recent US healthcare reform measures have already generated much noise in the life sciences sector. However, the sector's long-term focus is centred on the world's emerging economies.

As specialists gather for the annual Biotechnology Industry Organization meeting in Chicago this week, they do so against a backdrop that has already changed – with the prospect of much more to come.

Already last year, Mr Obama started making alterations, with measures including lifting long-standing restrictions on stem cell research, and putting forward influential nominees to run institutions from the Food and Drug Administration to the National Institutes of Health.

His stimulus package helped lay the foundations for a shift to electronic patient records, comparative effectiveness research to judge the value of medical interventions more rigorously, and efforts to boost disease prevention and health promotion.

Healthcare reform, in spite of its many shortcomings, will begin to expand insurance coverage, offering the prospect of a larger market for companies that can demonstrate the value of their products.

There will be pain ahead, with Leerink Swann, the healthcare specialist group, estimating rebates, discounts and taxes mean the long-term costs for the drug industry may exceed $100bn.

Several US companies, including Eli Lilly, have issued earnings downgrades, although some are sceptical about the extent of the net negative impact.

Andrew Witty, chief executive of GlaxoSmithKline, says that, despite a modest dip in US sales so far this year, "I'm increasingly confident about where our business is headed. All the signs are that it is stabilising."

Intense lobbying allowed the industry to rebuff fresh calls for reimportation of drugs being sold at lower prices in Canada, and to win lengthy periods of "data exclusivity", which will slow the introduction of cheaper "biosimilars" even after patents on biological medicines expire.

That means innovative pharmaceutical companies may potentially feel less pain than other parts of the healthcare sector, including insurers and providers.

The reform package will also help improve disclosure, with new federal transparency requirements requiring drug companies to publish their payments to doctors for the first time.

That comes at a time when US regulators – nervous about the globalisation of the industry and especially the drive towards low-cost outsourced manufacturing based abroad – are stepping up factory inspections and warnings.

There is also growing scrutiny of industry-funded continuing medical education and other questionable ethical practices. GSK and regulators alike are currently under criticism for the extent of "informed consent" given to patients in its Tide trial for its diabetes drug Avandia.

AstraZeneca was forced last month to pay $520m and sign a corporate integrity agreement, following alleged mismarketing of its antipsychotic Seroquel, ahead of litigation by patients seeking compensation for side-effects they claim are linked to the drug.

But most investors are more concerned about the longer term prospects of returns from new markets, as sales of traditional drugs in established markets look sluggish.

There is little optimism in western Europe, where spiralling budget deficits since 2008 are triggering cutbacks in public spending.

A number of countries have already imposed aggressive reductions in drug payments; others are likely to follow. Japan is also stagnant.

The result of pressures in established markets is unprecedented diversification: nearly all the large pharmaceutical companies, and many of their smaller and speciality peers, are expanding into fast-growing emerging markets, in particular China.

Many are also broadening their product range, shifting away from reliance on patented medicines into animal health, generic drugs, vaccines, consumer healthcare and related activities to smooth the uncertainties of prescription drugs.

While volumes rise, the downside is lower margins, as well as the structural uncertainties of the developing "pharmemerging" markets, where much

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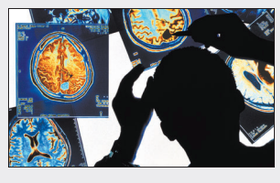
Electronic records Progress is slower than hoped for, and costs are higher, to modernise medical records, writes **Nicholas Timmins** **Page 4**



Poor find unhealthy choices are cheaper

Chronic diseases

Rowenna Davis says risk factors are more prevalent in developing countries

Conventional theory had it that only westerners could afford to die as a result of lifestyle choices – by over-consumption of food, cigarettes and alcohol and too little exercise.

People in the developing world were assumed to die of infectious diseases "beyond their control", such as malaria, cholera or tuberculosis. But this divide seems to have broken down.

Of all global deaths, 60 per cent are now caused by non-communicable ("lifestyle" or "chronic") diseases, and a full 80 per cent of those occur in developing countries.

Ala Alwan, assistant director-general at the World Health Organization (WHO) explains: "More people die in developing countries from non-communicable diseases because exposure to the risk factors – tobacco, being overweight, physical inactivity and alcohol – are more prevalent.

"High calorie diets tend to be cheaper than healthy diets and we know poorer people tend to smoke and drink more than average."

In short, their over-consumption comes not despite their poverty but because of it. Dr Alwan notes that developing world healthcare systems are also less well equipped to deal with the consequences.

Caught in time, one-third of cancers are treatable and about half of long-term complications associated with diabetes can be avoided.

But without effective intervention, the results can be devastating.

Every year in the developing world, an estimated 8m people die prematurely as a result of non-communicable diseases – with "prematurely" defined as at less than 60 years old.

In many developing countries, the commonest cause of gangrene and amputation is now untreated diabetes.

Of course, all this has a big impact on development. According to the WHO, a 10 per cent drop in the deaths associated with non-communicable diseases would have an impact on some key development goals equivalent to a decade of growth.

"Developing countries face a huge loss in productivity as a result of disability and premature death," says Dr Alwan, "On top of that, a huge amount of money has to be diverted from other causes to pay for treatment."

Such conditions may pose challenges, but they also offer opportunities for drugs companies.

In the case of Eli Lilly, a US-based pharmaceutical manufacturer, almost 90 per cent of its operations are now focused on non-communicable rather than infectious diseases, with a particular focus on diabetes.

Ala Alwan: 'Poorer people tend to smoke and drink more than average'

"We're seeing a big increase in sales in developing countries: China, India, Russia, Brazil, Mexico," says Thane Wettig, vice-president of global marketing for Lilly Diabetes.

According to Mr Wettig, the biggest obstacle to treatment in the developing world is not cost – his company offers different prices to countries with different budgets – but government policy.

"Governments allocate far fewer resources to non-communicable diseases than infectious ones, particularly when you take into account their respective mortality and morbidity rates," he says.

There are also practical problems of distribution. Diabetes medicines require refrigeration, but few patients can afford this. As a result, drugs quickly go off and people sometimes have to walk miles to clinics to replenish supplies.

Given that treatment can be expensive and complicated, policymakers are taking a step back along the disease chain and trying to stop people from falling ill.

Preventive measures are simple and cost-effective. Public bans on smoking and tobacco advertising can be implemented and tax increases on alcohol and unhealthy foods can raise revenue. So why don't more countries take action?

"Vested interests are a major constraint," says Dr Alwan, "The clearest example is the tobacco industry. Their marketing campaigns are impeding preventive efforts . . . and they have huge lobbying power."

Another problem, says Dr Alwan, is a lack of support from development agencies: "Although national prevention programmes are low-cost and evidence-based, they are not a priority among international agencies and donors."

A global action plan calls on governments and development agencies to improve monitoring, prevention and treatment of "lifestyle diseases" by 2013.

There is a long way to go. Just 8 per cent of the WHO's budget is spent on non-communicable diseases, compared with 35 per cent on communicable ones.

Reforms get started with small but certain steps

US healthcare

Anna Fifield considers how changes will affect patients, doctors and insurance companies

President Barack Obama might have achieved a political milestone with his overhaul of the US's inefficient healthcare system, but it will be years before the practical effects are felt.

For all the controversy that the reform effort generated in Washington – where protesters rallied against a "government takeover of healthcare" and labelled Mr Obama a "socialist" – relatively little will change immediately.

The biggest components of the 2,457-page bill that the president signed into law in March do not kick in until 2014. The legislation requires US citizens and residents to buy health insurance and involves subsidies and insurance market reforms.

However, the first signs of change will come fairly soon.

Starting this year, children will be allowed to stay on their parents' health insurance policies until age 26; insurers will not be able to deny children coverage on the grounds of pre-existing health problems; and the prescription drug "doughnut hole" – the gap that means the elderly have to pay the full cost of some medicines – will be closed.

"So, on the one hand, the law might not provide the kind of help people are expecting in the first few years," says Drew Altman, president of the Kaiser Family Foundation, a non-partisan policy group. "On the other hand, the sky will not immediately fall, as many people seem to believe it might. In fact, most people will see little or no change to their healthcare arrangements."

Mr Obama acknowledged that the reform package – which fell far short of what he initially envisaged – would not solve every problem in the $2,500bn healthcare system.

The reforms will extend coverage to 32m uninsured Americans, meaning about 94 per cent of the population will have health insurance once all the provisions take effect in 2018. Many will buy subsidised coverage from the health insurance exchanges that states are due to establish in 2014.

But even then, about 23m people will remain uninsured, about a third of whom will be undocumented immigrants.

After more than a year of politicking, there is still a lot of confusion among Americans about what impact the reforms will have, with many still doubting the changes are in their best interest.

According to the latest Gallup poll, 45 per cent said the reforms were a good thing, while 49 per cent said they were bad.

The Medicare Rights Center, a non-profit organisation for "older adults and people with disabilities", has been receiving a "steady stream" of calls about the changes, says Joseph Baker, the centre's president. "I would call them the 'worried well'," he says.

"They don't feel any impact now, but are worried that there might be a negative impact."

Some of the $940bn cost of the bill over the first decade will be recouped through savings in the Medicare scheme.

"We focus on the relief they will see in drug costs and primary care, and explain that the cost-savings will happen over many years," Mr Baker says. "Most folks calm down after that."

A US doctor talks to a patient as Barack Obama signs the healthcare reform bill into law on March 23 Getty

Doctors are also uncertain about how the reforms will affect them.

"Some physicians are confused because of the misinformation," says Lori Heim, president of the American Academy of Family Physicians, which supported the bill.

> After more than a year of politicking, there is still a lot of confusion about what impact the reforms will have

"They think there are going to be cuts in their Medicare payments, as commissions look at what services are under- or over-valued, but they have nothing to be concerned about there, because family physicians have been undervalued for years," she says.

The initial changes will also reduce administration. "Every time an insurance company changes its policies, we get caught in the middle," Dr Heim says. "We've all had patients who get sick and then their insurance companies drop them, so we end up trying to treat the patient and dealing with their insurer."

But doctors also warn of the challenges – by most physician organisation estimates, the US will need 50,000 more primary care doctors to deal with the influx of patients when insurance becomes mandatory.

There has been plenty of opposition among business to their reforms.

The loudest squeals have come from the insurance industry, which came under sustained attack from the Obama administration for what it said were unfair practices.

Insurance companies will face tough new regulations, but they will also have the opportunity to sell insurance to 32m new customers.

The final bill did not set up a rate review authority that would have had the power to cap premium increases, as Mr Obama had wanted, because of Congressional rules.

Karen Ignagni, president of the America's Health Insurance Plans industry group, repeatedly said the reforms will do nothing to contain healthcare costs.

"The access expansions are a significant step forward, but this legislation will exacerbate the healthcare costs crisis facing many working families and small businesses," Ms Ignagni said after the reforms were enacted.

She added that the administration should look at ways to control what hospitals and other providers charge.

Cross-border care stuck in waiting room

EU legislation

Stanley Pignal on efforts to give patients the right to access health services anywhere in Europe

When Antoine Elkhoury, a Swedish dentist, started noticing pangs of pain in his neck six years ago, his first instinct was to go through the Swedish health service for care. But after two operations left him unable to swallow and in constant pain, he took matters into his own hands.

Like thousands of patients every year in the European Union, Mr Elkhoury sought treatment in another country and claimed the money back– after much effort – from his home country's health system.

In his case, consultations in the UK, Germany and an operation in Spain finally resolved his injury. But he thinks he is lucky to have recouped most of the €20,000 of €23,000 he spent, although the process took five years.

"We are all in the EU. If it's a doctor in Sweden or in Spain who cures me – it really shouldn't matter," he says. "There should be free movement for patients. Like football players: if they have the right to play wherever they want in Europe, why should I not have the right to get medical treatment wherever I want?"

Mr Elkhoury's view is supported by the European Court of Justice (ECJ) in Luxembourg. Over the past decade, it has ruled repeatedly that European treaties give patients the right to access healthcare anywhere in the EU.

The principle it sticks to is that if a patient is unable to get a procedure done through the domestic health provider, that patient can go to another EU country – typically to a private hospital – and then be reimbursed to a level equivalent of what it would have cost at home.

That has not yet been translated into a reality. Proposals to legislate along the lines laid down by the court were first tabled by the European Commission in 2008, but are stalled because national governments cannot agree on the detail.

The focus of the cross-border health proposal is planned care, as opposed to emergency care for those who fall ill or have an accident while visiting another EU country. In the latter case, the European Health Insurance Card system ensures any emergency care is invoiced to the patient's country of origin.

A similar piece of legislation governs the health costs of British retirees living in Spain, for example, to ensure the Spanish government does not shoulder a burden that should be borne by Britain.

But nothing comparable exists for planned care. In part, this is because the issue is muddied by an ideological debate about private versus public healthcare.

The cross-border proposal would give patients the right to free private healthcare, but not in their home country. That is taboo for health authorities in many countries, who want "their" patients to use the domestic system.

It also attempts to reconcile vastly different healthcare systems. Britain mostly relies on its state-run National Health Service to deliver procedures, for example, whereas the Netherlands relies on a network of private insurers.

Questions over how to deal with the administrative burden is one reason why the bill is stalled.

"Nobody loves the cross-border healthcare directive," admits one EU diplomat. "You're effectively telling health ministers that part of their budget will end up overseas. But some version of it is going to happen: the ECJ has ruled it must."

However, it will not be for a while yet: Spain, which holds the rotating presidency of the EU in the first half of 2010, has been the most stubbornly opposed to the proposal.

It claims a cross-border system might leave it €2bn a year out of pocket – an amount other diplomats challenge. Portugal, Greece and Poland also oppose it.

"Spain doesn't like the idea of Spanish patients going overseas to get planned health procedures. It mostly has to do with their health system being administered by the regions, which have trouble dealing with each other, let alone foreign providers," says one person close to the talks.

The Commission, for its part, says it will keep on pushing for a legislative answer, though it stressed that only about 1 per cent of patients are concerned.

Aides to John Dalli, who looks after the health portfolio, say he is keen to find a solution to the impasse, but admits the situation is "tricky".

Mr Elkhoury now sits on the board of a Scandinavian association of patients with neck injuries lobbying for easier cross-border health. He estimates 95 per cent of patients he meets are not reimbursed, often because they fall through bureaucratic cracks. "You have to get prior approval from your health authority to be sure of getting your money back, and that is not always easy," he says.

His vision is that if cross-border healthcare could be made to work, a network of specialist clinics might be created to help patients across the bloc with complex problems, such as spine injuries or rare diseases.

But for now his focus is to make cross-border care more accessible:

"Why should I have to wait for a year or more to get medical attention when there is a doctor in the EU who can cure me? It makes no sense."

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Drug groups feel price pressure around the globe

Pharmaceuticals

But the larger ones continue to seek to develop new products, says **Andrew Jack**

President Barack Obama's health reforms were long and drawn-out to negotiate and will prove still more protracted to implement fully. But they have already prompted some pharmaceutical companies to diversify in order to survive.

The drug industry worked closely with the White House in an effort to reduce its pain, but long-term gains from increased healthcare insurance coverage are currently outweighed by the short-term squeeze of larger "rebates" – discounts on drugs sold to government medical programmes – and an excise tax to come.

In recent weeks, Eli Lilly, Bristol-Myers Squibb and Johnson & Johnson were among the large US pharmaceutical companies that adjusted earnings forecasts downwards for the current financial year, warning of pressure on sales in the world's largest medicines market.

More modest tweaks have been made by a number of European companies with US operations, including GlaxoSmithKline of the UK and Novo Nordisk of Denmark.

Both said during their first quarter results presentations that they expected a small drop in aggregate US sales during 2010, with similar or larger declines next year.

Despite the focus on the US, pricing pressures on drug companies are also being felt elsewhere around the world.

A recent report by Citi, the US investment bank, cautioned: "We believe cuts to European government budgets present a greater underappreciated risk in 2010."

It argued that the smaller, less diversified speciality companies would be hardest hit, led by Almirall of Barcelona, Spain, and Merck KGaA of Darmstadt, Germany.

With budget deficits as a proportion of gross domestic product particularly high in the UK, France and Spain, cuts in healthcare are in prospect – and reducing spending on commodities such as drugs is likely to prove an easier target than hospital closures or job and wage reductions for medical staff.

Already, Turkey has introduced substantial explicit across-the-board price cuts, and Germany and Spain have imposed reductions.

Others, led by Greece, have done so by default, accumulating large unpaid bills as the country struggles with large public sector debts.

> After the mega-mergers of 2009, most bankers are sceptical there will be much activity in the months ahead

There are intensifying pressures elsewhere.

Charles Ditkoff, global head of healthcare investment banking at Bank of America Merrill Lynch, argues that the Japanese market offers little domestic growth, as the government seeks to pare health costs, driving companies to look abroad for expansion.

That helps explain Astellas' unusual decision, for a Japanese company, to launch a hostile cross-border bid for OSI in the US, following its failure to acquire CV Therapeutics last year.

Following Roche's initially hostile full takeover of Genentech in the US in 2009, its Swiss rival Novartis began its own assertive buy-out at Alcon, the eyecare specialist, despite vocal objections from minority investors over the price.

A second recent Japanese takeover – by Sankyo, of Ranbaxy, the Indian generic drugs company – reflected the industry-wide trend for bold diversification.

Andrew Witty, the chief executive of GlaxoSmithKline, has made much of shifting his group away from "white pills in western markets", most recently this year pushing down this traditional segment of the business to just over a quarter of total sales.

In its place has come fresh investment in generics, consumer health, dermatology and vaccines; and far greater expansion in emerging markets, where economic growth is driving up healthcare spending, in contrast to the stagnation in many richer countries.

Sanofi-Aventis of France has also sought to expand its portfolio, reinvesting in Merial, an enlarged joint-venture for animal health with Merck, the New Jersey-based US group, alongside generic deals and initial steps into glucose monitoring.

Even after Pfizer acquired Wyeth last year in the US, it has retained an appetite for acquisitions, with a recent bid for Ratiopharm of Germany, the generics company, although it ultimately lost out to Teva of Israel. It continues to look for partners, after sealing initial deals in India last year. And AstraZeneca, the Anglo-Swedish group that was one of the last large drug companies to resist a shift into generic drugs, has recently changed tack, arguing that it too is interested in alliances to expand in developing countries and sustain sales of medicines even after patents expire.

After the surge in mega-mergers of 2009, most bankers doubt there will be much activity on such a scale in the months ahead.

What seems certain – as larger companies continue to seek to enrich their pipelines and accelerate their desire to outsource research and development – is that fresh deals will be done with biotech companies.

Investors grow wary of small-scale drug developers

UK biotech

Medical device companies may now find more favour as a safer investment, says **John O'Doherty**

Over the past tumultuous year, biotech groups, in common with businesses across the UK, have struggled to access financing. Many have found the going too tough.

One example is Alizyme, which went into administration in July last year. The group had been developing an anti-obesity drug, which had reached late-stage clinical trials in Japan. However, a lack of funding and uncertainties surrounding licensing payments from its development partners pushed it out of business.

It was followed soon after by York Pharma, the dermatology specialist, which went into administration after it was unable to repay in full a $1m loan it received from Uluru, the US dermatology group.

However, a number of biotech companies were able to access funding to keep going – not by securing lines of credit, but by issuing equity.

Last May, the drug developer Lipoxen raised £2.9m to help fund its blood-clotting product, and in October last year, Sinclair Pharma raised £18m in a share issue, which it used to buy two drugs from Belgium's Solvay for treating burns.

Phytopharm, which develops drugs for Parkinson's and motor neuron disease, has been another of the successes. In October, it announced positive results for its Parkinson's treatment, and its shares initially quintupled on the news. Thanks to the trial results, the group was able to raise £25m in December to further its research.

Lombard Medical, which makes stents used to keep arteries around the heart open, also tapped investors for cash. In January last year, the group raised £6.4m and this January, it secured a further £13m to spend over the course of this year, until such time as it hopes to receive approval in the US for its Aorfix stent.

More recently, Vernalis, which develops oncology and neuropathic pain drugs, raised £28m in a placing last month.

"It hasn't been great, but then I'd argue that it hasn't been terribly bad either," says Shawn Manning, a biotech analyst at Singer Capital, of the recent investment climate.

While funding difficulties may have pushed some companies to the wall, industry watchers believe that what could be more damaging for the long-term health of a volatile sector is not a general lack of appetite for financing small companies,

> 'What we will be entering into for UK biotech in particular is a sort of desert period'

but a specific biotech-related unease.

This was intensified recently by upsets to some companies' revenue plans, most of which were due to high-profile drug or licensing failures.

Investors in Ark Therapeutics lost out in December, when the European Medicines Agency said it was not going to approve the group's Cerepro treatment for brain cancer. The shares are now trading about 70 per cent below their December levels.

Last month, shares in Antisoma fell more than 70 per cent in one day on news that one of its key lung cancer drugs in development did not prolong life in humans.

Also in March, shares in the drug delivery group Vectura lost almost a quarter of their value over a few days. The falls were triggered by a decision from Sandoz, the generics arm of Novartis, to relinquish its rights to Vectura technology on a generic lung drug.

Even Vernalis had a bump in March, less than a fortnight after its placing. Its shares dropped almost 30 per cent, after results from a study of its drug for diabetes-induced neuropathic pain showed little difference from a group given a placebo treatment.

"It hasn't done us any favours for 2010, because if you look back on some of the companies that raised money recently they've gone away and that money is down the drain now and they had complete failures," says Andy Smith, a biotech fund manager at Axa Framlington, who foresees difficulties in funding for the year ahead.

"It puts people off investing any more money into the sector, having believed what the companies said, raised money and then lost it again. I think what we will be entering into for UK biotech in particular, is a sort of desert period."

But notwithstanding the disappointments, there is still considerable scope for large returns.

"There are parts of UK life sciences that have done very well, such as diagnostics companies, which had a fantastic 2009," says Paul Cuddon, a biotech analyst at KBC Peel Hunt.

While he agrees that investors are now more wary of small-scale drug developers with only one drug candidate, he reckons that pharmaceutical groups with broader pipelines, as well as medical device companies may now find more favour, as a safer way of investing in the life sciences market.

"Although therapeutic biotech hasn't done very well, medical devices have had a fantastic year, and that's where we're looking for the next round of appetite to come from.

"You want broad revenue spread with multiple pipeline candidates. Those are the sorts of things that investors find interesting."

The genetically modified crop marches on

Agriculture and food

Types introduced so far have benefited farmers rather than consumers, writes **Clive Cookson**

In agricultural biotechnology, the big theme is still the march of genetically modified crops across the world's farmland.

While farmers have yet to adopt genetic engineering or cloning of animals to a significant extent – even in the GM-friendly US, fears of consumer resistance to biotech meat and milk outweigh any likely benefits – they have embraced biotech plants in some of the world's most important growing regions.

The most authoritative annual survey of GM planting, carried out by the International Service for the Acquisition of Agri-biotech Applications, showed a 7 per cent annual increase last year in the area covered to 134m hectares (330m acres) in 25 countries.

But GM food crops are still concentrated in the western hemisphere. The US accounts for almost half the world's GM planting (64m hectares), followed by Brazil (21.4m ha) and Argentina (21.3m ha).

Although India and China are big biotech growers, their GM crops are almost entirely cotton, cultivated for fibre rather than food. The picture may change soon in China, where regulators issued biosafety certificates in November for insect-resistant rice and "phytase" maize (which has an added gene to make the crop more digestible in animal feed).

But GM food had a setback in India in February, when the government unexpectedly rejected an application to grow an insect-resistant strain of brinjal (aubergine) and demanded more safety tests.

"Agbio" companies continue to face strong consumer and political resistance to GM crops in Europe, where only 95,000ha were grown last year – mainly insect-resistant maize in Spain.

The industry celebrated a success in March in its long struggle to get more crops approved in Europe. After a 13-year wait, the European Commission allowed BASF of Germany to plant its GM potato called Amflora to produce industrial starch – but not spuds for human or animal consumption.

Many other GM crops, approved elsewhere in the world, are still waiting for a go-ahead from the EC. Three more GM maize products are believed to be at the front of the queue.

Worldwide, the GM scene is dominated by four crops (soyabeans, maize, cotton and canola or oilseed rape), two traits (herbicide tolerance and insect resistance) and one company (Monsanto).

Herbicide-tolerant genes let the farmer spray a broad-spectrum weedkiller, usually Monsanto's RoundUp, to kill all weeds without harming the crop. The Bt insect resistance gene, derived from *Bacillus thuringiensis* bacteria, reduces the amount of pesticide required to protect the crop.

Crops with combined or "stacked" traits are becoming increasingly important. This year, Monsanto will launch SmartStax maize, which has eight added genes coding for three traits. It is herbicide-tolerant and protects against insects.

GM products so far have delivered their direct benefits to the farmer rather than the consumer. A report last month by the National Academy of Sciences in Washington DC said: "Many US farmers who grow genetically engineered crops are realising substantial economic and environmental benefits, such as lower production costs, fewer pest problems, reduced use of pesticides and better yields, compared with conventional crops."

A new wave of GM crops, to be released over the next few years, may bring more obvious benefits to the consumer, in the form of better nutritional qualities, and to agricultural production, in the form of more resistance to stresses such as drought, salinity and extremes of temperature.

An important development will be the commercial launch of drought-tolerant GM maize, scheduled for 2012.

Although GM gets all the attention, there are alternative ways to use science to improve crops. For example Australia's CSIRO announced last month a salt-tolerant wheat that yields 25 per cent more on saline soils than its parent variety.

The Australian scientists isolated two salt tolerance genes in *Triticum monoccum*, a wheat species that grows on poor, arid soils in the Middle East, and introduced them into durum wheat, which is widely cultivated for pasta production – through non-GM breeding aided by the latest molecular marking technology.

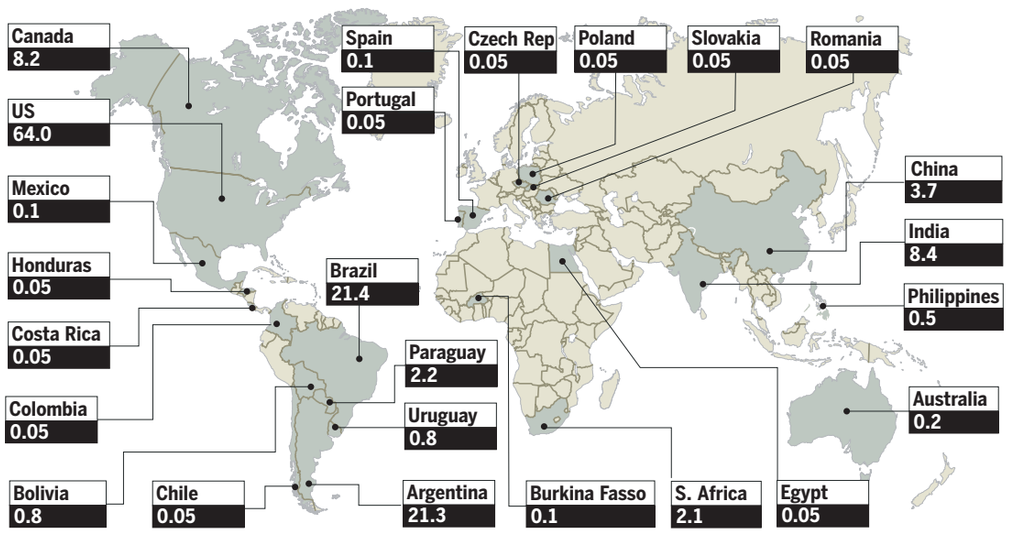
A more general way of introducing new traits into crops without inserting foreign genes is "site-directed mutagenesis". Cibus, a privately owned company based in San Diego, is a leader here with its proprietary Rapid Trait Development System or RTDS. This uses the plant's own genetic machinery to change its DNA.

Cibus has reached agreements with a variety of companies and organisations – most recently the Flax Council of Canada – to use RTDS on their crops. Stephen Evans-Freke, Cibus chairman, says the technology makes it possible to commercialise new traits more quickly than GM, because regulatory approval is much more straightforward when no external genes are introduced.

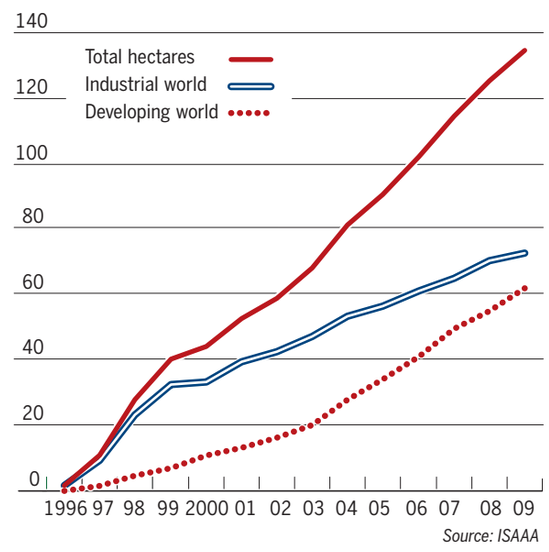
Biotech crops

Global area, 2009
By country (Million hectares)

14 million farmers in 25 countries planted 134 million hectares in 2009, an increase of 7% or 9 million hectares over 2008



Global growth in area
Million hectares



Source: ISAAA

Price hangs on patient outcomes

Charging schemes

Andrew Jack finds some drug companies choosing to be paid by results

When the UK government's medicines advisory body expressed doubts nearly a decade ago about the value of using several new drugs for multiple sclerosis, the Department of Health came up with a ground-breaking compromise to avoid the political backlash.

It proposed an experiment by which it would pay for the medicines – Avonex, Betaferon, Rebif and Copaxone – at a discount to the manufacturers' prices, on condition that their effects were monitored closely.

If they performed much better or worse than initially claimed, the price would be modified accordingly.

The government's advisory body – the National Institute for Health and Clinical Excellence (Nice) – has been keenly watched around the world for its pioneering efforts to ensure new drugs offer cost as well as clinical benefits. So has the multiple sclerosis "risk sharing scheme" itself.

On paper, it offered a tempting solution to the uncertainties of assessing innovative treatments before significant data have been collected in ordinary patients, rather than the smaller number recruited to the more artificial set-up of a trial.

But the experience, in practice, is a cautionary tale for healthcare systems everywhere seeking better value for money from pharmaceutical companies, by taking innovative approaches to pricing that are more closely linked to patient outcomes.

It took from 2002 until 2005 before 5,500 patients were recruited into the MS scheme, and until 2007 for the first evaluation phase to be completed.

The results were only finally made public in the British Medical Journal at the end of last year. They were inconclusive, with the authors arguing it was too soon to judge whether or not the drugs had provided value. No changes in pricing were recommended.

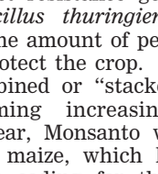
Some researchers who followed the programme questioned its value from the start. They argued it was ethically impossible to exclude MS patients, which meant it was difficult to establish a "control" group not taking the new drugs, against which to measure their impact.

In the period since, critics have said that the scheme locked in an approach using drugs which have since become outmoded, while stalling the introduction of subsequent innovations.

"There are serious questions about why this scheme has failed to deliver," says Simon Gillespie, chief executive of the MS Society. "The Department of Health should face up to the reality that their scheme is not fit for purpose."

Yet pharmaceutical companies have since adapted and adopted many more innovative pricing schemes.

"It is not uncommon for some classes of drugs to be effective in only one in three patients who take them," says Steve Black, health systems specialist at PA Consulting Group, who cites anti-cancer treatments and psychoactive medicines. "We might have to spend tens of thousands before knowing whether a drug will have any effect."



Simon Gillespie: 'The [MS] scheme is not fit for purpose'

In the UK, after Nice rejected Janssen Cilag's drug Velcade for multiple myeloma – a cancer of the white blood cells – in 2006, the company agreed a risk-sharing scheme by which the NHS would pay only for that sub-group of patients in which it showed significant benefit.

A dozen variations on such outcome-based schemes have since been introduced in the country, ranging from money-back guarantees on drugs to free treatment beyond an agreed number of paid-for doses, such as Lucentis for age-related macular degeneration – an eye disease that causes loss of vision.

Elsewhere, a similar pattern is taking hold. Nathan Swilling, a partner at Simon-Kucher, a German consultancy, says risk-sharing for expensive new cancer drugs, such as Bayer's Nexavar, has become all but obligatory in Italy.

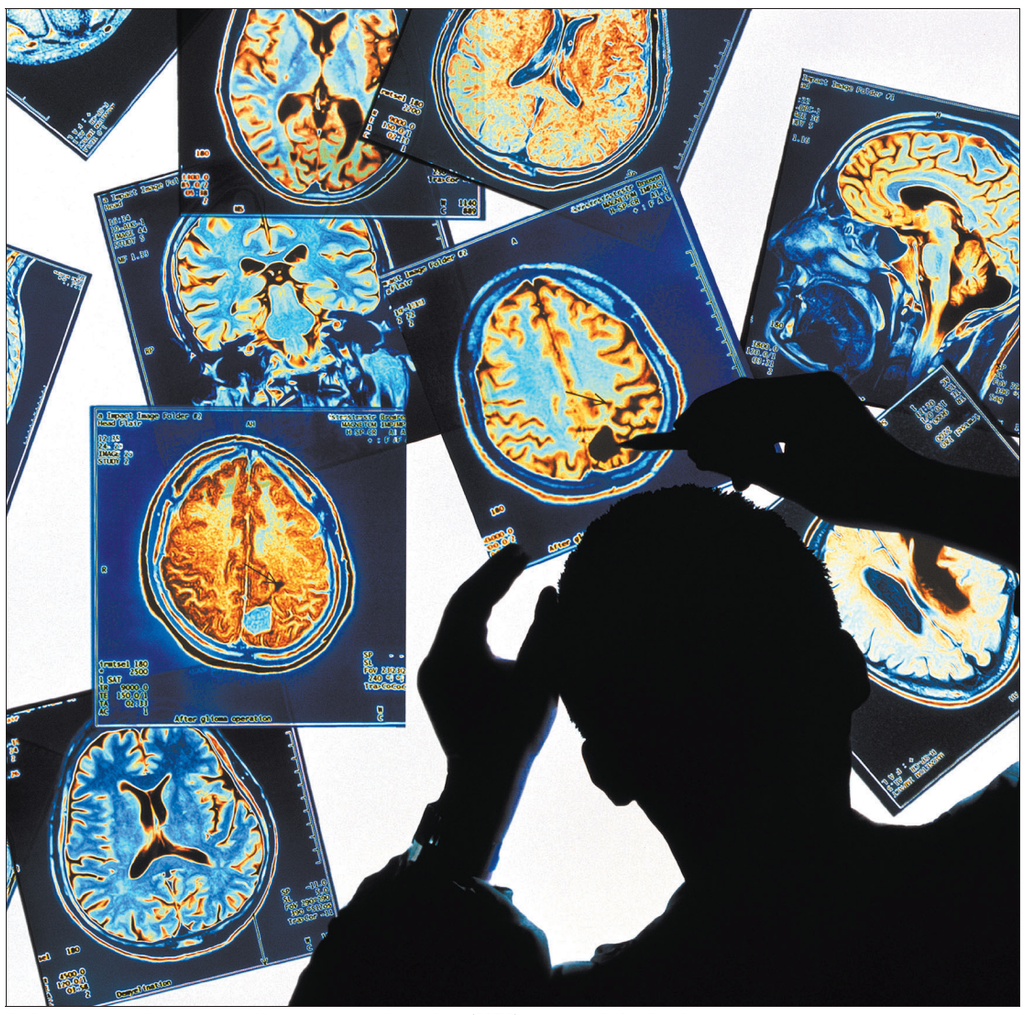
The drugs are offered at half the list price for up to three months, and then at the full price in the smaller group of patients who respond to treatment.

In Germany, Novartis has agreed with two sick funds to offer refunds for patients who suffer bone fractures after taking Aclasta for osteoporosis. It believes its drug, taken once-yearly by injection, significantly improves outcomes by boosting compliance compared with alternatives requiring daily or weekly pills.

One challenge is finding meaningful measurements to assess patients' progress, and which can be credited directly to the drug under test. The risk to drug companies, is that once schemes are agreed, they spread to other markets, and become generalised discounts.

But faced with the alternative – a growing reluctance on the part of health authorities to reimburse – companies increasingly accept that linking charges to outcomes is a price worth paying.

Possibilities multiply for nerve cell regrowth



A doctor examines magnetic resonance imaging (MRI) scans of the brain — Science Photo Library

Regenerative medicine

Clive Cookson looks at therapies under test to tackle disease and injury of the brain or nervous system

Regenerative medicine has immense potential for renewing failing or damaged tissues throughout the body, from the skin on the surface to organs deep inside. But the most exciting prospect is for regeneration of the brain and nervous system, both because the unmet medical need is so great and because the science is so challenging.

There are two complementary approaches to neural regeneration. The more traditional one is cell therapy – putting new neurons – nerve cells – or their progenitor cells into the brain or nervous system.

The first transplants of foetal neurons into Parkinson's disease patients took place in the 1980s – with mixed results – and today several companies are on the brink of clinical trials of therapies based on stem cells.

They include: ReNeuron of the UK, which is about to test neural stem cells in stroke patients; and Geron, from California, which plans to treat acute spinal injury with nerve cells derived from human embryonic stem cells.

The other possibility is to stimulate the latent power of some human neurons to regenerate themselves. Scientists have long known that neurogenesis takes place in more primitive organisms, including some fish and amphibians, but one of the dogmas of 20th century neuroscience – that adult humans do not make new brain cells – was only overturned in the late 1990s.

The discovery then of adult neurogenesis at the Salk Institute in California has inspired a great wave of research, as scientists and biotechnology companies look for ways to increase the low natural level of brain cell generation, without risking the cancer that might accompany unnatural neural growth.

"Very little is known still about human neurogenesis, because it is difficult to look at the growth of neurons in the living human brain," says Mike Modo of the Institute of Psychiatry in London. "But in postmortems of stroke victims, there is clear evidence of neurogenesis after the stroke."

Sygnis Pharma, a German biotechnology company, wants to achieve this effect with a protein called "granulocyte colony stimulating factor" or G-CSF, produced naturally in the brain after a stroke – apparently acting both to reduce cell death in the acute phase and to stimulate subsequent regeneration of blood vessels and neurons.

After successful animal tests, Sygnis is undertaking a clinical trial to assess the efficacy of its G-CSF treatment – which the company calls AX200. About 350 stroke patients are taking part in the double-blinded trial; half will receive an infusion of AX200 and the other half a placebo saline solution.

Results are expected in the middle of next year.

A Swedish company, NeuroNova, is following a similar approach with two neuro-stimulating proteins – both in early clinical trials. One is a formulation of "platelet-derived growth factor" (PDGF) to treat Parkinson's disease; the other contains "vascular endothelial growth factor" (VEGF) for amyotrophic lateral sclerosis (known in the US as Lou Gehrig's disease), the most common form of motor neuron disease.

> 'Very little is known about neurogenesis because it is difficult to look at the growth of neurons in the living human brain'

A third neurogenesis company, BrainCells of San Diego, is taking a different tack. It is pursuing the discovery made in 2003 by one of its founders, René Hen of Columbia University, that antidepressant drugs achieve some of their effects by stimulating the growth of neurons in the hippocampus, a brain area involved in learning and memory.

In contrast to Sygnis and NeuroNova, whose early work is focusing on proteins that might help people with serious or acute brain disease, BrainCells is concentrating initially on "small molecule" chemicals that people can take as pills or capsules, with a screening programme that has looked at hundreds of potential drugs to find the ones that best trigger the proliferation of new neurons in cell cultures.

Two of its drugs are already giving promising results in clinical trials with patients suffering from severe depression and anxiety, who do not respond to existing antidepressants.

In terms of results, there may not be much practical difference between the two approaches to brain repair – transplanting neurons and stimulating the brain's intrinsic growth potential – because animal experiments suggest that cell transplants are particularly good at stimulating neurogenesis. This is because the very presence of newly transplanted cells seems to help the brain repair itself, by activating its own "endogenous" stem cells and growth factors.

Mr Modo says that in cases of serious brain injury or disease, a third component may be necessary for effective treatment. Shrinkage and neuronal death often leave a hole in the brain, which transplanted and regenerated cells cannot fill on their own.

A potential solution then is to add a scaffold, made from biocompatible materials and laden with neurostimulating factors, which can guide and support the cells as they grow.

Neural regeneration may be a young field, with much still to prove, but it is one of the fastest growing and most exciting in the whole of bioscience.

Electronic records Making slow progress

Across the world, the drive to create electronic medical records is making progress slower than hoped for, while costs are higher.

"They are not a quick fix," says Joe Swedish, the chief executive of Trinity Health, a US hospital provider, which has invested $400m in an electronic record for 8,000 physicians at 44 hospitals.

That judgment can be echoed in England, where an ambitious, decade-long £12bn drive to deliver an electronic record to 50m of its citizens is at least four years late, and will not be delivered in full in any foreseeable future.

Billed as the world's biggest civilian IT programme, the UK's Connecting for Health suffers from what might be called the "prophet in its own country" syndrome. Some achievements are admired from abroad: people in England see only the failures.

Growing numbers of Britain's primary care physicians, its family doctors, send patients' records electronically when a patient moves home – cutting weeks of waiting when written folders of notes had to be transferred. The country has replaced X-ray film with digital images, saving money, improving diagnostic accuracy and avoiding lost films that repeatedly led to wasted hospital appointments and unnecessary repeat X-rays.

With mixed success, a hospital appointment can be booked electronically, with choice over where and when patients are seen. A communication system known as "the spine" holds databases that include a single number for every patient, ensuring accurate identity.

And there are the beginnings of a summary care record, available nationally round the clock, carrying details of patients' medication and allergies that can help with out-of-hours emergency treatment.

"People who come and look at this from abroad are really impressed by much of what we have done," says Christine Connelly, the health department's chief information officer.

Many "buts" follow, however. Some so large that the future of the programme is in the balance. For the core aim of the programme was a complete electronic record, to be rolled out from 2005, accessed from hospital, primary care and community settings.

To do that, huge contracts were let not to health IT specialists but to IT integrators such as CSC, Accenture, Fujitsu and BT to install systems. Initially three, but soon only two key software packages were chosen.

This was a highly centralised solution – one spectacularly different from what could have been the alternative approach: defining what should be in the record and what it should look like, setting communication standards, and then letting the health system buy from a catalogue of approved products.

Had the integrators had good product to hand, the centralised approach might well have worked. It did with digital imaging, when the programme took existing packages of hardware and software and rolled them out across the country in less than two years.

But for the record software, it turned out that iSoft's package was good at providing the data the NHS needed for payment mechanisms but lacked the clinical record, while the other package, Cerner's, had the opposite problem.

On top of that, installing hospital patient administration systems that underpin everything for payment and the electronic record has proved far tougher than anyone imagined.

The result has been massive delays and multiple missed deadlines. The future of the huge contract held by CSC is in doubt. And while BT has performed appreciably better on its regional contract in London, the scale of what it was to deliver has been cut back. Roll-out of the summary care record has been halted in much of the country until there is public awareness of what it implies.

Even the ministers in charge now accept that this mighty programme will no longer deliver the comprehensive solution originally envisaged.

The new government due shortly in the UK will have to decide whether it is worth ploughing on, or if a radical revamp can be afforded, given the costs of cancellation and constrained public spending. The future of Connecting for Health hangs in the balance.

Nicholas Timmins

Regulation undergoes review on both sides of the Atlantic

Medical devices

Joseph Milton looks at approval procedures

From bandages to X-ray machines, thermometers to pacemakers, the term "medical device" encompasses a broad and diverse range of healthcare products.

The Medical and Healthcare Products Regulatory Agency (MHRA), which regulates such devices in the UK, says 80,000 types are used in British healthcare.

The market for medical devices is large and often overlooked and expanding rapidly, both in the US and in Europe. Market research company Datamonitor estimates the global market grew 9 per cent from £172bn ($266bn) to £187bn between 2007 and 2008.

The European market was worth £46.5bn in 2009, while in the US, 2010 revenues are estimated at £97bn – a compound annual growth rate of 6.5 per cent over the past decade – according to strategic consultants Frost & Sullivan.

Medical devices have grown in complexity and prevalence, and European and US regulatory systems – devised in simpler times – are being reviewed and revised.

Revisions to the European system came into force this March, and US regulation is under review. Medical device regulation differs between the US and Europe, although the two systems overlap in places.

Before the revisions, the European regulatory framework had been unchanged since 1998. Rene van de Zande, president of Emergo Group, a consultancy that advises medical device manufacturers worldwide, says: "Over the past 10 years, enforcement was lacking. Now everything comes with enforcement."

US regulation, overseen by the Food and Drug Administration (FDA), has been periodically tweaked since its introduction in 1976, but the entire system is now under review by both the FDA and the Institute of Medicine (IOM) of the National Academies, and may be overhauled.

Both regions require manufacturers to register with the relevant authority and implement "Quality Management Systems" (QMS), ensuring that design, manufacturing processes and labelling are up to standard.

New devices are classified into one of three groups based on potential risk to patients, each with different regulatory requirements.

Class I devices range from examination gloves to handheld surgical instruments. They are the least risky, and subject to minimal regulatory scrutiny. Class II includes surgical needles and X-ray machines, while Class III devices, subject to the strictest regime, include pacemakers and cerebral stimulators. Class III devices are mainly implanted in the body and sustain or support life.

In Europe, QMS and technical files are required for all new devices. For Class III devices, design dossiers must also be provided.

These documents and systems are audited by representatives, appointed in the UK by the MHRA. Finally, a Declaration of Conformity – confirming that the device complies with the applicable directives – is submitted.

CE Certificates, which certify a product has met EU requirements, are then issued for new devices.

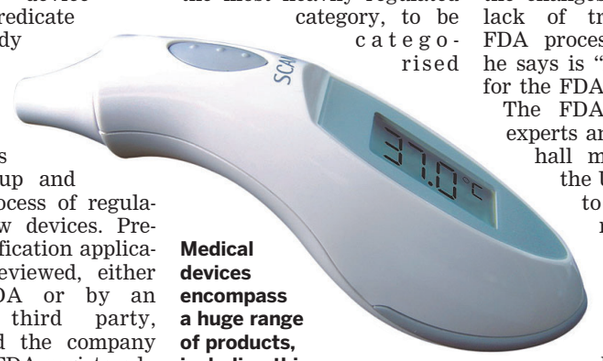
In the US, Class II devices require what is termed "Premarket Notification 510(k)" clearance. By showing that a "substantially equivalent" device – termed a predicate – has already passed the 510(k) step successfully, manufacturers can speed up and ease the process of regulation for new devices. Premarket Notification applications are reviewed, either by the FDA or by an appointed third party, cleared, and the company and device FDA registered.

Mr van de Zande says that third-party review of 510(k) relieves the pressure on the FDA, but has been criticised.

Dick Thompson of the FDA says third party review was recently withdrawn for radioactive devices, although there are no plans to abandon the third party review programme as a whole.

New Class III devices require FDA-approved clinical trials, followed by application for Premarket Approval (PMA) and inspection of manufacturing facilities.

Producing predicates can allow devices that might otherwise fall into Class III, the most heavily regulated category, to be categorised instead as Class II.



Medical devices encompass a huge range of products, including this ear thermometer

Mr van de Zande says this is a problem: "They take bits of devices which are already cleared, and combine them into a 510(k)." These are known as multiple, or split predicates, and the new device may bear little relation to those used as predicates.

Mr Thompson says: "There are some concerns with how predicates are defined and used. The Agency is in the process of gathering comments to determine whether there are in fact problems, what [these] are and what can be done about them.

Mr van de Zande hopes the changes will address a lack of transparency in FDA processes, something he says is "important, both for the FDA and industry".

The FDA is consulting experts and holding town hall meetings around the US to contribute to an improved regulatory system.

Mr Thompson says that nobody knows what the changes will be.

Focus shifts over to the emerging economies

Continued from Page 1

healthcare spending is in the form of out-of-pocket expenditure by individual patients.

Another tactic in Europe and increasingly the US is experimentation with new approaches to pricing linked more explicitly to the demonstrable value of drugs.

There is a fresh emphasis on patient compliance, symbolised by Novartis' recent deal with Proteus to create a "chip in a pill" to monitor adherence to dosing regimes.

For the biotech sector, the "engine" that creates drugs, there are signs of hope. A report by Ernst & Young suggests that established centres in the US, Europe, Canada and Australia had an aggregate net profit for the first time last year of $3.7bn, after net losses of $1.8bn in 2008.

As large pharmaceutical groups start to cut costs in their own formerly sacrosanct research and development divisions, they will be spending more on in-licensing – buying the rights to other companies' products – and acquisitions.

Yet there is also a price to pay. Andrew Baum, pharmaceutical analyst with Morgan Stanley, worries that intensifying competition driven by outsourcing drug discovery could lead to overpayment. "The companies may end up destroying value," he says.

Just as fundamentally, the Ernst & Young data suggest that much of biotech's new-found profitability has been the result of its own intensifying round of cost-cutting in research budgets.

Investment was down 21 per cent in 2009 after years of high growth.

Coupled with the difficulties for smaller companies in seeking funding, there are longer term worries that the consequence will be shrinkage in the collective industry pipeline.

Some culling may be justified, but it raises the prospect of an uncertain future for promising treatments.

With patent expiries gathering pace and few signs of blockbusters on the scale of the past, there is much talk of collaborative alliances between companies and academic centres, and "open innovation" to help close the gap.

Kasim Kutay, a partner at Moelis, an investment bank, says he has seen considerable interest from other companies in the decision of GSK and Pfizer to merge their HIV drugs that are both in development and on the market into the joint-venture ViiV Healthcare.

Companies are seeking new ways to share risks, such as AstraZeneca's partnerships with Merck on cancer medicines and Bristol-Myers Squibb on diabetes, or Eli Lilly's co-funded drug development projects with Quintiles, a clinical research group.

Last year's round of pharmaceutical company mega-mergers helped defer the pain of growing patent expiries, but did little to assuage investors' concerns that research and development remains highly risky and wasteful.

Mr Kutay says: "Many shareholders are sceptical of the hype around mega-mergers beyond cost-cutting. They don't buy the argument about scale benefits and boosting research and development productivity."

In future, innovation will be required from the drug industry, not only in science, to develop medicines, but also in management and commercial strategies to persuade cautious payers to buy those products, which clearly show both clinical value and cost effectiveness.