2004 approvals: the demise of the blockbuster?

The rise in approval numbers is good news, but the list illustrates companies' future growth models.

Simon Frantz

In a year filled with bad news for the drug industry, one reason for cheer is that the total number of New Molecular Entities (NMEs) approved by the FDA was 31, the highest since 1999 (see ONLINE FIG. 1).

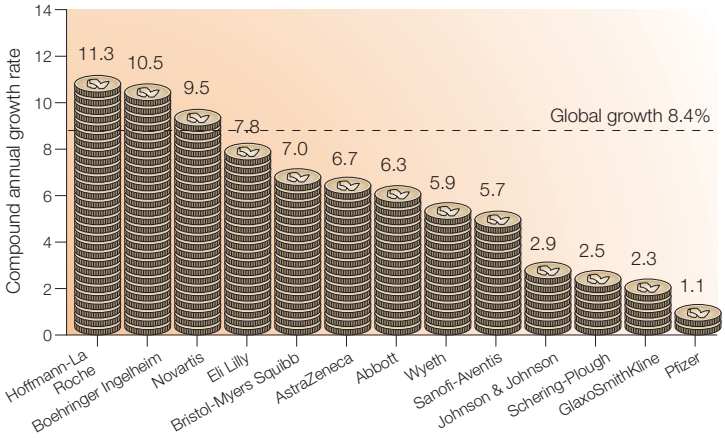
On the surface, it seems that R&D productivity is back on track following the low of 17 NMEs approved in 2002. But a closer inspection of the list shows a distinct lack of approvals from big pharmaceutical companies — Pfizer, Lilly and Aventis being the notable exceptions (see ONLINE TABLE 1).

Yet it wasn't long ago that analysts and company representatives were saying that these companies needed to produce as many as two or three blockbusters a year to maintain double-digit growth.

"The blockbuster drug concept is alive and well, but the blockbuster model to sustain double-digit growth is dead," says Irena Melnikova, Senior Research Analyst at Life Science Insights.

Revenue growth has relied heavily on blockbusters in recent years. The Boston Consulting Group estimates that 80% of growth for the 10 biggest pharmaceutical companies during the last decade came from blockbusters.

The number of blockbusters launched has dropped since then, and the rate of patent expirations is increasing. Between now and 2007, the best-selling drugs coming off-patent could place around US $30 billion in sales at risk, says a report from the management consulting firm A. T. Kearney.



Growing pains: Predicted compound annual growth rate of large pharmaceutical companies during 2003–2008. Average based on the top 50 drug companies worldwide in 2003 based on prescription drug sales. SOURCE PRODUCTVIEW, WOODMACKENZIE, DECEMBER 2004

Also, some potential blockbusters are not realizing their full potential. High-profile drug withdrawals such as rofecoxib (Vioxx; Merck), disappointing trial results with drugs such as gefitinib (Iressa; AstraZeneca), and pressure from consumer groups about safety issues with rosuvastatin (Crestor; AstraZeneca) are affecting sales revenues. Pricing pressures from governments are likely to further reduce sales growth.

The level of R&D spending as a percentage of sales that is required to sustain 10% growth itself keeps growing, says Melnikova. In 1980, it took only 7% of sales, rising to 25% in 1990 and again to 40% in 2001. "Obviously, this model is not sustainable," says Melnikova.

All of which will hit revenue growth. The average compound annual growth rate for large pharmaceutical companies during 2003–2008 is predicted to be around 8.4% (see figure), significantly below the industry's historical US growth rate of around 12–15%.

Companies such as Bristol-Myers Squibb, Abbott and Wyeth have moved away from blockbusters to targeted treatments to drive growth, convinced in part by the success of

imatinib (Gleevec; Novartis) and bevacizumab (Avastin; Genentech). Some, including Novartis, are branching out further into the generics market, whereas generics companies are now moving into R&D.

Whether there are enough blockbusters in the pipeline to fill the gap is perhaps doubtful. Rimonabant (Accomplia; Sanofi–Aventis) for obesity and smoking, and torcetrapib (Pfizer) for dyslipidaemia are potential blockbusters. Other big-sellers on the horizon include CTLA4Ig (Abatacept; Bristol-Myers Squibb) for rheumatoid arthritis and a nanoparticle injectable form of paclitaxel (Abraxane; American Pharmaceutical Partners) for cancer.

But beyond that, analysts say that companies are struggling to produce blockbusters, and should instead concentrate on producing 3–4 $500+ million-selling-drugs.

And, with growing scrutiny of safety issues raised by Vioxx and other COX2 inhibitors, the days in which companies could rely on blockbusters to drive growth seem to have come to an end.

Iressa failure raises fears about accelerated approvals

Concerns that the regulatory bar might be raised for oncology drugs.

Simon Frantz

If gefitinib (Iressa) becomes the first oncology drug to be withdrawn after receiving accelerated approval from the FDA, the impact might not just be felt by its manufacturer AstraZeneca.

With the FDA facing pressure from other quarters claiming that it prizes speed before safety, researchers are worried that this could affect all cancer drugs going through the accelerated approval process.

The potential benefit of novel treatments for patients with fatal diseases means that the FDA is willing to accept treatments on the basis of positive surrogate endpoint data rather than clinical effect.

Iressa was approved in 2003 with data from single-arm Phase II studies showing that it reduced tumour proliferation in patients with advanced non-small-cell lung cancer who had not responded to other treatments.

As there is always a chance that surrogate endpoints might not correlate with clinical benefit, the so-called subpart H regulatory guidelines of the accelerated approval process stipulate that the company continues with clinical trials after the drug is marketed.

AstraZeneca was asked to run a confirmatory study to show that Iressa's ability to shrink lung tumours would lead to improved survival, and this failed.

The FDA hasn't completed its evaluation of Iressa, and so couldn't comment on whether it will ask AstraZeneca to withdraw Iressa from the market, or whether it will reassess the accelerated approval process.

But it is entirely rational to decide to trade off the risk of a false positive for the general good of earlier approvals, says Stephen George, Professor of Biostatistics at Duke University Medical Center. "Despite all the hype about potential early

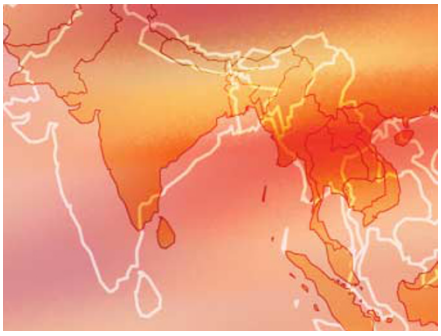
Fine print TRIPS up multinational and Indian companies

Does the new intellectual property regime in India spell the end for generic production of branded drugs? Not quite.

Simon Frantz

Years of expectation and apprehension finally ended on 1 January as India began a new era of drug discovery.

The Trade Related Intellectual Property (TRIPS) agreement of the World Trade Organization, signed by India in 1995, mandates that the country adopts a product patent regime for food and medicines by the beginning of this year.



India has begun a new era of patent law

With only process patents available for pharmaceuticals since 1970, India blossomed into a US $5-billion drug industry by using reverse engineering to make and sell generic copies of branded drugs. In 2003, more than 60,000 generic brands in 60 therapeutic areas were available in India.

The TRIPS agreement not only allows multinational drug companies to launch new products and manufacture them exclusively in India, but it also allows them to put pressure on Indian companies to withdraw generic forms of branded drugs.

In response, many generics companies, such as Ranbaxy and Dr Reddy's, are already using their experience in chemistry and manufacturing, combined with low costs, to seek alternative revenue streams, including creating novel drugs, strategic marketing alliances and expanding manufacturing capacities.

"As we see it, any company, whether bulk drug producer or formulator, with a research focus and intellectual property awareness will thrive," says a spokesperson for Ranbaxy.

But if multinational companies think that this marks the end of a system that led to every major blockbuster drug being developed into at least 10 generic brands in India, they should think again.

First, the TRIPS agreement only applies to products invented after 1 January 1995. "This covers only around 5% of the branded drugs that are currently sold here," says Amar Lulla, joint managing director of Cipla. For example, Cipla can continue selling its version of the HIV drug AZT.

Second, the estimated 12,000 mailbox applications that were filed for product patents are only being opened and examined from 1 January. Generics manufacturers can freely manufacture their drugs while mailbox applications lie unprocessed.

Whether the Indian Patent Office has the capabilities to deal with this backlog quickly is open to question. The national patent offices housed only 46 examiners before 1 January. Now, 250 examiners have been recruited to handle the increased workload, with a further 50 to be recruited this year.

markers of efficacy in many diseases, there is at present no way to permit such early decisions without increasing the risk of a wrong decision."

One way of avoiding erroneous conclusions from Phase II trials would be to require Phase III interim data, as is the case for accelerated approvals of HIV drugs.

"This was the case for accelerated approval of oxaliplatin in colorectal cancer," says George. "There was a built-in analysis of a surrogate endpoint used for accelerated approval with the same study used as a more definitive analysis after further follow-up to confirm or refute the early finding."

"I hope that the FDA do not overreact and do not abrogate the accelerated approval approach," says Len Lichtenfeld, Chief Medical Oficer at the American Cancer Society. "We need to consider whether it is better for patients to delay approval of a potentially valuable drug, or whether to approve and monitor it."

Iressa has shown that the monitoring system can pick up drugs that fail to show a survival benefit, says Lichtenfeld. "It may not be a perfect system, but you can't let the perfect be the enemy of the good."

The Indian government has estimated that it will take up to 30 months to process these applications, and it could take a couple for years to award patents.

"Enforcement remains a major concern, and we will be cautious about launching major innovations in India, until the environment is more secure," says Steve Brown, spokesperson for AstraZeneca, which has already set up a research centre in Bangalore that focuses on tuberculosis research.

One bone of contention for Indian companies is that the definition of patentability is unclear. The new law has introduced the term 'mere new use' rather than just 'new use' for a drug. This, say Indian companies, does not clarify whether variations that extend the patent life of a drug will not be patentable.

Indian companies would like the scope of patentability to be restricted to new chemical entities, and fear that the new laws will result in a series of litigations.

But this shouldn't discourage domestic companies says a spokesperson for Ranbaxy. "A stronger patent regime will bring in opportunities in every area. It will be entirely up to us to grab the opportunities and prosper or behave like ostriches."

NEWS IN BRIEF

FDA rejects OTC statins

An FDA advisory committee has again rejected Merck's and Johnson & Johnson's bid to sell a non-prescription, low-dose version of a statin. The panel voted 20 to 3 against over-the-counter (OTC) sales of a 20-mg dose of lovastatin (Mevacor) because of concerns that it could not be used safely without physician guidance. Although panel members did not doubt the efficacy of the statin, some said that Merck's 'actual use' study, which simulates pharmacies selling OTC Mevacor, failed to show that consumers could properly decide whether to take the treatment. The FDA rejected earlier proposals for non-prescription statins from Merck and others, most recently in 2000, but UK authorities approved the use of OTC statins in 2004. Despite the setback, Bristol-Myers Squibb said it still plans to seek FDA clearance to sell an OTC version of pravastatin (Pravachol).

Pharmacogenomics chip approved

Roche has received approval from the FDA to market its first microarray-based test. The AmpliChip CYP450 identifies cytochrome P4502D6 genotype variations to predict drug metabolism. The test was launched in Europe in 2004, but the FDA had delayed its decision, questioning whether the test needed a pre-market application, because it is a complicated device with specific directions that, if misused, has the potential to harm patients through misdiagnoses. Sales of the AmpliChip CYP450 could reach US $100 million a year, according to Roche, compared with average peak annual sales of US $10–20 million for other diagnostics.

Bayer buys back rights to impotence drug

Bayer has agreed to pay €208 million (US $272 million) to GlaxoSmithKline to regain sole marketing rights outside of the United States for the impotence drug vardenafil (Levitra). Bayer hopes that the move will help lift earnings. Analysts say that the move fits in with Bayer's moves to focus on Europe and fields in which it has successful products, but reflects the weak sales performance of Levitra in comparison to its competitors. Pfizer's sildenafil (Viagra) still dominates the field, with more than 70% of the market share in the USA, whereas Lilly's tadalafil (Cialis) controls about 19%.

New initiatives to provide greater access to drug data

The International Federation of Pharmaceutical Manufacturers and Associations, along with three other industry associations covering Europe, the United States and Japan, said they will be creating a freely accessible online registry of current and completed drug trials. The registry will publish detailed information about all clinical trials, other than exploratory Phase I studies. Participation is voluntary, but the scheme already has backing from GlaxoSmithKline, Pfizer, AstraZeneca, Merck, Novartis and Sanofi-Aventis. Also, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) will open up its drug safety monitoring system. Patients will in future be able to view anonymous data on suspected adverse drug reactions on the MHRA Web site.

Arguments over missing Prozac documents

Eli Lilly is defending itself against what it says are inaccurate statements made about the company and its antidepressant fluoxetine (Prozac) in the *British Medical Journal*. According to a news story in the 1 January issue, the *BMJ* received documents from an anonymous source suggesting a link between Prozac and suicide attempts and violence, which had gone missing during a 1994 lawsuit. The case against Lilly was on behalf of victims of a workplace shooting in Louisville, Kentucky, by Joseph Wesbecker, who was prescribed Prozac a month before the shootings. Lilly's lawyers have notified the *BMJ* that the article is "inaccurate and defamatory", and said that all their relevant data had been previously submitted to the FDA. The *BMJ* said it had validated its information and forwarded the documents on to the FDA, but it will address Lilly's concerns after reviewing them.

Risks of HIV drug withheld

Nevirapine (Viramune; Boehringer-Ingelheim), used to block HIV transmission between mothers and babies in Africa, is at the centre of controversy over its safety. Viramune reduces the chances of HIV transmission by up to 50%, but can also promote drug-resistant forms of the virus and has been linked to potentially fatal liver toxicity. According to documents obtained by the Associated Press, US officials knew about the problems as early as January 2002 from trial data, but did not tell President Bush before he authorized shipping the drug to Africa as part of a US $500-million initiative. The FDA has now issued a warning that Viramune could cause liver damage, but the World Health Organisation said that it would continue recommending use of the drug, as the benefits outweigh the toxicity problems.

PATENTWATCH

Alza's patent upheld

The US Court of Appeals for the Federal Circuit has upheld the decision of the Vermont District Court that Alza's patent (US 4,588,580) covering transdermal-patch administration of the narcotic painkiller fentanyl is infringed by Mylan Laboratories, not invalid and not unenforceable. On appeal, Mylan argued that the claims were not correctly construed and that the patent was unenforceable due to inequitable conduct.

Prior to the '580 patent, transdermal patches used huge excesses of drug with high solubility to maintain the necessary concentration gradient for prolonged delivery. This design was inappropriate for a narcotic due to the large excesses of controlled substance that remained in discarded patches. The inventors of the '580 patent discovered that the skin permeability of fentanyl was highly dependent on the chemical form of the drug, and that incorporating the drug in the patch in the form of a base, rather than the more common fentanyl citrate, achieved satisfactory delivery rates. The patch is sold by Janssen as Duragesic.

Did a prior-art patent (US 4,470,962), which claimed the possibility of using a fentanyl citrate patch, render the '580 patent invalid? The district court ruled that it was clear from the prosecution history that the claims contained in the '580 patent referred to the base form of fentanyl and excluded the citrate form, therefore the '962 patent did not anticipate or render obvious the '580 patent. The court also focussed on the construction of the claim term 'skin permeable'. Both the prosecution history and the specification disclaimed fentanyl citrate, because it was unsuitable for transdermal administration and therefore not classed as a 'skin-permeable form' of fentanyl. Finally, the district court found that although during the prosecution history of the patent one statement had the potential to be misleading, there was no evidence of the requisite intent to deceive in order to conclude inequitable conduct.

ALZA Corp. and Janssen Pharmaceutica v Mylan Laboratories:
http://www.fedcir.gov/opinions/04-1344.doc

Promoter sequence not novel

The United States Court of Appeals for the Federal Circuit has upheld a previous decision to deny the patent application US 8,822,509 filed by James F. Crish and Robert L. Eckert, which discloses the isolation and sequencing of the promoter sequence of human involucrin (hINV), a protein that interacts with keratin within epithelial cells.

Claims in the application that refer to a portion of the nucleotide sequence containing the promoter were rejected because they were deemed to be anticipated by two publications authored by Crish. Both papers used plasmids that contained an identical promoter region and one paper disclosed the complete structure of the promoter. However, according to the Apellants, because neither paper specifically disclosed the nucleotide sequence described in the patent application the papers were not prior art.

The board rejects this claim on the basis that the promoter region of hINV was specifically identified by size and location in the previous papers, and that the identification and characterization (that is, sequencing) of a prior-art material does not make it novel. Furthermore, because the plasmids used in both papers necessarily contain the sequence of interest, the Court of Appeals ruled that the pending claims are anticipated by the plasmid in the prior art, and that the Apellants have provided no evidence that the plasmids used in the patent application and the Crish publication were different.

How safe is Safe harbour?

The US Supreme Court has agreed to review a lower court ruling concerning the breadth of patent protection for research experiments carried out by drug companies that infringe patents. The Drug Price Competition and Patent Term Extension Act, also known as the Hatch–Waxman Act, created a 'safe harbour' exemption that permits drug manufacturers to perform experiments needed to obtain FDA approval of their drugs without incurring liability for patent infringement, even if their activities infringe patent rights.

Biotechnology company Integra alleged that Merck and Scripps infringed patents owned by Integra relating to peptides involved in interactions between cell surfaces and the extracellular matrix. Scripps identified several potential antitumour peptide candidates and selected the most promising peptide by conducting experiments to evaluate the specificity, efficacy and toxicity of the peptide candidates for various diseases. The Appeals Court held that these activities did not fall under the safe harbour because they were exploratory in nature and not done solely for purposes reasonably related to the development and submission of information to the FDA. The court reasoned that the safe-harbour provision in the Hatch–Waxman Act was intended only to promote the growth of generic drugs.

However, in a brief submitted to the Supreme Court by the government, it is argued that the current decision of the court of appeals reflects an incorrect view of the law, which is likely to restrict the development of new drugs. The brief holds that creating a distinction between preclinical and clinical research is a misreading of the law, and, in addition, that this is a misunderstanding of the type of information required by the FDA for evaluating potential new drugs.

Merck v Integra Lifesciences, Case number 03-1237

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PATENT PRIMER

Patent infringement

Luke Kempton

The life-sciences press is peppered with headlines such as 'Court holds that Ranbaxy did not infringe GSK patent' and 'Court awards Applied Medical Resources Corp., $43.5 million because Tyco Corporation had infringed Applied's patent'. But what amounts to an infringement? How does the court decide whether Ranbaxy can make its generic version of the antibiotic Ceftin or that Tyco has to pay such a large sum?

A granted patent gives the owner a monopoly: only the owner, or someone with his permission, can make, sell or use a product or process that falls within that monopoly. The scope of this monopoly is set out in the claims of the patent. Each claim — and there may be many in a single patent — sets out a number of features or elements that define the invention.

An example of a claim is 'Use of rapamycin for the preparation of a medicament for inhibiting organ- or tissue-transplant rejection in a mammal in need thereof'. This is the principal claim in a UK patent owned by American Home Products (AHP) that was the subject of litigation in the United Kingdom against Novartis in 2001. In order to infringe a claim, a product or process has to have all of the elements of the claim. So, if someone was using rapamycin to treat heart disease they would not infringe the claim, because they were not using the organ-transplant rejection element of the claim. At the other extreme, if a product falls within the literal wording of the claim then that clearly is an infringement.

The Protocol

The difficulty arises when a third party's product or process is similar to a patented invention but does not fall within the literal wording of a claim. Does the claim cover it? Under harmonized patent law in Europe, the patent should not be limited to the literal meaning of any term in a claim (the patentee should have a fair degree of protection), but the protection cannot extend outside the claims such that the claims only serve as a guideline. In the UK the court has, since 1982, applied a structured test known as the 'Protocol Questions' to apply these principles to the facts of a particular case. However, in a landmark decision of 21 October 2004 in the case of *Amgen v TKT*, the House of Lords held that the Protocol Questions are only really relevant to claims in which figures or measurements are used. Now the only compulsory question is, 'what would the skilled person have understood the patentee to have used the language of the claim to mean?'

In relation to the rapamycin claim, AHP argued that the term 'rapamycin' covered a derivative of rapamycin developed by Novartis. The UK decided that the term 'rapamycin', as used in the patent, meant rapamycin alone and could not be broadened to cover rapamycin derivatives (for more information see BOX).

Doctrine of equivalents

The US courts take a different approach to dealing with the issue of non-literal infringement. They determine whether there is 'equivalence' between each of the elements of the accused product or process (rather than the accused product or process as a whole) and the claimed elements of the patented invention; this is the so-called 'doctrine of equivalents'. Factors that are taken into account to determine whether an element is equivalent include the purpose for which an element is used in a patent and whether persons reasonably skilled in the technology would have known of the interchangeability of an element not contained in the patent with one that was.

In the US, to prevent the unfair broadening of the scope of a claim, the doctrine is limited by a further doctrine called 'prosecution history (or file wrapper) estoppel'. This doctrine applies when a claim is amended in the course of the application for a patent — that is, during its prosecution before the US Patent & Trademark Office. If the amendment results in the narrowing of the scope of a claim, then, subject to some provisos, the patentee cannot later argue that anything falling outside the literal meaning of that element and covered by the original broader claim is an equivalent. Competitors can therefore rely on the estoppel to ensure that their own devices will not be found to infringe other patents by equivalence. This doctrine has been subject to intensive scrutiny throughout the courts in the US during the past few years in the *Festo* case.

Balanced protection

So, in both the UK and the US (and indeed other countries of the world), the general principle is that a claim of a patent should not be limited to the strict, literal interpretation of the words of a claim because that would unfairly limit the patentee's monopoly. But, on the other hand, a claim should not be construed so broadly as to cover devices or processes that a patentee had not considered when creating his invention and which third parties, on reading the patent, could not reasonably have supposed would fall within the claim.

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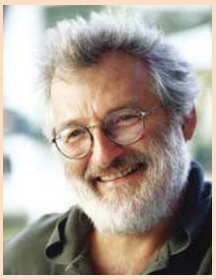
AMERICAN HOME PRODUCTS VERSUS NOVARTIS

Rapamycin was known as an antifungal antibiotic, but in 1989 Professor Sir Roy Calne discovered that it also had an immunosuppressive effect. This invention was patented under the title 'Use of rapamycin and derivatives and prodrugs thereof…', but no derivatives had been found or were described in the patent. Novartis developed the rapamycin derivative SDZ RAD, which AHP claimed infringed its patent. The UK Court of Appeal (*AHP v Novartis* [2001] RPC 159) held that the patent claims were limited to rapamycin alone and that Novartis' derivative, SDZ RAD, did not fall within the claims. This was because although SDZ RAD worked in the same way as rapamycin, at the time the patent was filed a skilled person could not have predicted how many derivatives would have an immunosuppressive effect or indeed whether any and/or which would . In addition, throughout the specification of the patent the word rapamycin was used to denote the molecule itself and derivatives were referred to as such. In contrast, derivatives were not mentioned in the claims.

AN AUDIENCE WITH...

Sir John Sulston



Sir John Sulston, former Director of the Wellcome Trust Sanger Institute

Sir John Sulston is the former director of the Wellcome Trust Sanger Institute in Hinxton, Cambridge, UK. He graduated from the University of Cambridge in 1963, and has worked mainly on the nematode worm *Caenorhabditis elegans*, but latterly has been involved with the sequencing of the human genome. Sulston is a Fellow of the Royal Society, and is an honorary fellow of Pembroke College, Cambridge. He shared the Nobel Prize in Physiology or Medicine in 2002 for his work on the regulation of organ development and programmed cell death. Sulston is a proponent of open resource research and has recently turned his attention to championing new approaches to treating neglected diseases.

Which is more pressing — providing cheap drugs for neglected diseases or the infrastructure to deliver them?

It depends on the disease and the society in question, but we should not regard them as either/or. Improvements in drug supply will drive the expansion of health services, but without new medicines the efficacy of health services is limited. Médecins Sans Frontières has an extraordinarily good medical delivery system, but had to set up its own initiative to collaborate on affordable cures for sleeping sickness. In Cape Town in 2002 the Treatment Action Campaign told me that their patients probably adhere to the antiretroviral regime as well as those in the United States. So the main issue is drug availability.

Have other industries been targeted in the way pharma has over issues in the developing world — essentially being asked to forego profits and ROI?

Indeed they have. Fairtrade coffee has been so successful in taking market share that Nescafe and Kraft are setting up their own competing 'fair' brands. Nestlé has also been strongly attacked for years over attempting to stop breast feeding in developing countries, and Monsanto has been targeted for maintaining seed prices by preventing farmers from saving seed. Until recently pharma had it easier than most, perhaps because it has exploited the mystery surrounding drug discovery to create a highly profitable but fundamentally inefficient industry. Around one-third of pharma's revenue is profit and another third goes into marketing — twice as much as is invested in R&D. This allows the industry to hit every UK physician with £20,000 of advertising per year, and in the US advertise directly to the consumer as well. Pharma also spends huge sums on lobbying the US and EU governments to craft bilateral agreements and free-trade areas that undercut the intellectual property rights of poorer countries. The industry does not and cannot produce medicines purely for neglected diseases, because there is no profit to be had, but what it can do is make medicines that have already been developed for rich markets available at production cost to poor markets. This is not a call to forgo profits, because there are no high-price sales there anyway.

To produce new drugs for the truly neglected diseases we need a different system that doesn't depend on return on capital. Pharma has a lot of scientific talent locked up in its labs, and partnership schemes can allow them and their currently unwanted products to be used for the benefit of humanity.

How can we stop cheap drugs being re-imported into the developed world?

With difficulty, but I never understand why this objection is raised, given that the world is full of tariff barriers that are more or less effectively enforced by customs officials. The real issue is counterfeiting. Nobody wants unregistered and untested counterfeit drugs of unknown quality floating around the world. It is far better to agree to discounted exports and/or generic licensing, under supervision of the World Health Organization and conditions of transparent distribution. This will be much easier if we move away from market-driven research, in which drug prices are set artificially high in the first place.

What model should pharma adopt to enable non-market-driven drug discovery?

In addition to some of the approaches already discussed, a more political approach is to provide new incentives: government money could be provided for work on an 'orphan disease'. For example, we heard recently that the UK government has guaranteed GlaxoSmithKline payment for a malaria vaccine of unproven efficacy. However, the discipline of the market place is lost, and in light of GSK recently withholding information regarding paroxetine, some strong umpiring is clearly necessary.

More radical suggestions include the treaty proposed by Hubbard and Love, in which all nations agree to spend ~0.1% of their GDP on R&D for medicines. All nations spend about this much anyway, because about 10% of the purchase price of drugs goes back to R&D, and countries, rich and poor, spend about 1% of GDP on medicines. The value of the contributions would be weighted to reflect the extent that the research is made public and applied to the most important goals, and R&D would be supported by a mixture of direct funding and rewards to successful teams. Production of drugs would be carried out by a separate competitive market.

In order to move forward with these initiatives we need more input from publicly funded labs in early parts of the drug pipeline and less regard being paid to intellectual property of basic discovery. The World Intellectual Property Organization needs to facilitate open collaborative agreements, rather than simply enforcing existing patent law as the US Patent and Trademark Office would have it do.

So what is the role of pharma in this? To desist from the lobbying that obstructs change, and to re-invent itself: R&D decoupled from production, working in partnership and helping to deliver real global health care. The huge sales forces will have to go, as will exorbitant returns on capital. It will be painful and cannot happen overnight, but surely it's better to plan for a soft landing than to merge and merge until the final crash.