

Pharma 2005

An Industrial Revolution in R&D



This paper addresses the problems currently besetting the pharmaceutical industry, the resulting need to achieve a dramatic increase in the number and quality of new drugs emerging from the pipeline, and the many opportunities which exist for improving that flow. It quantifies the effects of soaring research and development costs, sluggish sales growth and shorter product lifecycles; explores the implications of the new technologies and new sciences, including the need for fundamentally different skills; and looks at the likely impact of these changes in terms of regulation. It also addresses some of the changes taking place in the social framework within which the industry operates, including the growing power of the consumer and the trend towards self-medication. All point to the fact that the industry must learn to create affordable new drugs, and that it will only be able to do so if it totally transforms the way in which it performs R&D.

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1 Introduction

When Felix Hoffman produced aspirin, he turned Bayer, the dye-maker for which he worked, into the world's first drug company. The birth of the pharmaceutical industry epitomises its subsequent development. Over the past hundred years, it has successively adapted to advances in medicine, biology, epidemiology, economics and information technology. This ability to evolve in response to new sources of scientific knowledge has served it well. The top 20 companies alone are collectively capitalised at about \$1.3 trillion. Even more importantly, they have delivered total shareholder returns (TSR) – capital growth plus dividends – of more than 20% a year over the past five years.

But evolution is generally a process of slow change and the industry now faces a challenge of absolutely unprecedented scale. Soaring R&D costs, shortening product lifecycles and sluggish sales growth have combined to produce a climate more hostile than anything it has previously encountered – a climate in which only the smartest managements will survive.

Over the past seven years the top 20 companies have seen their R&D spend more than double in nominal terms. If this pattern continues unchanged for the next seven years, R&D costs per company will rise from an average \$1.2 billion to around \$2.5 billion a year by the year 2005 – a spend that is (assumes R&D costs per drug of \$500m and \$350m at today's prices) enough to produce between 26 and 37 new drugs respectively each over the next seven years. But this would represent a four- to six-fold increase in the number of new drugs currently emerging from the R&D pipelines of the top 20 companies, a level of productivity that is hardly conceivable. In other words, the number of new drugs put out by each company between now and the year 2005 would need to approach the 45 new drugs per annum currently produced by the *entire* industry.

If, as seems more likely, the top 20 companies peg their R&D spend to sales revenues (which are projected to grow worldwide at 7% a year over the next seven years), they can expect to spend an average \$1.9 billion a year by the year 2005. This would then enable each to produce between 22 and 31 drugs (assumes R&D costs per drug of \$500m and \$350m at today's prices) over the same period. But it, too, would put an enormous strain on their R&D operations.

Moreover, even if the top 20 companies succeed in handling such a large output, the returns they yield may still fall far short of what they have formerly delivered. About 90% of all new drugs earn less than \$180m* a year. Our research shows that, if the top 20 companies are to deliver sales growth of 7% a year in line with the industry forecasts, they will need to dramatically improve their R&D productivity or ensure that every drug they produce is a billion-dollar blockbuster.

If they fail to do either, the total shareholder returns they produce will plummet. With R&D costs of \$350m per drug and average annual sales of \$265m (the industry norm), those returns will more than halve. With costs of \$500m per drug and average annual sales of \$265m, they will fall to a level that would be dire for shareholders and management alike.

But the suffering is unlikely to be equally distributed. Confronted with rising costs and a slowdown in sales, some companies have been making strenuous efforts to improve their productivity. Some have also begun to focus on the most promising leads – the sort that will generate revenues like Prozac – and jettison the also-rans in the R&D pipeline.

This and much more is what all the world's leading companies must do, if they wish to survive in their current form. "Sticking to the present course of action is simply not an option," says Dr Steve Arlington, head of pharmaceutical research and development consulting at PricewaterhouseCoopers. "Those companies which cannot dramatically increase both the number and quality of the drugs they produce will go the way of the dinosaurs," he concludes.

* Based on data contained in "Strategic Management of R&D in the Pharmaceutical Industry", PJB Publications 1995, adjusted to 1998 values by PwC

2 Symptoms of Stress

The soaring cost of R&D

Industry sources suggest that the pharmaceutical and biotechnology industries worldwide will spend about \$39 billion on R&D this year. US-based companies are expected to invest about \$21.1 billion. Europe will account for at least another \$14.1 billion.

But big as these numbers are, they are likely to grow bigger still if the industry continues on its current path. Ten years ago, total R&D expenditure in the US was \$6.5 billion – barely a third of the figure today. It is expected to rise by 11% this year alone. In Europe, the increase has been smaller. Even so, it was 5.3% between 1996 and 1997, the last year for which details are available.

The 1998 report on R&D strategies by the Centre for Medicines Research (CMR) International confirms this upward trend. In 1997, 38 of the companies participating in its annual surveys invested \$23.64 billion in R&D – a mean expenditure of \$0.62 billion per company and an 8% increase (at constant exchange rates) on 1996.

A slowdown in sales

As R&D costs have soared, prescription sales have moved into the doldrums. In the 1980s, the pharmaceutical industry typically spent 10% of sales revenues on R&D, in a market growing at about 11% a year. Data from CMR International suggests that the situation is now very different. In 1997, prescription pharmaceutical sales at 35 respondent companies reached an estimated \$122.2 billion, up just 6% at constant exchange rates on the previous year. With mean sales of \$3.49 billion per company, the average R&D spend represented 17.5% of sales.

Predictably, the industry leaders performed somewhat better, with sales rising by an average 14%. But even they found the R&D pipeline a heavy burden, with expenditure (at a mean \$1.26 billion per company) accounting for 16.8% of sales. Moreover, given current consensus sales forecasts of just 6-7% growth per annum, they will find it difficult to keep up this pace.

The price of innovation

The rise in R&D expenditure is partly attributable to the fact that there are more drugs in the pipeline. In March 1998, there were 3,278 drugs in pre-clinical testing, up from 3,102 in 1997 and 2,853 in 1996 – suggesting that the industry leaders have begun to rectify the “innovation deficit” first identified by Professor Jürgen Drews, former president of International R&D at Hoffman-La Roche, in 1995.

The world's top 20 pharmaceutical companies spent \$17.9 billion on R&D in 1993. Professor Drews calculated that, between them, they therefore had about 894 projects in preclinical trials. However, given a success rate of 40% for discovery compounds, only 358 drugs could be expected to pass this stage. And only 10% of those – 36 drugs – would ever reach the market. Take into account a typical portfolio turnover rate of four years and the top 20 companies could each expect to produce just 0.45 new chemical entities (NCEs) per year.

Compare this with the current position at Pfizer, and it is easy to see how much has changed. With plans to launch 23 products by the year 2001, Pfizer is clearly not suffering from an innovation deficit. It has also rewarded shareholders with TSR in excess of 40% per annum over the past five years.

But Pfizer has the richest pipeline in the industry. Many companies are not nearly so well placed. Though they have closed the innovation gap, they are still unable to produce sufficient drugs to sustain double-digit sales growth – a fact which suggests that other problems have appeared. Where once the block was a dearth of drugs in discovery, it is now the quality of those leads and development of the plenitude of drugs competing for resource. In short, the industry will be forced to make some difficult choices.

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The development lag

The latest report on R&D Strategies from CMR International provides some evidence of this lag in development. At the end of 1996, 41 respondent companies had 350 new active substances (NASs) in Phase II trials or beyond. Based on present attrition rates, they could therefore expect to market an estimated 167 NASs over the next five years.

Since the same companies collectively produced only 93 new molecular entities (more than 90% of NASs are also NMEs) in the previous five years, this would represent a significant improvement. Even so, at a mean of 4.07 NASs over half a decade, it still amounts to less than one NAS per company per year.

It also falls far short of the publicly stated plans of some of the industry giants. Rhône-Poulenc Rorer, for example, aims to secure approvals for between one and two new chemical or genetic entities a year; Glaxo Wellcome intends to bring three new medicines to the market annually by the year 2000; and Bristol-Myers Squibb hopes to produce 30 new drugs for development by the year 2003, a three-fold increase on its performance in 1997.

However, research shows that they will be very hard pushed to achieve these targets. The report from CMR International states, for example, that "the much publicised stretch goal of some of the major companies to produce three new products per annum is probably achievable in any one year, but sustainability is uncertain". In fact, the recent increase in the number of drugs reaching the market is partly attributable to the progress made by the US Food and Drug Administration (FDA) in dealing with a backlog of applications. Our own analysis indicates that the situation could be far worse than CMR International's report implies.

The heart of the problem

Current sales projections suggest that the industry's turnover will grow by 7% a year. If the top 20 companies are to achieve this growth, they will each need, on average, to generate \$28.9 billion in sales between now and the year 2005. But, in order to do so, they must boost the number of new drugs coming out of their pipelines quite dramatically. We have considered three possible scenarios using our ValueBuilder™ model*.

Scenario 1

In the first scenario we have assumed that R&D costs are not expressed as a function of sales revenues (which is quite common); rather, they rise in line with past performance at 10.8% per annum in nominal terms. We have also assumed that total costs per approved drug are \$350m at today's prices; that revenues per drug average \$265m a year – the industry norm; and that sales growth is driven by the number of new drugs that come through the R&D pipeline. Our analysis shows that, in these circumstances, the industry's TSR will fall from nearly 30% per annum, for a basket of 15 of the top companies, to about 10% per annum and that 37 new drugs will need to be approved between now and the year 2005. Naturally, some companies will do much better than others.

Scenario 2

In fact, this is probably optimistic, given that costs per approved drug are likely to be somewhat higher. The US Office of Technology Assessment puts them at \$400m in 1994 dollars; research from Lehman Brothers estimates them at \$608m (including fixed costs), although new technologies could eventually deliver considerable savings; and recent reports suggest they could be as much as \$660m.

We have therefore re-computed the figures, assuming total costs of \$500m per approved drug at today's prices, revenues of \$265m per drug and R&D expenditure rising at 10.8% per year in nominal terms. This results in a further erosion of TSR to levels that would be disastrous for the shareholders and executive management alike, and that 26 new drugs will need to be approved between now and the year 2005.

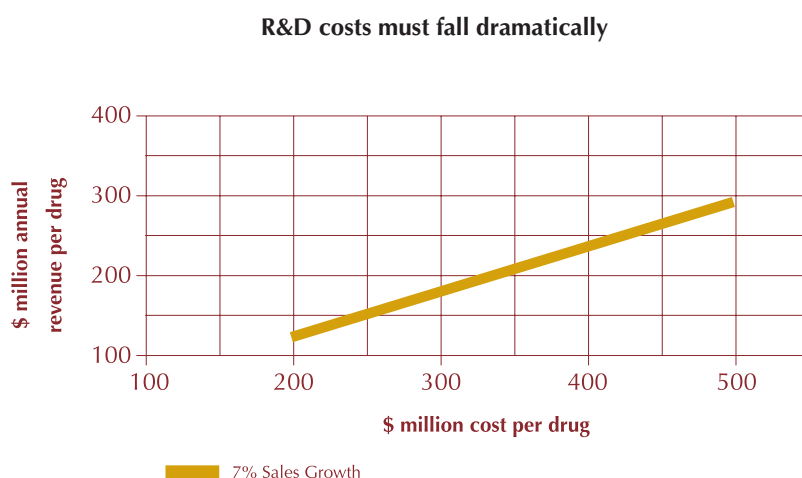
* ValueBuilder™ is a global trademark which represents our unique process of value creation, preservation and realisation. It includes PharmaValueBuilder™, which evaluates Big Pharma companies and – most critically – shows their sensitivity to changing assumptions of risk, growth and return.

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Scenario 3

In our third scenario, sales are projected to grow in line with the industry forecasts of 7% per annum, while R&D expenditure rises in proportion to sales growth. This approach has enabled us to explore the inter-relationship between improved productivity in the innovation engine of the business (measured by costs per approved drug) and the success of the sales and marketing function in exploiting the commercial opportunity presented by the new product (measured by annual revenue per new drug).

We have used our shareholder value model to calculate the correlations that exist between these two variables and have illustrated the results below.



If the industry is to achieve sales growth of 7% per annum, it must slash its R&D costs. It will need to cut costs per drug for the 90% or so of all drugs which bring in less than \$180m a year to just \$280m – a saving of between 20% (on costs of \$350m) and 44% (on costs of \$500m). It is this improvement in the efficiency of R&D spend that will deliver the new drugs required to achieve the 7% sales growth.

The numbers game

What seems clear from these numbers is that some companies are heading for a crash unless they can rethink their approach so completely that R&D costs and lead times plummet, generate additional sales revenues with blockbuster drugs or move into brand new markets. Companies which provide treatments the public genuinely wants – since there is no evidence that demand is slowing down – will be able to maintain their lead. Those which do not will be taken over, forced to merge with their fellow laggards or compelled to retrench into niche operations like animal health, which generate much lower rates of return.

Exactly how many industry giants will stay giants is difficult to forecast, but we believe that significant industry restructuring on a scale in excess of the aborted Glaxo Wellcome/SmithKline Beecham deal will become prevalent. Indeed, we think there could be as few as 13 top companies by the year 2005. Sir Mark Richmond, Glaxo's former Head of Research Worldwide, goes further. "We could see just three major pharmaceutical-healthcare providers, each with a cloud of satellites – subordinate companies specialising in vaccines, biologicals and the rest," he says.

One thing is certain: whatever the numbers are, "Big Pharma" will look very different by the year 2005. It has no choice but to adopt a new strategic, tactical and operational management model consistent with the fundamental drivers of this new paradigm – and to do so fast.

3 A Revolution in the Making

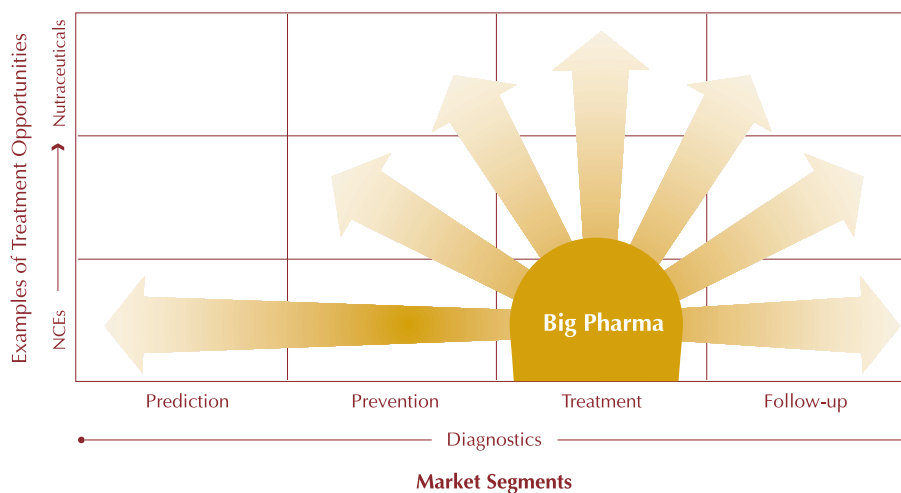
Compound opportunities

So is new technology the answer? Combinatorial chemistry and high throughput screening (HTS) have certainly transformed the early stages of the R&D process. Over the past few years, they have delivered a ten-fold increase in the number of compounds which can be generated for assays and a 100-fold increase in the number of compounds which can be screened.

These tools have become still more important in the context of the new treatment areas now emerging. Over the past 50 years, the pharmaceutical industry has directed its entire efforts at less than 500 targets. But within the next decade the Human Genome Project aims to sequence the entire human genome, containing about 80,000-100,000 genes.

The implications for R&D are massive. If 5% of the proteins encoded in the human genome have therapeutic value and a further 20,000 represent possible biological targets (in line with industry forecasts), there would be some 25,000 new targets. And even if only a quarter of them prove to have genuine potential, this would still represent a 14-fold improvement on the current situation.

Moreover, apart from producing new targets, genetic screening will provide the means with which to identify genotypes and thus to predict who is at risk from what, together with the side effects of any medication. The focus of treatment will also expand from cure to the reversal of pathology in conditions such as epilepsy and Alzheimer's disease. So the industry's remit looks set to grow significantly. Where once it made pills and lotions, it will be increasingly involved in prediction, prevention and follow-up treatments.



In addition to such changes, the shifting demographic profile has begun to stimulate demand for new medicines. With the ageing of the population, conditions such as osteoporosis, arthritis and dementia have come to the fore. Higher lifestyle expectations have had a similar effect, sparking the search for better drugs to treat problems such as obesity, acne and erectile dysfunction. The extraordinary interest generated by Viagra is an example of just how much call there is for such medications.

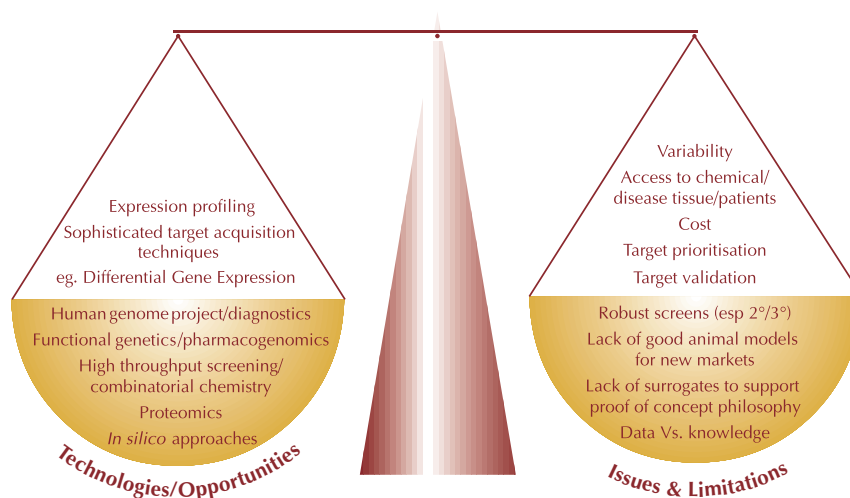
This revolution heralds some enormous opportunities. Over the next few years, the industry will see an explosion in the number of leads it can explore; an expansion in the number of conditions requiring treatment; and a growing role within the healthcare chain.

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Compound challenges

But though the opportunities are huge, so are the challenges and simply pushing more drugs down the pipeline will not sort them out. The pharmaceutical industry must improve the quality of the drugs it produces, either by being much more selective at a much earlier stage in the R&D process or by completely changing the parameters in which it operates to ensure that it gets better results.

By the year 2005, today's technologies will be mature. Combinatorial chemistry and HTS will no longer provide a competitive advantage. If anything, they will merely increase the pressure further down the pipeline, as the search for genuinely ground-breaking drugs makes development and manufacturing much more exacting.



Genomics will not solve this problem. The exponential increase in the number of targets will bring its own risks, including a substantial rise in the ratio of R&D costs to sales until returns on investment feed through; and price competition from a plethora of products in any one therapeutic area. It will also fragment the market. If disease-based research establishes that there are five sub-sets of asthma requiring five different treatments, for example, the market for any one product will shrink considerably – even if the overall market expands as a result of new opportunities to treat patients who have failed to respond to previous medications or suffered adverse side effects.

Today's Key Skills	2005 Key Skills
Genomics/Proteomics	Increased emphasis on today's skills plus:
Bioinformatics	Business focused approach in R&D
Pharmacogenetics	Managing across virtual organisations
Knowledge engineering	Diagnostics as product development opportunities
Engineering (automation)	Non-invasive imaging technology
Global, X-functional teamworking	Gene therapy/DNA vaccine approaches
Project management	Portfolio management
Integration	Environmental auditing

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All these trends will put enormous pressure on the regulatory authorities, as they struggle to cope with a flood of applications for new drugs for ever more specialised conditions. They will also produce a massive increase in the volume of data with which the industry and its regulators have to grapple. The change is reflected in the new skills, like knowledge management, and new words, like bioinformatics (coined to describe the marriage of biology and IT), now entering the industry.

But knowledge management will be only one of the new skills required in the brave new world of “e-R&D”. With computer-generated molecular libraries and chemical screens, *in silico* tests for toxicity, metabolism and bioavailability, and virtual clinical trials, the role of “traditional” chemistry will be changed beyond all recognition. The industry will want very different skills from those available today.

The critical question, then, is how it can combat these challenges and make the most of the opportunities.

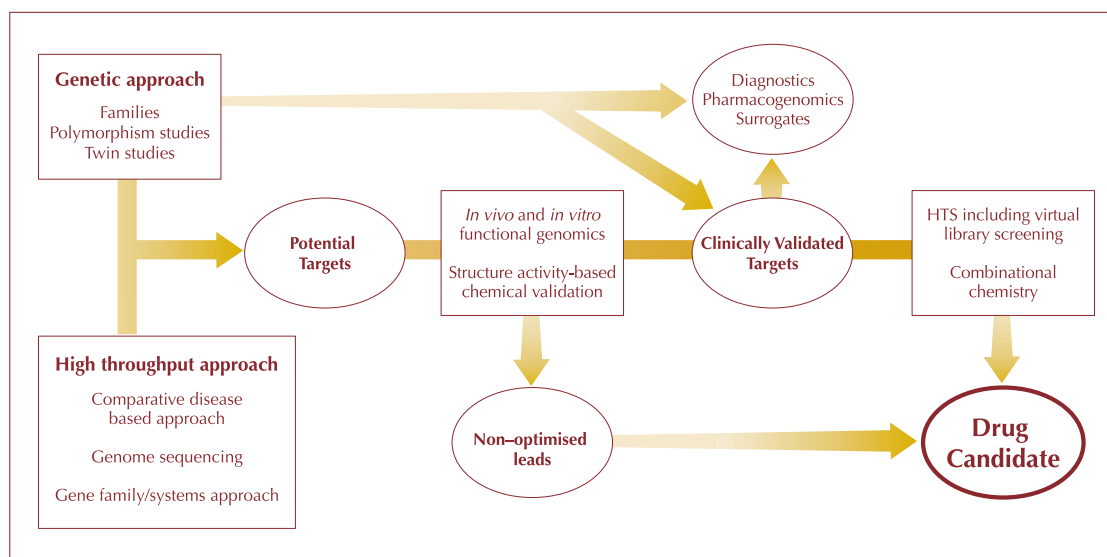
4 Getting a Head Start

Gene genie

By the year 2005, it is likely that the chemical “letters” which make up the DNA in human cells will not merely be decoded, they will also be at least partly assembled as “words” and “sentences” with meaning, thus addressing the shift from genetic codes to the linkage with disease. Genomics promises to create new leads and new areas of business; it will open up the markets for diagnostic testing, preventative medicines, follow-up treatments and even support services such as lifestyle counselling.

It will also begin to dictate what gets researched. When one version of diabetes is much more common than another, it clearly makes sense to focus on the version with the biggest patient population and potential returns on investment. But this creates other problems. R&D directors used to deciding what takes place in the laboratory may not welcome the change. Patients with rare versions of an illness may raise even stronger objections. In short, genomics brings with it profound ethical and commercial implications.

The opportunities it affords have also spawned a host of potential rivals. In 1997, according to *Nature Biotechnology* (Volume 16, May 1998), there were 380 quoted biotechnology companies and over 1,000 privately owned biotech companies worldwide. This year alone they will spend an estimated \$9.0 billion on genetic research.



Companies involved in the emerging sciences have had a considerable impact on Big Pharma as demonstrated by the fact that between 10% and 20% of its R&D budget is now thought to be devoted to genomics. But their success has done more than influence the direction of its research. It also suggests that economies of scale are no longer as important as they were.

Stripped of this advantage, the industry leaders will have to look to their laurels. They will need to determine how much to invest in gene research in the short term; how to steer their R&D operations into the most potentially productive areas; how to spread their risk by embracing the next wave of new technologies; and how to cope with the financial demands involved in doing so.

The big screen

High-tech solutions such as combinatorial chemistry, pharmacophore technology and HTS will certainly not enable Big Pharma to fend off its rivals. On the contrary, the new technologies will lower the barriers to drug discovery and make patent walls easier to defeat. What distinguishes the leaders from the also-rans will be the quality of their compound libraries and ease of access to the information within those libraries. The ability to maximise the benefits of HTS, by extending the range and accuracy of the assays and harnessing the knowledge they generate, will also be vital.

The home run

Smart systems of any sort are only tools; smart people are another matter entirely. Yet many research scientists tell us that they do not find working in large organisations conducive to originality, lateral thinking and innovation. The industry leaders must therefore learn to foster a creative culture without losing control of the purse strings: no easy task.

But this assumes that research scientists continue to work within a conventional corporate environment. In fact, some companies have already made efforts to change that environment: Rhône-Poulenc Rorer has, for example, created Gencell, a loosely affiliated network of 14 companies specialising in the emerging sciences, while Novartis recently announced that it was forging research alliances with academia.

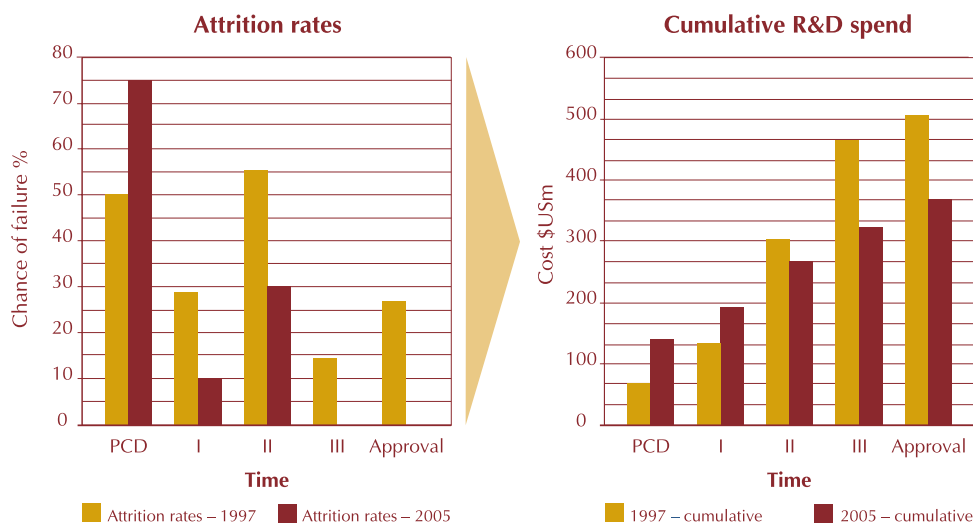
However, the mechanisation of the early-stage discovery process could culminate in something much more radical, such as the development of drug discovery factories and “tele-labs”. By the year 2005, the most successful pharmaceutical companies may be emulating some of the “baby biotech” firms with research scientists, linked by powerful intranet facilities, working from home.

5 Taking the Lead

The killing fields

In December 1997, Glaxo Wellcome announced that it had achieved a significant cut in the attrition rate for drugs entering preclinical trials. It brought 18 NCEs to exploratory development that year, triple the number which Glaxo and Wellcome had jointly produced in 1994. Moreover, only four of the 28 NCEs that entered exploratory development in 1996 and 1997 were dropped before entering full development – a 14.3% failure rate, compared with the industry average of about 33%.

This translates into a 29% chance of ultimate success, almost three times the average in 1994. It also highlights the enormous benefits which improvements at the preclinical stage can deliver. Attrition rates vary considerably, depending on both the company and the therapeutic category. Traditionally, however, many companies have delayed selecting the “winners” and spiking the “losers” until they are in clinical testing; about 30% of all compounds are dropped in Phase I and 50% in Phase II trials.



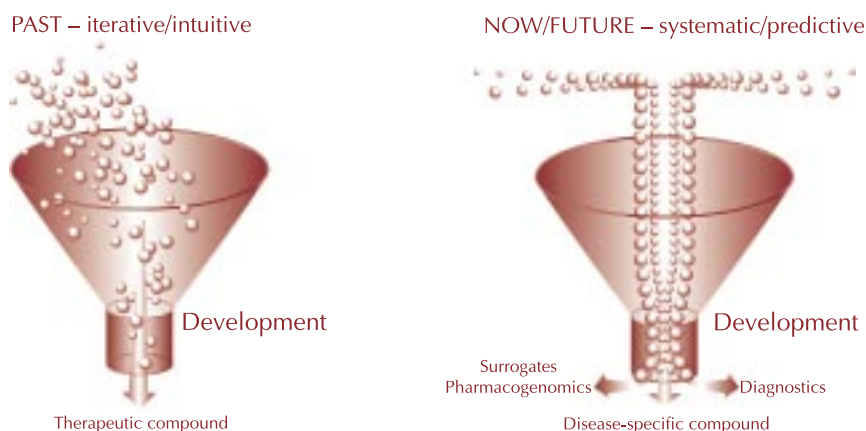
Given the increasing number of drug candidates in the pipeline, more complex development and manufacturing processes, greater volumes of data, growing regulatory requirements and the need to reduce lead times, this is too late. Preclinical trials must become the “killing fields” for any drug that does not fully live up to expectations in terms of its safety, efficacy and commercial viability. Although the pharmaceutical industry has traditionally been characterised by indecision, it must now become much more decisive.

A bridge too far

If it is to bring the selection process forward, it will need to move further towards *in silico*, *in vitro* and *ex vivo* testing from *in vivo* testing, at the preclinical stage of development; and tailor those tests much more carefully. It must move from an iterative and intuitive way of doing things to systematic, predictive processes that will rapidly identify disease targets in commercially viable disease segments.

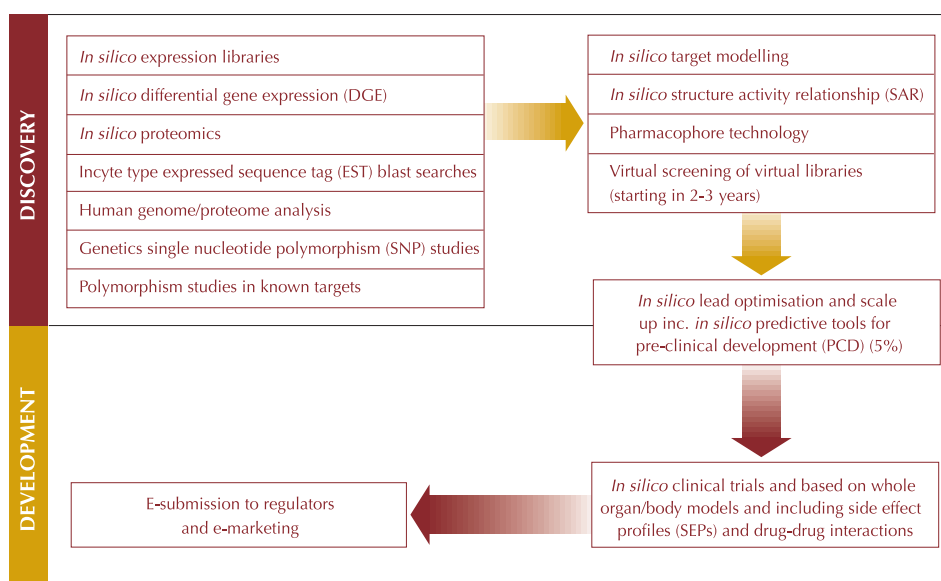
It will also have to create a culture that blends scientific curiosity and hard-nosed commercialism, with preclinical teams capable of producing detailed risk/benefit analyses, development and contingency plans. If they do not have any blockbusters in the pipeline, for example, they must work out how to produce a portfolio of minnows which collectively

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yield the same returns. Several leading companies have already made strides in this respect, through the integration of marketing with R&D.

But transferring skills traditionally associated with preclinical into late stage discovery, and skills traditionally associated with clinicals into early development, is only an interim measure. Changes already on the horizon suggest that the preclinical stage will soon be a bridge nobody needs.



Emerging *in silico* techniques and technologies such as single cell differential gene expression and target searches in Expressed Sequence Tag libraries marketed by companies like Incyte will enable the industry to identify targets with the ideal physiological and pathological characteristics. Pharmacophore technology, *in silico* lead optimisation, scale-up and preclinical trials will follow. Computer modelling will even provide the tools with which to perform *in silico* clinical trials, based on whole organ body models that test for everything, including side effect profiles and drug-drug interactions – although it is doubtful that the regulators will accept such evidence for some time. In short, within a few years, the industry will be able to move straight from the test tube to man (if not to the marketplace).

6 Testing, Testing, Testing...

Running out of patients

Between 1991 and 1995, the average number of clinical trials required to get a drug to market rose from 36 to 68. The trials also became more complex. Over the past decade, the average number of assessments per trial has nearly doubled, as has the average number of patients involved in each trial.

Pharmacogenomics – the study of genetic variations between individuals and how they influence the way in which people respond to a particular drug – looks likely to modify this trend. It will soon enable the industry to target drugs much more precisely. Indeed, it even paves the way for mass customisation, with “bespoke medicines” tailored to a patient’s specific biological traits.

On the one hand, then, pharmacogenomics will reduce the number of patients needed in any one trial, by making it much easier to target people with a specific genetic profile. On the other, it will increase the number of trials needed to test different drugs for different versions of the same disease.

But though pharmacogenomics promises to simplify the way in which clinical trials are conducted, the increasing demand for pharmaco-economic data may have the opposite effect. Healthcare purchasers everywhere have begun to focus on value for money. This will change the nature of the data that is collected.

Moreover, both changes will be far outstripped by the pressure further up the pipeline as a result of shorter development times and higher success rates in discovery and preclinical testing. In the short term, we estimate that the net effect of these improvements could be a nearly six-fold rise in demand for the resources (patients and trial personnel) required to conduct clinical trials. In the long term, *in silico* techniques and the drive to address the inefficiencies inherent in such studies will solve the problem by truncating the clinical trials process.

Virtual bodies

Greater competition for patients and investigators, and the rising cost of clinical trials, have triggered one of the boldest experiments in the history of the pharmaceutical industry: an attempt to test products without any human exposure. Companies like Pharsight are using preclinical data to create populations of software “people” designed to behave like the real thing. But virtual trials will probably cut the amount of clinical resources required by 10% at best in the short term (although the savings may be much greater later on). Remote data entry and other advances could save another 20%, so there will still be a massive shortfall.

Most patients in Phase II or III trials are currently recruited at specialist referral centres. This pool is not big enough to meet the industry’s needs. An increasing number of companies are therefore recruiting patients through primary care providers, the Internet and even television. But as patients become better informed, they may become more selective about the sort of trials in which they agree to participate.

Private investigators

Access to many people will also be increasingly restricted by health maintenance organisations (HMOs) and site management organisations (SMOs). In Europe these are, for the most part, loosely affiliated groups of investigators who conduct trials on a commercial basis. However, as access to patients becomes an increasingly valuable asset, and demand for outcomes and pharmaco-economic research grows, they are likely to become very much more powerful. By the year 2005, the market may well be dominated by between five and 10 quoted SMOs with collective control over tens of millions of patients transcending national boundaries.

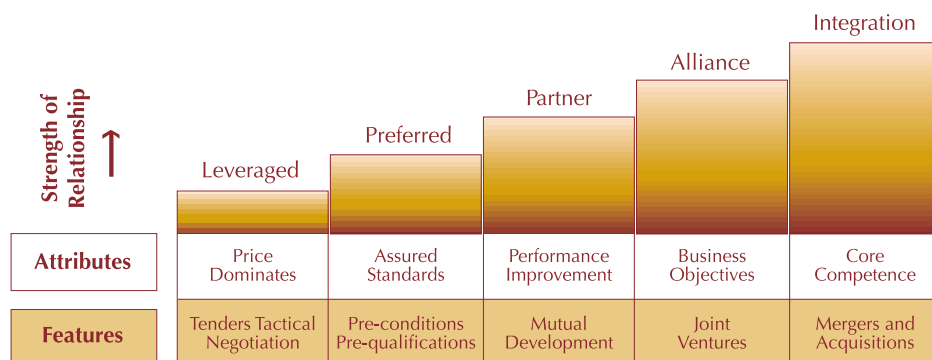
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Outside forces

The danger that it will be starved of a crucial resource is one of several factors driving the industry into external collaborations. Most large pharmaceutical companies still treat contract research organisations (CROs) as “hired help” rather than an expert resource. But given the number of projects on their books, many CROs already have better access to patients than the companies which employ them. This will increase, as they expand the range of services they offer, build on the close relationships they enjoy with “baby biotech” and, in some cases, join forces with SMOs.

If the CROs and SMOs hold a strong deck of cards, however, so do the HMOs. And since they are primarily interested in pharmaco-economic data – information which clinical trials have not traditionally collected – access to their patient pools is likely to be contingent on performing trials that give them the data they require.

Thus the need for patients and outcomes data will change the balance of power between Big Pharma and the rest of the healthcare chain. The large pharmaceutical companies will have to forge new alliances with CROs, HMOs and SMOs – or buy them. They will also have to learn how to manage those relationships properly and how to address the resulting ethical dilemmas, such as whether the HMOs to which they are linked should have access to drugs from other companies.



People power

When AIDS patient groups learned that Wellcome was developing AZT, they obtained copies of the protocols, visited the company and made suggestions about how to improve the clinical trials. They also took to the streets in an effort to ensure that the drug was tested and approved as rapidly as possible, even though it did not meet the normal criteria for safety and efficacy. For the victims of AIDS, the promise of a few extra years outweighed the risk of taking an as yet unproven drug. The FDA ruled in its favour.

Consumer clout has traditionally featured little in an industry dominated by the demands of regulators and doctors. Scientific conventions about proof of concept determine what gets asked and what gets measured, although much of this data is redundant and has nothing to do with how patients feel: few people, for example, could detect a four point decrease in their Hamilton depression rating scale, yet this counts as a clinically significant outcome.

But things are changing. In a 1996 survey of US Internet users carried out by FIND/SVP, 38% of all respondents actively sought health and medical information. Moreover, the traffic is not just one-way. Some AIDS patient groups now conduct self-administered trials and publish the data on the Internet for the use of other patients and the industry itself.

A better educated customer base will have an enormous impact on the whole healthcare industry, says Jonathan Peck, vice-president of the Institute of Alternative Futures. “If you want to see the model for tomorrow’s marketplace, look back to the AIDS patients who went to their doctors knowing more about experimental therapies and alternative care options than the physicians who cared for them.” People power will “force every healthcare business to learn how to operate in smart markets”, he adds.

An Industrial Revolution in R&D

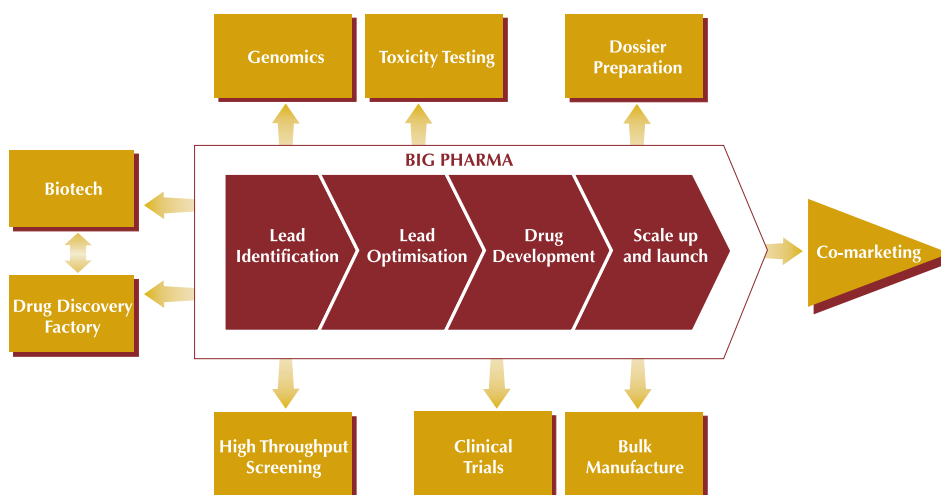
In short, as the public becomes more knowledgeable, it will start to call some of the shots. The 33% rise in US direct-to-consumer advertising, from \$900m to \$1.2 billion, over the past year alone reflects the industry's growing awareness of its importance, but this is just one manifestation of the change. Consumers will increasingly influence the decisions companies make about which treatment areas to tackle, the sorts of questions they ask in clinical trials and the criteria on which a drug is judged.

Trials and errors

What gets measured differently gets done differently and, for other reasons too, the industry will have to change its clinical procedures. Most companies design trials without using information from studies in other therapeutic areas, even though the data could help them to design better trials. They also use a wide range of systems, with little standardisation, including paper-based case reports completed on site and then keyed or scanned into a central computer.

This fragmented approach will no longer work, as improvements in discovery and preclinical trials push more drugs more rapidly down the pipeline and the studies themselves become more complex. The leading companies are therefore starting to build proper data warehouses with information in easily retrievable formats; to borrow from studies in other treatment areas to design better trials; and to input the results of those trials electronically, so that the data can be used for other trials as well as in preparing a dossier for the regulators.

They will also need to alter the way in which they allocate resources. Most large pharmaceutical companies still operate on a functional basis, with budgets and power vested in different areas of the business. When those areas have different (sometimes conflicting) priorities, the project suffers. A far more effective way of slicing the cake is to create a horizontal structure, with budgets vested in specific project teams – including manufacturing and marketing – which can then “buy” what they need from the various functions. Pursued to its logical conclusion, this approach enables a company to identify its core processes and how much it can outsource, thereby releasing capital for further R&D.



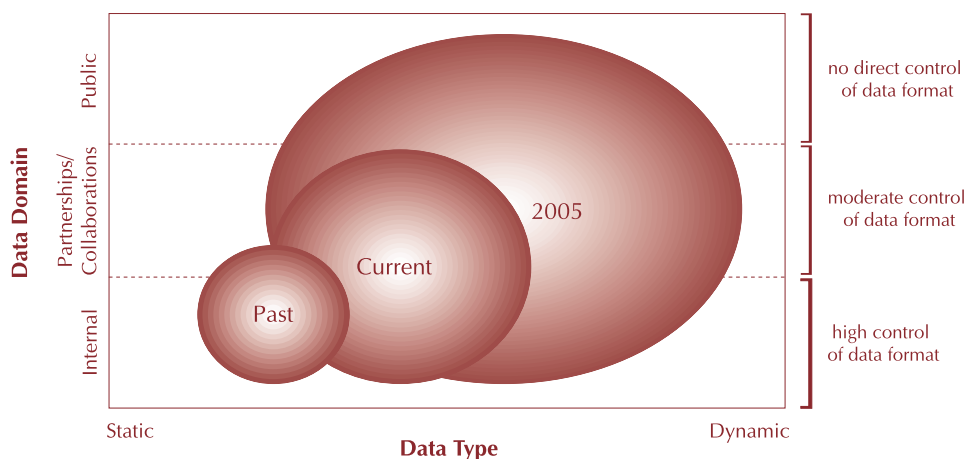
It also puts the project itself centre stage, optimises the use of finite resources and may even cut lead times dramatically. Preclinical and clinical studies typically take about seven years in total. However, several leading companies with which we have worked have cut development times within some key operations to half the industry average, by reorganising their business from a set of separate activities conducted in several different functions into a single integrated process.

7 Turning Data into Knowledge

The tip of the molecular iceberg

With state-of-the-art combinatorial chemistry, it is now possible to synthesize 10^3 - 10^4 compounds per chemist-year. This is many times the few hundred compounds a chemist could turn out using traditional methods. It is also just the tip of the molecular iceberg.

The number of virtual "organic" compounds that can be made from carbon, hydrogen, oxygen, nitrogen and sulphur is effectively infinite – as much as 10^{100} , for example. Assume an increase in computing power of the magnitude we have seen over the past decade and *in silico* screening, and the pharmaceutical industry will soon be able to synthesize 10^{10} compounds – one million more than the current level per chemist-year.



The new technologies look set to generate many gigabytes of additional data. Indeed, they have already begun to do so. In its recent report on *Entering the Third Generation of Pharmaceutical R & D*, Glaxo Wellcome estimated that HTS has produced a 10-fold increase in its network traffic. Plans to adopt denser screening plates and more complex library design will add a second order of magnitude and the company estimates that internally-generated data alone will soon expand the load on its computer infrastructure by a factor of 100.

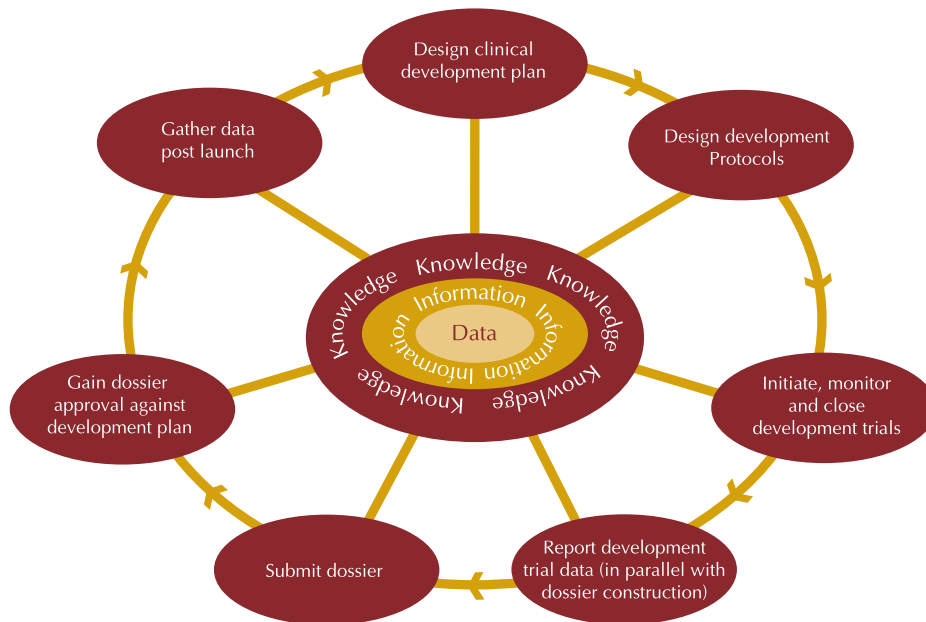
The growing volume and complexity of clinical trials will likewise expand the sheer quantity of data that needs to be processed. But what the industry itself creates is only part of the story; it must also be able to manage the data produced by its partners. Over the past decade the number of strategic alliances has more than doubled, from 248 to 635 per annum. It is likely to keep rising, as the industry leaders forge further links with biotech companies, CROs, SMOs and HMOs. We estimate that in certain therapeutic areas outcomes evidence alone may double the volume of clinical data. Such feedback data will shape the design of subsequent trials and improve the quality of development programmes.

Creating a virtuous circle of data

Most pharmaceutical companies are currently ill-equipped to deal with this information onslaught. They have no defined data standards, no common architecture and no central depot from which staff can easily access the experience of colleagues elsewhere in the business. Fortunately, however, the technology will soon be available to assist in solving many of these problems.

By the year 2005, web-based approaches to data management will have matured sufficiently to provide a portal to multiple data sources, dispensing with the need for standardised formats altogether. The data will be indexed to create a taxonomy of knowledge and distributed on a widespread basis. Thus staff will have “plug and play” access to the data, wherever they sit in the product development chain. Whether they work in early stage discovery, late stage development, in head office, at home or at the premises of a partner organisation, they will be able to call up the same files with the same ease.

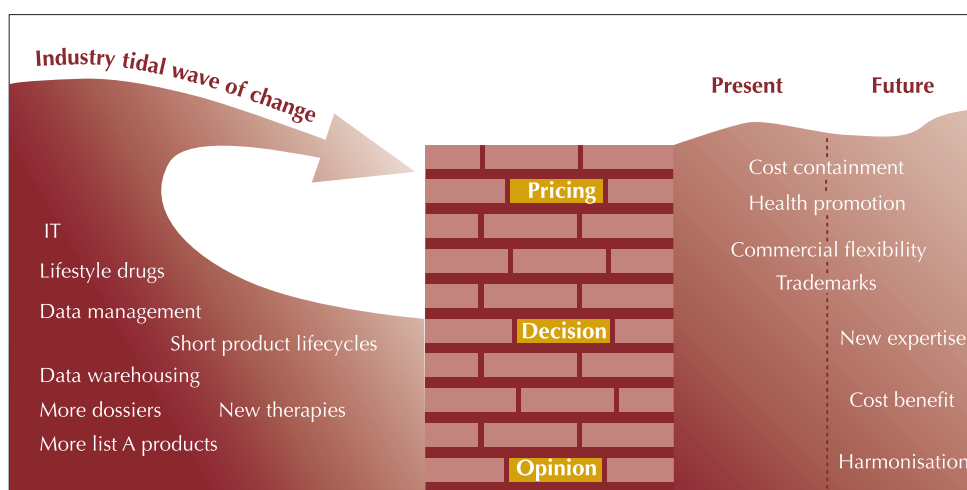
But putting the right electronic links in place is only half the battle; the other is creating the right human links. Without a systematic way of capturing data, there will be nothing to call on. Without a corporate culture that fosters learning, the data will remain data and never get translated into knowledge. Proper knowledge management systems depend on setting project milestones specifically to document the data that has been collected; appointing staff with the skills to manage distributed data; and ensuring that the people employed by the organisation actually use it to improve what they do subsequently. The power of outcomes analysis and its use in the development process has yet to be fully realised.



8 Working with the Watchdogs

A tidal wave of dossiers

The pharmaceutical companies are by no means the only part of the R&D chain at risk of being overwhelmed by a tidal wave of data. The regulatory authorities sitting at the end of the pipeline with far less resources face problems too. The surge in the number of drug candidates produced by the new technologies will ultimately translate into a huge rise in the number of applications for new drugs landing on the desks of the FDA, European Medicines Evaluation Agency (EMA) and other regulatory bodies.



The complexity of the dossiers supporting those applications will also increase, as the new fields of research start to yield fruit. Many of the new gene and protein therapies will raise medical and ethical issues outside the previous experience of the regulators, as will the evidence produced by virtual trials. Those with a national remit, for example, will need to scrutinise the pharmacogenomic data rigorously, to determine whether it applies to the populations they cover. And some drugs will simply be so specialised that the patient population on which they can be tested is too small to provide statistically conclusive results.

These changes are likely to alter the very nature of regulation. When tiny samples of data on highly specialised drugs are all that is available, the industry's arbiters will be forced to shift from corroboration of the facts to evaluation of the risks and benefits. They will also be forced to rely to a much greater extent on the companies which have developed those drugs, since they will be the sole experts.

Speeding up the process

The pressure on the regulators will be compounded by the growing power of public opinion. With greater access to healthcare data, consumer demand for fast-track approval of drugs designed to treat emotive conditions will rise.

In fact, the regulators have already made considerable headway on this front: figures published by the FDA, for example, show that the mean approval time for NMEs fell from 32.4 months in 1987 to 16.2 months in 1997. The FDA and EMA have also set up fast-track systems for drugs in critical treatment areas, and some of the other regulators could now follow suit.

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But the need to provide a mechanism for dealing with drugs so highly targeted that they cannot be tested on a sufficient number of patients may well result in a more far-reaching change. With conditional approvals – where a drug is given a restricted licence, pending satisfactory evidence from post-marketing trials – times to market could be cut without forfeiting regulatory control.

Firm allies

The job of the regulatory bodies could also be made much easier with electronic dossiers that use consistent information architecture, software and conventions. As Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research (CDER), says: "Over the long term CDER's goal is a fully integrated, fully standardised electronic submission that is searchable across submissions."

Given this impetus, it is likely that, by the year 2005, electronic dossiers will be standardised. They may even be replaced by virtual submissions – where trial data is saved on a continuous basis and stored on a central server accessible to research company and regulator alike.

Virtual submissions would enable the regulatory bodies to assess evidence on a rolling basis, rather than waiting for a formal application. But they would also provide an opportunity for much closer dialogue and this might produce an even bigger change. It could rewrite the relationship between the industry and its custodians. Past differences behind them, the two would become partners in the shared enterprise of getting good treatments to the patients who need them as quickly as possible.

9 Rewriting the social contract

The pharmaceutical industry is not just an entity by itself, though; it operates within a social framework. This, too, is changing. As governments and healthcare purchasers throughout the world struggle to control the soaring healthcare bill, so consumers will be expected to foot an increasing share of the costs.

There is evidence that this is already happening, with the development of over-the-counter line extensions like Zantac. But at what point should it stop? Most states will probably continue to shoulder the burden for treatment of life-threatening conditions in the very poor. New drugs like Viagra and Xenical (the obesity medication), in which the boundary between clinical illness and quality of life is blurred in the mind of the patient, are another matter. Spurred by the threat of a black hole in their budgets, many governments may want to keep such drugs entirely in the private domain because of the difficulties involved in clarifying the distinction between illness and lifestyle.

However, this would create two or more tiers of medical provision. It would also break with everything that has previously characterised medical ethics. At present, although the monied classes can afford to see a consultant and leap the queue, they still get the same drugs as the poor. For both ethical and commercial reasons, then, the industry must totally transform its R&D to create affordable drugs. If governments will not pay for its products and individuals are unable to do so, it will have no customer base.

The shift towards self-medication raises other issues. With an increasing number of products available over the counter, patients must be much better informed. The same is true of the new lifestyle drugs. A pill that keeps the pounds off will do nothing to counteract the damage from many hours spent slumped in front of the television. If patients are to use such drugs properly, they will need to become partners in the healthcare chain.

The pharmaceutical industry must shoulder some of the responsibility for this process of education. It must also be prepared to tackle some uncomfortable ethical questions; dismissing such issues as things outside its province will not win it any friends. And it will certainly need friends in the tough years ahead, for, as Professor Julian Hilton of Telos Consulting remarks, "The old way of doing R&D is about to implode."

In short, today's model will certainly not suffice. The financial pressures the industry faces; the new skills it will require as a result of the fundamental change in its core activities; the greatly increasing complexity of those activities; the fact that neither new technologies nor new sciences will provide any easy answers: all dictate the need for a totally different approach. What works today will not work tomorrow. If they want to be part of that future, the world's leading pharmaceutical companies must cast off today's paradigms for tomorrow's untrodden path.

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