

Diverging paths, difficult choices

Pharma is poised on a knife-edge. Major scientific and technological advances, together with socio-demographic changes, rising demand for medicines and trade liberalisation, will revive its fortunes in another decade. But in the meantime it faces some fundamental challenges – challenges that will entail making difficult decisions over the next few years.

Good news. The scientific foundation on which Pharma rests is improving exponentially, thanks to advances in genetics and genomics, a huge leap in our understanding of disease and massive improvements in the technologies used to collect and analyse biomedical data. In 2001, it cost \$95 million to read an entire human genome¹. Today, two manufacturers are developing machines that can do so for as little as \$1,000 – in a matter of hours².

Technological developments have also paved the way for electronic medical record systems that capture vast quantities of outcomes data. And with sophisticated data sharing, processing and mining techniques, scientists can make better sense of what they see.

The global market for medicines is simultaneously growing, as the world's population increases, ages and becomes more sedentary, and many of the former barriers to free trade fall. Indeed, the market could be worth nearly \$1.6 trillion by 2020 – up from \$1.08 trillion in 2011³.

...and bad

In some respects, then, Pharma's prospects have never looked more promising. But neither have they ever looked so poor. The industry's output has flatlined for the past decade. Its corporate culture is sclerotic. And the commercial climate is becoming much harsher.

In short, if Pharma is to prosper in the future, it

must first ensure that it has a future – and many of the conditions that will determine what happens in 2020 are already in place. Most, if not all, of the products that will be launched by then are already in the pipeline. Many of the senior executives who will be at the helm have already been earmarked for high office or appointed. And changing the culture of a large organisation can take years.

Value for money is the new mantra

Healthcare expenditure as a percentage of GDP is climbing everywhere – and it is climbing most steeply in the mature markets where the industry has historically made most of its money. This trend is unsustainable.

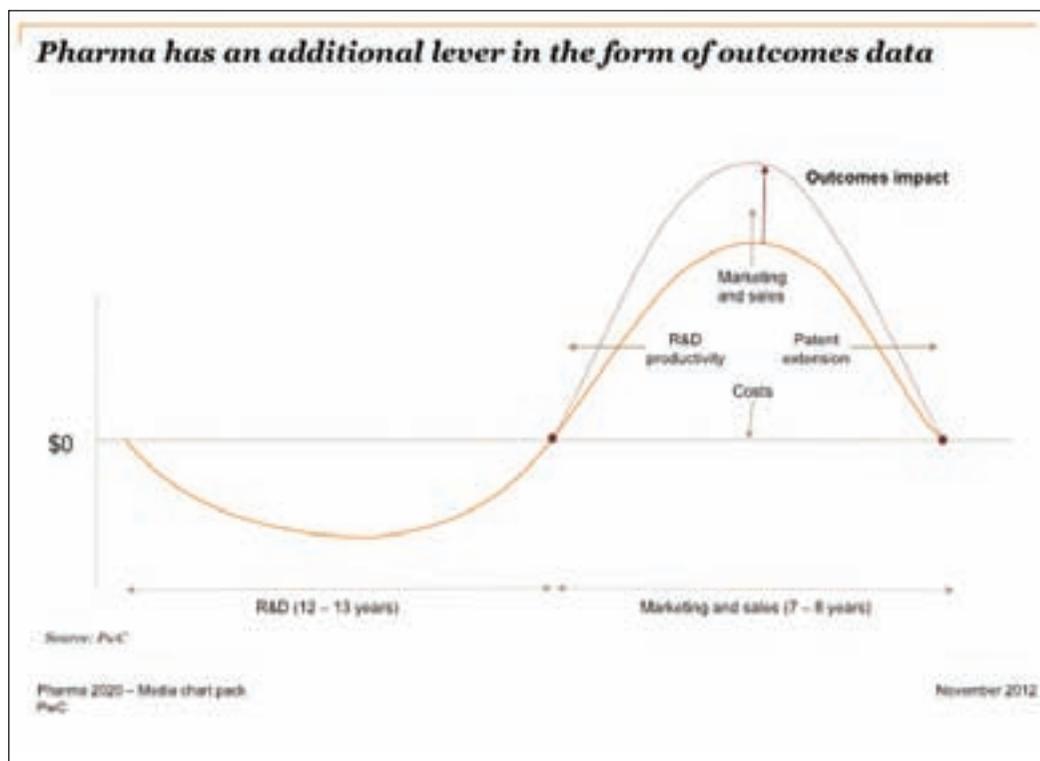
The Affordable Care Act, AMNOG and other such reforms testify to the pressure healthcare payers in the mature economies are experiencing. Faced with a crushing financial, demographic and epidemiological burden, they want more value for their money. And they want hard evidence to back any claims that a new medicine is better than rival therapies.

This has profound implications for Pharma. It must either offer more value without charging more or remove costs from another part of the healthcare system to make room for the higher prices it is charging. And, in either case, it must provide proof of the value it is offering.

So, rather than using the 'profit' levers on which it has traditionally relied, the industry must now

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Figure 1
Pharma must now pull a new lever in the form of outcomes data



resort to another lever: namely, outcomes. It must demonstrate the worth of its products with real-world evidence of lower mortality and morbidity rates or savings in total healthcare costs (Figure 1). And pulling the outcomes lever will entail major changes – particularly in development, where Pharma will have to take greater heed of the views of healthcare payers and providers.

The growth markets aren't the answer

The situation in the growth markets is somewhat different. Expenditure on medicines is rising far faster in these countries than it is elsewhere. But serving the growth markets is very difficult, not least because they vary so much. Moreover, patients in the growth economies typically have to foot a larger share of their own healthcare costs than patients in the mature economies. And per capita healthcare spending is far too low to support biologics costing thousands of dollars.

At present, then, the growth markets lack the power to reward innovation. So, even if Pharma succeeds in capturing more custom from the roughly 80% of people who live outside the developed world, this won't be enough to offset price erosion in the mature markets.

Pharma's core challenge

Pharma's future in every part of the globe there-

fore hinges on its ability to make more innovative medicines more economically – and to prove the value those medicines deliver. So how can the industry improve its R&D productivity? We think there are two aspects to the problem: one scientific, the other managerial. We'll start with the scientific issues.

Frontloading the R&D process

The most important decision a pharma company makes during the R&D process is which target or mechanism to focus on. It usually starts by collating evidence drawn largely from the public domain to create a hypothesis about the role of a mechanism in a given disease. But there is rarely a single, compelling piece of data validating the mechanism's role in the underlying pathophysiology of the disease. Furthermore, very little is known about the feasibility of intervening pharmacologically or demonstrating the desired clinical effect at this point.

In other words, the company has to decide on a course of action before it has much information to go on – and the stakes are very high. If it makes the wrong choice, it could end up eight or nine years later with a failure that has cost a billion dollars or more.

So it is crucial to find out as much as possible about the role a particular mechanism plays in

disease before embarking on an expensive development programme. Yet, on average, the industry spends only 7% of its R&D budget on target selection and validation (Figure 2). We believe that investing more money in translational medicine and innovative, early clinical studies to validate targets would reduce the risk of losing a lot more money further down the line.

Making the most of genetics and genomics

Many companies also continue to rely on animal models, although these have proved a relatively insensitive means of predicting efficacy in man. But with whole-genome association studies and next-generation sequencing (NGS), we now have a suite of tools with which to probe and predict the impact of different mechanisms in human populations before conducting clinical trials.

An example? High-density lipoprotein (HDL) levels are associated with heart disease. Yet trials of cholesterylester transfer protein (CETP) inhibitors have shown no beneficial effect on cardiovascular outcomes, despite raising HDL-cholesterol levels. Why not? Genetic analysis of the link between various alleles known to exclusively affect HDL levels and the incidence of myocardial infarction strongly suggests that the relationship is correlative, rather than causal⁴.

Large-scale population studies, coupled with

NGS, can also point to new regions for research. And though both genetics and genomics currently play quite a small role in the laboratory, this is an area of study that is advancing very rapidly. So we believe that, by 2020, Pharma should be investing as much as 20% of its R&D budget in genetics and genomics.

The industry should also draw on the growing number of large population and patient cohorts with well-characterised phenotypes. Together with better biomarker screening technologies and cheaper genomic technologies, this will help it decipher the messages encoded in our genes and develop targeted medicines for many diseases, much as it is now doing with cancer.

Focusing to play

Investing more in the early part of the discovery process and capitalising on the potential of genomics are by no means the only things Pharma can do to improve its productivity. Many companies investigate numerous diseases and spread themselves very thin. We think it would be better to focus on a few therapeutic areas and collaborate with the best people in the field.

Most industry executives now recognise the merits of ‘open innovation’. Several traditional rivals have entered into co-development pacts⁵. And 10 companies recently formed a non-profit organisation to

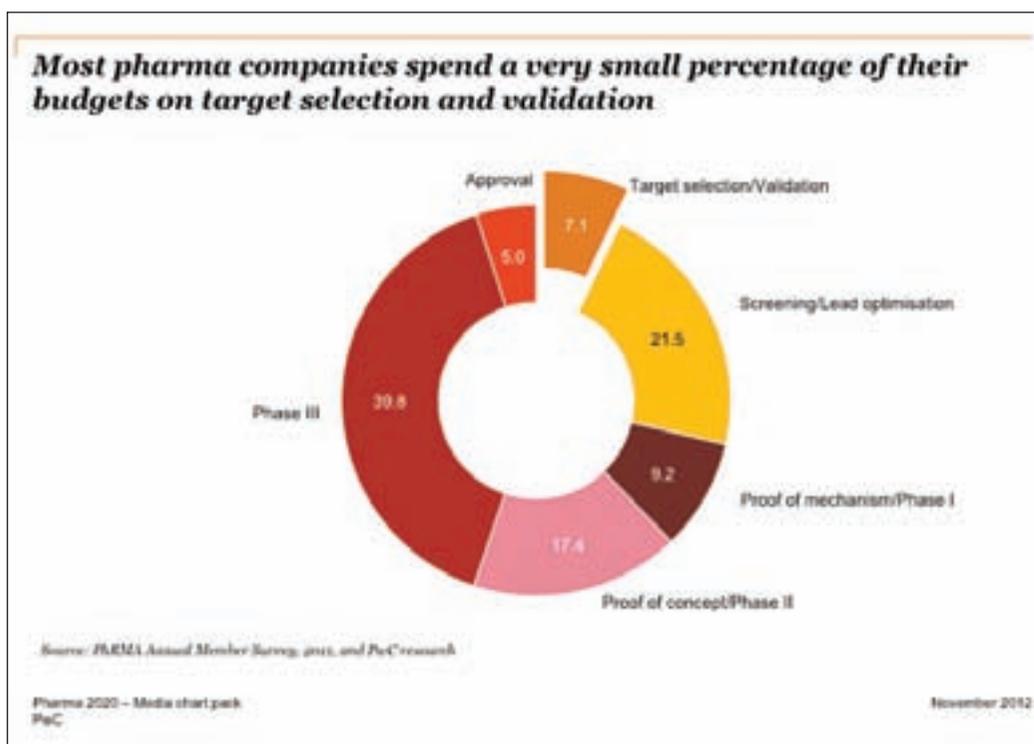


Figure 2: Most companies spend relatively little on target selection and validation

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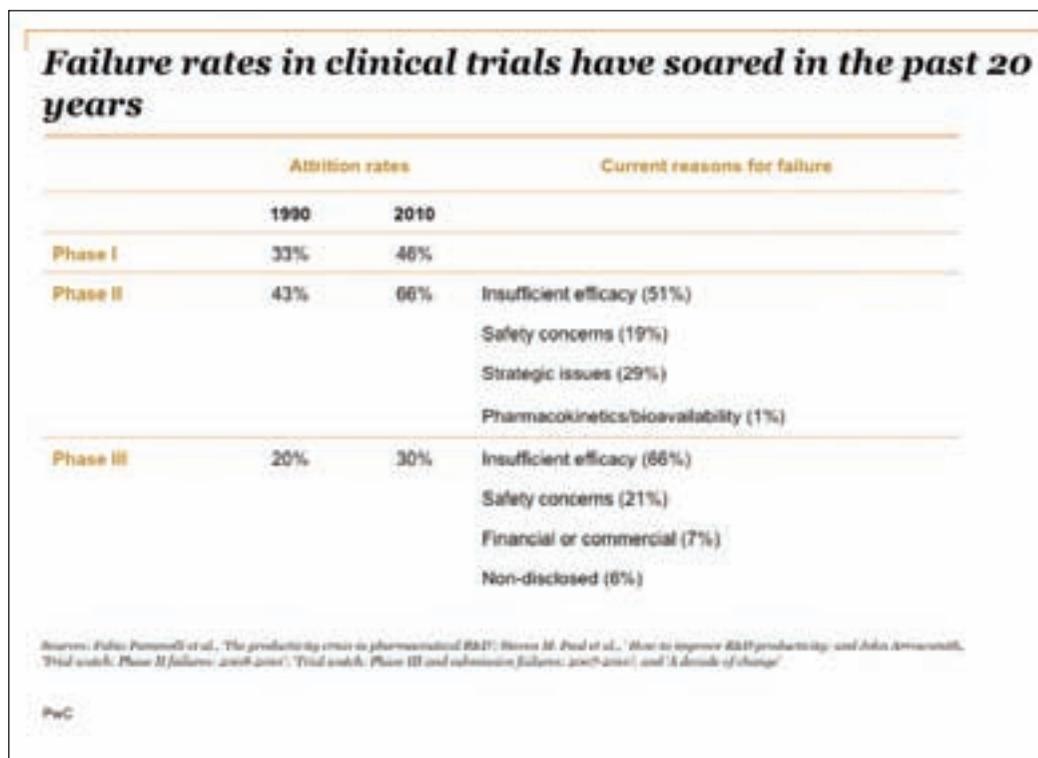


Table 1: Failure rates in clinical trials have soared in the past 20 years

solve common drug development problems⁶. This pattern will continue. By 2020, most precompetitive challenges will probably be tackled collectively. But collaboration with fellow experts is only part of the equation; the other is specialisation.

Cutting to the chase

If Pharma is to convince healthcare payers of the value of the medicines it develops, it will also need to provide the sort of information they require – and that means changing the development process itself. Randomised controlled trials are designed to measure the safety and efficacy of new treatments in strict conditions, not to assess how well they work in the real world.

Novel forms of testing, such as n-of-1 trials and in-life trials, can provide insights traditional trials cannot yield. N-of-1 trials are particularly useful for detecting variations in efficacy, for example, while in-life trials reveal how well a product works in everyday practice.

The regulators are more open to such methods than many companies realise. The European Medicines Agency has explicitly stated that it will consider evidence from sequential n-of-1 trials⁷. And the US Food and Drug Administration recently approved Xarelto for the prevention of strokes in patients with atrial

fibrillation after a large in-life trial⁸. But the industry will certainly have to liaise more closely with the agencies in designing trials that use unconventional formats.

Turning to new treatment types

So Pharma can improve the speed and skill with which it develops new medicines in various ways. But these are not its only options. New treatment types also offer grounds for hope.

Advances in vaccinology have facilitated the development of a new generation of vaccines for a much wider range of diseases. Prophylactic vaccines for meningococcal disease and malaria are already on the horizon, for example⁹. Several promising therapeutic vaccines for non-infectious conditions have also entered the pipeline, including a 'universal' vaccine that trains the body to recognise and destroy tumour cells by itself¹⁰.

Regenerative medicine offers another route forward and some organisations have already made considerable headway. In late 2010, US biotech firm Organovo created the first blood vessels to be bioprinted with cells cultured from a single person¹¹. The General Hospital of Chinese Armed Police Forces is now performing a Phase II trial on the use of umbilical cord stem cells in treating

motor neuron disease¹². And Advanced Cell Technology has started testing retinal pigment epithelium made from embryonic stem cells to treat Stargardt's disease¹³.

Such therapies will obviously require much more complex development, manufacturing and distribution processes than those used to produce conventional medicines. But some of them will also generate enormous clinical and commercial value because they provide a permanent solution. Indeed, they are likely to be tomorrow's blockbusters.

Making more informed decisions

We have discussed the scientific reasons for Pharma's diminishing productivity in the laboratory – and how the industry can address them. But managerial factors play a big role, too, and one of the biggest factors is poor decision-making.

Attrition rates in late-stage development have climbed steeply over the past 20 years (Table 1)¹⁴. Between 2007 and 2010 alone, 83 compounds failed in Phase III or during the submission process, and two-thirds of them foundered because of insufficient efficacy¹⁵.

So, to quote equities analyst Andrew Baum, Pharma is “failing late, failing more and failing expensively”¹⁶. Why? We think it is because many companies cannot manage the relationship between risk and value very effectively. They are also over-optimistic.

Such companies would fare better if they pruned their portfolios to focus on the compounds with the greatest probability of success, using two key yardsticks: therapeutic expertise and the risk/value ratio of each compound. In doing this, they should pay as much attention to commercial risks as they do to technical risks and draw on all the information at their disposal.

When most drugmakers measure risk, for example, they concentrate how novel a target or mechanism is, the degree of confidence in rationale and so forth. They spend much less time considering issues like whether a product offers enough improvement on the existing alternatives. Similarly, when they measure potential value, they give insufficient thought to what payers or providers think. A few honourable exceptions exist, but they are very few indeed.

Building a balanced portfolio

The next step is to build a balanced portfolio, just as investment managers try to do when they are managing financial assets. Responsible fund managers do not bet all their clients' money on risky assets that might, with luck, deliver big returns.

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Yet many pharmaceutical companies do just that.

In our view, combining a few highly speculative compounds with some bread-and-butter products that will generate a steady income is wiser. It is also essential to appoint an independent committee of senior executives to appraise each molecule objectively and monitor the portfolio continuously, since a clinical pathway can be completely redesigned in six months.

It is equally important to compare that portfolio with those of rival companies, because this is how investors think. Our analysis of the pipelines of the industry majors shows that the value generated by R&D varies significantly from one to another. Two factors – therapeutic focus and the ability to manage risk – account for some of these differences. The companies with the most valuable pipelines have decided on the rules by which they are playing and stuck to them.

Adopting a more discriminating approach has two advantages. First, it frees up resources for the candidates a company chooses to focus on, which increases the odds of getting them to market. Second, it helps the company reduce its R&D costs. And even if it only succeeds in lowering its costs without increasing its output, it has still improved its productivity.

Creating a more innovative corporate culture

Neither scientific nor managerial improvements will suffice, however, unless the industry can recover from its cultural malaise. As venture capitalist Bruce Booth recently noted, Big Pharma's culture has been "homogenised, purified, sterilised, whipped, stirred [and] filtered" to such an extent that it has "lost its ability to ferment the good stuff required to innovate"¹⁷.

So how can the industry's top figures reinvigorate their companies? They can bring fresh blood to the board by recruiting people from more diverse backgrounds. They can also lay down clear guidelines about the kind of innovation they want, tell investors how much they plan to spend on R&D over the next few years and stick to their guns in the face of short-termism.

In addition, they can remove layers of unnecessary middle management and create autonomous teams that report straight to the head of R&D. They can build networks that cut through the barriers between different business units and organisations to encourage genuine collaboration. And they can use the sort of measures and rewards that truly stimulate innovation, including incentives for terminating weak candidates as fast as possible.

The road to renewal

To sum up, the scientific and technological progress we are now making will bring a golden era of renewed productivity and prosperity. But capitalising on these advances will require major changes in Pharma's culture and working practices. Its paramount challenge is to create more value for patients, providers and payers – and thus for shareholders.

Clearly, the path each company takes will depend on its individual aims and circumstances. That path may be hard: strewn with impediments, forking in unforeseen ways, demanding decisions that are very difficult. But those companies that survive the journey will reap significant gains. In another decade, they will have the means to start developing medicines that render some of the most serious diseases from which we now suffer curable. **DDW**

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