Pressures for change in the pharmaceutical industry

MAKING NEW MEDICINES

One area of Innogen's research on global health innovation investigates the sustainability of multinational pharmaceutical companies. Our interdisciplinary approach encouraged us to look to the interactions between innovation and regulation for an explanation of the relative lack of innovativeness in developing new medicines. Our work suggests the need for a radical rethink both of the systems of innovation themselves, and of the existing governance systems as they influence each other.

As part of Innogen's stakeholder engagement we have discussed our ideas widely with industry, regulatory bodies and OECD. We have given presentations at workshops, national and international conferences. We also had the opportunity to have private conversations with the Vice Presidents for Regulatory Affairs of three of the biggest multinational pharmaceutical companies who agreed with our diagnosis of the current state of affairs and challenged us to tell them what to do about it.

In this feature, **Professor Joyce Tait** provides a background to Innogen's work in this area.

PRESSURES FOR CHANGE IN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry, colloquially known as 'big pharma' is often in the news with items ranging from revolutionary new drugs to stem cell and tissue therapies for currently incurable diseases such as diabetes or Parkinson's. However, much news coverage remains more negative in tone with criticism of the power of multinationals or of risky side effects of drugs.

A parallel theme in professional and business journals is the precarious nature of future company finances. The current drug discovery process is both expensive and slow. Developing a single new product from the lab bench to the bedside can take more than 12 years and cost more than $1 billion. Only large, multinational pharmaceutical companies, big pharma, can afford the time and cost needed to develop products all the way to market. They are then in a position to make very large profits if the drug fills a major market where there are no competing products. This 'blockbuster' drug development model, which until recently has been the mainstay of the pharmaceutical industry, depends on a stream of new, potentially blockbuster, products coming through development pipelines to maintain profit levels as existing drugs come off patent.

For more than ten years, analysts have been claiming that this drug discovery and development model is fundamentally unsustainable. The pharmaceutical sector has been accused of a failure of innovative capacity and of placing too great a focus on incremental, rather than radical, innovation. However, these symptoms are characteristic of an industry sector that has reached maturity.

'New research that has the potential to deliver public benefits may fail to do so because of the lengthy and expensive drug development process.'

Drugs have been developed for all the easy targets and they are now off-patent generic products no longer attracting high profit margins. There is also increased competition with companies from China and India entering global generic markets. It has become increasingly difficult to find new products that are effective enough to compete with existing product ranges, safe enough to pass regulatory scrutiny, and cheap enough to manufacture.

So far, problems of maturity have manifested themselves in a series of small crises every few years and each of these has been met by the industry with a round of restructuring of its innovation pipelines or changing targeting strategies. There is a strong 'bandwagon' effect here in that a particular innovation approach will spread like a wave among the large companies, only to be replaced after a few years by another tactic which again spreads among most of the major companies.

'Regulation is the factor that has enabled the overall structure of the pharmaceutical sector to remain unchanged for the last fifty years, despite numerous potentially path-breaking scientific discoveries.'

However, so far we have seen only short term, often very expensive, coping strategies. None has turned out to be the answer to the long term pipeline problem but the dominance of the multinational pharmaceutical companies has remained unassailable, even as research and technology trajectories move in a direction that does not always gel with a blockbuster approach.

Examples of strategies to make the development process more cost-effective over the past ten years include:

- **outsourcing early stage R&D to stimulate innovation**
- **setting up small, independent units within the company to stimulate innovation**
- **broadening the company's focus to target all major therapeutic areas to make the development process more cost-effective**
- **narrowing the company's focus to cover only areas of particular strength, also to improve the cost-effectiveness of the development process**

A HISTORICAL LOOK AT THE PHARMACEUTICAL INDUSTRY

So far, most of the successful life science innovations have been 'incremental' or 'path-dependent' in that they are easily accommodated within the current big pharma innovation model. Companies capitalise on new scientific discoveries by innovating around the margins of existing product development systems to do what they have always been doing, only do it better or more efficiently.

More rarely an innovation is potentially 'disruptive' or 'path-breaking', stepping outside existing paradigms, leading to discontinuities in innovation pathways, to major shifts in product types and their place in the market, and even to the creation of new industry sectors or radical re-structuring of existing sectors.

In some ways, innovation in the pharmaceutical sector has been surprisingly resistant to 'path-breaking' change, despite difficulties in markets, the steady build-up of an onerous regulatory system, huge development costs and a lengthy development life span. In contrast, over the past fifty years, the information and communication technology (ICT) sector has experienced several waves of disruption from a series of radical innovations so that it now bears no resemblance to the industry that existed in the 1960s. This type of fundamental, path-breaking change usually comes when a small, unknown company has a good idea, develops a new product which succeeds spectacularly and changes the whole shape of the market place and of the company and sector structures; Microsoft and Google would be prime examples in the ICT sector.

'The successful development of smarter life science products in the 21st century will depend on the development of very much smarter regulatory systems.'

Yet, if anything, the pharmaceutical sector has invested more money, from public and private sources, in research and development than the ICT sector. The reason behind some of the investment, particularly in the early stages when biotechnology was new, was the assumption that this might lead to the 'next big thing', the path-breaking innovation where a small company could become a multinational in its own right, with a winning strategy that was different from incumbent multinationals.

Two of today's innovative technologies that could potentially lead to disruptive change in pharmaceutical company strategies are pharmacogenetics and stem cell therapies:

Pharmacogenetics

Our genes influence our susceptibility to particular diseases and drug side effects. Pharmacogenetics is a new approach to drug development based on knowledge gained from gene sequencing. Understanding people's variable responses to drugs could lead to more effective design of clinical trials and improve disease diagnostics, drug discovery and development. The resulting 'personalised medicine' approach has been widely publicised, although it would be more accurate to describe it as 'group-based' rather than 'personalised'.

An example is the drug Herceptin, a treatment for the 25-30% of breast cancer patients who have multiple copies of a gene that predisposes them to the disease. As Herceptin is of little benefit to patients who do not have this pre-disposition, it can only be prescribed after a genetic diagnostic test. For a company this means that, as well as developing the drug for a smaller market (only those women with multiple copies of a particular gene), they also have to bear the cost of developing the diagnostic test. This is one reason why such drugs are very expensive.

The personalised medicine approach of 'finding the right medicine for the right patient' would segment the market and reduce the profit base for new drugs that are even more expensive than normal to develop.

To avoid these disruptive impacts, the market area with the greatest attraction for big pharma is the development of drugs that work in all genetic sub-groups. Applications that segment markets into smaller sub-groups, with greater public benefits but lower profit margins will not be developed, leading to conflicting priorities between commercial and public health agendas.

This demonstrates why new research that has the potential to deliver public benefits may fail to do so because of the lengthy and expensive drug development process and the need for companies to charge high prices to cover the costs of this process and also to fund future drug development.

Stem Cell Therapies

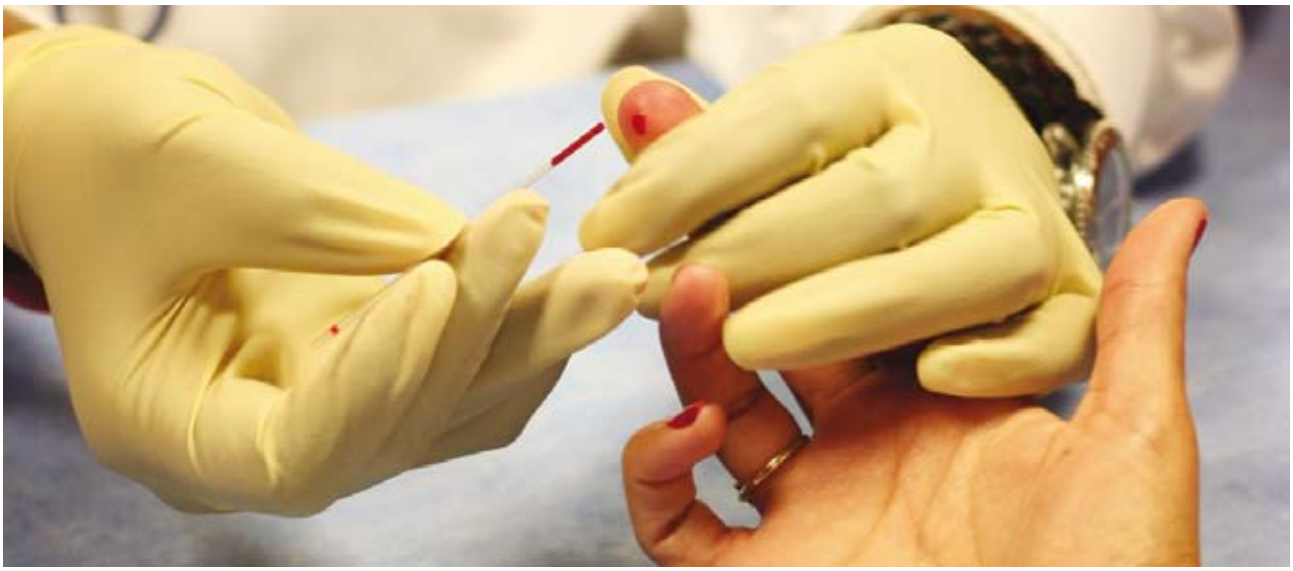
Stem cell therapies are another example where good ideas from basic research may face a difficult if not impassable route to market. Research on stem cells from a number of sources (adult, embryonic, foetal, umbilical cord blood) could potentially lead to innovative tissue-based treatments for incurable diseases such as diabetes, multiple sclerosis, or Parkinson's disease.

There is strong interest in this area from some big pharma companies, but there is no well-defined progression of stages from the basic stem cell through to the final therapeutic product and until recently there was no regulatory system in place for the products. The development path for stem cells will be radically different from the one taken for drug development. Handling living material, maintaining its integrity and freedom from contamination, and delivering it to patients, all require different facilities and skills sets from those needed to develop chemical drugs. The scale of operation is also much smaller. Indeed, for stem cells as therapies, there are virtually no points of contact with the pharmaceuticals innovation system.

The interest of big pharma companies in stem cell technology mainly relates to their use in clinical trials for conventional drugs to improve predictions of drug effects on human tissues. Thus the main impact of stem cells on big pharma companies is likely to be to facilitate chemical drug development, rather than to develop cures for currently incurable diseases. If such therapies were developed, rather than contributing to the profits of drug companies, they would undermine the markets for some blockbuster drugs. They therefore promise (or threaten) to set up an alternative, competing innovation route with a disruptive impact on traditional pharma companies.

However, if the regulatory systems being developed for tissue therapies continue to be based on a clinical trials approach similar to that for drugs, they will be too expensive for small companies to develop and unattractive to large companies. The result may be that we see far fewer stem cell therapies than expected on the basis of clinical potential.

Investments in biotechnology were expected to help the pharmaceutical industry to move on to a new high value-added life science-based innovation model, but while there has indeed been spectacular scientific progress this has not yet delivered major new revenue streams or radically new innovation models. Most investors now assume that they will support a new biotechnology firm (NBF) only until it becomes large enough or successful enough to be taken over by, or to license its technology to, a multinational. Fundamental change seems increasingly necessary and even inevitable, but at the same time increasingly unimaginable.



PATH DEPENDANT INNOVATION: THE ROLE OF REGULATORY SYSTEMS

Regulatory systems in Europe and the USA have been a significant factor in the almost entirely 'path dependant' innovation in the pharmaceutical sector since the 1960s. These regulatory systems, operated by the US Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA), create insurmountable barriers to entry for any small company with a new idea. The result is that the small companies in this sector have to rely on the large multinationals to take their products through clinical trials to a market place; with the consequence that only products that fit with the strategies of multinational companies (i.e. path-dependent innovations) will be developed.

Regulation is the factor that has enabled the overall structure of the pharmaceutical sector to remain unchanged for the last fifty years, despite numerous potentially path-breaking scientific discoveries.

Regulation is also reinforcing a situation where current innovation models are increasingly unsustainable and at the same time it is discouraging new developments that could bring about the necessary change. Tensions are building up within the system as a result of this rigidity, like a pressure cooker with a defective safety valve.

'For stem cells as therapies, there are virtually no points of contact with the pharmaceuticals innovation system.'

Taleb, in his book *The Black Swan: The Impact of the Highly Improbable*, describes the kind of situation where there is a widespread feeling that 'this can't continue'. The build-up of multiple pressures could lead to rapid, perhaps chaotic, change, but we are unable to predict what might be the eventual trigger for change and what the outcomes will be, who will be the winners and who will be the losers. Also, the longer the unsustainable situation is allowed to continue and to build up internal tensions, the more drastic the eventual change. The current global financial crisis is an illustration of this kind of event, and this crisis could indeed be the trigger that exposes the weakness of the multinational pharmaceutical companies.

FORESIGHT – PREDICTING AND ENGINEERING FUNDAMENTAL CHANGE

The Organisation for Economic Co-operation and Development (OECD) asked Innogen to develop scenarios on the future of the global health care sector for 2015-2030. We developed these scenarios from two perspectives:

(i) where the sector constructively embraced radical change and

(ii) where it continued as today with piecemeal changes in response to increasingly frequent crises.

MANAGED RADICAL CHANGE SCENARIO

Under this scenario, dramatic and fundamental change in the pharmaceutical innovation system was enabled by equally fundamental changes to regulatory systems. This would involve the development of new, smarter approaches to drug development. If industry, regulators and stakeholder groups collaborated to enable such changes to take place, the prize could be considerable. Healthcare systems, while remaining profitable, could deliver a more equitable distribution of benefits and a more cost-effective translation of innovative developments 'from bench to bedside'.

> 'Fundamental change in the pharmaceutical innovation system was enabled by equally fundamental changes to regulatory systems.'

Our imaginary outcome involved discussions at CEO level about new business strategies that led to the formation of a joint company involving two major multinational companies, one pharmaceutical and one ICT. The joint company would gain first mover advantage in what they perceived was the way forward for the sector: a new co-ordinated mode of operation which became known as Networked Health Care (NHC). Healthcare became predominantly a service industry, co-ordinating the activities of a range of public and private sector providers to deliver drugs, information, services, treatments, and related products to patients.

An important aspect of the NHC approach was the involvement of several different types of company and product within the same networked organisation. The key to its profit model was that the most powerful industry partner was no longer acting as a technology gate-keeper, inhibiting (with the unwitting aid of regulatory systems) the development of innovations that did not contribute to the big pharma approach to health care. While the profit base of any individual item in the portfolio of a NHC-based company was not comparable to that of a block-buster drug, the co-ordinated delivery of a range of drugs and therapies, each with a more modest profit base, proved to be a more viable and resilient approach in the long term.

The success of this model led to its uptake by others in the ICT and pharmaceuticals sectors, and the fact that the route to market for health care products was increasingly brokered by such companies meant that contributing companies could succeed financially with a much wider range of innovation strategies than was previously the case. The fruits of public and private investment in life sciences began to emerge in new and often-unexpected ways, stimulated by new types of partnership bringing together companies and individuals with biochemical, chemical, IT, physics and engineering expertise.

By 2030 the long term winners were the companies that, faced with a need for creative change, had been able to re-structure their innovation models, even if it meant making many current products and processes redundant. Companies that aggressively defended the status quo in a rapidly changing environment gained in the short term but did not retain their dominance in the long run.

MUDDLING THROUGH SCENARIO

In the absence of major shocks to the system, the pharmaceutical sector could continue to be populated by companies seeking to maximise their short term advantages from life science innovation. In normal circumstances these are admirable survival tactics but much less so if the underlying model is unsustainable. Difficulties in finding new products to fill development pipelines and a lack of income to fund new developments led to intense, often dysfunctional, competition between major companies. It also encouraged practices that were portrayed by public groups as unethical.

> 'Companies in the sector experienced a slow decline to become generic drug producers with a greatly diminished R&D base.'

Companies in the sector experienced a slow decline to become generic drug producers with a greatly diminished R&D base. There were numerous missed innovation opportunities; dysfunctional competition between and within companies; and relationships with regulators were adversarial rather than collaborative.

Barring a complete collapse of the world economy, technological innovation is likely to be the main determinant of future healthcare scenarios provided this can be facilitated by smarter regulatory systems. Recent events thus raise the question whether the current global economic shocks could lead to a period of chaotic turbulence in the pharmaceutical sector, rather than the managed change envisaged in the first scenario or the slow decline to become producers of commodity chemicals envisaged in the second case.

FORESIGHT AS ENGINEERING CHANGE RATHER THAN PREDICTING CHANGE

Increasingly Foresight aims, not just to predict change, but to determine how change can be achieved to benefit society. If one finds the right levers, and is able to align system components to be sufficiently flexible, change can take place surprisingly rapidly. However, outcomes will always be uncertain, being determined by interactions among drivers and actors in complex and unpredictable ways. Having the right people in the right place at the right time and creating appropriate incentives for change are all part of the complex toolkit needed to deliver benefits from Foresight but they do not guarantee success.

The kind of change needed to shift large scale entrenched systems like the pharmaceutical industry or regulatory agencies has been described as 'turning round an oil tanker', but even once you have turned the oil tanker round, it is still an oil tanker. Achieving the Managed Radical Change scenario would be equivalent to converting the oil tanker into a smaller, more multifunctional mother ship in charge of a fleet of smaller, faster vessels capable of taking off in many directions while remaining well connected with one another.

LOOKING AHEAD

How can the current mis-match between the nature of new life science innovations, the kind of company that can best exploit these innovations, public and patient expectations of new drugs and treatments, and regulatory systems that were designed around 20th century models of drug development, be reconciled?

'It has become increasingly difficult to find new products that are effective enough to compete with existing product ranges, safe enough to pass regulatory scrutiny, and cheap enough to manufacture.'

Research conducted by Innogen suggests that there are serious blockages to radical transformation of the drug discovery system. The potential for change is there, in that at least some seeds exist. Science and technologies are moving in new directions in stem cells, biomarkers, pharmacogenetics, and synthetic biology, to give some current examples, and science based on genetic understanding is beginning to change some practices of drug and vaccine development. At the same time, recently, there have been more efforts to close the gaps that deny development of, and access to, drugs and vaccines for a majority of the world's population. But so far, there have been no big breakthroughs in the regulatory and delivery climate that might open up possible new waves of radical innovation.

In our view the key to change, showing how it could be done not merely recognising that it is needed, would require joint action by industry managers, regulators and a range of other stakeholders (such as patients, health systems, research funders, including funds like the Wellcome Trust, Cancer Research UK and the Bill and Melinda Gates Foundation) with a good awareness of the pressures and opportunities for change.

The interactions between innovation and regulation in life sciences are crucial, particularly the process by which regulation not only prevents harmful products from reaching the market, but also determines the entire shape of the industry sector. These interactions determine which companies dominate and which are subservient, which are the winning innovation strategies and even which countries are able to play in this lucrative game.

Leading science managers and practitioners now think that new scientific developments are gaining momentum and have potential to force a change, although there have been similar bouts of optimism in the past. The key requirement is for the regulatory environment to change to accommodate a broader range of innovation models. We are therefore suggesting that the successful development of smarter life science products in the 21st century will depend on the development of very much smarter regulatory systems.

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