EDUCATE, INNOVATE

Pharma, academia and biotech – could a balanced mix of the three be the perfect combination for drug discovery? Ray Hill of Imperial College London talks to Steve Coomber about potential pitfalls, culture clashes and how to deal with fragile relationships between key industry players.

Contributor profile

From 2002–2008 Professor Ray Hill was executive director, licensing and external research, Europe for Merck Sharp & Dohme Research Laboratories. He is now visiting professor in neuroscience and mental health and honorary business development advisor at Imperial College London, and visiting professor at a number of other UK universities.

These are challenging times for big pharma. It takes between ten and 15 years and over $800 million (£500 million) to develop a new medicine. Despite billions of dollars expended on R&D, and huge advances in technology and knowledge, the average number of first-in-class drugs approved each year by the US Food and Drug Administration (FDA) over the last decade remains static. As productivity declines and R&D costs spiral, pharmaceutical companies are increasingly looking for new ways to innovate, turning to alliances with academia and biotech. Yet such relationships are fraught with difficulties, not least the challenge of overcoming cultural barriers, explains Ray Hill, visiting professor of pharmacology at Imperial College London.

The innovation challenge

Today's major pharmaceuticals are facing an increasingly tough innovation challenge, says Hill, who has 20 years of experience working for Merck, in licensing, external research and drug discovery. 'Even with the new insights and technology we have, when a compound enters phase one clinical trials, it probably has a 10% chance of becoming a marketed product,' he says.

In fact, the ability to understand drug mechanisms and put drugs appropriately into clinical trials has not changed much over recent years. One study, says Hill, shows that while there was a marked increase in the number of compounds going into Phase I and then Phase II clinical trials between 1997 and 2007, the number of compounds progressing to final-stage Phase III clinical trials did not increase.

The diminishing returns on R&D spend highlight big pharma's problems. In the US, total pharma company spend on R&D rocketed from $16 billon (£10 billion) in

1993 to $40 billion (£25 billion) in 2006. Yet only 24 first-in-class drugs were approved by the FDA in 2008, 18 in 2006 and 2007, and an average of 26 a year in the six years prior to 2006. Productivity has remained resolutely static, if not declined slightly, while spending has markedly increased.

Expectations for efficacy and safety appear to increase annually. Hill points to recent concerns about the cardiotoxicity risk associated with drugs that interfere with the hERG potassium channel and may cause acquired long QT syndrome. 'Twenty years ago drugs were marketed in ignorance of this channel,' he says. 'If we tested all drugs on the market at the moment I'm sure we would find some that show activity against this channel. But, for pharmacodynamic reasons, it's safe to use them.

'These days you have a cellular screen for activity against this channel, and at very early-stage testing any drug showing significant activity is dumped. Molecules that would previously have gone down the pipeline are eliminated because of this theoretical risk. The public should expect the safest drugs, and the best-available technology be used to make them safe, but the more molecules thrown away because of unwanted activity, the harder it is to select the activity you do want.'

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This combination of factors creates an increased dependence of big pharma on licensed-in products and technology. The pace of technological change means that, no matter how big a company is, it is less likely to have all the internal resources required to do the whole drug development job, from drug discovery through to market. Consequently, many big pharmaceutical companies are changing their innovation strategy, and moving to more open innovation models, with an increased emphasis on collaboration, cooperation and partnership with biotech firms and academic institutions. Companies like GlaxoSmithKline, Merck and others have announced that a significant proportion of their R&D budget will be spent outside their company.

Culture clash

There has always been an important relationship between academia and the pharmaceutical industry, but it is a relationship that has changed significantly over the last two decades. 'Going back 25 years or so, it was true to say that the really top-quality scientists didn't go into industry. It was seen as a second-rate career choice,' says Hill. 'So there was a period of time when the real cutting-edge science could only be found in the universities.'

In the early 1980s, however, some distinguished scientists decided to move from academia and work in drug discovery and the pharma industry. Universities became a breeding

ground for pharma industry personnel, as well as conducting the blue skies research that eventually became drug discovery projects. At the same time a new layer of small biotech companies has emerged, between the universities and big companies. Some of these biotech firms have spun out of the universities, while some have come out of closed projects from pharma. Although pharmaceutical companies understand the need to collaborate and form alliances with academia and biotech, managing those relationships can be a challenge, says Hill. 'One barrier is cultural,' he explains. 'Their motives are very different. The academics' reason for being there is to advance their reputation, and that of their university, by publishing prestigious papers and hopefully making significant scientific discoveries. Essentially, it is curiosity-driven unmanaged research, and while it has been successful in the past, it is an entirely different mindset to the way industry looks at things.'

UKDDC PROMOTES ACADEMIA

In March 2009 the UK Drug Discovery Consortium was officially launched. The aim of the group is to research and develop new molecule therapeutics through non-industry organisations. It hopes to offer an alternative source of quality drug leads and candidates for pharma, biotech and public private partnerships; enhance the profile of non-industry-based drug discovery in the UK; provide education and training for building integrated drug discovery operations in academic settings; share knowledge and know-how between consortium members for more effective drug discovery programmes; and give consortium members access to specialised resources in a cost-effective manner.

Sometimes industry invests in that type of research and then tries to manage it in the way that it would manage internal projects. That approach may be some way from what the principal investigator in the academic laboratory had envisaged. In this situation, the arrangement can fall apart quite early on in the project simply because the people are not good at working together. Equally, for the major pharmaceutical companies, throwing lots of money at an academic laboratory and then standing back and saying, 'see you in three years, when you have been successful' requires lots of courage. Big pharma and industry laboratories are under pressure to provide shareholder value; they are used to balancing the budget every month and making sure that money is spent on something that is going to be productive.

Researchers working in biotech firms have often worked in big pharma at some stage in their careers. As a result, they may feel constrained by the bureaucracy of a big company and its very hierarchical structure. People in small biotech firms tend to like the fact that they have several different jobs in the firm, and don't need to ask a superior if it is okay to do certain things, believes Hill. 'Biotech firms are very agile and able to change their direction and jump on a new idea very quickly, whereas a big company probably organises a series of committee meetings,' he says. 'When biotech companies are bought by big companies there is a danger you will change the culture of the small company and the key people you bought the company to get hold of will then leave.'

Taking control of a biotech without changing its culture, and reducing productivity, is therefore a real challenge. While there is no magic bullet, more companies are adopting the approach pioneered by Johnson & Johnson; running the biotech as part of the bigger company as far as budgets are concerned, but in terms of its scientific management and the way that it runs, leaving it alone as much as possible and preserving its original culture, as that was one of the main reasons for buying the firm in the first place.

Managing relationships

Whether big pharma is linking up with a university, group of universities or a biotech firm, says Hill, if you want to avoid the possible negative effects of culture clash, then that relationship must be managed. Otherwise it is all too easy to lose productivity or people, or be left with a tense standoff between the parties, because they are not talking the same research language. One effective solution is to use professionally trained personnel, often in the form of an alliance management group, as intermediaries that work to make sure that this relationship functions properly.

'For example, the group I started for Merck in Europe was a licensing and external research group, staffed by scientists who all had at least ten years of drug discovery experience, and a good publication record and were respected by the academic community,' says Hill. 'We acted as ambassadors, as the first point of contact with universities and biotechs, making sure that the way we started our dialogue with the potential partner was appropriate.'

There is no question that the world is changing and we have entered a period of flux where big pharma is searching for the most effective drug discovery model for the future. Whatever that model turns out to be, those major pharmaceutical firms that find ways of working effectively with a range of partners are likely to be the big winners in the long run. 'The democratisation of drug discovery means that universities and small companies can now do the things that ten years ago only big companies could do,' Hill concludes. 'The real value of scientific discovery is the same, whether it comes from academia, from a biotech or from a big company. The game that the big companies have got to play is to try and be extremely aware of what is going on elsewhere.' WPF